NONINVASIVE VITAL SIGNS SURGICAL MONITOR FOR CONSCIOUS MICE AND RATS

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Anesthesia and Surgical Research

Isoflurane Induces Learning Impairment That Is Mediated by Interleukin 1β in Rodents

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0051431

Wednesday, December 12, 2012

Cao L, Li L, Lin D, Zuo Z

... The settings were adjusted to maintain the end tidal CO 2 at ~32 mm Hg. Rectal temperature was maintained at 37°C ±0.5°C. Heart rate and SpO 2 were measured continuously during anesthesia with a MouseOx™ Pulse Oximeter (Harvard Apparatus, Holliston, MA). ...

Postoperative cognitive decline is a clinical syndrome. Volatile anesthetics are commonly used during surgery. It is conceivable that volatile anesthetics may contribute to postoperative cognitive decline. Isoflurane can impair cognitive functions of animals under certain conditions. However, the mechanisms for this impairment are not clear. Here, male 18-month old Fisher 344 rats or 10-week old mice were exposed to 1.2 or 1.4% isoflurane for 2 h. Our studies showed that isoflurane impaired the cognitive functions of the rats in Barnes maze. Isoflurane-exposed rats had reduced freezing behavior during the training sessions in the fear conditioning test. This isoflurane effect was attenuated by lidocaine, a local anesthetic with anti-inflammatory property. Rats that had training sessions and were exposed to isoflurane 30 min later had freezing behavior similar to that of control animals. Isoflurane increased the expression of interleukin 1β (IL-1β), interleukin-6 and activated caspase 3 in the hippocampus of the 18-month old rats. IL-1β positive staining was co-localized with that of NeuN, a neuronal marker. The increase of IL-1β and activated caspase 3 but not interleukin-6 was attenuated by lidocaine. Isoflurane also impaired the cognitive functions of 10-week old C57BL/6J mice and increased IL-1β in their hippocampi. However, isoflurane did not affect the cognitive functions of IL-1β deficient mice. Our results suggest that isoflurane impairs the learning but may not affect the recall of the aged rats. IL-1β may play an important role in this isoflurane effect.

Anaesthesia and physiological monitoring during in vivo imaging of laboratory rodents: considerations on experimental outcomes and animal welfare

www.google.com/url?q=http://www.ejnmmires.com/content/pdf/2191-219X-2-44.pdf&sa=D&sntz=1&usg=...

Monday, October 1, 2012

Jordi L Tremoleda, Angela Kerton and Willy Gsell

The implementation of imaging technologies has dramatically increased the efficiency of preclinical studies, enabling a powerful, non-invasive and clinically translatable way for monitoring disease progression in real time and testing new therapies. The ability to image live animals is one of the most important advantages of these technologies. However, this also represents an important challenge as, in contrast to human studies,

imaging of animals generally requires anaesthesia to restrain the animals and their gross motion. Anaesthetic agents have a profound effect on the physiology of the animal and may thereby confound the image data acquired. It is therefore necessary to select the appropriate anaesthetic regime and to implement suitable systems for monitoring anaesthetised animals during image acquisition. In addition, repeated anaesthesia required for longitudinal studies, the exposure of ionising radiations and the use of contrast agents and/or imaging biomarkers may also have consequences on the physiology of the animal and its response to anaesthesia, which need to be considered while monitoring the animals during imaging studies. We will review the anaesthesia protocols and monitoring systems commonly used during imaging of laboratory rodents. A variety of imaging modalities are used for imaging rodents, including magnetic resonance imaging, computed tomography, positron emission tomography, single photon emission computed tomography, high frequency ultrasound and optical imaging techniques such as bioluminescence and fluorescence imaging. While all these modalities are implemented for non-invasive in vivo imaging, there are certain differences in terms of animal handling and preparation, how the monitoring systems are implemented and, importantly, how the imaging procedures themselves can affect mammalian physiology. The most important and critical adverse effects of anaesthetic agents are depression of respiration, cardiovascular system disruption and thermoregulation. When anaesthetising rodents, one must carefully consider if these adverse effects occur at the therapeutic dose required for anaesthesia, if they are likely to affect the image acquisitions and, importantly, if they compromise the well-being of the animals. We will review how these challenges can be successfully addressed through an appropriate understanding of anaesthetic protocols and the implementation of adequate physiological monitoring systems.

Differential actions of isoflurane and ketamine-based anaesthetics on cochlear function in the mouse

http://www.sciencedirect.com/science/article/pii/S0378595512002031

Monday, October 1, 2012

Jennie M.E. Cederholm, Kristina E. Froud, Ann C.Y. Wong, Myungseo Ko, Allen F. Ryan, Gary D. Housley

... The cardio-pulmonary status of the animals, and the depth of anaesthesia, was monitored using an oxymeter (MouseOx ® , STARR Life Sciences). Experiments were alternated between isoflurane and K/X/A anaesthetics. 2.2. Auditory brainstem response. ...

Isoflurane is a volatile inhaled anaesthetic widely used in animal research, with particular utility for hearing research. Isoflurane has been shown to blunt hearing sensitivity compared with the awake state, but little is known about how isoflurane compares with other anaesthetics with regard to hair cell transduction and auditory neurotransmission. The current study was undertaken in C57Bl/6J and C129/SvEv strains of mice to determine whether isoflurane anaesthesia affects hearing function relative to ketamine-based anaesthesia. Cochlear function and central auditory transmission were assessed using auditory brainstem response (ABR) and distortion product otoacoustic emission (DPOAE), comparing thresholds and input/output functions over time, for isoflurane vs. ketamine/xylazine/acepromazine anaesthesia. ABR thresholds at the most sensitive region of hearing (16 kHz) were initially higher under isoflurane anaesthesia. This reduced hearing sensitivity worsened over the 1 h study period, and also became evident with broadband click stimulus. Ketamine anaesthesia provided stable ABR thresholds. Although the growth functions were unchanged over time for both anaesthetics, the slopes under isoflurane anaesthesia were significantly less. Cubic (2f1–f2) DPOAE

thresholds and growth functions were initially similar for both anaesthetics. After 60 min, DPOAE thresholds increased for both groups, but this effect was significantly greater with ketamine anaesthesia.
The isoflurane-mediated increase in ABR thresholds over time is attributable to action on cochlear nerve activation, evident as a right-shift in the P1-N1 input/output function compared to K/X/A. The ketamine-based anaesthetic produced stable ABR thresholds and gain over time, despite a right-shift in the outer hair cell – mediated DPOAE input/output function.

Contribution of microRNA-203 to the isoflurane preconditioning-induced neuroprotection

http://www.sciencedirect.com/science/article/pii/S0361923012001013

Wednesday, August 1, 2012

Lin Cao, Chenzhuo Feng, Liaoliao Li, Zhiyi Zuo

... Rectal temperature was maintained at 37 °C ± 0.5 °C. Heart rate and pulse oximeter oxygen saturation (SpO 2) were measured continuously during anesthesia with a MouseOx™ Pulse Oximeter (Harvard Apparatus, Holliston, MA). ...

A prior exposure to isoflurane, a common volatile anesthetic, provides neuroprotection (isoflurane preconditioning). To determine the role of microRNAs in this protection, we performed microRNA array assay on cerebral cortex harvested from rats exposed to isoflurane or isoflurane-exposed rat B35 neuron-like cells. We showed that isoflurane significantly increased microRNA-203 expression in B35 neuron-like cells. The microRNA-203 expression in rat cerebral cortex also trended to increase after isoflurane exposure. Over-expression of microRNA-203 increased the tolerance of B35 cells to oxygen-glucose deprivation and the expression of phospho-Akt, a protein kinase that promotes cell survival. Isoflurane preconditioning also reduced the injury of these cells after oxygen-glucose deprivation. These results suggest that isoflurane preconditioning-induced neuroprotection may involve increased expression of microRNA-203. This finding provides the initial evidence that micoRNA-203 is a target for isoflurane in the brain.

Inhalation Anesthesia-Induced Neuronal Damage and Gene Expression Changes in Developing Rat Brain

http://versita.metapress.com/content/057j056316824536/

Tuesday, July 10, 2012

Fang Liu, Lei Guo, Jie Zhang, Shuo W. Rainosek, Leming Shi, Tucker A. Patterson, Quan-Zhen Li, Natalya Sadovova, Joseph P. Hanig, Merle G. Paule, William Slikker, Jr., Cheng Wang

.. The control group received mock anesthesia (air was used as a substitute). Oxygen saturation was measured with a small clip that attached to an appendage (eg a foot) on the animal's body using MouseOx system (Starr Life Sciences Corp, Oakmont, PA, USA). ...

Nitrous Oxide (N2O), an N-methyl-D-aspartate (NMDA) receptor antagonist, and isoflurane (ISO), which acts on multiple receptors including postsynaptic gamma-aminobutyric acid (GABA) receptors, are frequently used inhalation anesthetics, alone or as a part of a balanced anesthetic regimen administered to pregnant women and to human neonates and infants requiring surgery. The current study investigated histological features and gene expression profiles in response to prolonged exposure to N2O or ISO alone, and their combination in developing rat brains. Postnatal day 7 rats were exposed to clinically-relevant concentrations of N2O (70%), ISO (1.0%) or N2O plus ISO (N2O + ISO) for 6 hours. The neurotoxic effects were evaluated and the brain tissues were harvested for RNA extraction 6 hours after anesthetic administration. The prolonged exposure to N2O + ISO produced elevated neuronal cell death as indicated by an increased number of TUNEL-positive cells in frontal cortical levels compared with control. No significant neurotoxic effects were observed in animals exposed to N2O or ISO alone. DNA microarray analysis revealed gene expression changes after N2O, ISO or N2O + ISO exposure. Differentially expressed genes (DEGs) from the N2O + ISO group were significantly associated with 45 pathways directly related to brain functions. Although the gene expression profiles from animals exposed to N2O or ISO alone were remarkably different from those of the control group, the pathways of these genes involved were not closely associated with neurons. These findings provide novel insights into the mechanisms by which N2O + ISO cause neurotoxicity in the developing brain, suggesting multiple factors are involved in the neuronal cell deathinducing effects (cascades) of N2O + ISO.

Hyperalgesia by low doses of the local anesthetic lidocaine involves cannabinoid signaling: An fMRI study in mice

http://www.painjournalonline.com/article/S0304-3959(12)00207-2/abstract

Friday, May 11, 2012

Simone C. Bosshard, Joanes Grandjean, Aileen Schroeter, Christof Baltes, Hanns U. Zeilhofer, Markus Rudin

Abstract

Lidocaine is clinically widely used as a local anesthetic inhibiting propagation of action potentials in peripheral nerve fibers. Correspondingly, the functional magnetic resonance imaging (fMRI) response in mouse brain to peripheral noxious input is largely suppressed by local lidocaine administered at doses used in a clinical setting. We observed, however, that local administration of lidocaine at doses 100× lower than that used clinically led to a significantly increased sensitivity of mice to noxious forepaw stimulation as revealed by fMRI. This hyperalgesic response could be confirmed by behavioral readouts using the von Frey filament test. The increased sensitivity was found to involve a type 1 cannabinoid (CB1) receptor-dependent pathway as global CB1 knockout mice, as well as wild-type mice pretreated systemically with the CB1 receptor blocker rimonabant, did not display any hyperalgesic effects after low-dose lidocaine. Additional experiments with nociceptor-specific CB1 receptor knockout mice indicated an involvement of the CB1 receptors located on the nociceptors. We conclude that low concentrations of lidocaine leads to a sensitization of the nociceptors through a CB1 receptor-dependent process. This lidocaine-induced sensitization might contribute to postoperative hyperalgesia.

Low frequency stimulation of the perforant pathway generates anesthesia-specific variations in neural activity and BOLD responses in the rat dentate gyrus.

http://www.ncbi.nlm.nih.gov/pubmed/21863039

Wednesday, February 1, 2012

Krautwald K, Angenstein F.

Abstract

To study how various anesthetics affect the relationship between stimulus frequency and generated functional magnetic resonance imaging (fMRI) signals in the rat dentate gyrus, the perforant pathway was electrically stimulated with repetitive low frequency (i.e., 0.625, 1.25, 2.5, 5, and 10 Hz) stimulation trains under isoflurane/N(2)O, isoflurane, medetomidine, and α-chloralose. During stimulation, the blood oxygen level-dependent signal intensity (BOLD response) and local field potentials in the dentate gyrus were simultaneously recorded to prove whether the present anesthetic controls the generation of a BOLD response via targeting general hemodynamic parameters, by affecting mechanisms of neurovascular coupling, or by disrupting local signal processing. Using this combined electrophysiological/fMRI approach, we found that the threshold frequency (i.e., the minimal frequency required to trigger significant BOLD responses), the optimal frequency (i.e., the frequency that elicit the strongest BOLD response), and the spatial distribution of generated BOLD responses are specific for each anesthetic used. Concurrent with anesthetic-dependent characteristics of the BOLD response, we found the pattern of stimulus-induced neuronal activity in the dentate gyrus is also specific for each anesthetic. Consequently, the anesthetic-specific influence on local signaling processes is the underlying cause for the observation that an identical stimulus elicits different BOLD responses under various anesthetics.

Determination of Minimum Alveolar Concentration for Isoflurane and Sevoflurane in a Rodent Model of Human Metabolic Syndrome

http://www.anesthesia-analgesia.org/content/114/2/297.short

Tuesday, December 13, 2011

Dinesh Pal, PhD, Meredith E. Walton, BA, William J. Lipinski, MS, Lauren G. Koch, PhD, Ralph Lydic, PhD, Steve L. Britton, PhD and George A. Mashour, MD, PhD

Abstract

BACKGROUND: Morbid obesity affects the pharmacokinetics and pharmacodynamics of anesthetics, which may result in inappropriate dosing. We hypothesized that obesity significantly alters the minimum alveolar concentration (MAC) for isoflurane and sevoflurane. To test this hypothesis, we used a rodent model of human metabolic syndrome developed through artificial selection for inherent low aerobic capacity runners (LCR) and high aerobic capacity runners (HCR). The LCR rats are obese, display phenotypes homologous to those characteristic of human metabolic syndrome, and exhibit low running endurance. In contrast, HCR rats have high running endurance and are characterized by improved cardiovascular performance and overall health.

METHODS: Male and female LCR (n = 10) and HCR (n = 10) rats were endotracheally intubated and maintained on mechanical ventilation with either isoflurane or sevoflurane. A bracketing design was used to determine MAC; sensory stimulation was induced by tail clamping. An equilibration period of 30 minutes was provided before and between the consecutive tail clamps. Two-tailed parametric (unpaired t test) and nonparametric (Mann–Whitney test) statistics were used for the comparison of MAC between LCR and HCR rats. The data are reported as mean ± SD along with the 95% confidence interval. A P value of <0.05 was considered statistically significant.

RESULTS: The MAC for isoflurane in LCR rats (1.52% ± 0.13%) was similar to previously reported isoflurane-MAC for normal rats (1.51% ± 0.12%). The HCR rats showed a significantly higher isoflurane-MAC (1.90% ± 0.19%) than did the LCR rats (1.52% ± 0.13%) (P = 0.0001). The MAC for sevoflurane was not significantly different between LCR and HCR rats and was similar to the previously published sevoflurane-MAC for normal rats (2.4% ± 0.30%). There was no influence of sex on the MAC of either isoflurane or sevoflurane.

CONCLUSION: Obesity and associated comorbidities do not affect anesthetic requirements as measured by MAC in a rodent model of metabolic syndrome. By contrast, high aerobic capacity is associated with a higher MAC for isoflurane and may be a risk factor for subtherapeutic dosing.

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Dynamic determination of oxygenation and lung compliance in murine pneumonectomy Read More: http://informahealthcare.com/doi/abs/10.3109/01902148.2011.561399

http://informahealthcare.com/doi/abs/10.3109/01902148.2011.561399

Wednesday, June 1, 2011

Barry C. Gibney, Grace S. Lee, Jan P. Houdek,Miao Lin, Lino F. Miele, Kenji Chamoto, Moritz A. Konerding, Akira Tsuda, and Steven J. Mentzer

Thoracic surgical procedures in mice have been applied to a wide range of investigations, but little is known about the murine physiologic response to pulmonary surgery. Using continuous arterial oximetry monitoring and the FlexiVent murine ventilator, the authors investigated the effect of anesthesia and pneumonectomy on mouse oxygen saturation and lung mechanics. Sedation resulted in a dose-dependent decline of oxygen saturation that ranged from 55% to 82%. Oxygen saturation was restored by mechanical ventilation with increased rate and tidal volumes. In the mouse strain studied, optimal ventilatory rates were a rate of 200/minute and a tidal volume of 10 mL/kg. Sustained inflation pressures, referred to as a “recruitment maneuver,” improved lung volumes, lung compliance, and arterial oxygenation. In contrast, positive end-expiratory pressure (PEEP) had a detrimental effect on oxygenation; an effect that was ameliorated after pneumonectomy. These results confirm that lung volumes in the mouse are dynamically determined and suggest a threshold level of mechanical ventilation to maintain perioperative oxygen saturation.

Monitoring of Vital Signs for Long-Term Survival of Mice under Anesthesia

http://cshprotocols.cshlp.org/content/2011/2/pdb.prot5563.short

Saturday, January 1, 2011

Andrew J. Ewald, Zena Werb and Mikala Egeblad

Anesthesia protocols for mice have been optimized, as described here, to achieve long-term imaging (up to 40 h) and facilitate survival through careful monitoring of the mice during anesthesia. Isoflurane anesthesia is the preferred method, because it can be adjusted quickly as needed during the experiment. Critical for the long survival times under anesthesia is the use of the lowest possible dose of anesthesia, which is identified by corneal reflex and monitoring of breath and heart rate, blood-oxygenation levels, and vascular distension

using an oximeter probe. It is critical that the carrier gas for isoflurane is humidified. In addition, it is essential to keep mice warm and to compensate for loss of fluid by supplementing with saline. Alternative approaches rely on injectable anesthetics, which do not require dedicated equipment or high-ventilation rates in the imaging room. However, injectable anesthetics are harder to dose for image sessions of >6-10 h.

Anesthetic Considerations for the Study of Murine Tumor Models

http://www.springerlink.com/content/p3k300676018w12t/

Saturday, January 1, 2011

Thies Schroeder, Siqing Shan and Mark W. Dewhirst

Abstract

This chapter is to provide researchers with an overview over the requirements, challenges, and current solutions of rodent anesthesia in preclinical cancer research. Since the overwhelming majority of research is currently done in mouse models, rather than rats or other rodents, the review will focus predominantly on mouse strains. We will provide a range of hands-on protocols and suggestions on the application of the most commonly used rodent anesthesia procedures.

Behavioral Studies

Haploinsufficiency of the E3 Ubiquitin Ligase C-Terminus of Heat Shock Cognate 70 Interacting Protein (CHIP) Produces Specific Behavioral Impairments

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0036340
Friday, May 11, 2012

McLaughlin B, Buendia MA, Saborido TP, Palubinsky AM, Stankowski JN, et al.

The multifunctional E3 ubiquitin ligase CHIP is an essential interacting partner of HSP70, which together promote the proteasomal degradation of client proteins. Acute CHIP overexpression provides neuroprotection against neurotoxic mitochondrial stress, glucocorticoids, and accumulation of toxic amyloid fragments, as well as genetic mutations in other E3 ligases, which have been shown to result in familial Parkinson's disease. These studies have created a great deal of interest in understanding CHIP activity, expression and modulation. While CHIP knockout mice have the potential to provide essential insights into the molecular control of cell fate and survival, the animals have been difficult to characterize in vivo due to severe phenotypic and behavioral dysfunction, which have thus far been poorly characterized. Therefore, in the present study we conducted a battery of neurobehavioral and physiological assays of adult CHIP heterozygotic (HET) mutant mice to provide a better understanding of the functional consequence of CHIP deficiency. We found that CHIP HET mice had normal body and brain weight, body temperature, muscle tone and breathing patterns, but do have a significant elevation in baseline heart rate. Meanwhile basic behavioral screens of sensory, motor, emotional and cognitive functions were normative. We observed no alterations in performance in the elevated plus maze, light-dark preference and tail suspension assays, or two simple cognitive tasks: novel object recognition and spontaneous alternation in a Y maze. Significant deficits were found, however, when CHIP HET mice performed wire hang, inverted screen, wire maneuver, and open field tasks. Taken together, our data indicate a clear subset of behaviors that are altered at baseline in CHIP deficient animals, which will further guide whole animal studies of the effects of CHIP dysregulation on cardiac function, brain circuitry and function, and responsiveness to environmental and cellular stress.

Assessment of locomotion in chlorine exposed mice by computer vision and neural networks

http://jap.physiology.org/content/112/6/1064.short

Thursday, March 15, 2012

Aristotelis S. Filippidis, Sotirios G. Zarogiannis, Alan Randich, Timothy J. Ness, and Sadis Matalon

... These measurements were repeated with air breathing mice. Peripheral oxygen saturation was assessed periodically with a MouseOx pulse oximeter equipped with a neck collar according to manufacturer instructions (STARR Lifesciences.). Video capture and acquisition. ...

Assessment of locomotion following exposure of animals to noxious or painful stimuli can offer significant insights into underlying mechanisms of injury and the effectiveness of various treatments. We developed a novel method to track the movement of mice in two dimensions using computer vision and neural network algorithms. By using this system we demonstrated that mice exposed to chlorine (Cl2) gas developed impaired locomotion and increased immobility for up to 9 h postexposure. Postexposure administration of buprenorphine, a common analgesic agent, increased locomotion and decreased immobility times in Cl2- but not air-exposed mice, most likely by decreasing Cl2-induced pain. This method can be adapted to assess the effectiveness of various therapies following exposure to a variety of chemical and behavioral noxious stimuli.

Hypertension, Hypotension & Other Cardiovascular Disorders

Oxygen Inhalation Improves Survival Time of Mice with Acute Intra-abdominal Hypertension and Protects Liver Cells

http://www.sciencedirect.com/science/article/pii/S0041134512003314

Friday, June 1, 2012

Q. He, L. Cai, S. Zhang, Y. Chen, G. Liu, C. Zhang

... 9. Data Collection and Statistical Analyses. A noninvasive pulse-blood oxygen monitor (MouseOx, STARR, Oakmont, PA) for small animals used to determine the survival of mice at high IAP was represented as mean values ± standard deviations. ...

Objective
The objectives of this study were to establish a mouse model of sustainable, stable acute intra-abdominal hypertension (IAH), seeking to observe the survival time and liver functions at different intra-abdominal pressures (IAP), and to investigate changes after oxygen therapy.
Methods
Sixty Kunming mice were assigned to 4 groups with an average of 15, 20, 30, or 40 cmH2O IAP. The 40 cmH2O group seemed to be appropriate for follow-up experiments. The 45 mice added to the cohort were assigned into 3 groups administered an average of 50%, 80%, and 100% O2, respectively. Liver and blood samples were used to compare the rates of apoptosis using the TUNEL assay as well as alanine aminotransferase (ALT), aspartate aminotransferase (AST); Caspase-3, 9, MDA, and SOD concentrations.
Results
Most animals in the 15 and 20 cmH2O groups survived 8 hours. The average survival for the 30 and 40 cmH2O groups were 4.54 ± 0.54 hours and 2.04 ± 0.44 hours, respectively ($P < .01$). As the oxygen concentration increased, the survival time was prolonged among the 40 cmH2O IAP group ($P < .01$), and the member of apoptotic hepatic cells decreased ($P < .01$), with a concomittent decrease in caspase 3 and 9 as well as malondialdehyde, although superoxide dismutase showed the opposite results.
Conclusion
The present work using a mouse model for acute IAH showed oxygen inhalation to improve host survival and protect liver cells.

The A2B adenosine receptor modulates pulmonary hypertension associated with interstitial lung disease

http://www.fasebj.org/content/26/6/2546.short

Tuesday, March 13, 2012

Harry Karmouty-Quintana, Hongyan Zhong, Luis Acero, Tingting Weng, Ernestina Melicoff, James D. West||, Anna Hemnes||, Almut Grenz, Holger K. Eltzschig, Timothy S. Blackwell||, Yang Xia, Richard A. Johnston, Dewan Zeng, Luiz Belardinelli and Michael R. Blackburn

Abstract

Development of pulmonary hypertension is a common and deadly complication of interstitial lung disease. Little is known regarding the cellular and molecular mechanisms that lead to pulmonary hypertension in patients with interstitial lung disease, and effective treatment options are lacking. The purpose of this study was to examine the adenosine 2B receptor (A2BR) as a regulator of vascular remodeling and pulmonary hypertension secondary to pulmonary fibrosis. To accomplish this, cellular and molecular changes in vascular remodeling were monitored in mice exposed to bleomycin in conjunction with genetic removal of the A2BR or treatment with the A2BR antagonist GS-6201. Results demonstrated that GS-6201 treatment or genetic removal of the A2BR attenuated vascular remodeling and hypertension in our model. Furthermore, direct A2BR activation on vascular cells promoted interleukin-6 and endothelin-1 release. These studies identify a novel mechanism of disease progression to pulmonary hypertension and support the development of A2BR antagonists for the treatment of pulmonary hypertension secondary to interstitial lung disease.—Karmouty-Quintana, H., Zhong, H., Acero, L., Weng, T., Melicoff, E., West, J. D., Hemnes, A., Grenz, A., Eltzschig, H. K., Blackwell, T. S., Xia, Y., Johnston, R. A., Zeng, D., Belardinelli, L., Blackburn, M. R. The A2B adenosine receptor modulates pulmonary hypertension associated with interstitial lung disease.

Nimodipine-Induced Hypotension but Not Nitroglycerin-Induced Hypotension Preserves Long- and Short-Term Memory in Adult Mice

http://www.anesthesia-analgesia.org/content/114/5/1034.short

Friday, February 24, 2012

Michael Haile, MD, Samuel Galoyan, PhD, Yong-Sheng Li, MD,Barry H. Cohen, PhD, David Quartermain, PhD, Thomas Blanck, MD, PhD and Alex Bekker, MD, PhD

... Data were expressed as mean percent of the baseline value. In addition a MouseOx pulse oximetry device (STARR Life Sciences, Allison Park, PA) was used to measure oxygen saturation (Spo 2) and heart rate. Statistics. The ...

BACKGROUND: Acute hypotension may be implicated in cognitive dysfunction. l-Type calcium channel blockers in the setting of hypoxia are protective of learning and memory. We tested the hypothesis that hypotension induced by nimodipine (NIMO) and nicardipine (NICA) would be protective of long- and short-term memory compared to hypotension induced by nitroglycerin (NTG).

METHODS: Forty Swiss-Webster mice (30 to 35 g, 6 to 8 weeks) were randomized into 4 groups for IP injection immediately after passive avoidance (PA) learning on day 0: (1) NTG (30 mg/kg); (2) NICA (40 mg/kg); (3) NIMO (40 mg/kg); and (4) saline. PA training latencies (seconds) were recorded for entry from a suspended platform into a Plexiglas tube where a shock (0.3 mA; 2-second duration) was automatically delivered. On day 2 latencies were recorded during a testing trial during which no shock was delivered. Latencies >900 seconds were assigned this value. Lower testing latency is indicative of an impairment of long-term associative memory. Forty-nine additional mice were randomized into similar groups for object recognition testing (ORT) and given IP injections on day 0. ORT measures short-term memory by exploiting the tendency of mice to prefer novel objects where a familiar object is present. On day 5 during training, 2 identical objects were placed in a circular arena and mice explored both for 15 minutes. A testing trial was

conducted 1 hour later for 3 minutes after a novel object replaced a familiar one. Mice with intact memory spend about 65% of the time exploring the novel object. Mice with impaired memory devote equal time to each object. Recognition index (RI) is defined as the ratio of time spent exploring the novel object to time spent exploring both objects was the measure of memory. Mean arterial blood pressure (MAP), cerebral bloodflow, and body and brain oxygenation (Po2) studies were done in separate groups of mice to determine the dosages for matched degrees of hypotension and the physiological profile of each treatment.

RESULTS: The median PA latencies for the different conditions were as follows: NTG (219.5 ± 93.5 second semi-interquartile range [SIQR]), NICA (372.5 ± 75.5 second SIQR), NIMO (540 ± 200 second SIQR) and saline (804 ± 257.5 second SIQR). Rank methods were used to analyze the PA latencies for significant differences. NTG latency was significantly shorter than NIMO latency (P = 0.012) and saline latency (P = 0.006), but not NICA latency (P = 0.126). ORT RI values showed a similar pattern. We found that NTG RI (47.2 ± 5.9% SEM) was different from NIMO RI (60.2 ± 4.6% SEM, P = 0.031) and different from saline RI (66.9 + 3.7% SEM, P = 0.006). Physiological experiments showed that MAP decreased to 45 to 50 mm Hg in all animals who became minimally responsive to external stimuli within 10 to 15 minutes of injection. Intergroup differences for MAP, body and brain oxygenation, and cerebral bloodflow were not statistically significant.

CONCLUSION: Acute hypotension induced by NIMO was protective of 2 categories of memory formation relevant to the clinical posttreatment period. Both immediate long-term associative memory consolidation as measured by the PA learning paradigm and delayed short-term working memory function as measured by the ORT paradigm were significantly improved compared to matched levels of hypotension induced by NTG. These results indicate the utility of further investigation of l-type calcium channel blockers as a potential means of preserving cognition in the setting of hypotensive and low flow states.

Blockade of Integrin αvβ3 Enhances Vascular Leak in Mice by Inhibiting Endothelial Cortical Actin Formation

http://ajrccm.atsjournals.org/content/early/2011/10/06/rccm.201108-1381OC.full.pdf

Thursday, October 6, 2011

George Su, Amha Atakilit, John T Li, Nanyan Wu, Mallar Bhattacharya, Jieling Zhu, Jennifer E. Shieh, Elizabeth Li, Robert Chen, Stephen Sun, Cynthia P. Su, and Dean Sheppard

... Pulse oximetry: Five consecutive sustained readings for at least 30 seconds were averaged using

the MouseOx® system (Starr Life Sciences, Oakmont, Pennsylvania). Primary lung endothelial

cells: Mouse lungs were perfused to clear, harvested en bloc, minced ...

Diabetes Depresses Synaptic Transmission in Sympathetic Ganglia by Inactivating nAChRs through a Conserved Intracellular Cysteine Residue

http://www.cell.com/neuron/retrieve/pii/S089662731000468X

Thursday, June 24, 2010

Verónica Campanucci, Arjun Krishnaswamy, Ellis Cooper

Abstract
Most people with diabetes develop severe complications of the autonomic nervous system; yet, the underlying causes of many diabetic-induced dysautonomias are poorly understood. Here we explore the idea that these dysautonomias results, in part, from a defect in synaptic transmission. To test this idea, we investigated cultured sympathetic neurons and show that hyperglycemia inactivates nAChRs through a mechanism involving an elevation in reactive oxygen species and an interaction with highly conserved cysteine residues located near the intracellular mouth of the nAChR channel. Consistent with this, we show that diabetic mice have depressed ganglionic transmission and reduced sympathetic reflexes, whereas diabetic mice expressing mutant postsynaptic nAChRs that lack the conserved cysteine residues on the α3 subunit have normal synaptic transmission in sympathetic ganglia and normal sympathetic reflexes. Our work suggests a new model for diabetic-induced dysautonomias and identifies ganglionic nAChRs as targets of hyperglycemia-induced downstream signals.

Correlation of Blood Flow and Systemic Physiology in Mice Tumor Models in Photodynamic Therapy

http://www.opticsinfobase.org/abstract.cfm?URI=BIOMED-2010-BSuD84

Sunday, April 11, 2010

Hsing-Wen Wang, Steven Schenkel, Rickson C. Mesquita, Arjun G. Yodh, and Theresa M. Busch

Blood flow in mice tumor models was measured with Diffuse Correlation Spectroscopy and compared to concurrent physiology monitoring. Positive correlations were (not) found between flow and heart (breath) rate during anesthesia periods.

Severe spontaneous bradycardia associated with respiratory disruptions in rat pups with fewer brain stem 5-HT neurons

http://ajpregu.physiology.org/content/296/6/R1783.abstract

Saturday, April 11, 2009

Kevin J. Cummings, Kathryn G. Commons, Kenneth C. Fan, Aihua Li, and Eugene E. Nattie

Abstract

The medullary 5-HT system has potent effects on heart rate and breathing in adults. We asked whether this system mitigates the respiratory instability and bradycardias frequently occurring during the neonatal period. 5,7-Dihydroxytryptamine (5,7-DHT) or vehicle was administered to rat pups at postnatal day 2 (P2), and we then compared the magnitude of bradycardias occurring with disruptions to eupnea in treated and vehicle control littermates at P5–6 and P10–12. We then used a novel method that would allow accurate assessment of the ventilatory and heart rate responses to near square-wave challenges of hypoxia (10% O2), hypercapnia (5 and 8% CO2 in normoxia and hyperoxia), and asphyxia (8% CO2-10% O2), and to the induction of the Hering-Breuer inflation reflex (HBR), a potent, apnea-inducing reflex in newborns. The number of 5-HT-positive neurons was reduced ~80% by drug treatment. At both ages, lesioned animals had considerably larger bradycardias during brief apnea; at P5–6, average and severe events were ~50% and 70% greater, respectively, in lesioned animals (P = 0.002), whereas at P10–12, events were ~ 23% and 50% greater (P = 0.018). However, lesioning had no effect on the HR responses to sudden gas challenge or the HBR. At P5–6, lesioned animals had reduced breathing frequency and ventilation (VE), but normal VE relative to metabolic rate (VE/VO2). At P10–12, lesioned animals had a more unstable breathing pattern (P = 0.04) and an enhanced VE response to moderate hypercapnia (P = 0.007). Within the first two postnatal weeks, the medullary 5-HT system plays an important role in cardiorespiratory control, mitigating spontaneous bradycardia, stabilizing the breathing pattern, and dampening the hypercapnic VE response.

In vivo study of the mitochondrial dysfunction during ischemia and the effect of oxidative stress on cell proliferation

https://circle.ubc.ca/handle/2429/7676

Wednesday, April 1, 2009

Liu, Ran

Abstract

Ion influx and water imbalance are major causes of injury during ischemia. Knowledge of the instantaneous subcellular structural and functional changes occurring in vivo, both during ischemia and immediately after the onset of reperfusion, have not been well characterized, mainly due to the extremely rapid progression of these events. To better understand the mechanisms underlying injury during ischemia in vivo, here, we examine mitochondrial function using the bilateral common carotid artery occlusion model of stroke. Mitochondrial membrane potential (Ym) was examined using two-photon fluorescence imaging of the dye Rhodamine123, as an indicator of mitochondrial function. We demonstrate that mitochondrial permeability transition pore-induced Ym collapse occurs during ischemia concurrently with plasma membrane potential depolarization, and repolarized rapidly during reperfusion. Furthermore, we show that inhibition of Ym collapse with cyclosporine A does not result in any detectable attenuation of dendritic structural damage– either during the stroke event or 2 hours afterwards. Thus, these data suggest that mitochondrial dysfunction is an early event during stroke and could contribute to delayed injury at later time points. Oxidative stress is another proposed mechanism of ischemic injury, given that anti-oxidant proteins play a vital role in brain cell survival. To study the chronic effect of elevated oxidative stress in vivo, we examined cell proliferation within neurogenic regions of the brain of adult mice with compromised anti-oxidant defences (Sut mice). Sut mice possess a natural truncation mutation in the gene Slc7a11 resulting in a malfunctional cystine/glutamate exchanger (xCT). Under normal conditions, xCT supply intracellular cyst(e)ine for the production of

glutathione, a major cellular anti-oxidant. Using bromodeoxyuridine labelling as an indicator of newborn cells, we found that the rate of subventricular-zone (SVZ) cell proliferation when normalized to tissue area was comparable between Sut and control mice. However, the cell proliferation rate within the denate gyrus (DG) was elevated in Sut mice. These results demonstrate that xCT expression plays a role in regulating cellular proliferation in the DG, but not the SVZ of adult mice. Futhermore, our in vivo observations clearly indicate that in the absence of xCT ongoing cellular proliferation can still persist.

A comparison of efficacy between conventional and modified methods of the chronic myocardial ischemia/reperfusion model

http://www.ajol.info/index.php/ajb/article/view/66074

Thursday, January 1, 2009

H-T Liu, F Li, Y-M Wang, WB Lau, L Tao, Y Yuan, H-C Wang

Abstract

The objective of this study is to develop and compare the efficacy of a modified versus conventional rat model of chronic myocardial ischemia/reperfusion. Sixty Sprague Dawley (SD) rats were randomly

divided into two groups, a modified group (mask respiratory support and short-time chest-opening) and a conventional group (tracheal intubation and long-time chest-opening). Operation time, surgical success rate, survival rate and infarct size were investigated. In addition, the post-operative living state of the rats was observed. In the perioperative period, the surgical success rate was greater in the modified model ($P < 0.05$ vs. conventional model). Both chest-opening time and spontaneous

respiration recovery time were significantly shorter in the modified group versus the conventional model ($P < 0.001$). Postoperative resumption of normal behaviors and activities was quicker in the modified surgical group, which demonstrated a statistically significant mortality benefit compared to

the conventional group ($P < 0.001$). Infarct size, assessed via triphenyltetrazolium chloride staining, was without statistical difference between the 2 groups ($P > 0.05$). The modified method offers advantages of simplicity, efficiency and independent conduct. Its employment enhances the success rate of the chronic rat myocardial ischemia/reperfusion model.

Age-related cardiac muscle sarcopenia: Combining experimental and mathematical modeling to identify mechanisms

http://www.sciencedirect.com/science/article/pii/S0531556507003002

Saturday, December 15, 2007

Jing Lina, Elizabeth F. Lopeza, Yufang Jinf, Holly Van Remmend, Terry Baucha, Hai-Chao Hang, Merry L. Lindsey

Abstract

Age-related skeletal muscle sarcopenia has been extensively studied and smooth muscle sarcopenia has been recently described, but age-related cardiac sarcopenia has not been previously examined. Therefore, we evaluated adult (7.5 ± 0.5 months; n = 27) and senescent (31.8 ± 0.4 months; n = 26) C57BL/6J mice for cardiac sarcopenia using physiological, histological, and biochemical assessments. Mice do not develop hypertension, even into senescence, which allowed us to decouple vascular effects and monitor cardiac-dependent variables. We then developed a mathematical model to describe the relationship between age-related changes in cardiac muscle structure and function. Our results showed that, compared to adult mice, senescent mice demonstrated increased left ventricular (LV) end diastolic dimension, decreased wall thickness, and decreased ejection fraction, indicating dilation and reduced contractile performance. Myocyte numbers decreased, and interstitial fibrosis was punctated but doubled in the senescent mice, indicating reparative fibrosis. Electrocardiogram analysis showed that PR interval and QRS interval increased and R amplitude decreased in the senescent mice, indicating prolonged conduction times consistent with increased fibrosis. Intracellular lipid accumulation was accompanied by a decrease in glycogen stores in the senescent mice. Mathematical simulation indicated that changes in LV dimension, collagen deposition, wall stress, and wall stiffness precede LV dysfunction. We conclude that age-related cardiac sarcopenia occurs in mice and that LV remodeling due to increased end diastolic pressure could be an underlying mechanism for age-related LV dysfunction.

Keywords

Aging; Sarcopenia; Cardiac; Hypertrophy; Fibrosis

Signaling from 1- and 2-adrenergic receptors is defined by differential interactions with PDE4

http://www.nature.com/emboj/journal/v27/n2/full/7601968a.html

Monday, December 3, 2007

Wito Richter, Peter Day, Rani Agrawal, Matthew D Bruss, Sébastien Granier, Yvonne L Wang, Søren G F Rasmussen, Kathleen Horner, Ping Wang, Tao Lei, Andrew J Patterson, Brian Kobilka and Marco Conti

Abstract

1- and 2-adrenergic receptors (ARs) are highly homologous, yet they play clearly distinct roles in cardiac physiology and pathology. Myocyte contraction, for instance, is readily stimulated by 1AR but not 2AR signaling, and chronic stimulation of the two receptors has opposing effects on myocyte apoptosis and cell survival. Differences in the assembly of macromolecular signaling complexes may explain the distinct biological outcomes. Here, we demonstrate that 1AR forms a signaling complex with a cAMP-specific phosphodiesterase (PDE) in a manner inherently different from a 2AR/-arrestin/PDE complex reported previously. The 1AR binds a PDE variant, PDE4D8, in a direct manner, and occupancy of the receptor by an agonist causes dissociation of this complex. Conversely, agonist binding to the 2AR is a prerequisite for the recruitment of a complex consisting of -arrestin and the PDE4D variant, PDE4D5, to the receptor. We

propose that the distinct modes of interaction with PDEs result in divergent cAMP signals in the vicinity of the two receptors, thus, providing an additional layer of complexity to enforce the specificity of1- and 2-adrenoceptor signaling.

Keywords:-adrenergic receptor, cAMP, cardiac myocyte, cyclic nucleotide phosphodiesterase, PDE

Moderate Pulmonary Arterial Hypertension in Male Mice Lacking the Vasoactive Intestinal Peptide Gene

http://www.cardiology.stonybrook.edu/pdfs/Kort.2007.Circulation.pdf

Monday, March 19, 2007

Sami I. Said, MD; Sayyed A. Hamidi, MD; Kathleen G. Dickman, PhD; Anthony M. Szema, MD; Sergey Lyubsky, MD; Richard Z. Lin, MD; Ya-Ping Jiang, MD; John J. Chen, PhD; James A. Waschek, PhD; Smadar Kort, MD

Background—Vasoactive intestinal peptide (VIP), a pulmonary vasodilator and inhibitor of vascular smooth muscle

proliferation, has been reported absent in pulmonary arteries from patients with idiopathic pulmonary arterial

hypertension (PAH). We have tested the hypothesis that targeted deletion of the VIP gene may lead to PAH with

pulmonary vascular remodeling.

Methods and Results—We examined VIP knockout (VIP/) mice for evidence of PAH, right ventricular (RV) hypertrophy, and pulmonary vascular remodeling. Relative to wild-type control mice, VIP/ mice showed moderate RV hypertension, RV hypertrophy confirmed by increased ratio of RV to left ventricle plus septum weight, and enlarged, thickened pulmonary artery and smaller branches with increased muscularization and narrowed lumen. Lung sections also showed perivascular inflammatory cell infiltrates. No systemic hypertension and no arterial hypoxemia existed to explain the PAH. The condition was associated with increased mortality. Both the vascular remodeling and RV remodeling were attenuated after a 4-week treatment with VIP.

Conclusions—Deletion of the VIP gene leads to spontaneous expression of moderately severe PAH in mice during air breathing. Although not an exact model of idiopathic PAH, the VIP/ mouse should be useful for studying molecular mechanisms of PAH and evaluating potential therapeutic agents. VIP replacement therapy holds promise for the treatment of PAH, and mutations of the VIP gene may be a factor in the pathogenesis of idiopathic PAH.

Hypoxia & Inhalation Studies

Effect of progesterone on respiratory response to moderate hypoxia and apnea frequency in developing rats

http://www.sciencedirect.com/science/article/pii/S156990481200331X

Friday, February 1, 2013

Aida Bairam, Delphine Lumbroso, Vincent Joseph

.. Furthermore, the effect of progesterone on oxygen desaturation and bradycardia during apnea was evaluated under baseline conditions and during the steady state of hypoxia using a pulse oximetry system for small rodents (MouseOx, STARR Life Sciences, Oakmont, PA, USA ...

We used whole-body plethysmography and pulse oximetry to assess the effects of acute administration of progesterone (4 mg/kg, i.p.) on normoxic ventilation, hypoxic ventilatory response (HVR: FiO2 = 12% over 20 min), metabolism, and apnea frequency in rats on postnatal (P) days P1, P4, P7, and P12. Arterial oxygen saturation was continuously measured, and apneas were discriminated based on the degree of associated desaturation, at least 5 units less than the value before the desaturation. In normoxia, progesterone did not alter ventilation, metabolism or the coefficient of variation of minute ventilation at any age studied when compared with the control group (saline). However, it decreased apnea frequency and apnea associated with desaturation only in P1 rats. In hypoxia: progesterone increased the peak HVR in P4 and P7 rats, increased the steady-state HVR (mean at 15–20 min of exposure) in P1, P4 and P7 without affecting the rats' metabolic rate, decreased the coefficient of variation of minute ventilation in P4 and P7 rats, and finally, decreased apnea frequency only in the P1 rats with no effect on apnea associated with desaturation at any age. We conclude that acute administration of progesterone has no effect on baseline ventilation, but it increases HVR in rats younger than 7days, and decreased the frequency of apnea only in P1 rats.

Thermoneutrality Modifies the Impact of Hypoxia on Lipid Metabolism

http://ajpendo.physiology.org/content/early/2012/12/17/ajpendo.00515.2012.abstract

Tuesday, December 18, 2012

Jonathan C Jun, Mi-Kyung Shin, Qiaoling Yao, Ronald Devera, Shannon Bevans-Fonti, and Vsevolod Y. Polotsky

.. cage 96 accompanied by four un-instrumented mice. Mouse oxygen saturation (SaO2) and breath rate were 97 measured using a MouseOx neck cuff and StarrLink

Hypoxia has been shown to rapidly increase triglycerides in mice by decreasing plasma lipoprotein clearance. However, the usual temperature of hypoxic exposure is below thermoneutrality for mice, which may increase thermogenesis and energy requirements resulting in higher tissue lipid uptake. We hypothesize that decreased lipid clearance and ensuing hyperlipidemia are caused by hypoxic suppression of metabolism at cold

temperatures and therefore, would not occur at thermoneutrality. Twelve-week old, male C57BL6/J mice were exposed to 6 hours of 10% O2 at usual temperature (22°C) or thermoneutrality (30°C). Acclimation to 22°C increased lipid uptake in the heart, lungs, and brown adipose tissue, resulting in lower plasma triglyceride and cholesterol levels. At this temperature, hypoxia attenuated lipid uptake in most tissues, thereby raising plasma triglycerides and LDL cholesterol. Thermoneutrality decreased tissue lipid uptake, and hypoxia did not cause a further reduction in lipid uptake in any organs. Consequently, hypoxia at thermoneutrality did not affect plasma triglyceride levels. Unexpectedly, plasma HDL cholesterol increased. The effect of hypoxia on white adipose tissue lipolysis was also modified by temperature. Independent of temperature, hypoxia increased heart rate and glucose; and decreased activity, body temperature, and glucose sensitivity. Our study underscores the importance of ambient temperature for hypoxia research, especially in studies of lipid metabolism.

Monitoring Hypoxia Induced Changes in Cochlear Blood Flow and Hemoglobin Concentration Using a Combined Dual-Wavelength Laser Speckle Contrast Imaging and Doppler Optical Microangiography System

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0052041

Tuesday, December 18, 2012

Roberto Reif, Jia Qin, Lei Shi, Suzan Dziennis, Zhongwei Zhi, Alfred L. Nuttall, Ruikang K. Wang

.. Body temperature was maintained at 37.0°C ± 0.5. End-tidal CO 2 (V9004 capnograph; Surgivet, Waukesha, Wis), heart rate, and blood oxygen saturation (MouseOx; Starr Life Science, Oakmont, Pa) were monitored and kept within physiologic ranges. ...

Purpose: To develop high-spatial-resolution magnetic resonance (MR) microangiography techniques to image the rat ocular circulation.
Materials and Methods: Animal experiments were performed with institutional Animal Care Committee approval. MR microangiography (resolution, 84 × 84 × 84 μm or 42 × 42 × 84 μm) of the rat eye (eight rats) was performed by using a custom-made small circular surface coil with an 11.7-T MR unit before and after monocrystalline iron oxide nanoparticle (MION) injection. MR microangiography measurements were made during air, oxygen, and carbogen inhalation. From three-dimensional MR microangiography, the retina was virtually flattened to enable en face views of various retinal depths, including the retinal and choroidal vascular layers. Signal intensity changes within the retinal or choroidal arteries and veins associated with gas challenges were analyzed. Statistical analysis was performed by using paired t tests, with $P < .05$ considered to indicate a significant difference. Bonferroni correction was used to adjust for multiple comparisons.
Results: The central retinal artery, long posterior ciliary arteries, and choroidal vasculature could be distinguished on MR microangiograms of the eye. With MR microangiography, retinal arteries and veins could be distinguished on the basis of blood oxygen level–dependent contrast. Carbogen inhalation–enhanced MR microangiography signal intensity in both the retina ($P = .001$) and choroid ($P = .027$) compared with oxygen inhalation. Carbogen inhalation showed significantly higher signal intensity changes in the retinal arteries ($P = .001$, compared with oxygen inhalation), but not in the veins ($P = .549$). With MION administration, MR microangiography depicted retinal arterial vasoconstriction when the animals were breathing oxygen ($P = .02$, compared with animals breathing air).
Conclusion: MR microangiography of the eye allows depth-resolved imaging of small angiographic details of

the ocular circulation. This approach may prove useful in studying microvascular pathologic findings and neurovascular dysfunction in the eye and retina.

Measuring tumor cycling hypoxia and angiogenesis using a side-firing fiber optic probe

http://onlinelibrary.wiley.com/doi/10.1002/jbio.201200187/abstract

Friday, December 14, 2012

Bing Yu1, Amy Shah, Bingqing Wang, Narasimhan Rajaram, Quanli Wang, Nirmala Ramanujam, Gregory M. Palmer, Mark W. Dewhirst

... A mouse pulse oximeter (Mouse Ox, Starr Life Science Corp., Allison Park, PA) was also clamped on to the left foot of the rat and ... while both the tissue oxygenation measured by the side-firing probe (Figure8(b)) and arterial blood oxygenation recorded by the MouseOx (Figure 8 ...

Hypoxia and angiogenesis can significantly influence the efficacy of cancer therapy and the behavior of surviving tumor cells. There is a growing demand for technologies to measure tumor hypoxia and angiogenesis temporally in vivo to enable advances in drug development and optimization. This paper reports the use of frequency-domain photon migration with a side-firing probe to quantify tumor oxygenation and hemoglobin concentrations in nude rats bearing human head/neck tumors administered with carbogen gas, cycling hypoxic gas or just room air. Significant increase (with carbogen gas breathing) or decrease (with hypoxic gas breathing) in tumor oxygenation was observed. The trend in tumor oxygenation during forced cycling hypoxia (CH) followed that of the blood oxygenation measured with a pulse oximeter. Natural CH was also observed in rats under room air. The studies demonstrated the potential of the technology for longitudinal monitoring of tumor CH during tumor growth or in response to therapy. (© 2012 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim)

Effects of hypoxia on cochlear blood flow in mice evaluated using Doppler optical microangiography

http://biomedicaloptics.spiedigitallibrary.org/article.aspx?articleid=1372932%20

Monday, October 1, 2012

Suzan Dziennis ; Roberto Reif ; Zhongwei Zhi ; Alfred L. Nuttall ; Ruikang K. Wang

Reduced cochlear blood flow (CoBF) is a main contributor to hearing loss. Studying CoBF has remained a challenge due to the lack of available tools. Doppler optical microangiography (DOMAG), a method to quantify single-vessel absolute blood flow, and laser Doppler flowmetry (LDF), a method for measuring the relative blood flow within a large volume of tissue, were used for determining the changes in CoBF due to systemic hypoxia in mice. DOMAG determined the change in blood flow in the apical turn (AT) with single-vessel resolution, while LDF averaged the change in the blood flow within a large volume of the cochlea (hemisphere with ~1 to 1.5 mm radius). Hypoxia was induced by decreasing the concentration of oxygen-

inspired gas, so that the oxygen saturation was reduced from >95% to ~80% . DOMAG determined that during hypoxia the blood flow in two areas of the AT near and far from the helicotrema were increased and decreased, respectively. The LDF detected a decrease in blood flow within a larger volume of the cochlea (several turns averaged together). Therefore, the use of DOMAG as a tool for studying cochlear blood flow due to its ability to determine absolute flow values with single-vessel resolution was proposed.

Decreased VEGF expression and microvascular density, but increased HIF-1 and 2α accumulation and EPO expression in chronic moderate hyperoxia in the mouse brain

http://www.sciencedirect.com/science/article/pii/S0006899312011419

Thursday, August 30, 2012

Girriso F. Benderroa, Xiaoyan Sunb, Youzhi Kuangb, Joseph C. LaManna

... Arterial oxygen saturation (SaO 2), which is hemoglobin oxygen saturation in arterial blood, was recorded in a subgroup of mice kept in normoxia or hyperoxia using a MouseOx™ Pulse Oximeter (STARR Life Sciences Corp., Oakmount, PA), as described earlier (Benderro and ...

Normal brain function is dependent on continuous and controlled oxygen delivery. Chronic moderate hypoxia leads to angiogenesis, suggesting a modulatory role for oxygen in determining capillary density. The objective of this study was to determine physiologic and brain angiogenic adaptational changes during chronic moderate normobaric hyperoxia in mice. Four-month old C56BL/6J mice were kept in a normobaric chamber at 50% O2 for up to 3 weeks. Normoxic littermates were kept in the same room outside the chamber. Freshly collected or fixed brain specimens were analyzed by RT-PCR, Western blot analysis and immunohistochemistry. Results show accumulation of hypoxia inducible factors 1 and 2α (HIF-1 and 2α), and increased expression of erythropoietin (EPO), cyclooxygenase-2 (COX-2) and angiopoietin-2 (Ang-2). Conversely, vascular endothelial growth factor (VEGF), and VEGF receptor-2 (KDR/Flk-1), Peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) and prolylhydroxylase-2 (PHD-2) expressions were decreased. VEGF mRNA level was diminished but there was no change in HIF-1α mRNA and von Hippel Lindau E3 ubiquitin ligase (VHL) protein expression. Microvascular density was significantly diminished by the end of the 3rd week of hyperoxia. Overall, our results are: (1) increased expression of the potent neuroprotective molecule, EPO; (2) diminished expression of the potent angiogenic factor, VEGF; and (3) decreased microvascular density. We can, therefore, conclude that brain microvascular density can be controlled by HIF-independent mechanisms, and that brain capillary density is a continuously adjusted variable with tissue oxygen availability as one of the controlling modulators.

Photoacoustic tomography can detect cerebral hemodynamic alterations in a neonatal rodent model of hypoxia-ischemia

http://www.ez.ane.pl/pdf/7223.pdf

Wednesday, August 22, 2012

Craig B. Sussman, Candace Rossignol, Qizhi Zhang, Huabei Jiang, Tong Zheng, Dennis Steindler, Linda Young, and Michael D. Weiss

.. imaging process by MouseOx® Pulse Oximeter (STARR Life Sciences™ Corp, Oakmont, PA). Post-imaging, the pups fully recovered on a heating gel pad and were then returned to their mother to nurse. The subjects were monitored ...

Hypoxic-Ischemic Encephalopathy (HIE) is one of the most recognized causes of neurological deficits in children. Cerebral blood flow (CBF) reductions, as seen with HIE, resulting in neuronal injury have not been evaluated in real-time. Photoacoustic Tomography (PAT) is a form of optical imaging which can detect cerebral hemodynamic alterations in a non-invasive, non-ionizing fashion via changes in hemoglobin optical absorption. Further, this technology has the potential to capture cerebral blood volume (CBV) fluctuations and perhaps CBF changes in real-time. We hypothesized that PAT can detect a reduction in cerebral hemoglobin optical absorption, and therefore CBF, in a neonatal model of hypoxia-ischemia. To investigate, P7 rats underwent right carotid artery ligation and exposure to 8% oxygen for 60 minutes while imaged with PAT every 20 minutes. Cerebral hemodynamic alterations, as measured by mean optical absorption (MOA), were calculated as a change from baseline. Global and regional MOA was analyzed using a linear mixed model. Global MOA was reduced within the right hemisphere as compared to the left during hypoxia. Regional differences in MOA were detected between the left and right sides for the middle and posterior cortical regions. Injury was confirmed using immunohistochemistry. We conclude that a reduction in global and regional MOA, and hence CBF, could be identified by PAT in a neonatal rat model of HIE. This is the first study described in the literature utilizing a neonatal rat model of HIE to demonstrate in vivo alterations in cerebral hemodynamics in a non-invasive and near real-time fashion.

The combination of theophylline and endothelin receptor antagonism improves exercise performance of rats under simulated high altitude

http://jap.physiology.org/content/early/2012/08/14/japplphysiol.01622.2011.short

Thursday, August 16, 2012

Daniel R. Radiloff, Yulin Zhao, Alina Boico, Chan Wu, Siqing Shan, Gregory Palmer, Karyn L. Hamilton, David C. Irwin, Gabi Hanna, Claude A. Piantadosi, and Thies Schroeder

.. bridge amp and PowerLab module. A pulse oximetry foot clip was applied to the left hind limb 150 of the animal (MouseOx, Starr Life Sciences) to record arterial hemoglobin oxygen saturation 151 (HbO2), and heart rate. The ...

Introduction: Decreased physical performance is a well-known consequence of rapid ascent to high altitude. Hypoxic pulmonary vasoconstriction (HPV) potentially limits cardiac output and systemic blood flow, thus preventing successful adaptation to rapid ascent. We hypothesized that pharmacological enhancement of the heart rate with theophylline, combined with reversal of HPV via endothelin blockade, could increase exercise performance at high altitude. Methods: Female Sprague Dawley rats were treated with combinations of 1) theophylline, 2) the endothelin receptor antagonists sitaxsentan/ambrisentan, and/or 3) phosphodiesterase-5

inhibitor sildenafil, and exposed to either a simulated high altitude (4,267 m) or 12% oxygen. Exercise capacity, peripheral blood flow, hemodynamics, and pulmonary leak were examined. Results: Combination treatment with theophylline and endothelin blockade, but not with the respective single compounds, significantly prolonged time run to fatigue under simulated high altitude. No such efficacy was found when theophylline was combined with sildenafil. Neither theophylline, nor sitaxsentan, or their combination influenced breathing rates and HbO2. Whereas under hypoxia, theophylline significantly increased muscular blood flow, and sitaxsentan increased tissue oxygenation; the combination improved both parameters, but in a reduced manner. Under hypoxia, the combination treatment but not the single compounds, significantly enhanced pulmonary arterial pressure (PAP) compared to controls (13.1 ± 6.3 vs. 11.9 ± 5.2 mmHg) whereas mean arterial pressure (MAP) remained unaffected. Pulmonary wet-to-dry weight ratios were unaffected by combination treatment. Conclusion: Concomitant dosing with a cardiac stimulant and endothelin antagonist can partially reverse loss of physical performance capacity under hypobaric hypoxia, independent from improving blood oxygen saturation.

Acute hypoxia induces hypertriglyceridemia by decreasing plasma triglyceride clearance in mice

http://ajpendo.physiology.org/content/303/3/E377.short

Tuesday, May 22, 2012

Jonathan C. Jun, Mi-Kyung Shin, Qiaoling Yao, Shannon Bevans-Fonti, James Poole, Luciano F. Drager, and Vsevolod Y. Polotsky

... Mice were kept on a 12:12-h light-dark cycle with lights on at 08:00 AM and off at 08:00 PM at 20–22°C. Heart rate and arterial oxygen saturation (SpO 2) were monitored using a neck oximeter (MouseOx, STARR Life Sciences, Pittsburgh, PA). ...

Obstructive sleep apnea (OSA) induces intermittent hypoxia (IH) during sleep and is associated with elevated triglycerides (TG). We previously demonstrated that mice exposed to chronic IH develop elevated TG. We now hypothesize that a single exposure to acute hypoxia also increases TG due to the stimulation of free fatty acid (FFA) mobilization from white adipose tissue (WAT), resulting in increased hepatic TG synthesis and secretion. Male C57BL6/J mice were exposed to FiO2 = 0.21, 0.17, 0.14, 0.10, or 0.07 for 6 h followed by assessment of plasma and liver TG, glucose, FFA, ketones, glycerol, and catecholamines. Hypoxia dose-dependently increased plasma TG, with levels peaking at FiO2 = 0.07. Hepatic TG levels also increased with hypoxia, peaking at FiO2 = 0.10. Plasma catecholamines also increased inversely with FiO2. Plasma ketones, glycerol, and FFA levels were more variable, with different degrees of hypoxia inducing WAT lipolysis and ketosis. FiO2 = 0.10 exposure stimulated WAT lipolysis but decreased the rate of hepatic TG secretion. This degree of hypoxia rapidly and reversibly delayed TG clearance while decreasing [3H]triolein-labeled Intralipid uptake in brown adipose tissue and WAT. Hypoxia decreased adipose tissue lipoprotein lipase (LPL) activity in brown adipose tissue and WAT. In addition, hypoxia decreased the transcription of LPL, peroxisome proliferator-activated receptor-γ, and fatty acid transporter CD36. We conclude that acute hypoxia increases plasma TG due to decreased tissue uptake, not increased hepatic TG secretion.

Intralipid Fat Emulsion Decreases Respiratory Failure in a Rat Model of Parathion Exposure

http://onlinelibrary.wiley.com/doi/10.1111/j.1553-2712.2012.01337.x/full

Thursday, May 17, 2012

Courtney Dunn, Steven B. Bird MD, Romolo Gaspari MD, PhD

Abstract

Therapies exist for acute organophosphate (OP) exposure Background: but mortality rates remain high (10% to 20%). Currently, treatment focuses on reversing the resultant cholinergic excess effects through the use of atropine. Intralipid fat emulsion (IFE) has been used to treat lipophilic drug ingestions and theoretically would be beneficial for some OP agents.

The hypothesis was that IFE would decrease the acute Objectives: respiratory depressant effects following lethal OP exposure using a lipophilic OP agent (parathion).

The authors used a previously validated animal model of OP Methods: poisoning with detailed physiologic respiratory recordings. The model consisted of Wistar rats anesthetized but spontaneously breathing 100% oxygen. Airflow, respiratory rate, tidal volume, mean arterial pressure, and pulse rate were digitally recorded for 120 minutes following OP exposure or until respiratory failure. Three study groups included parathion alone (n = 6), parathion and IFE 5 minutes after poisoning (n = 6), and parathion and IFE 20 minutes after poisoning (n = 6). In all groups, parathion was given as a single oral dose of 54 mg/kg (four times the rat oral 50% population lethal dose [LD50]). Three boluses of IFE (15 mg/kg/min) were given over 3 minutes, 20 minutes apart, starting either 5 or 20 minutes after poisoning. Timing of IFE was based on parathion kinetics. In one study group IFE was initiated 5 minutes after poisoning to coincide with initial absorption of parathion. In another study group IFE was given at 20 minutes to coincide with peak intravenous (IV) parathion concentration. Primary outcome was percentage of animals with apnea. Secondary outcome was time to apnea.

Animals exposed to parathion alone demonstrated a steady Results: decline in respiratory rate and tidal volume postexposure, with apnea occurring a mean of 51.6 minutes after poisoning (95% confidence interval [CI] = 35.8 to 53.2 minutes). Animals treated with IFE 5 minutes postexposure demonstrated no difference in mean time to apnea (44.5 minutes vs. 51.6 minutes, p = 0.29) or number of animals with respiratory arrest (100% vs. 100%, p = 1.00). Animals treated with IFE 20 minutes postexposure demonstrated a significantly prolonged mean time to apnea (95.3 minutes vs. 51.6 minutes, p = 0.002), but there was no difference in number of animals with respiratory arrest (100% vs. 66.7%, p = 0.45).

All animals exposed to 4 × LD50 of oral parathion Conclusions: demonstrate apnea and respiratory arrest. IFE given immediately after oral parathion does not prolong time to apnea. IFE given 20 minutes after oral exposure to parathion decreases the acute effects of the OP and prolongs the time to apnea.

Metabolic and cardiac signaling effects of inhaled hydrogen sulfide and low oxygen in male rats

http://jap.physiology.org/content/112/10/1659.short

Thursday, March 8, 2012

Asaf Stein, Zhengkuan Mao, Joanna P. Morrison, Michelle V. Fanucchi, Edward M. Postlethwait, Rakesh P. Patel, David W. Kraus, Jeannette E. Doeller, and Shannon M. Bailey

Abstract

Low concentrations of inhaled hydrogen sulfide (H2S) induce hypometabolism in mice. Biological effects of H2S in in vitro systems are augmented by lowering O2 tension. Based on this, we hypothesized that reduced O2 tension would increase H2S-mediated hypometabolism in vivo. To test this, male Sprague-Dawley rats were exposed to 80 ppm H2S at 21% O2 or 10.5% O2 for 6 h followed by 1 h recovery at room air. Rats exposed to H2S in 10.5% O2 had significantly decreased body temperature and respiration compared with preexposure levels. Heart rate was decreased by H2S administered under both O2 levels and did not return to preexposure levels after 1 h recovery. Inhaled H2S caused epithelial exfoliation in the lungs and increased plasma creatine kinase-MB activity. The effect of inhaled H2S on prosurvival signaling was also measured in heart and liver. H2S in 21% O2 increased Akt-PSer473 and GSK-3β-PSer9 in the heart whereas phosphorylation was decreased by H2S in 10.5% O2, indicating O2 dependence in regulating cardiac signaling pathways. Inhaled H2S and low O2 had no effect on liver Akt. In summary, we found that lower O2 was needed for H2S-dependent hypometabolism in rats compared with previous findings in mice. This highlights the possibility of species differences in physiological responses to H2S. Inhaled H2S exposure also caused tissue injury to the lung and heart, which raises concerns about the therapeutic safety of inhaled H2S. In conclusion, these findings demonstrate the importance of O2 in influencing physiological and signaling effects of H2S in mammalian systems.

Hypoxia activates nucleus tractus solitarii neurons projecting to the paraventricular nucleus of the hypothalamus

http://ajpregu.physiology.org/content/302/10/R1219.short

Wednesday, March 7, 2012

T. Luise King, Cheryl M. Heesch, Catharine G. Clark, David D. Kline and Eileen M. Hasser

Abstract

Peripheral chemoreceptor afferent information is sent to the nucleus tractus solitarii (nTS), integrated, and relayed to other brain regions to alter cardiorespiratory function. The nTS projects to the hypothalamic paraventricular nucleus (PVN), but activation and phenotype of these projections during chemoreflex stimulation is unknown. We hypothesized that activation of PVN-projecting nTS neurons occurs primarily at high intensities of hypoxia. We assessed ventilation and cardiovascular parameters in response to increasing severities of hypoxia. Retrograde tracers were used to label nTS PVN-projecting neurons and, in some rats, rostral ventrolateral medulla (RVLM)-projecting neurons. Immunohistochemistry was performed to identify nTS cells that were activated (Fos-immunoreactive, Fos-IR), catecholaminergic, and GABAergic following hypoxia. Conscious rats underwent 3 h normoxia (n = 4, 21% O2) or acute hypoxia (12, 10, or 8% O2; n = 5

each). Hypoxia increased ventilation and the number of Fos-IR nTS cells (21%, 13 ± 2; 12%, 58 ± 4; 10%, 166 ± 22; 8%, 186 ± 6). Fos expression after 10% O2 was similar whether arterial pressure was allowed to decrease (−13 ± 1 mmHg) or was held constant. The percentage of PVN-projecting cells activated was intensity dependent, but contrary to our hypothesis, PVN-projecting nTS cells exhibiting Fos-IR were found at all hypoxic intensities. Notably, at all intensities of hypoxia, ~75% of the activated PVN-projecting nTS neurons were catecholaminergic. Compared with RVLM-projecting cells, a greater percentage of PVN-projecting nTS cells was activated by 10% O2. Data suggest that increasing hypoxic intensity activates nTS PVN-projecting cells, especially catecholaminergic, PVN-projecting neurons. The nTS to PVN catecholaminergic pathway may be critical even at lower levels of chemoreflex activation and more important to cardiorespiratory responses than previously considered.

An Antagomir to MicroRNA Let7f Promotes Neuroprotection in an Ischemic Stroke Model

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0032662

Wednesday, February 29, 2012

Amutha Selvamani, Pratheesh Sathyan, Rajesh C. Miranda, Farida Sohrabji

We previously showed that middle-aged female rats sustain a larger infarct following experimental stroke as compared to younger female rats, and paradoxically, estrogen treatment to the older group is neurotoxic. Plasma and brain insulin-like growth factor-1 (IGF-1) levels decrease with age. However, IGF-1 infusion following stroke, prevents estrogen neurotoxicity in middle-aged female rats. IGF1 is neuroprotective and well tolerated, but also has potentially undesirable side effects. We hypothesized that microRNAs (miRNAs) that target the IGF-1 signaling family for translation repression could be alternatively suppressed to promote IGF-1-like neuroprotection. Here, we report that two conserved IGF pathway regulatory microRNAs, Let7f and miR1, can be inhibited to mimic and even extend the neuroprotection afforded by IGF-1. Anti-mir1 treatment, as late as 4 hours following ischemia, significantly reduced cortical infarct volume in adult female rats, while anti-Let7 robustly reduced both cortical and striatal infarcts, and preserved sensorimotor function and interhemispheric neural integration. No neuroprotection was observed in animals treated with a brain specific miRNA unrelated to IGF-1 (anti-miR124). Remarkably, anti-Let7f was only effective in intact females but not males or ovariectomized females indicating that the gonadal steroid environment critically modifies miRNA action. Let7f is preferentially expressed in microglia in the ischemic hemisphere and confirmed in ex vivo cultures of microglia obtained from the cortex. While IGF-1 was undetectable in microglia harvested from the non-ischemic hemisphere, IGF-1 was expressed by microglia obtained from the ischemic cortex and was further elevated by anti-Let7f treatment. Collectively these data support a novel miRNA-based therapeutic strategy for neuroprotection following stroke.

Epigenetic regulation of hypoxic sensing disrupts cardiorespiratory homeostasis

http://www.pnas.org/content/109/7/2515.short

Monday, January 9, 2012

Jayasri Nanduri,Vladislav Makarenko, Vaddi Damodara Reddy, Guoxiang Yuan, Anita Pawar, Ning Wang, Shakil A. Khan, Xin Zhang, Brian Kinsman, Ying-Jie Peng, Ganesh K. Kumar, Aaron P. Fox, Lucy A. Godley, Gregg L. Semenza and Nanduri R. Prabhakar

Abstract

Recurrent apnea with intermittent hypoxia is a major clinical problem in preterm infants. Recent studies, although limited, showed that adults who were born preterm exhibit increased incidence of sleep-disordered breathing and hypertension, suggesting that apnea of prematurity predisposes to autonomic dysfunction in adulthood. Here, we demonstrate that adult rats that were exposed to intermittent hypoxia as neonates exhibit exaggerated responses to hypoxia by the carotid body and adrenal chromaffin cells, which regulate cardio-respiratory function, resulting in irregular breathing with apneas and hypertension. The enhanced hypoxic sensitivity was associated with elevated oxidative stress, decreased expression of genes encoding antioxidant enzymes, and increased expression of pro-oxidant enzymes. Decreased expression of the Sod2 gene, which encodes the antioxidant enzyme superoxide dismutase 2, was associated with DNA hypermethylation of a single CpG dinucleotide close to the transcription start site. Treating neonatal rats with decitabine, an inhibitor of DNA methylation, during intermittent hypoxia exposure prevented oxidative stress, enhanced hypoxic sensitivity, and autonomic dysfunction. These findings implicate a hitherto uncharacterized role for DNA methylation in mediating neonatal programming of hypoxic sensitivity and the ensuing autonomic dysfunction in adulthood.

NMDA-dependent mechanisms only affect the BOLD response in the rat dentate gyrus by modifying local signal processing.

http://www.ncbi.nlm.nih.gov/pubmed/22167232

Wednesday, December 14, 2011

Tiede R, Krautwald K, Fincke A, Angenstein F.

Abstract

The role of N-methyl-D-aspartate (NMDA) receptor-mediated mechanisms in the formation of a blood oxygen level-dependent (BOLD) response was studied using electrical stimulation of the right perforant pathway. Stimulation of this fiber bundle triggered BOLD responses in the right hippocampal formation and in the left entorhinal cortex. The perforant pathway projects to and activates the dentate gyrus monosynaptically, activation in the contralateral entorhinal cortex is multisynaptic and requires forwarding and processing of signals. Application of the NMDA receptor antagonist MK801 during stimulation had no effect on BOLD responses in the right dentate gyrus, but reduced the BOLD responses in the left entorhinal cortex. In contrast, application of MK801 before the first stimulation train reduced the BOLD response in both regions. Electrophysiological recordings revealed that the initial stimulation trains changed the local processing of the incoming signals in the dentate gyrus. This altered electrophysiological response was not further changed by a subsequent application of MK801, which is in agreement with an unchanged BOLD response. When MK801 was present during the first stimulation train, a dissimilar electrophysiological response pattern was observed and corresponds to an altered BOLD response, indicating that NMDA-

dependent mechanisms indirectly affect the BOLD response, mainly via modifying local signal processing and subsequent propagation.

Hydrogen Sulfide Inhibits Hypoxia- But Not Anoxia-Induced Hypoxia-Inducible Factor 1 Activation in a von Hippel-Lindau- and Mitochondria-Dependent Manner

http://online.liebertpub.com/doi/abs/10.1089/ars.2011.3882

Thursday, December 8, 2011

Shinichi Kai, Tomoharu Tanaka, Hiroki Daijo, Hiroshi Harada, Shun Kishimoto, Kengo Suzuki, Satoshi Takabuchi, Keizo Takenaga, Kazuhiko Fukuda, and Kiichi Hirota

.. Blood pressure, heart rate, and peripheral O 2 saturation (SpO 2) during experiments were measured with a tail-cuff sphygmomanometer (model MK-1030; Muromachi Kikai, Tokyo, Japan) (41) and a MouseOx pulse oximeter (Starr Life Sciences, Oakmont, PA) (5). At the end of ...

Aims: In addition to nitric oxide and carbon monoxide, hydrogen sulfide (H2S) is an endogenously synthesized gaseous molecule that acts as an important signaling molecule in the living body. Transcription factor hypoxia-inducible factor 1 (HIF-1) is known to respond to intracellular reduced oxygen (O2) availability, which is regulated by an elaborate balance between O2 supply and demand. However, the effect of H2S on HIF-1 activity under hypoxic conditions is largely unknown in mammalian cells. In this study, we tried to elucidate the effect of H2S on hypoxia-induced HIF-1 activation adopting cultured cells and mice. Results: The H2S donors sodium hydrosulfide and sodium sulfide in pharmacological concentrations reversibly reduced cellular O2 consumption and inhibited hypoxia- but not anoxia-induced HIF-1α protein accumulation and expression of genes downstream of HIF-1 in established cell lines. H2S did not affect HIF-1 activation induced by the HIF-α hydroxylases inhibitors desferrioxamine or CoCl2. Experimental evidence adopting von Hippel-Lindau (VHL)- or mitochondria-deficient cells indicated that H2S did not affect neosynthesis of HIF-1α protein but destabilized HIF-1α in a VHL- and mitochondria-dependent manner. We also demonstrate that exogenously administered H2S inhibited HIF-1–dependent gene expression in mice. Innovation: For the first time, we show that H2S modulates intracellular O2 homeostasis and regulates activation of HIF-1 and the subsequent gene expression induced by hypoxia by using an in vitro system with established cell lines and an in vivo system in mice. Conclusions: We demonstrate that H2S inhibits hypoxia-induced HIF-1 activation in a VHL- and mitochondria-dependent manner. Antioxid. Redox Signal. 16, 203–216.

Hydrogen Sulfide Inhibits Hypoxia- But Not Anoxia-Induced Hypoxia-Inducible Factor 1 Activation in a von Hippel-Lindau- and Mitochondria-Dependent Manner

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Hydrogen Sulfide Inhibits Hypoxia- But Not Anoxia-Induced Hypoxia-Inducible Factor 1 Activation in a von Hippel-Lindau- and Mitochondria-Dependent Manner

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Shinichi Kai, Tomoharu Tanaka, Hiroki Daijo, Hiroshi Harada,Shun Kishimoto, Kengo Suzuki, Satoshi Takabuchi, Keizo Takenaga, Kazuhiko Fukuda, and Kiichi Hirota

Abstract

Aims: In addition to nitric oxide and carbon monoxide, hydrogen sulfide (H2S) is an endogenously synthesized gaseous molecule that acts as an important signaling molecule in the living body. Transcription factor hypoxia-inducible factor 1 (HIF-1) is known to respond to intracellular reduced oxygen (O2) availability, which is regulated by an elaborate balance between O2 supply and demand. However, the effect of H2S on HIF-1 activity under hypoxic conditions is largely unknown in mammalian cells. In this study, we tried to elucidate the effect of H2S on hypoxia-induced HIF-1 activation adopting cultured cells and mice. Results: The H2S donors sodium hydrosulfide and sodium sulfide in pharmacological concentrations reversibly reduced cellular O2 consumption and inhibited hypoxia- but not anoxia-induced HIF-1α protein accumulation and expression of genes downstream of HIF-1 in established cell lines. H2S did not affect HIF-1 activation induced by the HIF-α hydroxylases inhibitors desferrioxamine or CoCl2. Experimental evidence

adopting von Hippel-Lindau (VHL)- or mitochondria-deficient cells indicated that H2S did not affect neosynthesis of HIF-1α protein but destabilized HIF-1α in a VHL- and mitochondria-dependent manner. We also demonstrate that exogenously administered H2S inhibited HIF-1–dependent gene expression in mice. Innovation: For the first time, we show that H2S modulates intracellular O2 homeostasis and regulates activation of HIF-1 and the subsequent gene expression induced by hypoxia by using an in vitro system with established cell lines and an in vivo system in mice. Conclusions: We demonstrate that H2S inhibits hypoxia-induced HIF-1 activation in a VHL- and mitochondria-dependent manner. Antioxid. Redox Signal. 16, 203–216.

Arousal from sleep in response to intermittent hypoxia in rat pups is modulated by medullary raphe GABAergic mechanisms

http://ajpregu.physiology.org/content/302/5/R551.short

Wednesday, December 7, 2011

Robert A. Darnall, Robert W. Schneider, Christine M. Tobia, and Benjamin M. Zemel

Abstract

Arousal is an important defense against hypoxia during sleep. Rat pups exhibit progressive arousal impairment (habituation) with multiple hypoxia exposures. The mechanisms are unknown. The medullary raphe (MR) is involved in autonomic functions, including sleep, and receives abundant GABAergic inputs. We hypothesized that inhibiting MR neurons with muscimol, a GABAA receptor agonist, or preventing GABA reuptake with nipecotic acid, would impair arousal and enhance arousal habituation and that blocking GABAA receptors with bicuculline would enhance arousal and attenuate habituation. Postnatal day 15 (P15) to P25 rat pups were briefly anesthetized, and microinjections with aCSF, muscimol, bicuculline, or nipecotic acid were made into the MR. After a ~30-min recovery, pups were exposed to four 3-min episodes of hypoxia separated by 6 min of normoxia. The time to arousal from the onset of hypoxia (latency) was determined for each trial. Latency progressively increased across trials (habituation) in all groups. The overall latency was greater after muscimol and nipecotic acid compared with aCSF, bicuculline, or noninjected controls. Arousal habituation was reduced after bicuculline compared with aCSF, muscimol, nipecotic acid, or noninjected pups. Increases in latency were mirrored by decreases in chamber [O2] and oxyhemoglobin saturation. Heart rate increased during hypoxia and was greatest in muscimol-injected pups. Our results indicate that the MR plays an important, not previously described, role in arousal and arousal habituation during hypoxia and that these phenomena are modulated by GABAergic mechanisms. Arousal habituation may contribute to sudden infant death syndrome, which is associated with MR serotonergic and GABAergic receptor dysfunction.

Respiratory control and sternohyoid muscle structure and function in aged male rats: Decreased susceptibility to chronic intermittent hypoxia

http://www.sciencedirect.com/science/article/pii/S1569904811003934

Tuesday, November 22, 2011

J. Richard Skellya, Deirdre Edgea, Christine M. Shortta, James F.X. Jonesa, Aidan Bradfordb, Ken D. O'Hallorana

Abstract
Obstructive sleep apnoea syndrome (OSAS) is a common respiratory disorder characterized by chronic intermittent hypoxia (CIH). We have shown that CIH causes upper airway muscle dysfunction in the rat due to oxidative stress. Ageing is an independent risk factor for the development of OSAS perhaps due to respiratory muscle remodelling and increased susceptibility to hypoxia. We sought to examine the effects of CIH on breathing and pharyngeal dilator muscle structure and function in aged rats. Aged (18–20 months), male Wistar rats were exposed to alternating cycles of normoxia and hypoxia (90 s each; FIO2 = 5% O2 at nadir) or sham treatment for 8 h/day for 9 days. Following CIH exposure, breathing was assessed by whole-body plethysmography. In addition, sternohyoid muscle contractile and endurance properties were examined*in vitro*. Muscle fibre type and cross-sectional area, and the activity of key oxidative and glycolytic enzymes were determined. CIH had no effect on basal breathing or ventilatory responses to hypoxia or hypercapnia. CIH did not alter succinate dehydrogenase or glycerol phosphate dehydrogenase enzyme activities, myosin heavy chain fibre areal density or cross-sectional area. Sternohyoid muscle force and endurance were unaffected by CIH exposure. Since we have established that this CIH paradigm causes sternohyoid muscle weakness in adult male rats, we conclude that aged rats have decreased susceptibility to CIH-induced stress. We suggest that structural remodelling with improved hypoxic tolerance in upper airway muscles may partly compensate for impaired neural regulation of the upper airway and increased propensity for airway collapse in aged mammals.

Endothelin-1 mediates attenuated carotid baroreceptor activity by intermittent hypoxia

http://jap.physiology.org/content/112/1/187.short

Thursday, October 20, 2011

Ying-Jie Peng, Jayasri Nanduri, Xin Zhang, Ning Wang, Gayatri Raghuraman, Jeanne Seagard, Ganesh K. Kumar, and Nanduri R. Prabhakar

Abstract

The objectives of the present study were to examine the effects of intermittent hypoxia (IH) on arterial baroreflex function and assess the underlying mechanism(s). Experiments were performed on adult male rats treated with 14 days of IH (15 s of hypoxia, 5 min of normoxia; 8 h/day) or normoxia (control). Arterial blood pressures were elevated in IH-treated rats, and this effect was associated with attenuated heart rate and splanchnic sympathetic nerve responses to arterial baroreflex activation. In IH-treated rats, carotid baroreceptor responses to elevated sinus pressures were attenuated. Endothelin-1 (ET-1) levels were elevated in the carotid sinus region of IH-treated rats, and this effect was associated with increased endothelin converting enzyme (ECE) activity, which generates biologically active ET-1. ETA receptor antagonist prevented the effects of IH on carotid baroreceptor activity. In IH-treated rats, reactive oxygen species (ROS) levels were elevated in the carotid sinus region, and antioxidant treatment prevented the effects of IH on ET-1 levels, ECE activity, carotid baroreceptor activity, and baroreflex function. These results demonstrate that 1) IH attenuates arterial baroreflex function, which is in part due to reduced carotid baroreceptor responses to

elevated carotid sinus pressure, and 2) IH-induced carotid baroreceptor dysfunction involves reactive oxygen species-dependent upregulation of ET-1 signaling in the carotid sinus region.

Fentanyl activates hypoxia-inducible factor 1 in neuronal SH-SY5Y cells and mice under non-hypoxic conditions in a μ-opioid receptor-dependent manner

http://www.sciencedirect.com/science/article/pii/S0014299911007199

Friday, June 17, 2011

Hiroki Daijoa, Shinichi Kaia, Tomoharu Tanakaa, Takuhiko Wakamatsua, Shun Kishimotoa, Kengo Suzukia, b, Hiroshi Haradac, d, Satoshi Takabuchia, Takehiko Adachie, Kazuhiko Fukudaa, Kiichi Hirotaa,

Abstract

Hypoxia-inducible factor 1 (HIF-1) is the main transcription factor responsible for hypoxia-induced gene expression. Perioperative drugs including anesthetics have been reported to affect HIF-1 activity. However, the effect of fentanyl on HIF-1 activity is not well documented. In this study, we investigated the effect of fentanyl and other opioids on HIF-1 activity in human SH-SY5Y neuroblastoma cells, hepatoma Hep3B cells, lung adenocarcinoma A549 cells and mice. Cells were exposed to fentanyl, and HIF-1 protein expression was examined by Western blot analysis using anti-HIF-1α and β antibodies. HIF-1-dependent gene expression was investigated by semi-quantitative real-time reverse transcriptase (RT)-PCR (qRT-PCR) and luciferase assay. Furthermore, fentanyl was administered intraperitoneally and HIF-1-dependent gene expression was investigated by qRT-PCR in the brains and kidneys of mice. A 10-μM concentration of fentanyl and other opioids, including 1 μM morphine and 4 μM remifentanil, induced HIF-1α protein expression and HIF-1 target gene expression in an opioid receptor-dependent manner in SH-SY5Y cells with activity peaking at 24 h. Fentanyl did not augment HIF-1α expression during hypoxia-induced induction. HIF-1α stabilization assays and experiments with cycloheximide revealed that fentanyl increased translation from HIF-1α mRNA but did not stabilize the HIF-1α protein. Furthermore, fentanyl induced HIF-1 target gene expression in the brains of mice but not in their kidneys in a naloxone-sensitive manner. In this report, we describe for the first time that fentanyl, both in vitro and in vivo, induces HIF-1 activation under non-hypoxic conditions, leading to increases in expression of genes associated with adaptation to hypoxia.

Keywords

Fentanyl; Opioid; Hypoxia-inducible factor 1 (HIF-1); SH-SY5Y cells

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A neonatal mouse model of intermittent hypoxia associated with features of apnea in premature infants

http://www.sciencedirect.com/science/article/pii/S1569904811002047

Tuesday, June 14, 2011

Jun Caia, Chi Minh Tuonga, David Gozalc

Abstract

A neonatal mouse model of intermittent hypoxia (IH) simulating the recurring hypoxia/reoxygenation episodes of apnea of prematurity (AOP) was developed. C57BL/6 P2 pups were culled for exposure to either intermittent hypoxia or intermittent air as control. The IH paradigms consisted of alternation cycles of 20.9% O2 and either 8.0% or 5.7% O2 every 120 or 140 s for 6 h a day during daylight hours from day 2 to day 10 postnatally, i.e., roughly equivalent to human brain development in the perinatal period. IH exposures elicited modest to severe decrease in oxygen saturation along with bradycardia in neonatal mice, which were severity-dependent. Hypomyelination in both central and peripheral nervous systems was observed despite the absence of visible growth retardation. The neonatal mouse model of IH in this study partially fulfills the current diagnostic criteria with features of AOP, and provides opportunities to reproduce in rodents some of the pathophysiological changes associated with this disorder, such as alterations in myelination.

Keywords

Mouse model; Intermittent hypoxia; Infantile apnea; Apnea of prematurity; White matter

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Hypoxia-induced angiogenesis is delayed in aging mouse brain

http://www.sciencedirect.com/science/article/pii/S0006899311005130

Saturday, March 12, 2011

Girriso F. Benderroa, Joseph C. LaManna

Abstract

Chronic moderate hypoxia results in systemic and central nervous system adaptations that allow acclimatization. Long-term responses to hypoxia involve systemic physiological changes, metabolic regulation, and vascular remodeling. To investigate whether aging affects systemic and cerebral angiogenic adaptational changes in response to prolonged hypoxia, the present study assessed the responses of 4 month old (“young”) C57BL/6 mice and 24 month old (“aged”) C57BL/6 mice to chronic hypobaric hypoxia of 0.4 atm (290 torr). Compared to young mice, delayed body weight-loss recovery and a lag in polycythemic response were observed in aged mice. As previously shown, hypoxia inducible factor-1α (HIF-1α) accumulation was attenuated and vascular endothelial growth factor (VEGF) expression was decreased in the cerebral cortex of aged mice. Conversely, cyclooxygenase-2 (COX-2), angiopoietin-2 (Ang-2), and peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) protein upregulation were not affected in the aged mice. Despite an initial delay in cerebral angiogenic response in aged mice in the first week of hypoxia, no significant differences were observed in microvascular density between young and aged mice in normoxia and at 2 and 3 weeks of hypoxia. Taken together, these observations indicate that, even though the HIF-1 response to hypoxia is greatly attenuated, HIF-1 independent compensatory pathways are eventually able to maintain baseline and cerebral angiogenic adaptational changes to chronic hypoxia in aged mice. The delayed adaptive response, however, may result in decreased survival in the aged cohort.

Identification of a Novel Form of Noradrenergic-Dependent Respiratory Motor Plasticity Triggered by Vagal Feedback

http://neuro.cjb.net/content/30/50/16886.abstract

Wednesday, December 15, 2010

Arash Tadjalli , James Duffin , and John Peever

Abstract

The respiratory control system is not just reflexive, it is smart, it learns, and, in fact, it has a memory. The respiratory system listens to and carefully remembers how previous stimuli affect breathing. Respiratory memory is laid down by adjusting synaptic strength between respiratory neurons. For example, repeated hypoxic bouts trigger a form of respiratory memory that functions to strengthen the ability of respiratory motoneurons to trigger contraction of breathing muscles. This type of respiratory plasticity is known as long-term facilitation (LTF). Although chemical feedback, such as hypoxia, initiates LTF, it is unknown whether natural modulation of mechanical feedback (from vagal inputs) also causes motor plasticity. Here, we used reverse microdialysis, electrophysiology, neuropharmacology, and histology to determine whether episodic modulation of vagally mediated mechanical feedback is able to induce respiratory LTF in anesthetized adult rats. We show that repeated obstructive apneas disrupt vagal feedback and trigger LTF of hypoglossal motoneuron activity and genioglossus muscle tone. This same stimulus does not cause LTF of diaphragm activity. Hypoxic episodes do not cause apnea-induced LTF; instead, LTF is triggered by modulation of vagal feedback. Unlike hypoxia-induced respiratory plasticity, vagus-induced LTF does not require 5-HT2 receptors but instead relies on activation of α1-adrenergic receptors on hypoglossal motoneurons. In summary, we identify a novel form of hypoxia- and 5-HT-independent respiratory motor plasticity that is triggered by physiological modulation of vagal feedback and is mediated by α1-adrenergic receptor activation on (or near) hypoglossal motoneurons.

Neuronal death during combined intermittent hypoxia/hypercapnia is due to mitochondrial dysfunction

http://ajpcell.physiology.org/content/early/2010/03/31/ajpcell.00298.2009.abstract

Wednesday, March 31, 2010

Robert M. Douglas1,*, Julie Ryu1, Amjad Kanaan1, Maria del Carmen Rivero1, Laura J. Dugan1, Gabriel G. Haddad1, and Sameh S. Ali1

Abstract

Breathing-disordered states, such as in obstructive sleep apnea (OSA), which are cyclical in nature, have been postulated to induce neurocognitive morbidity in both pediatric and adult populations. The oscillatory nature of intermittent hypoxia, especially when chronic, may mimic the paradigm of ischemia/reperfusion in that

tissues and cells are exposed to episodes of low and high O2 and this may lead to oxidant stress. Therefore, we decided to explore the potential contribution of oxidant stress in our intermittent hypoxia/hypercapnia animal model and the role that mitochondria might play in this stress. Neonatal mice were exposed to intermittent hypoxia/hypercapnia for 10d and 2 weeks. Combined intermittent hypoxia/hypercapnia led to a marked increase in apoptotic cell death in the cerebral cortex. Oxygen consumption studies in isolated mitochondria from intermittent hypoxia/hypercapnia-exposed brains demonstrated significant reductions in both state 4 and state 3 respiratory activities by approximately 60% and 75%, respectively. Electron paramagnetic resonance (EPR) spectroscopy registered a significant increase in superoxide production during non-phosphorylating state 4 by 37% although superoxide leakage during state 3 didn't increase upon treatment. Neuronal superoxide-specific dihydroethidium-oxidation was also greater in exposed animals. These studies indicate that intermittent hypoxia/hypercapnia leads to oxidative stress due to mitochondrial response within the mouse CNS.

Chronic intermittent hypoxia augments chemoreflex control of sympathetic activity: Role of the angiotensin II type 1 receptor

http://www.sciencedirect.com/science/article/pii/S1569904810000492

Friday, February 12, 2010

Noah J. Marcusa, e, Yu-Long Lib, Cynthia E. Birdc, Harold D. Schultzd, Barbara J. Morgan

Abstract

Chronic exposure to intermittent hypoxia (CIH) increases carotid sinus nerve activity in normoxia and in response to acute hypoxia. We hypothesized that CIH augments basal and chemoreflex-stimulated sympathetic outflow through an angiotensin receptor-dependent mechanism. Rats were exposed to CIH for 28 days: a subset was treated with losartan. Then, lumbar sympathetic activity was recorded under anesthesia during 20-s apneas, isocapnic hypoxia, and potassium cyanide. We measured carotid body superoxide production and expression of angiotensin II type-1 receptor, neuronal nitric oxide synthase, and NADPH oxidase. Sympathetic activity was higher in CIH vs. control rats at baseline, during apneas and isocapnic hypoxia, but not cyanide. Carotid body superoxide production and expression of angiotensin II type 1 receptor and gp91phox subunit of NADPH oxidase were elevated in CIH rats, whereas expression of neuronal nitric oxide synthase was reduced. None of these differences were evident in animals treated with losartan. CIH-induced augmentation of chemoreflex sensitivity occurs, at least in part, via the renin–angiotensin system.

Keywords

Chemoreceptors; Angiotensin II; Superoxide; Angiotensin antagonist; Oxidative stress

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Treatment with the catalytic metalloporphyrin AEOL 10150 reduces inflammation and oxidative stress due to inhalation of the sulfur mustard analog 2-chloroethyl ethyl sulfide

http://www.sciencedirect.com/science/article/pii/S0891584910000729

Thursday, February 4, 2010

Heidi C. O'Neilla, Carl W. Whitea, b, Livia A. Veressc, Tara B. Hendry-Hoferb, Joan E. Loaderb, Elysia Mind, Jie Huangd, Raymond C. Rancourtb, Brian J. Day

Abstract
Sulfur mustard (bis-2-(chloroethyl) sulfide; SM) is a highly reactive vesicating and alkylating chemical warfare agent. A SM analog, 2-chloroethyl ethyl sulfide (CEES), has been utilized to elucidate mechanisms of toxicity and as a screen for therapeutics. Previous studies with SM and CEES have demonstrated a role for oxidative stress as well as decreased injury with antioxidant treatment. We tested whether posttreatment with the metalloporphyrin catalytic antioxidant AEOL 10150 would improve outcome in CEES-induced lung injury. Anesthetized rats inhaled 5% CEES for 15 min via a nose-only inhalation system. At 1 and 9 h after CEES exposure, rats were given AEOL 10150 (5 mg/kg, sc). At 18 h post-CEES exposure BALF lactate dehydrogenase activity, protein, IgM, red blood cells, and neutrophils were elevated but were decreased by AEOL 10150 treatment. Lung myeloperoxidase activity was increased after CEES inhalation and was ameliorated by AEOL 10150. The lung oxidative stress markers 8-OHdG and 4-HNE were elevated after CEES exposure and significantly decreased by AEOL 10150 treatment. These findings demonstrate that CEES inhalation increased lung injury, inflammation, and oxidative stress, and AEOL 10150 was an effective rescue agent. Further investigation utilizing catalytic antioxidants as treatment for SM inhalation injury is warranted.

Keywords
Antioxidants; Lung injury; Sulfur mustard; CEES; Free radicals

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Effect of intermittent hypoxia on atherosclerosis in apolipoprotein E-deficient mice

http://www.atherosclerosis-journal.com/article/S0021-9150(09)00848-X/abstract

Monday, November 9, 2009

Jonathan Jun, Christian Reinke, Djahida Bedja, Dan Berkowitz, Shannon Bevans-Fonti, Jianguo Li, Lili A. Barouch, Kathleen Gabrielson,Vsevolod Y. Polotsky

Abstract

Objective
Obstructive sleep apnea causes intermittent hypoxia (IH) and is associated with increased cardiovascular mortality. This increased risk may be attributable to more extensive or unstable atherosclerotic plaques in subjects with OSA. We studied the effect of chronic IH in atherosclerosis-prone mice.

Methods and results
Apolipoprotein E-deficient (ApoE−/−) mice fed a high cholesterol diet were exposed to 4 or 12 weeks of IH and compared to intermittent air-exposed controls. At 4 weeks, IH increased plaque size in the aortic sinus and the descending aorta. At 12 weeks, atherosclerosis progressed in all groups, but more rapidly in the descending aorta of IH-exposed animals. Plaque composition was similar between IH and controls. Between 4

and 12 weeks, there were progressive increases in blood pressure, with relatively stable increases in serum lipids and arterial stiffness.

Conclusions
IH accelerates atherosclerotic plaque growth in ApoE−/− mice without affecting plaque composition. The mechanisms may include non-additive increases in serum lipids, and cumulative increases in blood pressure.

Nimodipine Prevents Transient Cognitive Dysfunction After Moderate Hypoxia in Adult Mice

http://journals.lww.com/jnsa/Abstract/2009/04000/Nimodipine_Prevents_Transient_Cognitive.8.aspx

Wednesday, April 1, 2009

Haile, Michael MD*; Limson, Fred BA†; Gingrich, Kevin MD*; Li, Yong-Sheng MD‡; Quartermain, David PhD‡; Blanck, Thomas MD, PhD*; Bekker, Alex MD, PhD*

Abstract

Background: Cognitive changes associated with moderate hypoxia may be related to the elevation of cytosolic calcium (Ca2+) levels which may, in turn, affect neurotransmitter synthesis and metabolism. We tested whether treatment with nimodipine (NIMO), an L-type Ca2+ channel blocker, would preserve working memory after hypoxic hypoxia.

Methods: We randomized 157 Swiss-Webster, 30 to 35 g mice (6 to 8 wk) to 6 groups, which were exposed to the following gas mixtures for 1 hour: (1) O2 21%; (2) O2 21% followed by 0.1 mg/kg of subcutaneous NIMO; (3) O2 21% followed by vehicle (60% polyethylene glycol/40% methanol); (4) O2 10%; (5) O2 10% then NIMO; (6) O2 10% then vehicle. The Object Recognition Test (ORT) was given once either on Day 1 or Day 7 to assess changes in short-term memory. ORT exploits the tendency of mice to prefer novel over familiar objects. Two identical objects were placed in an arena for 15 minutes of training. During the testing 1 hour later, one of the objects was replaced by a new object. Recognition Index (RI) was used to compare performance. It is defined as the time spent exploring the novel object divided by the time spent exploring both objects, the novel plus the familiar, and this ratio is converted to a percentage. RI was analyzed with analysis of variance. Tukey Honestly Significant Difference tests were used for post hoc comparisons when appropriate. P values <0.05 were considered significant.

Results: RI for the control group was 68.3% (SE±3.6%). RI was 53.7% (SE±3.8%) for the 10% O2 group on the first posttreatment day. O2 saturation (SpO2) for the hypoxic group was 71.7% (SE±0.5%). By Day 7, RI for the 10% O2 group increased to 64.2% (SE±4.7%), which was not significantly different from control. On Day 1, RI was 68.6% (SE±5.2%) for hypoxic rodents treated with NIMO. These results were statistically significant. Low RI indicates impaired working memory and high RI indicates intact working memory. These results suggest that NIMO prevented impairment of working memory after moderate hypoxia.

Conclusions: NIMO reverses the disturbance of short-term working memory caused by moderate hypoxia in mice. The results may have implications for cognitive changes linked to Ca2+ homeostasis in the postoperative period.

Aerosolized Phosphoinositide 3-Kinase γ/δ Inhibitor TG100-115 [3-[2,4-Diamino-6-(3-hydroxyphenyl)pteridin-7-yl]phenol] as a Therapeutic Candidate for Asthma and Chronic Obstructive Pulmonary Disease

http://jpet.aspetjournals.org/content/328/3/758.abstract

Thursday, December 4, 2008

John Doukas, Lisa Eide, Karin Stebbins, Adrienne Racanelli-Layton, Luis Dellamary, Michael Martin, Elena Dneprovskaia, Glenn Noronha, Richard Soll, Wolfgang Wrasidlo, Lisette M. Acevedo and David A. Cheresh

Abstract

Phosphatidylinositol 3-kinases (PI3Ks) are key elements in the signaling cascades that lie downstream of many cellular receptors. In particular, PI3K δ and γ isoforms contribute to inflammatory cell recruitment and subsequent activation. For this reason, in a series of preclinical studies, we tested the potential of a recently developed small-molecule inhibitor of these two isoforms, TG100-115 [3-[2,4-diamino-6-(3-hydroxyphenyl)pteridin-7-yl]phenol], as a form of anti-inflammatory therapy for respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). To determine pharmacokinetic profiles, aerosolized formulations of the drug were delivered to mice by a nose-only inhalation route, yielding high pulmonary TG100-115 levels with minimal systemic exposure. Safety assessments were favorable, with no clinical or histological changes noted after 21 days of daily dosing. In a murine asthma model, aerosolized TG100-115 markedly reduced the pulmonary eosinophilia and the concomitant interleukin-13 and mucin accumulation characteristic of this disease. As a functional benefit, interventional dosing schedules of this inhibitor also reduced airway hyper-responsiveness. To model the pulmonary neutrophilia characteristic of COPD, mice were exposed to either intranasal lipopolysaccharide or inhaled smoke. Aerosolized TG100-115 again inhibited these inflammatory patterns, most notably in the smoke model, where interventional therapy overcame the steroid-resistant nature of the pulmonary inflammation. In conclusion, aerosolized TG100-115 displays pharmacokinetic, safety, and biological activity profiles favorable for further development as a therapy for both asthma and COPD. Furthermore, these studies support the hypothesis that PI3K δ and γ are suitable molecular targets for these diseases.

Development of the ACTH and corticosterone response to acute hypoxia in the neonatal rat

http://ajpregu.physiology.org/content/295/4/R1195.abstract

Wednesday, August 13, 2008

Eric D. Bruder, Jennifer K. Taylor, Kimberli J. Kamer, and Hershel Raff

Abstract

Acute episodes of severe hypoxia are among the most common stressors in neonates. An understanding of the development of the physiological response to acute hypoxia will help improve clinical interventions. The

present study measured ACTH and corticosterone responses to acute, severe hypoxia (8% inspired O2 for 4 h) in neonatal rats at postnatal days (PD) 2, 5, and 8. Expression of specific hypothalamic, anterior pituitary, and adrenocortical mRNAs was assessed by real-time PCR, and expression of specific proteins in isolated adrenal mitochondria from adrenal zona fascisulata/reticularis was assessed by immunoblot analyses. Oxygen saturation, heart rate, and body temperature were also measured. Exposure to 8% O2 for as little as 1 h elicited an increase in plasma corticosterone in all age groups studied, with PD2 pups showing the greatest response (~3 times greater than PD8 pups). Interestingly, the ACTH response to hypoxia was absent in PD2 pups, while plasma ACTH nearly tripled in PD8 pups. Analysis of adrenal mRNA expression revealed a hypoxia-induced increase in Ldlr mRNA at PD2, while both Ldlr and Star mRNA were increased at PD8. Acute hypoxia decreased arterial O2 saturation (SPO2) to ~80% and also decreased body temperature by 5–6°C. The hypoxic thermal response may contribute to the ACTH and corticosterone response to decreases in oxygen. The present data describe a developmentally regulated, differential corticosterone response to acute hypoxia, shifting from ACTH independence in early life (PD2) to ACTH dependence less than 1 wk later (PD8).

Double Oxygen–sensing Vector System for Robust Hypoxia/Ischemia-regulated Gene Induction in Cardiac Muscle In Vitro and In Vivo

http://www.nature.com/mt/journal/v16/n9/abs/mt2008136a.html

Tuesday, June 24, 2008

Ekaterina V Fomicheva, Immanuel I Turner, Terri G Edwards, Janet Hoff, Eric Arden, Louis G D'Alecy and Joseph M Metzger

Abstract

High-fidelity genetically encoded bio-sensors that respond to changes in cellular environmental milieu in disease offer great potential in a range of patho-physiological settings. Here a unique hypoxia-regulated vector-based system with double oxygen–sensing transcriptional elements was developed for rapid and robust hypoxia-regulated gene expression in the heart. Hypoxia-responsive cis elements were used in tandem with a single proline-modified oxygen-dependent degradation (ODD) domain of hypoxia-inducible factor-1α to form a double oxygen–sensing vector system (DOSVS). In adult cardiac myocytes in vitro, the DOSVS demonstrated a low background expression not different from baseline control in normoxia, and with 100% efficiency, robust, 1,000-fold induction upon hypoxia. In the heart in vivo, hypoxic and ischemic challenges elicited rapid 700-fold induction in living animals, exceeding that obtained by a high-fidelity constitutive cytomegalovirus (CMV) viral promoter. DOSVS also showed high temporal resolution in the heart in response to cyclical bouts of hypoxia in vivo. We propose that DOSVS will be valuable for a range of applications, including bio-sensing and therapeutic gene expression in the heart and other organ systems that are confronted by chronic or episodic hypoxic/ischemic stresses in vivo.

Epidermal Sensing of Oxygen Is Essential for Systemic Hypoxic Response

http://www.cell.com/retrieve/pii/S0092867408002894

Friday, April 18, 2008

Adam T. Boutin, Alexander Weidemann, Zhenxing Fu, Lernik Mesropian, Katarina Gradin, Colin Jamora, Michael Wiesener, Kai-Uwe Eckardt, Cameron J. Koch, Lesley G. Ellies, Gabriel Haddad, Volker H. Haase, M. Celeste Simon, Lorenz Poellinger, Frank L. Powell and Randall S. Johnson

Summary

Skin plays an essential role, mediated in part by its remarkable vascular plasticity, in adaptation to environmental stimuli. Certain vertebrates, such as amphibians, respond to hypoxia in part through the skin; but it is unknown whether this tissue can influence mammalian systemic adaptation to low oxygen levels. We have found that epidermal deletion of the hypoxia-responsive transcription factor HIF-1α inhibits renal erythropoietin (EPO) synthesis in response to hypoxia. Conversely, mice with an epidermal deletion of the von Hippel-Lindau (VHL) factor, a negative regulator of HIF, have increased EPO synthesis and polycythemia. We show that nitric oxide release induced by the HIF pathway acts on cutaneous vascular flow to increase systemic erythropoietin expression. These results demonstrate that in mice the skin is a critical mediator of systemic responses to environmental oxygen.

Influenza, Pneumonia, RSV & Other Acute Respiratory Disorders

Physostigmine Reverses Cognitive Dysfunction Caused by Moderate Hypoxia in Adult Mice

http://www.anesthesia-analgesia.com/content/105/3/739.abstract

Saturday, September 1, 2007

Alex Bekker, MD, PhD, Michael Haile, MD, Kevin Gingrich, MD, Leslie Wenning, BA, Alex Gorny, MD, David Quartermain, PhD and Thomas Blanck, MD, PhD

Abstract
BACKGROUND: Cognitive changes associated with moderate hypoxia in rodents may result from the diminished functioning of central cholinergic neurotransmission. We designed this study to examine whether treatment with physostigmine (PHY), an acetylcholinesterase inhibitor, could improve the impairment of working memory after hypoxic hypoxia.
METHODS: We randomized 90 Swiss Webster, 30–35 g mice (6–8 wks) to three hypoxia groups at fraction of inspired oxygen, FiO2 = 0.10 (1. no treatment; 2. PHY 0.1 mg/kg intraperitoneally administered immediately before; or 3. after hypoxia), or to two room air groups (given either no treatment or PHY after an insult). An object recognition test was used to assess short-term memory function. The object recognition test exploits the tendency of mice to prefer exploring novel objects in an environment when a familiar object is also present. During the 15 min training trial, two identical objects were placed in two defined sites of the box. During the test trial performed 1 h later, one of the objects was replaced by a new object with a different shape. The time spent exploring the two objects was automatically recorded by a video camera and associated software. The performance was analyzed with ANOVA, followed by *post hoc* comparisons using the Newman– Keuls test when appropriate. *P* values <0.05 were considered significant.
RESULTS: Untreated mice subjected to hypoxia at Fio2 = 0.1 spent significantly less time exploring a novel object on testing day 1 than did untreated mice breathing room air. Performance of the mice subjected to hypoxia, who received physostigmine after, but not before, the insult did not differ from the control group.
CONCLUSION: Moderate hypoxia impairs rodents' performance in a working memory task. It appears that changes are transient, because the cognitive functioning of the mice returned to the baseline level 7 days after treatment. Postinsult administration of PHY prevented deterioration of cognitive function. An increased level of acetylcholine in the central nervous system may be responsible for the improved performance of the hypoxia-treated mice.

IMPLICATIONS: Mild hypoxia (O2 saturation 70%) produces a transient impairment of short-term memory in adult mice. Physostigmine administered after hypoxic insult reverses cognitive dysfunction.

Viral acute lower respiratory infections impair CD8+ T cells through PD-1

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3408742/

Wednesday, August 1, 2012

John J. Erickson, Pavlo Gilchuk, Andrew K. Hastings, Sharon J. Tollefson, Monika Johnson, Melissa B. Downing,Kelli L. Boyd,Joyce E. Johnson, Annette S. Kim, Sebastian Joyce, and John V. Williams

Viruses are leading causes of severe acute lower respiratory infections (LRIs). These infections evoke incomplete immunity, as individuals can be repeatedly reinfected throughout life. We report that acute viral LRI causes rapid pulmonary CD8+ cytotoxic T lymphocyte (TCD8) functional impairment via programmed death–1/programmed death ligand–1 (PD-1/PD-L1) signaling, a pathway previously associated with prolonged antigenic stimulation during chronic infections and cancer. PD-1–mediated TCD8 impairment occurred acutely in mice following infection with human metapneumovirus or influenza virus. Viral antigen was sufficient for PD-1 upregulation, but induction of PD-L1 was required for impairment. During secondary viral infection or epitope-only challenge, memory TCD8 rapidly reexpressed PD-1 and exhibited severe functional impairment. Inhibition of PD-1 signaling using monoclonal antibody blockade prevented TCD8 impairment, reduced viral titers during primary infection, and enhanced protection of immunized mice against challenge infection. Additionally, PD-1 and PD-L1 were upregulated in the lungs of patients with 2009 H1N1 influenza virus, respiratory syncytial virus, or parainfluenza virus infection. These results indicate that PD-1 mediates TCD8 functional impairment during acute viral infection and may contribute to recurrent viral LRIs. Therefore, the PD-1/PD-L1 pathway may represent a therapeutic target in the treatment of respiratory viruses.

Dry deposition of pollutant and marker particles onto live mouse airway surfaces enhances monitoring of individual particle mucociliary transit behaviour

http://scripts.iucr.org/cgi-bin/paper_yard?mo5033

Sunday, July 1, 2012

M. Donnelley, K. S. Morgan, K. K. W. Siu and D. W. Parsons
... Body temperature was maintained using an infrared heat lamp and monitored with a rectal thermometer, and vital signs were monitored using a **MouseOx** pulse oximeter (STARR Lifesciences, USA). 2.4. Sample delivery. Owing **...**
Particles suspended in the air are inhaled during normal respiration and unless cleared by airway defences, such as the mucociliary transit (MCT) system, they can remain and affect lung and airway health. Synchrotron phase-contrast X-ray imaging (PCXI) methods have been developed to non-invasively monitor the behaviour of individual particles in live mouse airways and in previous studies the MCT behaviour of particles and fibres in the airways of live mice after deposition in a saline carrier fluid have been examined. In this study a range of common respirable pollutant particles (lead dust, quarry dust and fibreglass fibres) as well as marker particles (hollow glass micro-spheres) were delivered into the trachea of live mice using a dry powder insufflator to more accurately mimic normal environmental particulate exposure and deposition via inhalation. The behaviour of the particles once delivered onto the airway surface was tracked over a five minute period via PCXI. All particles were visible after deposition. Fibreglass fibres remained stationary throughout while all other particle types transited the tracheal surface throughout the imaging period. In all cases the majority of the particle deposition and any airway surface activity was located close to the dorsal tracheal wall. Both the individual and bulk motions of the glass bead marker particles were visible and their behaviour enabled otherwise hidden MCT patterns to be revealed. This study verified the value of PCXI for examining the post-deposition particulate MCT behaviour in the mouse trachea and highlighted that MCT is not a uniform process as suggested by radiolabel studies. It also directly revealed the advantages of dry particle delivery for establishing adequate particulate presence for visualizing MCT behaviour. The MCT behaviour and rate seen after dry particle delivery was different from that in previous carrier-fluid studies. It is proposed that dry particle delivery is essential for producing environmentally realistic particle deposition and studying how living airway surfaces handle different types of inhaled particles by MCT processes.

Respiratory Insufficiency Correlated Strongly with Mortality of Rodents Infected with West Nile Virus

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0038672

Thursday, June 14, 2012

John D. Morrey*, Venkatraman Siddharthan, Hong Wang, Jeffery O. Hall

West Nile virus (WNV) disease can be fatal for high-risk patients. Since WNV or its antigens have been identified in multiple anatomical locations of the central nervous system of persons or rodent models, one cannot know where to investigate the actual mechanism of mortality without careful studies in animal models. In this study, depressed respiratory functions measured by plethysmography correlated strongly with mortality. This respiratory distress, as well as reduced oxygen saturation, occurred beginning as early as 4 days before mortality. Affected medullary respiratory control cells may have contributed to the animals' respiratory insufficiency, because WNV antigen staining was present in neurons located in the ventrolateral medulla. Starvation or dehydration would be irrelevant in people, but could cause death in rodents due to lethargy or loss of appetite. Animal experiments were performed to exclude this possibility. Plasma ketones were increased in moribund infected hamsters, but late-stage starvation markers were not apparent. Moreover, daily subcutaneous administration of 5% dextrose in physiological saline solution did not improve survival or other disease signs. Therefore, infected hamsters did not die from starvation or dehydration. No cerebral edema was apparent in WNV- or sham-infected hamsters as determined by comparing wet-to-total weight ratios of brains, or by evaluating blood-brain-barrier permeability using Evans blue dye penetration into brains. Limited vasculitis was present in the right atrium of the heart of infected hamsters, but abnormal electrocardiograms for several days leading up to mortality did not occur. Since respiratory insufficiency was strongly correlated with mortality more than any other pathological parameter, it is the likely cause of death in rodents. These animal data and a poor prognosis for persons with respiratory insufficiency support the hypothesis that neurological lesions affecting respiratory function may be the primary cause of human WNV-induced death.

Innate lymphoid cells promote lung-tissue homeostasis after infection with influenza virus

http://www.nature.com/ni/journal/v12/n11/abs/ni.2131.html

Tuesday, August 2, 2011

Laurel A Monticelli,Gregory F Sonnenberg,Michael C Abt,Theresa Alenghat,Carly G K Ziegler,Travis A Doering,Jill M Angelosanto,Brian J Laidlaw,Cliff Y Yang,Taheri Sathaliyawala,Masaru Kubota,Damian Turner,Joshua M Diamond,Ananda W Goldrath,Donna L Farber,Ronald G Collman,E John Wherry& David Artis

Innate lymphoid cells (ILCs), a heterogeneous cell population, are critical in orchestrating immunity and inflammation in the intestine, but whether ILCs influence immune responses or tissue homeostasis at other mucosal sites remains poorly characterized. Here we identify a population of lung-resident ILCs in mice and humans that expressed the alloantigen Thy-1 (CD90), interleukin 2 (IL-2) receptor α-chain (CD25), IL-7

receptor α-chain (CD127) and the IL-33 receptor subunit T1-ST2. Notably, mouse ILCs accumulated in the lung after infection with influenza virus, and depletion of ILCs resulted in loss of airway epithelial integrity, diminished lung function and impaired airway remodeling. These defects were restored by administration of the lung ILC product amphiregulin. Collectively, our results demonstrate a critical role for lung ILCs in restoring airway epithelial integrity and tissue homeostasis after infection with influenza virus.

Differential Pathogenesis of Respiratory Syncytial Virus Clinical Isolates in BALB/c Mice

http://jvi.asm.org/content/85/12/5782.abstract

Tuesday, March 1, 2011

Kate L. Stokes, Michael H. Chi, Kaori Sakamoto,Dawn C. Newcomb, Michael G. Currier, Matthew M. Huckabee,Sujin Lee, Kasia Goleniewska, Carla Pretto, John V. Williams,Anne Hotard, Taylor P. Sherrill, R. Stokes Peebles Jr, and Martin L. Moore

Airway mucus is a hallmark of respiratory syncytial virus (RSV) lower respiratory tract illness. Laboratory RSV strains differentially induce airway mucus production in mice. Here, we tested the hypothesis that RSV strains differ in pathogenesis by screening six low-passage RSV clinical isolates for mucogenicity and virulence in BALB/cJ mice. The RSV clinical isolates induced variable disease severity, lung interleukin-13 (IL-13) levels, and gob-5 levels in BALB/cJ mice. We chose two of these clinical isolates for further study. Infection of BALB/cJ mice with RSV A2001/2-20 (2-20) resulted in greater disease severity, higher lung IL-13 levels, and higher lung gob-5 levels than infection with RSV strains A2, line 19, Long, and A2001/3-12 (3-12). Like the line 19 RSV strain, the 2-20 clinical isolate induced airway mucin expression in BALB/cJ mice. The 2-20 and 3-12 RSV clinical isolates had higher lung viral loads than laboratory RSV strains at 1 day postinfection (p.i.). This increased viral load correlated with higher viral antigen levels in the bronchiolar epithelium and greater histopathologic changes at 1 day p.i. The A2 RSV strain had the highest peak viral load at day 4 p.i. RSV 2-20 infection caused epithelial desquamation, bronchiolitis, airway hyperresponsiveness, and increased breathing effort in BALB/cJ mice. We found that RSV clinical isolates induce variable pathogenesis in mice, and we established a mouse model of clinical isolate strain-dependent RSV pathogenesis that recapitulates key features of RSV disease.

Pulmonary Gammaherpesvirus Infection and Pneumonitis Development Following Murine Bone Marrow Transplant.

http://deepblue.lib.umich.edu/handle/2027.42/86257

Saturday, January 1, 2011

Coomes, Stephanie Michael

Pulmonary complications are frequent following hematopoietic stem cell transplantation, including infections and pneumonitis. We have used a murine bone marrow transplant (BMT) model and murine gammaherpesvirus,

γHV-68, to study alterations in anti-viral immunity post-transplant. When challenged with γHV-68, BMT mice have reduced ability to control lytic viral replication in the lung, despite immune reconstitution. By day 21 post-infection the virus is latent, and BMT mice, but not control, develop pneumonitis with reduced oxygenation, fibrosis, inflammation, hyaline membranes, and foamy alveolar macrophages, a phenotype which persists 7 weeks post-infection. BMT mice have an increase in cells harvested by bronchoalveolar lavage (BAL), and this population is enriched in neutrophils, CD4, and CD8 cells. BAL fluid from BMT mice at day 21 has increased pro-fibrotic factors, including hydrogen peroxide, nitrite, and transforming growth factor-beta (TGFβ). Defective control of lytic virus infection in BMT mice is not related to impaired leukocyte recruitment or defective antigen presenting cell function. Rather, BMT lungs have decreased numbers of protective Th1 cells and increased numbers of Th17 cells in response to γHV-68. BMT mice are also characterized by an immunosuppressive lung environment at the time of infection that includes overexpression of TGFβ1, prostaglandin-E2, and increased Tregs. Neither pharmacological blockade of prostaglandin synthesis nor depletion of Tregs improved host defense. To understand the role of TGFβ, BMT mice were transplanted with transgenic bone marrow expressing dominant negative TGFβ receptor II in T cells (Tcell-DN-TGFβRII) or under the CD11c promoter (CD11c-DN-TGFβRII), blocking TGFβ signaling in CD4 and CD8 cells or CD11c-expressing cells, respectively. Tcell-DN-TGFβRII BMT mice have restored lytic viral load and improved Th1 response; these mice are largely protected from the pneumonitis phenotype. However, CD11cDN-TGFβRII BMT mice show increased susceptibility to lytic infection, similar to wild type BMT, and are only moderately protected from pneumonitis. Thus, our results indicate that overexpression of TGFβ1 following myeloablative BMT results in impaired T cell responses to viral infection, resulting in increased lytic viral load and pneumonitis. Our data provide new insight into the potential causes of impaired anti-viral immune responses and development of pneumonitis in hematopoietic stem cell transplant patients.

Pulse-oximetry accurately predicts lung pathology and the immune response during influenza infection

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2776688/

Monday, June 1, 2009

Verhoeven D, Teijaro JR, Farber DL. Department of Surgery, University of Maryland School of Medicine, Baltimore, MD 21210, USA.

In animal models of influenza, systemic weight loss is the primary indicator of morbidity from infection, which does not assess local lung pathology or the immune response. Here, we used a mouse-adapted pulse-oximeter as a non-invasive clinical readout of lung function during influenza infection in mice, and found direct correlations between oxygen saturation levels and lung pathology, that reflected the morbidity and survival from influenza infection. **We found blood oxygen levels to be a more accurate assessment than weight-loss morbidity in predicting lung pathology in hosts infected with different viral doses, and in assessing immune-mediated viral clearance in the lung.**

Low-Dose Arsenic Compromises the Immune Response to Influenza A Infection in Vivo

http://ehp03.niehs.nih.gov/article/info:doi/10.1289/ehp.0900911?282fee20

Wednesday, May 20, 2009

Courtney D. Kozul, Kenneth H. Ely, Richard I. Enelow, Joshua W. Hamilton

Background
Arsenic exposure is a significant worldwide environmental health concern. We recently reported that 5-week exposure to environmentally relevant levels (10 and 100 ppb) of As in drinking water significantly altered components of the innate immune response in mouse lung, which we hypothesize is an important contributor to the increased risk of lung disease in exposed human populations.

Objectives
We investigated the effects of As exposure on respiratory influenza A (H1N1) virus infection, a common and potentially fatal disease.

Methods
In this study, we exposed C57BL/6J mice to 100 ppb As in drinking water for 5 weeks, followed by intranasal inoculation with a sub lethal dose of influenza A/PuertoRico/8/34 (H1N1) virus. Multiple end points were assessed postinfection.

Results
Arsenic was associated with a number of significant changes in response to influenza, including an increase in morbidity and higher pulmonary influenza virus titers on day 7 post-infection. We also found many alterations in the immune response relative to As-unexposed controls, including a decrease in the number of dendritic cells in the mediastinal lymph nodes early in the course of infection.

Conclusions
Our data indicate that chronic As exposure significantly compromises the immune response to infection. Alterations in response to repeated lung infection may also contribute to other chronic illnesses, such as bronchiectasis, which is elevated by As exposure in epidemiology studies.

Post-infection A77-1726 blocks pathophysiologic sequelae of respiratory syncytial virus infection

http://ajrcmb.atsjournals.org/content/37/4/379.abstract

Sunday, May 17, 2009

IC Davis, ER Lazarowski, FP Chen, JM Hickman-Davis … - American Journal of Respiratory Cell and Molecular Biology, 2007 - Am Thoracic Soc

Despite respiratory syncytial virus (RSV) bronchiolitis remaining the most common cause of lower respiratory tract disease in infants worldwide, treatment has progressed little in the past 30 years. The aim of our study was to determine whether post-infection administration of *de novo* pyrimidine synthesis inhibitors could prevent the

reduction in alveolar fluid clearance (AFC) and hypoxemia that occurs at Day 2 after intranasal infection of BALB/c mice with RSV. BALB/c mice were infected intranasally with RSV strain A2. AFC was measured in anesthetized, ventilated mice after instillation of 5% bovine serum albumin into the dependent lung. Post-infection systemic treatment with leflunomide has no effect on AFC. However, when added to the AFC instillate, leflunomide's active metabolite, A77-1726, blocks RSV-mediated inhibition of AFC at Day 2. This block is reversed by uridine (which allows pyrimidine synthesis via the scavenger pathway) and not recapitulated by genistein (which mimics the tyrosine kinase inhibitor effects of A77-1726), indicating that the effect is specific for the *de novo* pyrimidine synthesis pathway. More importantly, when administered intranasally at Day 1, A77-1726, but not its vehicle dimethyl sulfoxide, maintains its beneficial effect on AFC and lung water content until Day 2. Intranasal instillation of A77-1726 at Day 1 also reduces bronchoalveolar lavage nucleotide levels, lung inflammation, and hypoxemia at Day 2 without impairing viral replication at Day 2 or viral clearance at Day 8. Post-infection intranasal or aerosolized treatment with pyrimidine synthesis inhibitors may provide symptomatic relief from the pathophysiologic sequelae of impaired AFC in children with RSV bronchiolitis.

Respiratory Insufficiency Correlated Strongly with Mortality of Rodents Infected with West Nile Virus

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JD Morrey, V Siddharthan, H Wang… - PLoS ONE, 2012 - dx.plos.org

... Pulse oximetry. Saturated arterial oxygen (SaO 2) measurements [27] were obtained from a mouse collar clip placed on the back of neck using the MouseOx™ pulse oximeter (**STARR Life Sciences**, Oakmont, PA) designed specifically to measure SaO 2 levels in mice. **...**

West Nile virus (WNV) disease can be fatal for high-risk patients. Since WNV or its antigens have been identified in multiple anatomical locations of the central nervous system of persons or rodent models, one cannot know where to investigate the actual mechanism of mortality without careful studies in animal models. In this study, depressed respiratory functions measured by plethysmography correlated strongly with mortality. This respiratory distress, as well as reduced oxygen saturation, occurred beginning as early as 4 days before mortality. Affected medullary respiratory control cells may have contributed to the animals' respiratory insufficiency, because WNV antigen staining was present in neurons located in the ventrolateral medulla. Starvation or dehydration would be irrelevant in people, but could cause death in rodents due to lethargy or loss of appetite. Animal experiments were performed to exclude this possibility. Plasma ketones were increased in moribund infected hamsters, but late-stage starvation markers were not apparent. Moreover, daily subcutaneous administration of 5% dextrose in physiological saline solution did not improve survival or other disease signs. Therefore, infected hamsters did not die from starvation or dehydration. No cerebral edema was apparent in WNV- or sham-infected hamsters as determined by comparing wet-to-total weight ratios of brains, or by evaluating blood-brain-barrier permeability using Evans blue dye penetration into brains. Limited vasculitis was present in the right atrium of the heart of infected hamsters, but abnormal electrocardiograms for several days leading up to mortality did not occur. Since respiratory insufficiency was strongly correlated with mortality more than any other pathological parameter, it is the likely cause of death in rodents. These animal data and a poor prognosis for persons with respiratory insufficiency support the hypothesis that neurological lesions affecting respiratory function may be the primary cause of human WNV-induced death.

Lung Cancer, COPD, Sleep Apnea & Other Chronic Respiratory Disorders

In vivo evaluation of venular glycocalyx during hemorrhagic shock in rats using intravital microscopy

http://www.sciencedirect.com/science/article/pii/S0026286212002014

Tuesday, January 1, 2013

Ivo Torres Filho, Luciana N. Torres, Jill L. Sondeen, I. Amy Polykratis, Michael A. Dubick

... Blood was collected into heparinized glass capillary tubes for hematocrit measurement (microhematocrit centrifuge model MB, Needthan HTS, MA). Hemoglobin O 2 saturation (SO 2) and respiratory rate (RR) were measured non-invasively (**MouseOx**, Starr Lifesciences). **...** Hemorrhage is responsible for a large percentage of trauma-related deaths but the mechanisms underlying tissue ischemia are complex and not well understood. Despite the evidence linking glycocalyx degradation and hemorrhagic shock, there is no direct data obtained in vivo showing glycocalyx thickness reduction in skeletal muscle venules after hemorrhage. We hypothesize that damage to the endothelial glycocalyx is a key element in hemorrhage pathophysiology and tested the hypothesis that hemorrhage causes glycocalyx degradation in cremaster muscle microvessels. We utilized intravital microscopy to estimate glycocalyx thickness in 48 microvessels while other microvascular parameters were measured using non-invasive techniques. Systemic physiological parameters and blood chemistry were simultaneously collected. We studied 27 post-capillary venules (< 16 μm diameter) of 8 anesthetized rats subjected to hemorrhage (40% of total blood volume). Six control rats were equally instrumented but not bled. Dextrans of different molecular weights labeled with FITC or Texas Red were injected. Glycocalyx thickness was estimated from the widths of the fluorescence columns and from anatomical diameter. While control rats did not show remarkable responses, a statistically significant decrease of about 59% in glycocalyx thickness was measured in venules after hemorrhagic shock. Venular glycocalyx thickness and local blood flow changes were correlated: venules with the greatest flow reductions showed the largest decreases in glycocalyx. These changes may have a significant impact in shock pathophysiology. Intravital microscopy and integrated systems such as the one described here may be important tools to identify mechanisms by which resuscitation fluids may improve tissue recovery and outcome following hemorrhage.

Neonatal caffeine treatment up-regulates adenosine receptors in brainstem and hypothalamic cardio-respiratory related nuclei of rat pups

http://www.sciencedirect.com/science/article/pii/S0014488612002701

Monday, October 1, 2012

Susana P. Gaytan, Rosario Pasaro

... and Caf groups (n = 190) were monitored (during 15 min) immediately before gavage and again 30 min after gavage (for another 15 min), to reduce the manipulation stress and obtain a regular

respiratory breathing, by means of a non-invasive sensor (**MouseOx** STARR Life **...**
While neonatal caffeine treatment is commonly used to alleviate apnea of prematurity in neonates and to improve neurological outcomes, its effects on adenosine A1 and A2A receptors (A1-R and A2A-R) are poorly known. We hypothesized that the central pharmacological action of caffeine is mediated by modification of the postnatal development of the adenosinergic system during a critical period. On postnatal days 2–6 (P2–P6) two groups of newborn rats were orally administered water plus glucose and/or caffeine at therapeutic doses to mimic the clinical use of caffeine in human neonates. Cardio-respiratory parameters were measured and the presence of A1-R and A2A-R and c-Fos protein was identified immunohistochemically in animals sacrificed from P2 to P11. % Haemoglobin saturation, and hearth and breath rates were significantly increased in caffeine-treated group (P5–P6). Significant differences were identified in the relative gene expression of A1-R and A2A-R, with an increase of A1-R labeling in the anterior hypothalamic area, ventromedial hypothalamic nucleus, parabrachial complex and ventrolateral medulla of the caffeine-treated group at P6. A moderate increase in A2A-R labeling was observed in ponto-medullary nuclei and other hypothalamic areas. An increase in c-Fos-positive labeled cells was found in the caffeine-treated group at P5–P6 within the same areas described above, with the most clear-cut increase seen in the arcuate nucleus. Indeed, increased A1-R and A2A-R gene expression was observed in both the brainstem and hypothalamus at P5. Up-regulation of adenosinergic maturation in central cardio-respiratory areas in caffeine-treated neonatal rats could explain the pharmacological effects of caffeine observed in premature infants.

Rosiglitazone Improves Insulin Sensitivity and Baroreflex Gain in Rats with Diet-Induced Obesity

http://jpet.aspetjournals.org/content/343/1/206.short

Wednesday, July 18, 2012

Ding Zhao, Belinda H. McCully, and Virginia L. Brooks

... Arterial oxygen levels were continuously monitored via a pulse oximeter (**Starr Life Sciences**, Inc, Oakmont, PA), and, if necessary, adjustments were made in tracheal catheter position to maintain oxygen levels at or above 95%. **...**
Obesity decreases baroreflex gain (BRG); however, the mechanisms are unknown. We tested the hypothesis that impaired BRG is related to the concurrent insulin resistance, and, therefore, BRG would be improved after treatment with the insulin-sensitizing drug rosiglitazone. Male rats fed a high-fat diet diverged into obesity-prone (OP) and obesity-resistant (OR) groups after 2 weeks. Then, OP and OR rats, as well as control (CON) rats fed a standard diet, were treated daily for 2 to 3 weeks with rosiglitazone (3 or 6 mg/kg) or its vehicle by gavage. Compared with OR and CON rats, conscious OP rats exhibited reductions in BRG (OP, 2.9 ± 0.1 bpm/mm Hg; OR, 4.0 ± 0.2 bpm/mm Hg; CON, 3.9 ± 0.2 bpm/mm Hg; $P < 0.05$) and insulin sensitivity (hyperinsulinemic euglycemic clamp; OP, 6.8 ± 0.9 mg/kg · min; OR, 22.2 ± 1.2 mg/kg · min; CON, 17.7 ± 0.8 mg/kg · min; $P < 0.05$), which were well correlated ($r2 = 0.49$; $P < 0.01$). In OP rats, rosiglitazone dose-dependently improved ($P < 0.05$) insulin sensitivity (12.8 ± 0.6 mg/kg · min at 3 mg/kg; 16.0 ± 1.5 mg/kg · min at 6 mg/kg) and BRG (3.8 ± 0.4 bpm/mm Hg at 3 mg/kg; 5.3 ± 0.7 bpm/mm Hg at 6 mg/kg). However, 6 mg/kg rosiglitazone also increased BRG in OR rats without increasing insulin sensitivity, disrupted the correlation between BRG and insulin sensitivity ($r2 = 0.08$), and, in OP and OR rats, elevated BRG relative to insulin sensitivity (analysis of covariance; $P < 0.05$). Moreover, in OP rats, stimulation of the aortic depressor nerve, to activate central baroreflex pathways, elicited markedly reduced decreases in heart

rate and arterial pressure, but these responses were not improved by rosiglitazone. In conclusion, diet-induced obesity impairs BRG via a central mechanism that is related to the concurrent insulin resistance. Rosiglitazone normalizes BRG, but not by improving brain baroreflex processing or insulin sensitivity.

SIRT1 protects against emphysema via FOXO3-mediated reduction of premature senescence in mice

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3366403/

Tuesday, May 1, 2012

Hongwei Yao, Sangwoon Chung, Jae-woong Hwang, Saravanan Rajendrasozhan, Isaac K. Sundar, David A. Dean, Michael W. McBurney, Leonard Guarente, Wei Gu, Mikko RÖnty, Vuokko L. Kinnula, and Irfan Rahman

Chronic obstructive pulmonary disease/emphysema (COPD/emphysema) is characterized by chronic inflammation and premature lung aging. Anti-aging sirtuin 1 (SIRT1), a NAD+-dependent protein/histone deacetylase, is reduced in lungs of patients with COPD. However, the molecular signals underlying the premature aging in lungs, and whether SIRT1 protects against cellular senescence and various pathophysiological alterations in emphysema, remain unknown. Here, we showed increased cellular senescence in lungs of COPD patients. SIRT1 activation by both genetic overexpression and a selective pharmacological activator, SRT1720, attenuated stress-induced premature cellular senescence and protected against emphysema induced by cigarette smoke and elastase in mice. Ablation of *Sirt1* in airway epithelium, but not in myeloid cells, aggravated airspace enlargement, impaired lung function, and reduced exercise tolerance. These effects were due to the ability of SIRT1 to deacetylate the FOXO3 transcription factor, since *Foxo3* deficiency diminished the protective effect of SRT1720 on cellular senescence and emphysematous changes. Inhibition of lung inflammation by an NF-κB/IKK2 inhibitor did not have any beneficial effect on emphysema. Thus, SIRT1 protects against emphysema through FOXO3-mediated reduction of cellular senescence, independently of inflammation. Activation of SIRT1 may be an attractive therapeutic strategy in COPD/emphysema.

Epigenetic regulation of hypoxic sensing disrupts cardiorespiratory homeostasis

http://www.pnas.org/content/109/7/2515.short

Monday, January 9, 2012

Jayasri Nanduri,Vladislav Makarenko, Vaddi Damodara Reddy, Guoxiang Yuan, Anita Pawar, Ning Wang, Shakil A. Khan, Xin Zhang, Brian Kinsman, Ying-Jie Peng, Ganesh K. Kumar, Aaron P. Fox, Lucy A. Godley, Gregg L. Semenza and Nanduri R. Prabhakar

Abstract

Recurrent apnea with intermittent hypoxia is a major clinical problem in preterm infants. Recent studies, although limited, showed that adults who were born preterm exhibit increased incidence of sleep-disordered breathing and hypertension, suggesting that apnea of prematurity predisposes to autonomic dysfunction in adulthood. Here, we demonstrate that adult rats that were exposed to intermittent hypoxia as neonates exhibit exaggerated responses to hypoxia by the carotid body and adrenal chromaffin cells, which regulate cardio-respiratory function, resulting in irregular breathing with apneas and hypertension. The enhanced hypoxic sensitivity was associated with elevated oxidative stress, decreased expression of genes encoding antioxidant enzymes, and increased expression of pro-oxidant enzymes. Decreased expression of the Sod2 gene, which encodes the antioxidant enzyme superoxide dismutase 2, was associated with DNA hypermethylation of a single CpG dinucleotide close to the transcription start site. Treating neonatal rats with decitabine, an inhibitor of DNA methylation, during intermittent hypoxia exposure prevented oxidative stress, enhanced hypoxic sensitivity, and autonomic dysfunction. These findings implicate a hitherto uncharacterized role for DNA methylation in mediating neonatal programming of hypoxic sensitivity and the ensuing autonomic dysfunction in adulthood.

State-specific Effects of Sevoflurane Anesthesia on Sleep Homeostasis: Selective Recovery of Slow Wave but Not Rapid Eye Movement Sleep

http://journals.lww.com/anesthesiology/Abstract/2011/02000/State_specific_Effects_of_Sevoflurane_Anesthesia.18.aspx

Tuesday, February 1, 2011

Pal, Dinesh Ph.D.*; Lipinski, William J. M.S.†; Walker, Amanda J. B.S.‡; Turner, Ashley M. B.S.‡; Mashour, George A. M.D,. Ph.D.§

Abstract

Background: Prolonged propofol administration does not result in signs of sleep deprivation, and propofol anesthesia appears to satisfy the homeostatic need for both rapid eye movement (REM) and non-REM (NREM) sleep. In the current study, the effects of sevoflurane on recovery from total sleep deprivation were investigated.

Methods: Ten male rats were instrumented for electrophysiologic recordings under three conditions: (1) 36-h *ad libitum* sleep; (2) 12-h sleep deprivation followed by 24-h *ad libitum*sleep; and (3) 12-h sleep deprivation, followed by 6-h sevoflurane exposure, followed by 18-h*ad libitum* sleep. The percentage of waking, NREM sleep, and REM sleep, as well as NREM sleep δ power, were calculated and compared for all three conditions.

Results: Total sleep deprivation resulted in significantly increased NREM and REM sleep for 12-h postdeprivation. Sevoflurane exposure after deprivation eliminated the homeostatic increase in NREM sleep and produced a significant decrease in the NREM sleep δ power during the postanesthetic period, indicating a complete recovery from the effects of deprivation. However, sevoflurane did not affect the time course of REM sleep recovery, which required 12 h after deprivation and anesthetic exposure.

Conclusion: Unlike propofol, sevoflurane anesthesia has differential effects on NREM and REM sleep homeostasis. These data confirm the previous hypothesis that inhalational agents do not satisfy the homeostatic need for REM sleep, and that the relationship between sleep and anesthesia is likely to be agent and state specific.

Non-invasive system for applying airway obstructions to model obstructive sleep apnea in mice

http://www.sciencedirect.com/science/article/pii/S1569904810003964

Tuesday, November 9, 2010

Alba Carreras, Yang Wang, David Gozal, Josep M. Montserrat, Daniel Navajas, Ramon Farré

Abstract
Obstructive sleep apnea (OSA) is characterized by recurrent upper airway obstructions during sleep. The most common animal model of OSA is based on subjecting rodents to intermittent hypoxic exposures and does not mimic important OSA features, such as recurrent hypercapnia and increased inspiratory efforts. To circumvent some of these issues, a novel murine model involving non-invasive application of recurrent airway obstructions was developed. An electronically controlled airbag system is placed in front of the mouse's snout, whereby inflating the airbag leads to obstructed breathing and spontaneous breathing occurs with the airbag deflated. The device was tested on 29 anesthetized mice by measuring inspiratory effort and arterial oxygen saturation (SaO2). Application of recurrent obstructive apneas (6 s each, 120/h) for 6 h resulted in SaO2 oscillations to values reaching 84.4 ± 2.5% nadir, with swings mimicking OSA patients. This novel system, capable of applying controlled recurrent airway obstructions in mice, is an easy-to-use tool for investigating pertinent aspects of OSA.

Keywords
Animal model; Upper airway Obstruction; Mouse model; Non-invasive system; Model sleep apnea;Respiratory disease

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The Asparaginyl Hydroxylase Factor Inhibiting HIF-1α Is an Essential Regulator of Metabolism

http://www.cell.com/cell-metabolism/retrieve/pii/S1550413110000690

Thursday, April 15, 2010

Na Zhang, Zhenxing Fu, Sarah Link, Johana Chicher, Jeffrey J. Gorman, DeeAnn Visk, Gabriel G. Haddad, Lorenz Poellinger, Daniel J. Peet, Frank Powell, Randall S. Johnson

Summary

Factor inhibiting HIF-1α (FIH) is an asparaginyl hydroxylase. Hydroxylation of HIF-α proteins by FIH blocks association of HIFs with the transcriptional coactivators CBP/p300, thus inhibiting transcriptional activation. We have created mice with a null mutation in the FIH gene and found that it has little or no discernable role in mice in altering classical aspects of HIF function, e.g., angiogenesis, erythropoiesis, or development. Rather, it is an essential regulator of metabolism: mice lacking FIH exhibit reduced body weight, elevated metabolic rate, hyperventilation, and improved glucose and lipid homeostasis and are resistant to high-fat-diet-induced weight gain and hepatic steatosis. Neuron-specific loss of FIH phenocopied some of the major metabolic phenotypes of the global null animals: those mice have reduced body weight, increased metabolic rate, and enhanced insulin sensitivity and are also protected against high-fat-diet-induced weight gain. These results demonstrate that FIH acts to a significant degree through the nervous system to regulate metabolism.

Non-invasive diagnosis of early pulmonary disease in PECAM-deficient mice using infrared pulse oximetry

http://www.sciencedirect.com/science/article/pii/S0014480009000938

Tuesday, July 28, 2009

Merideth A. Early, Marta Lishnevsky, John M. Gilchrist, David M. Higgins, Ian M. Orme, William A. Muller,Mercedes Gonzalez-Juarerro, Alan R. Schenkel

Abstract
Pulse oximetry is a common tool for detecting reduced pulmonary function in human interstitial lung diseases. It has not previously been used in a mouse model of interstitial lung disease. Further, platelet endothelial cell adhesion molecule deficient mice rarely show symptoms until disease is advanced.
Using blood oxygen saturation, different stages of disease could be identified in a non-invasive manner. These stages could be correlated to pathology. Collagen deposition, using Picrosirius Red, did correlate with blood oxygen saturation. These studies are the first to show the use of an infrared pulse oximetry system to analyze the progression of a fibrotic interstitial lung disease in a mouse model of the human diseases. Further, these studies show that an early alveolar damage/enlargement event precedes the fibrosis in this mouse model, a stage that represents the best targets for disease analysis and prevention. This stage does not have extensive collagen deposition. Most importantly, targeting this earliest stage of disease for therapeutic intervention may lead to novel treatment for human disease.

Blunted Hypoxic Pulmonary Vasoconstriction in Experimental Neonatal Chronic Lung Disease

http://171.66.122.149/content/178/4/399.abstract

Thursday, May 28, 2009

Gloria Juliana Rey-Parra, Stephen L. Archer, Richard D. Bland,Kurt H. Albertine, David P. Carlton, Soo-Chul Cho, Beth Kirby,Al Haromy, Farah Eaton, Xichen Wu and Bernard Thébaud

Abstract
Rationale: Neonatal chronic lung disease (CLD), caused by prolonged mechanical ventilation (MV) with O2-rich gas, is the most common cause of long-term hospitalization and recurrent respiratory illness in extremely premature infants. Recurrent episodes of hypoxemia and associated ventilator adjustments often lead to worsening CLD. The mechanism that causes these hypoxemic episodes is unknown. Hypoxic pulmonary vasoconstriction (HPV), which is partially controlled by O2-sensitive voltage-gated potassium (Kv) channels, is an important adaptive response to local hypoxia that helps to match perfusion and ventilation in the lung.
Objectives: To test the hypothesis that chronic lung injury (CLI) impairs HPV.
Methods: We studied preterm lambs that had MV with O2-rich gas for 3 weeks and newborn rats that breathed 95%-O2 for 2 weeks, both of which resulted in airspace enlargement and pulmonary vascular changes consistent with CLD.
Measurements and Main Results: HPV was attenuated in preterm lambs with CLI after 2 weeks of MV and in newborn rats with CLI after 2 weeks of hyperoxia. HPV and constriction to the Kv1.x-specific inhibitor, correolide, were preferentially blunted in excised distal pulmonary arteries (dPAs) from hyperoxic rats, whose dPAs exhibited decreased Kv1.5 and Kv2.1 mRNA and K+current. Intrapulmonary gene transfer of Kv1.5, encoding the ion channel that is thought to trigger HPV, increased O2-sensitive K+ current in cultured smooth muscle cells from rat dPAs, and restored HPV in hyperoxic rats.
Conclusions: Reduced expression/activity of O2-sensitive Kv channels in dPAs contributes to blunted HPV observed in neonatal CLD.

Breathing and sleep: measurement methods, genetic influences, and developmental impacts.

http://www.ncbi.nlm.nih.gov/pubmed/19506312

Thursday, January 1, 2009

Baekey DM, Feng P, Decker MJ, Strohl KP.

Abstract
Sleep-disordered breathing comprises alterations in respiratory rate, rhythm, and depth that present during sleep and may or may not be recognizable in breathing during wakefulness. Primary disorders include repetitive apneas, near apneas (hypopneas), or reductions in overall ventilation during sleep (hypoventilation), all of which lead to reductions in pulmonary gas exchange resulting in arousals, arrhythmia, hypercapnia, acidosis, and/or hypoxic stress responses such as pulmonary hypertension or polycythemia. Because the underlying mechanisms resulting in sleep-disordered breathing and its resulting comorbidities remain unclear, researchers use a variety of animal models to better understand the disorder. These models allow for conditioning paradigms, more detailed measurements of respiratory control, and the use of fewer preparations to provide a detailed picture of the individual components that contribute to breathing patterns. Both noninvasive and reduced methods are applicable with conditioned, inbred, and/or genetically manipulated animals to determine effect size and imply mechanisms. Research in animals has established preclinical models showing that intermediate traits of breathing pattern (e.g., responses to hypoxia, hypercapnia, and reoxygenation) vary according to genetic background and conditioning. Such findings permit new ideas about pathogenesis and prevention and form the rationale for observational and interventional studies in the human

population. In this article we focus on methods of investigating respiratory control and applicable rodent models.

Aerosolized Phosphoinositide 3-Kinase γ/δ Inhibitor TG100-115 [3-[2,4-Diamino-6-(3-hydroxyphenyl)pteridin-7-yl]phenol] as a Therapeutic Candidate for Asthma and Chronic Obstructive Pulmonary Disease

http://jpet.aspetjournals.org/content/328/3/758.long

Thursday, December 4, 2008

John Doukas, Lisa Eide, Karin Stebbins, Adrienne Racanelli-Layton,Luis Dellamary, Michael Martin, Elena Dneprovskaia, Glenn Noronha,Richard Soll, Wolfgang Wrasidlo, Lisette M. Acevedo andDavid A. Cheresh

Abstract
Phosphatidylinositol 3-kinases (PI3Ks) are key elements in the signaling cascades that lie downstream of many cellular receptors. In particular, PI3K δ and γ isoforms contribute to inflammatory cell recruitment and subsequent activation. For this reason, in a series of preclinical studies, we tested the potential of a recently developed small-molecule inhibitor of these two isoforms, TG100-115 [3-[2,4-diamino-6-(3-hydroxyphenyl)pteridin-7-yl]phenol], as a form of anti-inflammatory therapy for respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). To determine pharmacokinetic profiles, aerosolized formulations of the drug were delivered to mice by a nose-only inhalation route, yielding high pulmonary TG100-115 levels with minimal systemic exposure. Safety assessments were favorable, with no clinical or histological changes noted after 21 days of daily dosing. In a murine asthma model, aerosolized TG100-115 markedly reduced the pulmonary eosinophilia and the concomitant interleukin-13 and mucin accumulation characteristic of this disease. As a functional benefit, interventional dosing schedules of this inhibitor also reduced airway hyper-responsiveness. To model the pulmonary neutrophilia characteristic of COPD, mice were exposed to either intranasal lipopolysaccharide or inhaled smoke. Aerosolized TG100-115 again inhibited these inflammatory patterns, most notably in the smoke model, where interventional therapy overcame the steroid-resistant nature of the pulmonary inflammation. In conclusion, aerosolized TG100-115 displays pharmacokinetic, safety, and biological activity profiles favorable for further development as a therapy for both asthma and COPD. Furthermore, these studies support the hypothesis that PI3K δ and γ are suitable molecular targets for these diseases.

Phosphoinositide 3-kinases (PI3Ks) phosphorylate inositol lipids within cell membranes as an early step in the signaling cascades initiated by many ligand-receptor interactions (Vanhaesebroeck et al., 2001). The PI3K family can be divided into different classes based on subunit arrangement and substrate utility. For example, class IA isoforms, PI3Kα/β/δ, interact with tyrosine kinases such as growth factor receptor tyrosine kinases, and the class IB member PI3Kγ interacts with G-protein-coupled receptors. PI3Kα and β are broadly expressed across many tissues and control fundamental processes such as cellular proliferation; genetic deletion of either isoform is embryonically lethal (Vanhaesebroeck et al., 2005). In contrast, PI3Kδ and γ have a more restricted cellular distribution and a more focused role of mediating inflammatory responses; genetically deleted mice are not only viable but display reduced inflammatory responses (Hirsch et al., 2000; Yum et al., 2001; Hannigan et al., 2002; Laffargue et al., 2002; Ali et al., 2004).
Based on these profiles, one can appreciate that PI3Kδ and γ represent promising molecular targets in the development of novel anti-inflammatory agents. A relatively small number of PI3Kδ- and/or γ-specific

inhibitors have been tested in preclinical disease models (Sadhu et al., 2003; Barber et al., 2005; Camps et al., 2005; Doukas et al., 2006; Lee et al., 2006). We reported that a dual PI3Kγ/δ inhibitor named TG100-115 can diminish reperfusion injury to ischemic tissue after acute myocardial infarction (Doukas et al., 2006). Although TG100-115 was extended into the clinic for this indication, we also recognized its potential for use in other inflammatory-based settings because the combination of δ and γ isoform inhibition presents the opportunity to intervene across a broad range of cellular responses, including those induced by both receptor tyrosine kinases and G-protein-coupled receptors. For example, these two isoforms play nonredundant roles in the recruitment and activation of immune cells during inflammatory responses (Rommel et al., 2007); therefore, as an anti-inflammatory, a dual PI3Kγ/δ inhibitor may have extended benefits over isoform monoselective compounds. This is of particular relevance because there is building interest regarding the therapeutic potential of PI3K inhibitors in respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD) (Finan and Thomas, 2004; Adcock et al., 2006b; Ito et al., 2007;Krymskaya, 2007).

Asthma and COPD are driven by distinct immunologic processes (Barnes, 2008). Asthma is an allergic hypersensitivity involving a Th2-type immune response mounted by CD4+ T cells, with mast cells and eosinophils also playing important roles and neutrophils contributing in chronic severe disease. COPD initiates as an abnormal inflammatory response involving CD8+ T cells releasing Th1-type cytokines, with contributions from macrophages and neutrophils (Doherty, 2004;Welte and Groneberg, 2006; Baraldo et al., 2007). Clinical pictures also differ for the two diseases. Asthma presents as a nonprogressive airflow limitation that in most cases can be controlled with bronchodilators and corticosteroids. However, for many patients, symptom control is inadequate, and for the steroid-nonresponsive patient, new anti-inflammatories would be particularly welcome (Adcock and Ito, 2004; Barnes, 2004). COPD, in contrast, displays progressive airflow limitation, making longer term disease of increasingly serious impact. The disease is generally steroid nonresponsive; thus, anti-inflammatories that can prove efficacious in this setting are a clear need (Bailey and Tashkin, 2007).

As a means of assessing the potential of PI3K inhibitors as respiratory disease therapies, we conducted a series of preclinical studies focusing on aerosolized TG100-115. Aerosolization allowed for delivery of this compound to test animals by an inhalation route, the goal being to model a delivery system that could readily transfer to a clinical setting. In addition to favorable pharmacokinetic and safety profiles, we documented readily demonstrable anti-inflammatory activity in murine models of asthma and pulmonary neutrophilia (including smoke-induced neutrophilia, a steroid-resistant model of COPD) and functional improvements in the former.

The Role of NADPH Oxidase in Chronic Intermittent Hypoxia-Induced Pulmonary Hypertension in Mice

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2677439/

Thursday, October 23, 2008

Rachel E. Nisbet,Anitra S. Graves,Dean J. Kleinhenz, Heidi L. Rupnow, Alana L. Reed, Tai-Hwang M. Fan,Patrick O. Mitchell, Roy L. Sutliff, and C. Michael Hart

Abstract

Obstructive sleep apnea, characterized by intermittent periods of hypoxemia, is an independent risk factor for the development of pulmonary hypertension. However, the exact mechanisms of this disorder remain to be defined. Enhanced NADPH oxidase expression and superoxide ($O_2^{-\cdot}$) generation in the pulmonary vasculature play a critical role in hypoxia-induced pulmonary hypertension. Therefore, the current study explores the hypothesis that chronic intermittent hypoxia (CIH) causes pulmonary hypertension, in part, by increasing NADPH oxidase–derived reactive oxygen species (ROS) that contribute to pulmonary vascular remodeling and hypertension. To test this hypothesis, male C57Bl/6 mice and gp91phox knockout mice were exposed to CIH for 8 hours per day, 5 days per week for 8 weeks. CIH mice were placed in a chamber where the oxygen concentration was cycled between 21% and 10% O_2 45 times per hour. Exposure to CIH for 8 weeks increased right ventricular systolic pressure (RVSP), right ventricle (RV):left ventricle (LV) + septum (S) weight ratio, an index of RV hypertrophy, and thickness of the right ventricular anterior wall as measured by echocardiography. CIH exposure also caused pulmonary vascular remodeling as demonstrated by increased muscularization of the distal pulmonary vasculature. CIH-induced pulmonary hypertension was associated with increased lung levels of the NADPH oxidase subunits, Nox4 and p22phox, as well as increased activity of platelet-derived growth factor receptor β and its associated downstream effector, Akt kinase. These CIH-induced derangements were attenuated in similarly treated gp91phox knockout mice. These findings demonstrate that NADPH oxidase–derived ROS contribute to the development of pulmonary vascular remodeling and hypertension caused by CIH.

Keywords: hypoxia, pulmonary hypertension, nitric oxide, NADPH oxidase

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Integration in Respiratory Control: From Genes to Systems (Advances in Experimental Medicine and Biology) [Hardcover]

http://www.amazon.com/Integration-Respiratory-Control-Advances-Experimental/dp/0387736921

Thursday, November 15, 2007

Marc Poulin (Editor), Richard J. A. Wilson (Editor)

The neuronal circuit that generates breathing, the regulation of breathing, and its integration with other physiological systems is of utmost importance to human health. However, breathing abnormalities are common, and sleep apnea alone is estimated to affect 18 million in the United States. As one of the major complications of obesity, the prevalence of sleep apnea is likely to increase in the coming years. Congenital central hypoventilation syndrome (CCHS), asthma, Parkinson's disease, multiple sclerosis, spinal cord injury, and the pathophysiology of panic and related anxiety states also involve aspects of respiratory control. Integration in Respiratory Control: From Genes to Systems comprises the proceedings of the 10th Oxford Conference held at Lake Louise, Alberta, Canada, from the 19th to the 24th of September, 2006. This series of meetings was originally begun to bring physiologists and mathematicians together, in order to address critical issues in understanding the control of breathing. This volume includes the latest findings and developments at the genomic, cellular, and system levels that pertain to the physiology of cardio-respiratory control, including integrative physiology and modeling, central integration and neuromodulation, rhythm generation and plasticity, chemosensory transduction and signaling, pre- and post-natal development, and post-genomic perspectives.

Moderate Pulmonary Arterial Hypertension in Male Mice Lacking the Vasoactive Intestinal Peptide Gene

http://circ.ahajournals.org/content/115/10/1260.abstract

Monday, February 19, 2007

Sami I. Said, MD; Sayyed A. Hamidi, MD; Kathleen G. Dickman, PhD;Anthony M. Szema, MD; Sergey Lyubsky, MD; Richard Z. Lin, MD;Ya-Ping Jiang, MD; John J. Chen, PhD; James A. Waschek, PhD;Smadar Kort, MD

Background— Vasoactive intestinal peptide (VIP), a pulmonary vasodilator and inhibitor of vascular smooth muscle proliferation, has been reported absent in pulmonary arteries from patients with idiopathic pulmonary arterial hypertension (PAH). We have tested the hypothesis that targeted deletion of the VIP gene may lead to PAH with pulmonary vascular remodeling.
Methods and Results— We examined VIP knockout (VIP−/−) mice for evidence of PAH, right ventricular (RV) hypertrophy, and pulmonary vascular remodeling. Relative to wild-type control mice, VIP−/− mice showed moderate RV hypertension, RV hypertrophy confirmed by increased ratio of RV to left ventricle plus septum weight, and enlarged, thickened pulmonary artery and smaller branches with increased muscularization and narrowed lumen. Lung sections also showed perivascular inflammatory cell infiltrates. No systemic hypertension and no arterial hypoxemia existed to explain the PAH. The condition was associated with increased mortality. Both the vascular remodeling and RV remodeling were attenuated after a 4-week treatment with VIP.
Conclusions— Deletion of the VIP gene leads to spontaneous expression of moderately severe PAH in mice during air breathing. Although not an exact model of idiopathic PAH, the VIP−/− mouse should be useful for studying molecular mechanisms of PAH and evaluating potential therapeutic agents. VIP replacement therapy holds promise for the treatment of PAH, and mutations of the VIP gene may be a factor in the pathogenesis of idiopathic PAH.

Lung Injury & Mechanical Ventilation

Determinants of plasma copeptin: A systematic investigation in a pediatric mechanical ventilation model

http://www.sciencedirect.com/science/article/pii/S156990481200314X

Tuesday, January 15, 2013

Pietro L'Abate, Susanne Wiegert, Joachim Struck, Sven Wellmann, Vincenzo Cannizzaro

... system. Heart rate (HR) and oxygen saturation (SpO 2) were monitored via an animal pulse oximeter (MouseOx™, **STARR Life Sciences** Corporation™, Oakmont, PA, USA) by placing a non-invasive sensor on the tail. Peak **...**

Copeptin, the C-terminal part of the arginine vasopressin precursor peptide, holds promise as a diagnostic and prognostic plasma biomarker in various acute clinical conditions. Factors influencing copeptin response in the critical care setting are only partially established and have not been investigated systematically. Using an in vivo infant ventilation model (Wistar rats, 14 days old), we studied the influence of commonly occurring stressors in critically ill children. In unstressed ventilated rats basal median copeptin concentration was 22 pmol/L. In response to respiratory alkalosis copeptin increased 5-fold, while exposure to hypoxemia, high PEEP, hemorrhage, and psycho-emotional stress produced a more than 10-fold increase. Additionally, we did not find a direct association between copeptin and acidosis, hypercapnia, and hyperthermia. Clinicians working in the acute critical care setting should be aware of factors influencing copeptin plasma concentrations. Moreover, our results do have implications for animal studies in the field of stress research.

Diaphragm muscle atrophy in mouse following long-term mechanical ventilation

http://onlinelibrary.wiley.com/doi/10.1002/mus.23748/abstract

Wednesday, December 12, 2012

Huibin Tang PhD, Myung Lee BA, Amanda Khuong BS, Erika Wright BS, Joseph B. Shrager MD

.. Page 7 of 32 John Wiley & Sons, Inc. Muscle & Nerve Page 8. saturation were monitored continuously with the **MouseOX** Plus (Starr LifeSciences Corp., Oakmont, PA) via a sensor placed on a shaved leg. Heart rate was maintained at 320 ± 20 beats per minute. **...**

Introduction:

Mechanical ventilation (MV) is a life-saving measure, but full ventilator support causes ventilator-induced diaphragm atrophy (VIDA). Previous studies of VIDA have relied on human biopsies or a rat model. If MV can induce diaphragm atrophy in mouse, then mechanistic study of VIDA could be explored via genetic manipulation.

Results:

We show that 18 hours of MV in mice results in a 15% loss of diaphragm weight and a 17% reduction in fiber cross-sectional area. Important catabolic cascades are activated in this mouse model: transcription of the ubiquitin ligases atrogin and MuRF1, and the apoptotic marker Bim, are increased; the marker of autophagy, LC3, is induced at the protein level and shows a punctate distribution in diaphragm muscle fibers.

Conclusions:

This mouse model recapitulates the key pathophysiological findings of other models of VIDA, and it will enable the genetic manipulation required to fully explore the mechanisms underlying this important process.

Radioprotective Role in Lung of the Flaxseed Lignan Complex Enriched in the Phenolic Secoisolariciresinol Diglucoside (SDG)

http://www.rrjournal.org/doi/abs/10.1667/RR2980.1

Saturday, December 1, 2012

Melpo Christofidou-Solomidou , Sonia Tyagi , Ralph Pietrofesa , Floyd Dukes ,Evguenia Arguiri , Jason Turowski, Philip A. Grieshaber , Charalambos C. Solomides and Keith A. Cengel

... Evaluation of Cardiopulmonary Function Parameters Prior to sacrifice, at 16 weeks after irradiation, pulse oximetry was performed on conscious mice (n = 5/group) using a MouseOx noninvasive vital signs monitor (STARR Life Sciences Corp., Oakmont, PA). ...
While dietary wholegrain Flaxseed (FS) has potent anti-inflammatory, anti-fibrotic and antioxidant properties in murine models of acute and chronic lung injury, the main bioactive ingredient that contributes to these protective effects remains unknown. This study evaluated the lignan complex of FS (FLC) enriched in secoisolariciresinol diglucoside with respect to lung radioprotective and tumor radiosensitizing efficacy using a mouse model of thoracic radiation-induced pneumonopathy. C57/Bl6 mice were fed 0% FS, 10% FS, 10% FLC or 20% FLC for 3 weeks, then irradiated with a single fraction (13.5 Gy) of X-ray radiation treatment (XRT). Mouse survival was monitored for 4 months after irradiation and inflammatory lung parameters were evaluated in bronchoalveolar lavage (BAL) fluid. Gene and protein levels of protective antioxidant and phase II enzymes were evaluated in lung tissue using qPCR and protein levels were verified by immunoblotting. Prolonged administration of the FLC diet was well tolerated and was not associated with any toxicity. Importantly, comparable to the whole grain 10% FS diet, irradiated mice fed 10% and 20% FLC diets displayed improved survival. Improved hemodynamic measurements were also recorded in irradiated mice fed 10% FS or 10% FLC diet compared to irradiated 0% FS fed mice. Flaxseed lignan complex diet also attenuated polymorphonuclear infiltration and overall lung inflammation to levels comparable to those in nonirradiated mice. Flaxseed lignan complex, similarly to FS, up-regulated gene expression as well as protein levels of protective antioxidant enzymes such as heme oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase 1 (NQO1). Dietary FLC induced radiosensitizing effects in our murine model

of metastatic lung cancer. Importantly, protection of normal tissue does not thwart tumor cell death by radiation treatment. The dietary lignan complex of FS, mainly consisting of the phenolic secoisolariciresinol, is protective against radiation pneumonopathy in vivo while not hindering the tumoricidal effects of radiotherapy.

Mechanical ventilation reduces rat diaphragm blood flow and impairs oxygen delivery and uptake.

http://www.ncbi.nlm.nih.gov/pubmed/22846782

Monday, October 1, 2012

Davis RT 3rd, Bruells CS, Stabley JN, McCullough DJ, Powers SK, Behnke BJ.

Abstract

OBJECTIVES:
Although mechanical ventilation is a life-saving intervention in patients suffering from respiratory failure, prolonged mechanical ventilation is often associated with numerous complications including problematic weaning. In contracting skeletal muscle, inadequate oxygen supply can limit oxidative phosphorylation resulting in muscular fatigue. However, whether prolonged mechanical ventilation results in decreased diaphragmatic blood flow and induces an oxygen supply-demand imbalance in the diaphragm remains unknown.

DESIGN:
We tested the hypothesis that prolonged controlled mechanical ventilation results in a time-dependent reduction in rat diaphragmatic blood flow and microvascular PO2 and that prolonged mechanical ventilation would diminish the diaphragm's ability to increase blood flow in response to muscular contractions.

MEASUREMENTS AND MAIN RESULTS:
Compared to 30 mins of mechanical ventilation, 6 hrs of mechanical ventilation resulted in a 75% reduction in diaphragm blood flow (via radiolabeled microspheres), which did not occur in the intercostal muscle or high-oxidative hindlimb muscle (e.g., soleus). There was also a time-dependent decline in diaphragm microvascular PO2 (via phosphorescence quenching). Further, contrary to 30 mins of mechanical ventilation, 6 hrs of mechanical ventilation significantly compromised the diaphragm's ability to increase blood flow during electrically-induced contractions, which resulted in a ~80% reduction in diaphragm oxygen uptake. In contrast, 6 hrs of spontaneous breathing in anesthetized animals did not alter diaphragm blood flow or the ability to augment flow during electrically-induced contractions.

CONCLUSIONS:
These new and important findings reveal that prolonged mechanical ventilation results in a time-dependent decrease in the ability of the diaphragm to augment blood flow to match oxygen demand in response to contractile activity and could be a key contributing factor to difficult weaning. Although additional experiments are required to confirm, it is tempting to speculate that this ventilator-induced decline in diaphragmatic oxygenation could promote a hypoxia-induced generation of reactive oxygen species in

diaphragm muscle fibers and contribute to ventilator-induced diaphragmatic atrophy and contractile dysfunction.

Effects of Lecithinized Superoxide Dismutase and/or Pirfenidone Against Bleomycin-Induced Pulmonary Fibrosis

http://journal.publications.chestnet.org/article.aspx?articleid=1216044

Monday, October 1, 2012

Ken-Ichiro Tanaka, PhD; Arata Azuma, MD, PhD; Yuri Miyazaki; Keizo Sato, MD, PhD; Tohru Mizushima, PhD

Background: Idiopathic pulmonary fibrosis (IPF) involves lung injury induced by reactive oxygen species (ROS), such as superoxide anion, and fibrosis. Superoxide dismutase (SOD) catalyses the dismutation of superoxide anion to hydrogen peroxide. We recently reported that inhalation of lecithinized SOD (PC-SOD) ameliorated bleomycin-induced pulmonary fibrosis. We here studied effects of PC-SOD on bleomycin-induced pulmonary fibrosis and lung dysfunction and compared the results to those obtained with pirfenidone, a newly developed drug for IPF.
Methods: Lung mechanics (elastance) and respiratory function (FVC) were assessed using a computer-controlled ventilator. Respiratory function was evaluated by monitoring percutaneous arterial oxygen saturation (Spo2).
Results: Both inhalation of PC-SOD and oral administration of pirfenidone ameliorated bleomycin-induced pulmonary fibrosis and changes in lung mechanics. Administration of bleomycin produced a decrease in both FVC and Spo2. PC-SOD treatment led to significant recovery of both parameters, whereas pirfenidone improved only Spo2. PC-SOD suppressed the bleomycin-induced pulmonary inflammatory response and production of superoxide anions in the lung more effectively than pirfenidone. Furthermore, both PC-SOD and pirfenidone produced a therapeutic effect even when the drug was administered after the development of fibrosis. PC-SOD and pirfenidone also produced a synergistic therapeutic effect.
Conclusions: These results suggest that the superior activity of PC-SOD to pirfenidone against bleomycin-induced pulmonary fibrosis and lung dysfunction is due to its unique antioxidant activity. We propose that treatment of IPF with a combination of PC-SOD and pirfenidone could be therapeutically beneficial.

Intermedin Stabilized Endothelial Barrier Function and Attenuated Ventilator-induced Lung Injury in Mice

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0035832

Tuesday, May 1, 2012

Holger Christian Müller-Redetzky,Wolfgang Kummer,Uwe Pfeil,Katharina Hellwig,Daniel Will,Renate Paddenberg,Christoph Tabeling,Stefan Hippenstiel,Norbert Suttorp,Martin Witzenrath

... A urinary catheter was inserted. V T , RR, airway pressure, peripheral oxygen saturation and urine output were monitored (Pulmodyn, Hugo-Sachs-Electronics, March-Hugstetten, Germany; **MouseOx**, STARRLife-Sciences, Oakmont, PA, USA). **...**

Background

Even protective ventilation may aggravate or induce lung failure, particularly in preinjured lungs. Thus, new adjuvant pharmacologic strategies are needed to minimize ventilator-induced lung injury (VILI). Intermedin/Adrenomedullin-2 (IMD) stabilized pulmonary endothelial barrier function in vitro. We hypothesized that IMD may attenuate VILI-associated lung permeability in vivo.

Methodology/Principal Findings

Human pulmonary microvascular endothelial cell (HPMVEC) monolayers were incubated with IMD, and transcellular electrical resistance was measured to quantify endothelial barrier function. Expression and localization of endogenous pulmonary IMD, and its receptor complexes composed of calcitonin receptor-like receptor (CRLR) and receptor activity-modifying proteins (RAMPs) 1–3 were analyzed by qRT-PCR and immunofluorescence in non ventilated mouse lungs and in lungs ventilated for 6 h. In untreated and IMD treated mice, lung permeability, pulmonary leukocyte recruitment and cytokine levels were assessed after mechanical ventilation. Further, the impact of IMD on pulmonary vasoconstriction was investigated in precision cut lung slices (PCLS) and in isolated perfused and ventilated mouse lungs. IMD stabilized endothelial barrier function in HPMVECs. Mechanical ventilation reduced the expression of RAMP3, but not of IMD, CRLR, and RAMP1 and 2. Mechanical ventilation induced lung hyperpermeability, which was ameliorated by IMD treatment. Oxygenation was not improved by IMD, which may be attributed to impaired hypoxic vasoconstriction due to IMD treatment. IMD had minor impact on pulmonary leukocyte recruitment and did not reduce cytokine levels in VILI.

Conclusions/Significance

IMD may possibly provide a new approach to attenuate VILI.

Targeted Aerosolized Delivery of Ascorbate in the Lungs of Chlorine-Exposed Rats

http://online.liebertpub.com/doi/abs/10.1089/jamp.2011.0963

Tuesday, March 6, 2012

Andreas Bracher, Stephen F. Doran, Giuseppe L. Squadrito, Edward M. Postlethwait, Larry Bowen, and Sadis Matalon

Background: Chlorine (Cl2)-induced lung injury is a serious public health threat that may result from industrial and household accidents. Post-Cl2 administration of aerosolized ascorbate in rodents decreased lung injury and mortality. However, the extent to which aerosolized ascorbate augments depleted ascorbate stores in distal lung compartments has not been assessed.

Methods: We exposed rats to Cl2 (300 ppm for 30 min) and returned them to room air. Within 15–30 min postexposure, rats breathed aerosolized ascorbate and desferal or vehicle (mean particle size 3.3 μm) through a nose-only exposure system for 60 min and were euthanized. We measured the concentrations of reduced ascorbate in the bronchoalveolar lavage (BAL), plasma, and lung tissues with high-pressure liquid chromatography, protein plasma concentration in the BAL, and the volume of the epithelia lining fluid (ELF).

Results: Cl2-exposed rats that breathed aerosolized vehicle had lower values of ascorbate in their BAL, ELF, and lung tissues compared to air-breathing rats. Delivery of aerosolized ascorbate increased reduced ascorbate in BAL, ELF, lung tissues, and plasma of both Cl2 and air-exposed rats without causing lung injury. Based on mean diameter of aerosolized particles and airway sizes we calculated that approximately 5% and 1% of inhaled ascorbate was deposited in distal lung regions of air and Cl2-exposed rats, respectively. Significantly higher ascorbate levels were present in the BAL of Cl2-exposed rats when aerosol delivery was initiated 1 h post-Cl2.

Conclusions: Aerosol administration is an effective, safe, and noninvasive method for the delivery of low molecular weight antioxidants to the lungs of Cl2-exposed individuals for the purpose of decreasing morbidity and mortality. Delivery is most effective when initiated 1 h postexposure when the effects of Cl2 on minute ventilation subside.

Intravenous Immunoglobulin Prevents Murine Antibody-Mediated Acute Lung Injury at the Level of Neutrophil Reactive Oxygen Species (ROS) Production

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0031357

Friday, February 17, 2012

John W. Semple, Michael Kim, Jing Hou, Mark McVey, Young Jin Lee, Arata Tabuchi, Wolfgang M. Kuebler, Zhong-Wei Chai, Alan H. Lazarus

Transfusion-related acute lung injury (TRALI) is a leading cause of transfusion-associated mortality that can occur with any type of transfusion and is thought to be primarily due to donor antibodies activating pulmonary neutrophils in recipients. Recently, a large prospective case controlled clinical study of cardiac surgery patients demonstrated that despite implementation of male donors, a high incidence of TRALI still occurred and suggested a need for additional interventions in susceptible patient populations. To examine if intravenous immunoglobulin (IVIg) may be effective, a murine model of antibody-mediated acute lung injury that approximates human TRALI was examined. When BALB/c mice were injected with the anti-major histocompatibility complex class I antibody 34-1-2s, mild shock (reduced rectal temperature) and respiratory distress (dyspnea) were observed and pre-treatment of the mice with 2 g/kg IVIg completely prevented these symptoms. To determine IVIg's usefulness to affect severe lung damage, SCID mice, previously shown to be hypersensitive to 34-1-2s were used. SCID mice treated with 34-1-2s underwent severe shock, lung damage (increased wet/dry ratios) and 40% mortality within 2 hours. Treatment with 2 g/kg IVIg 18 hours before 34-1-2s administration completely protected the mice from all adverse events. Treatment with IVIg after symptoms began also reduced lung damage and mortality. While the prophylactic IVIg administration did not affect 34-1-2s-induced pulmonary neutrophil accumulation, bone marrow-derived neutrophils from the IVIg-treated mice displayed no spontaneous ROS production nor could they be stimulated in vitro with fMLP or 34-1-2s. These results suggest that IVIg prevents murine antibody-mediated acute lung injury at the level of neutrophil ROS production and thus, alleviating tissue damage.

Absence of Integrin αvβ3 Enhances Vascular Leak in Mice by Inhibiting Endothelial Cortical Actin Formation

http://ajrccm.atsjournals.org/content/185/1/58.short

Thursday, October 6, 2011

George Su, Amha Atakilit, John T. Li, Nanyan Wu, Mallar Bhattacharya, Jieling Zh, Jennifer E. Shieh, Elizabeth Li, Robert Chen, Stephen Sun, Cynthia P. Su and Dean Sheppard

Rationale: Sepsis and acute lung injury (ALI) have devastatingly high mortality rates. Both are associated with increased vascular leak, a process regulated by complex molecular mechanisms.

Objectives: We hypothesized that integrin αvβ3 could be an important determinant of vascular leak and endothelial permeability in sepsis and ALI.

Methods: β3 subunit knockout mice were tested for lung vascular leak after endotracheal LPS, and systemic vascular leak and mortality after intraperitoneal LPS and cecal ligation and puncture. Possible contributory effects of β3 deficiency in platelets and other hematopoietic cells were excluded by bone marrow reconstitution experiments. Endothelial cells treated with αvβ3 antibodies were evaluated for sphingosine-1 phosphate (S1P)–mediated alterations in barrier function, cytoskeletal arrangement, and integrin localization.

Measurements and Main Results: β3 knockout mice had increased vascular leak and pulmonary edema formation after endotracheal LPS, and increased vascular leak and mortality after intraperitoneal LPS and cecal ligation and puncture. In endothelial cells, αvβ3 antibodies inhibited barrier-enhancing and cortical actin responses to S1P. Furthermore, S1P induced translocation of αvβ3 from discrete focal adhesions to cortically distributed sites through Gi- and Rac1-mediated pathways. Cortical αvβ3 localization after S1P was decreased by αvβ3 antibodies, suggesting that ligation of the αvβ3 with its extracellular matrix ligands is required to stabilize cortical αvβ3 focal adhesions.

Conclusions: Our studies identify a novel mechanism by which αvβ3 mitigates increased vascular leak, a pathophysiologic function central to sepsis and ALI. These studies suggest that drugs designed to block αvβ3 may have the unexpected side effect of intensifying sepsis- and ALI-associated vascular endothelial leak.

Rescue of murine silica-induced lung injury and fibrosis by human embryonic stem cells

Thursday, June 30, 2011

P. Spitalieri, M.C. Quitadamo, A. Orlandi, L. Guerra, E. Giardina, V. Casavola, G. Novelli, C. Saltini and F. Sangiuolo

Alveolar type II pneumocytes (ATII cells) are considered putative alveolar stem cells. Since no treatment is available to repair damaged epithelium and prevent lung fibrosis, novel approaches to induce regeneration of injured alveolar epithelium are desired.

The objective of this study was to assess both the capacity of human embryonic stem cells (HUES-3) to differentiate in vitro into ATII cells and the ability of committed HUES-3 cells (HUES-3-ATII cells) to recover in vivo a pulmonary fibrosis model obtained by silica-induced damage.

In vitro differentiated HUES-3-ATII cells displayed an alveolar phenotype characterised by multi-lamellar body and tight junction formation, by the expression of specific markers such as surfactant protein (SP)-B, SP-C and zonula occludens (ZO)-1 and the activity of cystic fibrosis transmembrane conductance regulator-mediated chloride ion transport.

After transplantation of HUES-3-ATII cells into silica-damaged mice, histological and biomolecular analyses revealed a significant reduction of inflammation and fibrosis markers along with lung function improvement, weight recovery and increased survival. The persi

stence of human SP-C, human nuclear antigen and human DNA in the engrafted lungs indicates that differentiated cells remained engrafted up to 10 weeks.

In conclusion, cell therapy using HUES-3 cells may be considered a promising approach to lung injury repair.

Rescue of murine silica-induced lung injury and fibrosis by human embryonic stem cells

http://erj.ersjournals.com/content/early/2011/06/28/09031936.00005511.abstract

Thursday, June 30, 2011

P. Spitalieri, M.C. Quitadamo, A. Orlandi, L. Guerra, E. Giardina, V. Casavola, G. Novelli, C. Saltini and F. Sangiuolo

Abstract
Type II pneumocytes (ATII Cells) are considered as putative alveolar stem cells. Since no treatment is available to repair damaged epithelium and preventing lung fibrosis, novel approaches to induce regeneration of injured alveolar epithelium are desired.
The objective of this study was to assess both the capacity of human embryonic stem cells (HUES-3) to differentiate *in vitro* into ATII Cells and the ability of committed HUES-3 cells (HUES-3-ATII Cells) to recover *in vivo a* pulmonary fibrosis model obtained by silica-induced damage.
In vitro differentiated HUES-3-ATII Cells displayed alveolar phenotype characterized by multilamellar body and tight junction formation, by the expression of specific markers such as SP-B, SP-C and ZO-1 and the activity of CFTR-mediated chloride ion transport.
After transplantation of HUES-3-ATII Cells into silica-damaged mice, histological and biomolecular analyses revealed a significant reduction of inflammation and fibrosis markers along with lung function improvement, weight recovery and increased survival. The persistence of human SP-C, human nuclear antigen and human DNA in the engrafted lungs indicates that differentiated cells remained engrafted up to ten weeks.
In conclusion, cell therapy using HUES-3 cells may be considered a promising approach to lung injury repair.

Inducible disruption of autophagy in the lung causes airway hyper-responsiveness

http://www.sciencedirect.com/science/article/pii/S0006291X10023302

Thursday, December 23, 2010

Daisuke Inoue, Hiroshi Kubo, Keiko Taguchi, Takashi Suzuki, Masaaki Komatsu, Hozumi Motohashi, Masayuki Yamamoto

Abstract
Autophagy is a highly conserved process primarily known for its role in cellular adaptation to nutritional stress. This bulk protein degradation pathway relocates nutrients during starvation. Recent studies, however, have revealed essential roles of autophagy in various organs under normal conditions. Especially, autophagy is now recognized as the pathway responsible for the elimination of damaged proteins resulting from environmental stress. Lungs are constantly exposed to high oxygen tension and environmental chemicals. To investigate the importance of autophagy in lung physiology, we used an inducible system to ablate Atg7 expression, which is a protein essential for autophagy, in the respiratory epithelial cells of adult mice. We found that Atg7 deficiency caused swelling of bronchiolar epithelial cells and accumulation of p62, which links substrate proteins to the autophagy machinery. Bronchiolar epithelial cells, isolated by micro-dissection of lung tissues, had elevated expression of cytoprotective genes that are typically activated by Nrf2. Interestingly, Atg7-deficient lungs displayed hyper-responsiveness to cholinergic stimuli without apparent inflammatory signs. Swollen bronchiolar epithelial cells may have lead to mechanical airway constriction and lowered the threshold for the increase of airway resistance. This study demonstrates the critical role of autophagy in the lungs for the maintenance of pulmonary homeostasis.

MITIGATION OF CHLORINE GAS LUNG INJURY IN RATS BY POST EXPOSURE ADMINISTRATION OF SODIUM NITRITE

http://ajplung.physiology.org/content/early/2010/12/08/ajplung.00278.2010.abstract

Tuesday, December 7, 2010

Amit K Yadav, Stephen F. Doran, Andrey A. Samal, Ruchita Sharma,Kokilavani Vedagiri, Edward M. Postlethwait,Giuseppe Luciano Squadrito, Michelle V Fanucchi,L. Jackson Roberts II, Rakesh P Patel, and Sadis Matalon

Nitrite (NO2-) has been shown to limit injury to the heart, liver and kidneys in various models of ischemia-reperfusion injury. Currently, potential protective effects of systemic NO2- in limiting lung injury or enhancing repair have not been documented. We assessed the efficacy and mechanisms by which post-exposure intra-peritoneal injections of NO2- mitigate chlorine (Cl2) induced lung injury in rats. Rats were exposed to Cl2 (400 ppm) for 30 minutes and returned to room air. Nitrite (1mg/Kg) or saline were administered intraperitoneally at 10 min, 2, 4 and 6 hrs post exposure. Rats were sacrificed at 6 hrs or 24 h. Injury to airway and alveolar epithelia was assessed by quantitative morphology, protein concentrations, number of cells in bronchoalveolar lavage (BAL) and wet/dry lung weights. Lipid peroxidation was assessed by measuring lung F2-isoprostanes. Rats developed severe but transient hypoxemia. A significant increase of protein concentration, neutrophils numbers, airway epithelia in the BAL, and lung wet/dry weights was evident at 6 hrs post-Cl2 exposure. Quantitative morphology revealed extensive lung injury in the upper airways. Airway epithelial cells stained positive for TUNEL, but not caspase-3. Administration of NO2-

resulted in lower BAL protein levels, significant reduction in the intensity of the TUNEL positive cells and normal values of lung wet/dry weights. F2-isoprostane levels increased at six and 24 h post Cl2 exposure in both NO2- and saline injected rats. This is the first demonstration that systemic NO2- administration mitigates airway and epithelial injury.

Effect of low tidal volume ventilation on lung function and inflammation in mice

http://www.biomedcentral.com/1471-2466/10/21/

Thursday, October 21, 2010

Hans P Hauber, **Dörte Karp**, **Torsten Goldmann**, **Ekkehard Vollmer** and **Peter Zabel**

Background
A large number of studies have investigated the effects of high tidal volume ventilation in mouse models. In contrast data on very short term effects of low tidal volume ventilation are sparse. Therefore we investigated the functional and structural effects of low tidal volume ventilation in mice.

Methods
38 Male C57/Bl6 mice were ventilated with different tidal volumes (Vt 5, 7, and 10 ml/kg) without or with application of PEEP (2 cm H2O). Four spontaneously breathing animals served as controls. Oxygen saturation and pulse rate were monitored. Lung function was measured every 5 min for at least 30 min. Afterwards lungs were removed and histological sections were stained for measurement of infiltration with polymorphonuclear leukocytes (PMN). Moreover, mRNA expression of macrophage inflammatory protein (MIP)-2 and tumor necrosis factor (TNF)α in the lungs was quantified using real time PCR.

Results
Oxygen saturation did not change significantly over time of ventilation in all groups ($P > 0.05$). Pulse rate dropped in all groups without PEEP during mechanical ventilation. In contrast, in the groups with PEEP pulse rate increased over time. These effects were not statistically significant ($P > 0.05$). Tissue damping (G) and tissue elastance (H) were significantly increased in all groups after 30 min of ventilation ($P < 0.05$). Only the group with a Vt of 10 ml/kg and PEEP did not show a significant increase in H ($P > 0.05$). Mechanical ventilation significantly increased infiltration of the lungs with PMN ($P < 0.05$). Expression of MIP-2 was significantly induced by mechanical ventilation in all groups ($P < 0.05$). MIP-2 mRNA expression was lowest in the group with a Vt of 10 ml/kg + PEEP.

Conclusions
Our data show that very short term mechanical ventilation with lower tidal volumes than 10 ml/kg did not reduce inflammation additionally. Formation of atelectasis and inadequate oxygenation with very low tidal volumes may be important factors. Application of PEEP attenuated inflammation.

DCRoesemarcph aartricileson of the effect of lps and pam3 on ventilated lungs

Wednesday, October 20, 2010

Hans P Hauber, Dörte Karp, Torsten Goldmann, Ekkehard Vollmer and Peter Zabel

Abstract

Background: While lipopolysaccharide (LPS) from Gram-negative bacteria has been shown to augment inflammation in ventilated lungs information on the effect of Gram-positive bacteria is lacking. Therefore the effect of LPS and a lipopetide from Gram-positive bacteria, PAM3, on ventilated lungs were investigated.

Methods: C57/Bl6 mice were mechanically ventilated. Sterile saline (sham) and different concentrations of LPS (1 μg and 5 μg) and PAM3 (50 nM and 200 nM) were applied intratracheally. Lung function parameters and expression of

MIP-2 and TNFα as well as influx of neutrophils were measured.

Results: Mechanical ventilation increased resistance and decreased compliance over time. PAM3 but not LPS significantly increased resistance compared to sham challenge ($P < 0.05$). Both LPS and PAM3 significantly increased MIP-2 and TNFα mRNA expression compared to sham challenge ($P < 0.05$). The numbers of neutrophils were significantly increased after LPS at a concentration of 5 μg compared to sham ($P < 0.05$). PAM3 significantly increased the numbers of neutrophils at both concentrations compared to sham ($P < 0.05$).

Conclusions: These data suggest that PAM3 similar to LPS enhances ventilator-induced inflammation. Moreover, PAM3 but not LPS increases pulmonary resistance in ventilated

Publication Type:

Preexposure to hyperoxia causes increased lung injury and epithelial apoptosis in mice ventilated with high tidal volumes

http://ajplung.physiology.org/content/299/5/L711.abstract

Monday, September 6, 2010

1. Patrudu S. Makena,
2. Charlean L. Luellen,
3. Louisa Balazs,
4. Manik C. Ghosh,
5. Kaushik Parthasarathi,
6. Christopher M. Waters, and
7. Scott E. Sinclair

Abstract
Both high tidal volume mechanical ventilation (HV) and hyperoxia (HO) have been implicated in ventilator-induced lung injury. However, patients with acute lung injury are often exposed to HO before the application of mechanical ventilation. The potential priming of the lungs for subsequent injury by exposure to HO has not been extensively studied. We provide evidence that HO (90%) for 12 h followed by HV (25 μl/g) combined with HO for 2 or 4 h (HO-12h+HVHO-2h or -4h) induced severe lung injury in mice. Analysis of lung

homogenates showed that lung injury was associated with cleavage of executioner caspases, caspases-3 and -7, and their downstream substrate poly(ADP-ribose) polymerase-1 (PARP-1). No significant lung injury or caspase cleavage was seen with either HO for 16 h or HV for up to 4 h. Ventilation for 4 h with HO (HVHO) did not cause significant lung injury without preexposure to HO. Twelve-hour HO followed by lower tidal volume (6 μl/g) mechanical ventilation failed to produce significant injury or caspase cleavage. We also evaluated the initiator caspases, caspases-8 and -9, to determine whether the death receptor or mitochondrial-mediated pathways were involved. Caspase-9 cleavage was observed in HO-12h+HVHO-2h and -4h as well as HO for 16 h. Caspase-8 activation was observed only in HO-12h+HVHO-4h, indicating the involvement of both pathways. Immunohistochemistry and in vitro stretch studies showed caspase cleavage in alveolar epithelial cells. In conclusion, preexposure to HO followed by HV produced severe lung injury associated with alveolar epithelial cell apoptosis.

Toll-like Receptor 4-Myeloid Differentiation Factor 88 Signaling Contributes to Ventilator-induced Lung Injury in Mice

http://journals.lww.com/anesthesiology/Abstract/2010/09000/Toll_like_Receptor_4_Myeloid_Differentiation.23.aspx

Wednesday, September 1, 2010

Li, Huihua M.D.*; Su, Xiaoli M.D., Ph.D.†; Yan, Xuebin M.D., Ph.D.‡; Wasserloos, Karla M.S.§; Chao, Wei M.D., Ph.D.‖; Kaynar, A. Murat M.D.#; Liu, Zhao-Qian M.D., Ph.D.**; Leikauf, George D. Ph.D.††; Pitt, Bruce R. Ph.D.‡‡; Zhang, Li-Ming M.D.§§

Abstract

Background: The mechanisms of ventilator-induced lung injury, an iatrogenic inflammatory condition induced by mechanical ventilation, are not completely understood. Toll-like receptor 4 (TLR4) signaling *via* the adaptor protein myeloid differentiation factor 88 (MyD88) is proinflammatory and plays a critical role in host immune response to invading pathogen and noninfectious tissue injury. The role of TLR4-MyD88 signaling in ventilator-induced lung injury remains incompletely understood.

Methods: Mice were ventilated with low or high tidal volume (HTV), 7 or 20 ml/kg, after tracheotomy for 4 h. Control mice were tracheotomized without ventilation. Lung injury was assessed by: alveolar capillary permeability to Evans blue albumin, wet/dry ratio, bronchoalveolar lavage analysis for cell counts, total proteins and cytokines, results of histopathological examination of the lung, and plasma cytokine levels.

Results: Wild-type mice subjected to HTV had increased pulmonary permeability, inflammatory cell infiltration/lung edema, and interleukin-6/macrophage-inflammatory protein-2 in the lavage compared with control mice. In HTV, levels of inhibitor of κB α decreased, whereas phosphorylated extracellular signal-regulated kinases increased. TLR4 mutant and MyD88−/− mice showed markedly attenuated response to HTV, including less lung inflammation, pulmonary edema, cell number, protein content, and the cytokines in the lavage. Furthermore, compared with wild-type mice, both TLR4 mutant and MyD88−/− mice had significantly higher levels of inhibitor of κB α and reduced extracellular signal-regulated kinase phosphorylation after HTV.

Conclusions: TLR4-MyD88 signaling plays an important role in the development of ventilator-induced lung injury in mice, possibly through mechanisms involving nuclear factor-κB and mitogen-activated protein kinase pathways.

Simvastatin attenuates ventilator-induced lung injury in mice

http://www.biomedcentral.com/content/pdf/cc9209.pdf

Wednesday, April 14, 2010

Holger C Müller, Katharina Hellwig, Simone Rosseau, Thomas Tschernig, Andreas Schmiedl, Birgitt Gutbier, Bernd Schmeck, Stefan Hippenstiel, Harm Peters, Lars Morawietz, Norbert Suttorp, Martin Witzenrath

Abstract

Introduction: Mechanical ventilation (MV) is a life saving intervention in acute respiratory failure without alternative. However, particularly in pre-injured lungs, even protective ventilation strategies may evoke ventilatorinduced lung injury (VILI), which is characterized by pulmonary inflammation and vascular leakage. Adjuvant pharmacologic strategies in addition to lung protective ventilation to attenuate VILI are lacking. Simvastatin exhibited anti-inflammatory and endothelial barrier stabilizing properties in vitro and in vivo.

Methods: Mice were ventilated (12 ml/kg; six hours) and subjected to simvastatin (20 mg/kg) or sham treatment.

Pulmonary microvascular leakage, oxygenation, pulmonary and systemic neutrophil and monocyte counts and cytokine release in lung and blood plasma were assessed. Further, lung tissue was analyzed by electron microscopy.

Results: Mechanical ventilation induced VILI, displayed by increased pulmonary microvascular leakage and

endothelial injury, pulmonary recruitment of neutrophils and Gr-1 high monocytes, and by liberation of inflammatory cytokines in the lungs. Further, VILI associated systemic inflammation characterized by blood leukocytosis and elevated plasma cytokines was observed. Simvastatin treatment limited pulmonary endothelial injury, attenuated pulmonary hyperpermeability, prevented the recruitment of leukocytes to the lung, reduced pulmonary cytokine levels and improved oxygenation in mechanically ventilated mice.

Conclusions: High-dose simvastatin attenuated VILI in mice by reducing MV-induced pulmonary inflammation and hyperpermeability.

Chronic hypercapnia alters lung matrix composition in mouse pups

http://jap.physiology.org/content/early/2010/04/01/japplphysiol.00610.2009.abstract

Thursday, March 25, 2010

Julie Ryu, Gregory P. Heldt, Mary Nguyen, Orit Gavrialov, and Gabriel G. Haddad

Abstract
Rationale: Permissive hypercapnia, a stretch-limiting ventilation strategy, often results in high PaCO2. This strategy is associated with reduced morbidity and mortality in premature infants and its benefits have been attributed to diminished barotrauma. However, little is known about the independent effect of high CO2levels during the lung development. Methods: Mice were exposed to 8% CO2 or room air for 2 weeks either from postnatal day 2 through 17 or as adults (~2 months of age). Lungs were excised and processed for protein, RNA, histology and total lung volumes. Results: Histologic analysis demonstrated that alveolar walls of CO2-exposed mouse pups were thinner than those of controls and had twice the total lung volume. Molecular analysis revealed that several matrix proteins in the lung were down-regulated in mouse pups exposed to hypercapnia. Interstitial collagen type I α1, type III α1, elastin and fibronectin protein and mRNA levels were less than half of controls while collagen IV α5 was unaffected. This decrease in interstitial collagen could thus account for the thinning of the interstitial matrix and the altered lung biomechanics. Matrix metalloproteinase (MMP) -8, a collagenase that has specificity for collagen types I and III, increased in hypercapnic mouse pups suggesting increased collagen degradation. Moreover, tissue inhibitor of MMP (TIMP) -1, a potent inhibitor of MMP-8, was significantly decreased. However, unlike pups, adult mice exposed to hypercapnia demonstrated only a mild increase in total lung volumes and did not exhibit similar molecular or histologic changes. Conclusions: Although permissive hypercapnia may prevent lung injury from barotrauma, our study revealed that exposure to hypercapnia may be an important factor in lung remodeling and function, especially in early life.

Transplantation of Human Embryonic Stem Cell–Derived Alveolar Epithelial Type II Cells Abrogates Acute Lung Injury in Mice

http://www.nature.com/mt/journal/v18/n3/abs/mt2009317a.html

Tuesday, January 19, 2010

Dachun Wang, John E Morales, Daniel G Calame, Joseph L Alcorn and Rick A Wetsel

Respiratory diseases are a major cause of mortality and morbidity worldwide. Current treatments offer no prospect of cure or disease reversal. Transplantation of pulmonary progenitor cells derived from human embryonic stem cells (hESCs) may provide a novel approach to regenerate endogenous lung cells destroyed by injury and disease. Here, we examine the therapeutic potential of alveolar type II epithelial cells derived from hESCs (hES-ATIICs) in a mouse model of acute lung injury. When transplanted into lungs of mice subjected to bleomycin (BLM)-induced acute lung injury, hES-ATIICs behaved as normal primary ATIICs, differentiating into cells expressing phenotypic markers of alveolar type I epithelial cells. Without experiencing tumorigenic side effects, lung injury was abrogated in mice transplanted with hES-ATIICs, demonstrated by recovery of body weight and arterial blood oxygen saturation, decreased collagen deposition, and increased survival. Therefore, transplantation of hES-ATIICs shows promise as an effective therapeutic to treat acute lung injury.

High tidal volume ventilation is not deleterious in infant rats exposed to severe hemorrhage

http://researchrepository.murdoch.edu.au/2083/1/high_tidal_volume_ventil...

Friday, January 1, 2010

Background: Both high tidal volume (VT) ventilation and hemorrhage induce acute lung injury in adult rodents. It is not known whether injurious ventilation augments lung injury in infant rats exposed to severe hemorrhage.

Methods: Two week old rats were allocated to ventilation with VT 7 mL/kg and PEEP 5 cmH2O (low VT) or VT 21 mL/kg and PEEP 1 (high VT) for 4 h. Additional rats were subjected to volume-controlled hemorrhage and delayed saline resuscitation, followed by low VT or high VT ventilation for 4 h. Non-ventilated control groups were also included. Airway resistance and the coefficient of tissue elastance (H) were derived from respiratory input impedance measurements using the low-frequency forced oscillation technique. Pressure-volume curves were obtained at baseline and at the end of the study. Interleukin-6 (IL-6), macrophage inflammatory protein-2 (MIP-2), and tumor necrosis factor alpha (TNF-α) were determined in bronchoalveolar lavage fluid (BALF) and serum.

Results: In both healthy and hemorrhage-exposed animals high VT resulted in reduced H (better lung compliance), and increased transcutaneous oxygen saturation. IL-6 in BALF was greater in ventilated animals when compared to non-ventilated controls, but not different between ventilated groups. No significant differences were found for all other inflammatory mediators, total protein concentration in BALF, and histology.

Conclusion: High VT ventilation with low PEEP improves respiratory system mechanics without causing additional damage to healthy and hemorrhage-exposed infant rats after 4

3h of ventilation. This study highlights the tolerance to high VT ventilation in infant rats

and underscores the need for age-specific animal models.

Lung volume recruitment maneuvers and respiratory system mechanics in mechanically ventilated mice

http://www.sciencedirect.com/science/article/pii/S1569904809003218

Sunday, September 27, 2009

Vincenzo Cannizzaro, Luke J. Berry, Philip K. Nicholls, Graeme R. Zosky, Debra J. Turner,Zoltán Hantos, Peter D. Sly

Abstract

The study aim was to establish how recruitment maneuvers (RMs) influence lung mechanics and to determine whether RMs produce lung injury. Healthy BALB/c mice were allocated to receive positive end-expiratory pressure (PEEP) at 2 or 6 cmH2O and volume- (20 or 40 mL/kg) or pressure-controlled (25 cmH2O) RMs every 5 or 75 min for 150 min. The low-frequency forced oscillation technique was used to measure respiratory input impedance. Large RMs resulting in peak airway opening pressures (*P*ao) > 30 cmH2O did not increase inflammatory response or affect transcutaneous oxygen saturation but significantly lowered airway resistance, tissue damping and tissue elastance; the latter changes are likely associated with the bimodal pressure–volume behavior observed in mice. PEEP increase alone and application of RMs producing peak *P*ao below 25 cmH2O did not prevent or reverse changes in lung mechanics; whereas frequent application of substantial RMs on top of elevated PEEP levels produced stable lung mechanics without signs of lung injury.

Keywords
Pulmonary elastance; Airway resistance; Lung volume history; Recruitment maneuver; Mechanical ventilation

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Therapeutic effects of hypercapnia on chronic lung injury and vascular remodeling in neonatal rats

http://ajplung.physiology.org/content/297/5/L920.abstract

Wednesday, September 9, 2009

Azhar Masood, Man Yi, Mandy Lau, Rosetta Belcastro,Samuel Shek, Jingyi Pan, Crystal Kantores,Patrick J. McNamara, Brian P. Kavanagh, Jaques Belik, Robert P. Jankov, and A. Keith Tanswell

Permissive hypercapnia, achieved using low tidal volume ventilation, has been an effective protective strategy in patients with acute respiratory distress syndrome. To date, no such protective effect has been demonstrated

for the chronic neonatal lung injury, bronchopulmonary dysplasia. The objective of our study was to determine whether evolving chronic neonatal lung injury, using a rat model, is resistant to the beneficial effects of hypercapnia or simply requires a less conservative approach to hypercapnia than that applied clinically to date. Neonatal rats inhaled air or 60% O2 for 14 days with or without 5.5% CO2. Lung parenchymal neutrophil and macrophage numbers were significantly increased by hyperoxia alone, which was associated with interstitial thickening and reduced secondary crest formation. The phagocyte influx, interstitial thickening, and impaired alveolar formation were significantly attenuated by concurrent hypercapnia. Hyperoxic pups that received 5.5% CO2 had a significant increase in alveolar number relative to air-exposed pups. Increased tyrosine nitration, a footprint for peroxynitrite-mediated reactions, arteriolar medial wall thickening, and both reduced small peripheral pulmonary vessel number and VEGF and angiopoietin-1 (Ang-1) expression, which were observed with hyperoxia, was attenuated by concurrent hypercapnia. We conclude that evolving chronic neonatal lung injury in a rat model is responsive to the beneficial effects of hypercapnia. Inhaled 5.5% CO2 provided a significant degree of protection against parenchymal and vascular injury in an animal model of chronic neonatal lung injury likely due, at least in part, to its inhibition of a phagocyte influx.

Pulmonary Surfactant Surface Tension Influences Alveolar Capillary Shape and Oxygenation

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2746989/

Friday, February 6, 2009

Machiko Ikegami, Timothy E. Weaver, Shawn N. Grant, and Jeffrey A. Whitsett

Alveolar capillaries are located in close proximity to the alveolar epithelium and beneath the surfactant film. We hypothesized that the shape of alveolar capillaries and accompanying oxygenation are influenced by surfactant surface tension in the alveolus. To prove our hypothesis, surfactant surface tension was regulated by conditional expression of surfactant protein (SP)-B in *Sftpb*−/− mice, thereby inhibiting surface tension–lowering properties of surfactant *in vivo* within 24 hours after depletion of*Sftpb*. Minimum surface tension of isolated surfactant was increased and oxygen saturation was significantly reduced after 2 days of SP-B deficiency in association with deformation of alveolar capillaries. Intravascularly injected 3.2-μm-diameter microbeads through jugular vein were retained within narrowed pulmonary capillaries after reduction of SP-B. Ultrastructure studies demonstrated that the capillary protrusion typical of the normal alveolar–capillary unit was reduced in size, consistent with altered pulmonary blood flow. Pulmonary hypertension and intrapulmonary shunting are commonly associated with surfactant deficiency and dysfunction in neonates and adults with respiratory distress syndromes. Increased surfactant surface tension caused by reduction in SP-B induced narrowing of alveolar capillaries and oxygen desaturation, demonstrating an important role of surface tension–lowering properties of surfactant in the regulation of pulmonary vascular perfusion.

Keywords: surfactant protein-B, transgenic mice, pulmonary blood flow, acute respiratory distress syndrome, pulmonary vascular perfusion

Pulmonary surfactant is a complex mixture of lipids and associated proteins that are required for formation and stability of surfactant film in the alveolus. After secretion from type II epithelial cells, surfactant forms a lipid rich film that covers the entire alveolar surface, reducing surface tension at the air/liquid interface from

70 mN/m to near 0 mN/m (1). The reduction of alveolar surface tension is required for the maintenance of alveolar surface area, upon which respiration depends. Surfactant function requires the presence of surfactant protein (SP)-B, a small hydrophobic protein that is tightly associated with surfactant phospholipids in the alveolus (1, 2). In humans and mice, SP-B deficiency or mutations in *SFTPB* cause respiratory failure and death in adults and neonates (3–5). Conditional reduction of SP-B for 4 days in adult mice causes respiratory failure associated with abnormal high surface tension of the surfactant present in bronchoalveolar lavage fluid (BALF) (6–8). This conditional SP-B mouse provides a useful model for study of the influence of surface tension on lung structure, function, and inflammation in adult lung *in vivo*. The loss of surfactant surface activity influences the shape and function of cells beneath the surfactant film. For example, reduction in SP-B increases the surface tension of surfactant, influencing both cell shape and phagocytic activity of alveolar macrophages *in vivo*, providing support for the concept that surface tension influences cell shape and function in the alveolus (9).

Acute lung injury is a common cause of mortality and morbidity associated with high surface tension in the alveolus as a result of surfactant deficiency and dysfunction in both children and adults (10, 11). Concentrations of SP-B in BALF from patients with acute respiratory distress syndrome were decreased to 20 to 50% of normal (11). Pulmonary hypertension and intrapulmonary shunting is commonly associated with respiratory distress syndrome in neonates and adults, resulting in the impairment of ventilation perfusion or disrupting normal gas exchange.

The alveolar capillary unit consists of a region composed of both interstitial and epithelial components. In addition to alveolar pressure, other capillary compressive forces, including alveolar surface tension and tension in connective tissue fibers (12, 13), must be overcome for recruitment to occur. Because of the close apposition of the alveolar cell surfaces and epithelial component of vessels of the microcirculation, changes in surface tension may influence capillary blood flow via transmitted forces.

In the present study, we sought to test the hypothesis that decreased activity of pulmonary surfactant alters alveolar capillary shape that in turn influences alveolar capillary blood flow and gas exchange *in vivo*. For these studies, a mouse model in which the expression of SP-B in respiratory epithelial cells was conditionally controlled *in vivo* was used.

RESPIRATORY MECHANICS IN INFANT AND ADULT MICE MODELLING VENTILATOR-INDUCED LUNG INJURY

http://www.phd.szote.u-szeged.hu/Multidiszciplinaris_DI/Disszertaciok/20...

Thursday, January 1, 2009

Vincenzo CANNIZZARO, MD

SUMMARY

Mechanical ventilation is critical in the management of patients suffering respiratory failure. However, mechanical ventilation has also the potential to aggravate or induce lung injury. This injury is referred to as ventilator-induced lung injury (VILI). To better understand different aspects and mechanisms involved in VILI age-specific

animal models are desirable. However, animal models investigating VILI do not include measurements of accurate respiratory system mechanics and inadequately consider effects of confounding factors such as positive end-expiratory pressure (PEEP), oxygen, and lung volume recruitment maneuvers.

The current thesis was designed to investigate major determinants of VILI, namely high tidal volume (VT), inadequate PEEP, high oxygen concentrations, and stress and strain-induced release of inflammatory mediators. Thus, we aimed at investigating effects of high-VT ventilation and PEEP in infant mice, impact of supplemental oxygen in both infant and adult mice, and outcome of lung volume recruitment maneuvers (RM) in adult mice.

Different ventilation strategies in healthy infant and adult mice were compared in an interventional controlled manner. The following outcome variables were assessed: a) respiratory system impedance, partitioned into components representing the conducting airways and lung parenchyma, representing dynamic lung function measurements, b) thoracic gas volume, c) pressure-volume curves, characterizing quasi-static lung function measurements, d) inflammatory response, measuring differential cell counts, protein content, and cytokines in lung lavage fluid and serum, and e) histology, quantifiying structural changes and inflammation.

While high-VT ventilation produced lung injury in infant mice presumably via overdistension and loss of lung volume, high oxygen concentrations had no impact on respiratory system mechanics in either age group. In addition, we found in adult mice that PEEP increase alone and application of RMs producing peak airway opening pressures <25 cmH2O did not prevent or reverse changes in lung mechanics, whereas frequent application of substantial RMs on top of elevated PEEP levels produced

stable lung mechanics without signs of lung injury.

These findings underline the need for age-specific small animal models and

require that specification of ventilator settings are reported in all studies investigating

effects of mechanical ventilation in mice.

Publication Type:

Lung Injury & Mechanical Ventilation

Effects of Ethanol on Pulmonary Inflammation in Postburn Intratracheal Infection

http://journals.lww.com/burncareresearch/pages/articleviewer.aspx?year=2008&issue=03000&article=00008&type=abstract

Saturday, March 1, 2008

Murdoch, Eva L. BS*; Brown, Henry G. MD, PhD†; Gamelli, Richard L. MD‡; Kovacs, Elizabeth J. PhD*‡

Infectious complications are a major cause of mortality in trauma patients. Burn patients with prior ethanol exposure have a worse prognosis than those who sustain injury but had not been drinking. We examined pulmonary infection and lung pathology in mice given ethanol (1.2 g/kg) 30 minutes before being subjected to 13 to 15% total body surface area scald burn followed by intratracheal inoculation with *Pseudomonas aeruginosa* (1-2 × 103 colony-forming units [CFUs]). Survival was monitored for up to 48 hours. Sham control groups had 100% survival after intratracheal infection regardless of ethanol exposure. Infected burned animals had 55% survival; however, survival of infected mice exposed to ethanol and burn injury was significantly lower (27%, $P < .0001$). When pulmonary infection was evaluated, the lungs of sham groups were negative for bacterial colonies. In addition, at 24 hours there were no significant differences in lung CFUs from infected burned animals regardless of ethanol exposure (3.0 × 104). However, pulmonary bacterial content significantly decreased (1.2 × 10, $P < .02$) at 48 hours in mice given burn injury alone, where CFUs from the lungs of mice exposed to ethanol prior to burn did not decline (5.4 × 105). At the same time point, lungs from animals given ethanol and burn injury had about a 2-fold ($P < .02$) increase in leukocyte infiltration and vascular congestion, as well as decreased pulmonary oxygen saturation (82.8%, $P < .02$), when compared with other treatment groups. In summary, ethanol exposure in postburn intratracheal infection results in the inability to clear pulmonary infection marked by a prolonged pulmonary leukocyte accumulation and a decrease in pulmonary function.

Transfusion-related Acute Lung Injury

http://www.sciencedirect.com/science/article/pii/S088985880600195X

Wednesday, January 24, 2007

Chelsea A. Sheppard, MD, Lennart E. Lögdberg, MD, PhD, James C. Zimring, MD, PhD, Christopher D. Hillyer, MD

With the success of reducing the risk of transfusion-transmitted infectious diseases, noninfectious serious hazards of transfusion have come to the forefront with respect to transfusion safety. Transfusion-related acute lung injury has emerged as a dominant noninfectious serious hazard of transfusion. Improved understanding of its pathophysiology is needed to improve clinical strategies to deal with the risk. Such understanding, in turn, will depend on the continued progress in development of good model systems, in vitro and in vivo, for experimental studies. As the pathologic mechanisms are elucidated, a universal definition and strategies for the prevention and/or mitigation may become more tangible. This article reviews the clinical manifestations, evolving definition, incidence, pathophysiology, animal modeling, and donor screening and deferral algorithms as they relate to transfusion-related acute lung injury.

Absence of Integrin αvβ3 Enhances Vascular Leak in Mice by Inhibiting Endothelial Cortical Actin Formation

G Su, A Atakilit, JT Li, N Wu… - American journal of …, 2012 - Am Thoracic Soc

... Lung Evans Blue Extravasation Assay. See the online supplement for information. Pulse Oximetry. Five consecutive sustained readings for at least 30 seconds were averaged using the MouseOx system (**Starr Life Sciences**, Oakmont, PA). Primary Lung Endothelial Cells. **...**

Rationale: Sepsis and acute lung injury (ALI) have devastatingly high mortality rates. Both are associated with increased vascular leak, a process regulated by complex molecular mechanisms.

Objectives: We hypothesized that integrin αvβ3 could be an important determinant of vascular leak and endothelial permeability in sepsis and ALI.

Methods: β3 subunit knockout mice were tested for lung vascular leak after endotracheal LPS, and systemic vascular leak and mortality after intraperitoneal LPS and cecal ligation and puncture. Possible contributory effects of β3 deficiency in platelets and other hematopoietic cells were excluded by bone marrow reconstitution experiments. Endothelial cells treated with αvβ3 antibodies were evaluated for sphingosine-1 phosphate (S1P)–mediated alterations in barrier function, cytoskeletal arrangement, and integrin localization.

Measurements and Main Results: β3 knockout mice had increased vascular leak and pulmonary edema formation after endotracheal LPS, and increased vascular leak and mortality after intraperitoneal LPS and cecal ligation and puncture. In endothelial cells, αvβ3 antibodies inhibited barrier-enhancing and cortical actin responses to S1P. Furthermore, S1P induced translocation of αvβ3 from discrete focal adhesions to cortically distributed sites through Gi- and Rac1-mediated pathways. Cortical αvβ3 localization after S1P was decreased by αvβ3 antibodies, suggesting that ligation of the αvβ3 with its extracellular matrix ligands is required to stabilize cortical αvβ3 focal adhesions.

Conclusions: Our studies identify a novel mechanism by which αvβ3 mitigates increased vascular leak, a pathophysiologic function central to sepsis and ALI. These studies suggest that drugs designed to block αvβ3 may have the unexpected side effect of intensifying sepsis- and ALI-associated vascular endothelial leak.

Read Full Article

Neonatal Rodent Studies

Role of ATP and adenosine on carotid body function during development

http://www.sciencedirect.com/science/article/pii/S1569904812001577

Tuesday, January 1, 2013

Aida Bairam, Lalah M. Niane, Vincent Joseph

... arterial oxygen saturation (SpO 2) or heart rate (HR), we combined respiratory recordings using whole body plethysmography and measures of arterial SpO 2 and heart rate with an oximeter designed for small rodents (Mouse-Ox - STARR Life Sciences, Oakmont, PA, USA). ...

The carotid body is the main peripheral oxygen sensor involved in cardio-respiratory control under both normoxic and hypoxic conditions. This review focuses on data from newborn animals related to the involvement of the purinergic system in carotid body function during development. We describe the potential effects mediated by ATP and adenosine receptors on ventilation, chemoreceptor activity and their influence on respiratory instability, such as apnea. The conclusions that appear from this review is that in newborn rats, activation of ATP receptors increases the carotid body function although with no age dependent manner, regulates breathing under normoxia, and enhances the initial increase in ventilation in response to hypoxia (likely reflecting carotid body responses). However, activation of adenosine receptors may play a role on carotid body function under chronic conditions, such as intermittent hypoxia or exposure to the adenosine receptor antagonist caffeine. Under the later conditions, an indirect effects involving the carotid body dopaminergic system are observed.

Mesodermal Pten inactivation leads to alveolar capillary dysplasia-like phenotype

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3484434/

Thursday, November 1, 2012

Caterina Tiozzo,Gianni Carraro, Denise Al Alam, Sheryl Baptista, Soula Danopoulos, Aimin Li, Maria Lavarreda-Pearce, Changgong Li, Stijn De Langhe,Belinda Chan, Zea Borok, Saverio Bellusci, and Parviz Minoo

Alveolar capillary dysplasia (ACD) is a congenital, lethal disorder of the pulmonary vasculature. Phosphatase and tensin homologue deleted from chromosome 10 (Pten) encodes a lipid phosphatase controlling key cellular functions, including stem/progenitor cell proliferation and differentiation; however, the role of PTEN in mesodermal lung cell lineage formation remains unexamined. To determine the role of mesodermal PTEN in the ontogeny of various mesenchymal cell lineages during lung development, we specifically deleted Pten in early embryonic lung mesenchyme in mice. Pups lacking Pten died at birth, with evidence of failure in blood oxygenation. Analysis at the cellular level showed defects in angioblast differentiation to endothelial cells and an accompanying accumulation of the angioblast cell population that was associated with disorganized capillary beds. We also found decreased expression of Forkhead box protein F1 (Foxf1), a gene associated with the ACD human phenotype. Analysis of human samples for ACD revealed a significant decrease in PTEN and increased activated protein kinase B (AKT). These studies demonstrate that

mesodermal PTEN has a key role in controlling the amplification of angioblasts as well as their differentiation into endothelial cells, thereby directing the establishment of a functional gas exchange interface. Additionally, these mice could serve as a murine model of ACD.

Endothelin receptor antagonist has limited access to the fetal compartment during chronic maternal administration late in pregnancy

http://www.sciencedirect.com/science/article/pii/S0024320512000896

Saturday, March 3, 2012

Larry G. Thaete, Saira Khan, Sylvia Synowiec, Brian D. Dayton, Joy Bauch, Mark G. Neerhof

Abstract

Aims

Endothelin receptor A (ETA) antagonism normalizes fetal growth in several models of rodent fetal growth restriction (FGR). Our aims were to determine the levels of ETA antagonist in maternal and fetal plasma following chronic maternal administration, and to determine its impact on pregnancy outcome, survival and growth of rat pups.

Main methods

Timed pregnant rats were treated with one of two endothelin receptor antagonists or vehicle, from gestation day 14–21 (term = 22 days). The antagonists and their respective doses were ABT-546 (20 mg/kg/day) and FR139317 (12 mg/kg/day). On day 21, in six rats per group, maternal and fetal plasma ABT-546 was assayed by HPLC. Five additional rats in each group delivered spontaneously and nursed their pups through postpartum day 7. Viability of newborns, oxygen saturation, litter sizes, and pup weights were recorded on postpartum days 1 and 7.

Key findings

Fetal antagonist levels reached only 2% of maternal levels ($p < 0.01$). There were no significant differences among groups in length of gestation; litter size; survival, number and weight of live pups at birth and at 7 days postpartum; and tissue oxygen saturation.

Significance

Maternal administration of an ETA antagonist, at a dose sufficient to ameliorate FGR, has no adverse impact on survival and growth of neonatal rat pups. ETA antagonism, delivered maternally, produces sufficiently low fetal plasma levels of antagonist so as not to present a survival threat to the neonatal pups. The beneficial effects of maternally administered ETA antagonism on fetal growth occur in the maternal, not the fetal, compartment.

Keywords

Endothelin receptor antagonist; Rat; Pregnancy; Fetal; Neonatal

Oxydial/Hypoxydial

Circulating endothelial progenitor cells are reduced in rat oxygen-induced retinopathy despite a retinal SDF-1/CXCR4 and VEGF proangiogenic response

http://www.sciencedirect.com/science/article/pii/S0024320512003815

Monday, September 17, 2012

Amanda Villalvilla, Manuel Moro, Luis Arruza, Santiago Redondo, Arturo Fernández-Cruz, Raquel Fernández-Durango

.. Low Flow Bird MicroBlender (Care Fusion, San Diego, CA, USA) and HypoxyDial (STARR Life Sciences, Oakmont, PA, USA) blenders were used. Oxygen levels were continuosly monitored with Oxydig monitor (Drägerwer AG, Lübeck, Germany). ...

Aims
The purpose of this study is to investigate circulating endothelial progenitor cells (EPCs) and the signaling pathways involved in their recruitment in the ischemic retina of the 50/10 rat model of oxygen-induced retinopathy (OIR).

Main methods
Within 12 h after birth, litters of Sprague–Dawley rats and their mothers were exposed to alternating oxygen concentrations, followed by a room air exposition, to induce OIR. Retinopathy was quantified by ADPase stain in flat-mounted retinas and pre-ILM nuclei count in retinal sections. Semiquantitative real-time PCR and immunofluorescence were assessed in retinas to study stromal cell-derived factor 1 (SDF-1), its receptor CXCR4 and vascular endothelial growth factor (VEGF) expression. Circulating EPCs were evaluated by flow cytometry in peripheral blood.

Key findings
Our results showed increased immunolabelling of SDF-1 in endothelial cells and strong expression of CXCR4 in Müller cells in OIR retinas as compared to control retinas. We found increased levels of CXCR4 and VEGF mRNA in OIR retinas, especially during the vascular attenuation stage. The number of circulating EPCs was decreased in OIR rats as compared to control rats.

Significance
The decrease in circulating EPCs could be implied in vessel growth arrest during normal retinal development in OIR rats, while pro-angionenic signals released by Müller cells in the hypoxic retina could drive pathological neovascularization in the ischemic retina. These data warrant further studies to investigate new therapeutic approaches for ROP.

Keywords
Oxygen-induced retinopathy; Endothelial progenitor cells; Angiogenesis; CXCR4; SDF-1; Müller cells

Phosphorescent nanoparticles for quantitative measurements of oxygen profiles in vitro and in vivo

http://www.sciencedirect.com/science/article/pii/S0142961211014025

Tuesday, January 10, 2012

Nak Won Choi, Scott S. Verbridge, Rebecca M. Williams, Jin Chen, Ju-Young Kim, Russel Schmehl, Cornelia E. Farnum, Warren R. Zipfel, Claudia Fischbach, Abraham D. Stroock

Abstract

We present the development and characterization of nanoparticles loaded with a custom phosphor; we exploit these nanoparticles to perform quantitative measurements of the concentration of oxygen within three-dimensional (3-D) tissue cultures in vitro and blood vessels in vivo. We synthesized a customized ruthenium (Ru)-phosphor and incorporated it into polymeric nanoparticles via self-assembly. We demonstrate that the encapsulated phosphor is non-toxic with and without illumination. We evaluated two distinct modes of employing the phosphorescent nanoparticles for the measurement of concentrations of oxygen: 1) in vitro, in a 3-D microfluidic tumor model via ratiometric measurements of intensity with an oxygen-insensitive fluorophore as a reference, and 2) in vivo, in mouse vasculature using measurements of phosphorescence lifetime. With both methods, we demonstrated micrometer-scale resolution and absolute calibration to the dissolved oxygen concentration. Based on the ease and customizability of the synthesis of the nanoparticles and the flexibility of their application, these oxygen-sensing polymeric nanoparticles will find a natural home in a range of biological applications, benefiting studies of physiological as well as pathological processes in which oxygen availability and concentration play a critical role.

Keywords

Nanoparticle; Oxygen–sensing; Ruthenium phosphor; Poly(urethane acrylate nonionomer) (PUAN); Tissue engineering; Vascular oxygen concentration

Pharmacology & Toxicology

Toxicodynamics of rigid polystyrene microparticles on pulmonary gas exchange in mice: Implications for microemboli-based drug delivery systems

http://www.sciencedirect.com/science/article/pii/S0041008X12004632

Tuesday, January 15, 2013

H.L. Kutscher, D. Gao, S. Li, C.B. Massa, J. Cervelli, M. Deshmukh, L.B. Joseph, D.L. Laskin, P.J. Sinko

.. Arterial hemoglobin oxygen saturation (SpO2) in the blood was monitored on the mouseâ€™s thigh using a MouseOxÂ® pulse oximeter (STARR Life Sciences, Oakmont, PA) at 1 and 3 day pre-MP exposure and 1, 3, 5 and 7 day post-MP exposure. ...

The toxicodynamic relationship between the number and size of pulmonary microemboli resulting from uniformly sized, rigid polystyrene microparticles (MPs) administered intravenously and their potential effects on pulmonary gas exchange were investigated. CD-1 male mice (6–8 weeks) were intravenously administered 10, 25 and 45 μm diameter MPs. Oxygen hemoglobin saturation in the blood (SpO2) was measured non-invasively using a pulse oximeter while varying inhaled oxygen concentration (FIO2). The resulting data were fit to a physiologically based non-linear mathematical model that estimates 2 parameters: ventilation–perfusion ratio (VA/Q) and shunt (percentage of deoxygenated blood returning to systemic circulation). The number of MPs administered prior to a statistically significant reduction in normalized VA/Q was dependent on particle size. MP doses that resulted in a significant reduction in normalized VA/Q one day post-treatment were 4000, 40,000 and 550,000 MPs/g for 45, 25 and 10 μm MPs, respectively. The model estimated VA/Q and shunt returned to baseline levels 7 days post-treatment. Measuring SpO2 alone was not sufficient to observe changes in gas exchange; however, when combined with model-derived VA/Q and shunt early reversible toxicity from pulmonary microemboli was detected suggesting that the model and physical measurements are both required for assessing toxicity. Moreover, it appears that the MP load required to alter gas exchange in a mouse prior to lethality is significantly higher than the anticipated required MP dose for effective drug delivery. Overall, the current results indicate that the microemboli-based approach for targeted pulmonary drug delivery is potentially safe and should be further explored.

Activation of Protein Kinase C (PKC)α or PKCε as an Approach to Increase Morphine Tolerance in Respiratory Depression and Lethal Overdose

http://jpet.aspetjournals.org/content/341/1/115.short

Friday, January 6, 2012

Hong-Yiou Lin, Ping-Yee Law and Horace H. Loh

Abstract

Long-term use of opioids is hindered by respiratory depression and the possibility for fatal overdose in drug abusers. This is attributed to higher levels of tolerance that develops against antinociception than to respiratory depression. Identifying important mechanisms that would increase morphine respiratory depression and overdose tolerance could lead to the safer use of opioids. Because protein kinase C (PKC) activity mediates the development and maintenance of morphine antinociceptive tolerance, we hypothesized that activating PKCα or PKCε at the pre-Bötzinger complex (preBötC) can increase morphine tolerance in respiration and overdose. Laser microdissection and quantitative reverse transcriptase-polymerase chain reaction were used to compare the relative mRNA abundances of PKCα, γ, and ε between ventrolateral periaqueductal gray (vlPAG) and preBötC. To test whether PKCα or ε could enhance morphine tolerance in respiratory depression and overdose, lentivirus carrying the wild type, constitutively activated mutants, and small interference RNA against PKCα or ε was stereotaxically injected into the preBötC. Expression of constitutively active PKC (CAPKC) α or ε, but not wild-type PKC (WTPKC) α or ε, at the preBötC allowed rats to develop tolerance to morphine respiratory depression. In terms of lethality, expression of WTPKCε, CAPKCα, or CAPKCε at preBötC increased morphine tolerance to lethal overdose. CAPKCε-expressing rats developed the highest level of respiratory depression tolerance. Furthermore, when CAPKCε lentivirus was injected into the vlPAG, rats were able to develop significant antinociceptive tolerance at low doses of morphine that normally do not cause tolerance. The approach of increasing morphine respiratory depression and lethality tolerance by increasing PKCα or ε activity at preBötC could be used to make opioids safer for long-term use.

Activation of PKCα or PKCε as an approach to increase morphine tolerance in respiratory depression and lethal overdose

http://jpet.aspetjournals.org/content/early/2012/01/06/jpet.111.188235.short

Friday, January 6, 2012

Hong-Yiou Y. Lin, Ping-Yee Y. Law and Horace H. Loh

Abstract

Long-term use of opioids is hindered by respiratory depression and the possibility for fatal overdose in drug abusers. This is due to higher levels of tolerance that develops against antinociception than to respiratory depression. Identifying important mechanisms that would increase morphine respiratory depression and overdose tolerance could lead to the safer use of opioids. Since PKC activity mediates the development and maintenance of morphine antinociceptive tolerance, we hypothesized that activating PKCα or ε at the pre-Botzinger complex (preBotC) can increase morphine tolerance in respiration and overdose. Laser microdissection and qRT-PCR were used to compare the relative mRNA abundances of PKCα, γ, and ε between vlPAG vs. preBotC. To test whether PKCα or ε could enhance morphine tolerance in respiratory depression and overdose, lentivirus carrying the wild type (WT), constitutively activated mutants (CA), and siRNA against PKCα or ε were stereotaxically injected into the preBotC. Expressing CAPKCα or ε, but not WTPKCα or ε, at the preBotC allowed rats to develop tolerance to morphine respiratory depression. In terms of lethality, expressing either WTPKCε, CAPKCα, or CAPKCε at preBotC increased morphine tolerance to lethal overdose. CAPKCε expressing rats developed the highest level of respiratory depression tolerance. Furthermore, when CAPKCε lentivirus was injected into the vlPAG, rats were able to develop significant antinociceptive tolerance at low doses of morphine that normally do not cause tolerance. The approach of

increasing morphine respiratory depression and lethality tolerance by increasing PKCα or ε activity at preBotC could be used to make opioids safer for chronic use.

Postnatal morphine administration alters hippocampal development in rats

http://onlinelibrary.wiley.com/doi/10.1002/jnr.22750/full

Tuesday, October 4, 2011

Christopher M. Traudt, Ivan Tkac, Kathleen M. Ennis, Leah M. Sutton, Daniel M. Mammel, Raghavendra Rao

Morphine is frequently used as an analgesic and sedative in preterm infants. Adult rats exposed to morphine have an altered hippocampal neurochemical profile and decreased neurogenesis in the dentate gyrus of the hippocampus. To evaluate whether neonatal rats are similarly affected, rat pups were injected twice daily with 2 mg/kg morphine or normal saline from postnatal days 3 to 7. On postnatal day 8, the hippocampal neurochemical profile was determined using in vivo 1H NMR spectroscopy. The mRNA and protein concentrations of specific analytes were measured in hippocampus, and cell division in dentate gyrus was assessed using bromodeoxyuridine. The concentrations of γ-aminobutyric acid (GABA), taurine, and myo-insotol were decreased, whereas concentrations of glutathione, phosphoethanolamine, and choline-containing compounds were increased in morphine-exposed rats relative to control rats. Morphine decreased glutamic acid decarboxylase enzyme levels and myelin basic protein mRNA expression in the hippocampus. Bromodeoxyuridine labeling in the dentate gyrus was decreased by 60–70% in morphine-exposed rats. These results suggest that recurrent morphine administration during brain development alters hippocampal structure.

Critically ill preterm infants are frequently treated with prolonged courses of opiates to decrease pain and stress (Anand et al.,2004). The efficacy of such treatment is debated, but the clinical practice persists (Franck et al.,2000; Simons et al.,2003; Carbajal et al.,2005; Cignacco et al.,2008), because the effects of untreated pain are well established (Anand,2000; Duric and McCarson,2006). There are increasing concerns that opiates may have detrimental effects on neurodevelopmental outcomes. Neonatal morphine treatment with and without stress is associated with short-term changes in gene expression and cellular composition in the hippocampus (Vien et al.,2009; Juul et al.,2011) and long-term neurobehavioral deficits in rodents (McPherson et al.,2007; Boasen et al.,2009).

In adult rats, the neurochemical profile of the hippocampus is altered during morphine administration (Corrigall,1983; Simonato,1996; Gao et al.,2007), and hippocampus-mediated learning is impaired (Spain and Newsom,1991; Bhutta et al.,2001), possibly because of decreased neurogenesis in the dentate gyrus of the hippocampus (Eisch et al.,2000; Lledo et al.,2006).

To evaluate the safety of morphine for sedation in the absence of pain, we used a neonatal rat model of morphine administration (McPherson et al.,2007). We hypothesized that neonatal morphine administration would alter the neurochemical profile of the developing hippocampus and decrease neurogenesis in the dentate gyrus. The metabolites indexing neuronal and glial integrity, energy substrates and energy sufficiency, phospholipid biosynthesis, and amino acids and neurotransmitters in the developing hippocampus were assessed using high-field in vivo 1H NMR spectroscopy, followed by evaluation of mRNA and protein

expression of relevant analytes in the hippocampus. We assessed cell proliferation in the dentate gyrus using bromodeoxyuridine (BrdU) histochemistry and found that rat pups exposed to recurrent morphine administration had an altered neurochemical profile, decreased glutamic acid decarboxylase (GAD) and myelin basic protein (MBP) expressions in the hippocampus, and decreased incorporation of BrdU in the dentate gyrus.

Acute, Sublethal Cyanide Poisoning in Mice Is Ameliorated by Nitrite Alone: Complications Arising from Concomitant Administration of Nitrite and Thiosulfate as an Antidotal Combination

http://pubs.acs.org/doi/abs/10.1021/tx2001042

Monday, May 2, 2011

Leah K. Cambal , Megan R. Swanson , Quan Yuan , Andrew C. Weitz , Hui-Hua Li , Bruce R. Pitt , Linda L. Pearce *, and Jim Peterson

Sodium nitrite alone is shown to ameliorate sublethal cyanide toxicity in mice when given from 1 h before until 20 min after the toxic dose as demonstrated by the recovery of righting ability. An optimum dose (12 mg/kg) was determined to significantly relieve cyanide toxicity (5.0 mg/kg) when administered to mice intraperitoneally. Nitrite so administered was shown to rapidly produce NO in the bloodsteam as judged by the dose-dependent appearance of EPR signals attributable to nitrosylhemoglobin and methemoglobin. It is argued that antagonism of cyanide inhibition of cytochrome c oxidase by NO is the crucial antidotal activity rather than the methemoglobin-forming action of nitrite. Concomitant addition of sodium thiosulfate to nitrite-treated blood resulted in the detection of sulfidomethemoblobin by EPR spectroscopy. Sulfide is a product of thiosulfate hydrolysis and, like cyanide, is known to be a potent inhibitor of cytochrome c oxidase, the effects of the two inhibitors being essentially additive under standard assay conditions rather than dominated by either one. The findings afford a plausible explanation for an observed detrimental effect in mice associated with the use of the standard nitrite–thiosulfate combination therapy at sublethal levels of cyanide intoxication.

Novelty-evoked activity in open field predicts susceptibility to helpless behavior

http://www.sciencedirect.com/science/article/pii/S0031938410003124

Monday, August 30, 2010

Eimeira Padilla, Jason Shumake, Douglas W. Barrett, Genevieve Holmes, Eva C. Sheridan, F. Gonzalez-Lima

Abstract

Learned helplessness in animals has been used to model disorders such as depression and post-traumatic stress disorder (PTSD), but there is a lack of knowledge concerning which individual behavioral characteristics at baseline can predict helpless behavior after exposure to inescapable stress. The first aim of this study was to determine behavioral predictors of helplessness using the novel and familiar open-field tests, sucrose

consumption, and passive harm-avoidance tasks before learned helplessness training and testing. Individual differences in physiologic responses to restraint stress were also assessed. A cluster analysis of escape latencies from helplessness testing supported the division of the sample population of Holtzman rats into approximately 50% helpless and 50% non-helpless. Linear regression analyses further revealed that increased reactivity to the novel environment, but not general activity or habituation, predicted susceptibility to learned helplessness. During restraint stress there were no mean differences in heart rate, heart rate variability, and plasma corticosterone between helpless and non-helpless rats; however, a lower heart rate during stress was associated with higher activity levels during exploration. Our most important finding was that by using an innocuous screening tool such as the novel and familiar open-field tests, it was possible to identify subjects that were susceptible to learned helplessness.

A novel paradigm for assessing efficacies of potential antidotes against neurotoxins in mice

http://www.sciencedirect.com/science/article/pii/S0378427407009733

Wednesday, October 10, 2007

Daune L. Crankshaw David J.W. Goon, Jacquie E. Briggs, David DeLong, Michael Kuskowski, Steven E. Patterson, Herbert T. Nagasawa

Abstract

Historically, antidotal potencies of cyanide antagonists were measured as increases in the experimental LD50 for cyanide elicited by the antidotes. This required the use of high doses of cyanide following pre-treatment with the putative antidote. Since IACUC guidelines at our institutions strongly discourage LD50 determinations: we developed a new test paradigm that allowed for maximal survival of cyanide-treated animals with greatly reduced numbers of animals. Symptoms of cyanide toxicity include disruption of neuromuscular coordination, i.e., the righting reflex. Therefore, to establish a dose-response curve, the times required for recovery of this righting reflex with increasing doses of cyanide were measured. A cyanide dose that disrupted this righting reflex for approximately 1 h with minimal deaths was then selected. Using this paradigm, the current cyanide antidotes, viz., nitrite plus thiosulfate and hydroxocobalamin, as well as some potential cyanide antidotes that we developed, were evaluated pre- and post-cyanide. This allowed, for the first time, the assessment of the post-cyanide effectiveness of the current antidotes against cyanide poisoning in a live animal. In addition, some prototype compounds were found to exhibit antidotal efficacy not only when injected i.p. following cyanide, but also when administered orally 30 min before cyanide. Pre-cyanide oral efficacy suggests that such compounds have the potential of being administered prophylactically before exposure to cyanide. This new test paradigm was found to be a powerful tool for assessing the efficacies of some novel antidotes against cyanide and should be equally applicable for evaluating putative antidotes for other neurotoxins.

Keywords

Cyanide; Animal model; Recovery; Righting reflex; Oral efficacy

Shock Models

Ambient Oxygen Promotes Tumorigenesis

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0019785

Thursday, May 12, 2011

Ho Joong Sung, Wenzhe Ma, Matthew F. Starost, Cory U. Lago, Philip K. Lim, Michael N. Sack, Ju-Gyeong Kang, Ping-yuan Wang, Paul M. Hwang

Abstract

Oxygen serves as an essential factor for oxidative stress, and it has been shown to be a mutagen in bacteria. While it is well established that ambient oxygen can also cause genomic instability in cultured mammalian cells, its effect on de novo tumorigenesis at the organismal level is unclear. Herein, by decreasing ambient oxygen exposure, we report a ~50% increase in the median tumor-free survival time of p53−/− mice. In the thymus, reducing oxygen exposure decreased the levels of oxidative DNA damage and RAG recombinase, both of which are known to promote lymphomagenesis in p53−/− mice. Oxygen is further shown to be associated with genomic instability in two additional cancer models involving the APC tumor suppressor gene and chemical carcinogenesis. Together, these observations represent the first report directly testing the effect of ambient oxygen on de novo tumorigenesis and provide important physiologic evidence demonstrating its critical role in increasing genomic instability in vivo.

Sphingosine kinase 1 and sphingosine-1-phosphate receptor 2 are vital to recovery from anaphylactic shock in mice

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2860904/

Monday, April 19, 2010

Ana Olivera, Christoph Eisner, Yoshiaki Kitamura, Sandra Dillahunt, Laura Allende, Galina Tuymetova, Wendy Watford, Francoise Meylan, Susanne C. Diesner, Lingli Li, Jurgen Schnermann, Richard L. Proia, and Juan Rivera

Abstract

Sphingosine kinase 1 (SphK1) and SphK2 are ubiquitous enzymes that generate sphingosine-1-phosphate (S1P), a ligand for a family of G protein–coupled receptors (S1PR1–S1PR5) with important functions in the vascular and immune systems. Here we explore the role of these kinases and receptors in recovery from anaphylaxis in mice. We found that Sphk2–/– mice had a rapid recovery from anaphylaxis. In contrast, Sphk1–/– mice showed poor recovery from anaphylaxis and delayed histamine clearance. Injection of S1P into Sphk1–/– mice increased histamine clearance and promoted recovery from anaphylaxis. Adoptive cell

transfer experiments demonstrated that SphK1 activity was required in both the hematopoietic and nonhematopoietic compartments for recovery from anaphylaxis. Mice lacking the S1P receptor S1PR2 also showed a delay in plasma histamine clearance and a poor recovery from anaphylaxis. However, S1P did not promote the recovery of S1pr2–/– mice from anaphylaxis, whereas S1pr2+/– mice showed partial recovery. Unlike Sphk2–/– mice, Sphk1–/– and S1pr2–/– mice had severe hypotension during anaphylaxis. Thus, SphK1-produced S1P regulates blood pressure, histamine clearance, and recovery from anaphylaxis in a manner that involves S1PR2. This suggests that specific S1PR2 agonists may serve to counteract the vasodilation associated with anaphylactic shock.

Stroke & Brain Injury

A method for hypothermia-induction and maintenance allows precise body and brain temperature control in mice

http://www.sciencedirect.com/science/article/pii/S0165027012004621

Friday, February 15, 2013

Yongshan Moua, Brian J. Wilgenburgb, Yang-ja Leea, John M. Hallenbeck

... Oxygen saturation, heart rate, and respiratory rate were monitored by an Oximeter (**STARRLife Sciences** Corporation, Oakmont, PA) in survival experiments. The Oximeter was connected to the animal's neck via a CollarClip Sensor (Fig. 1B). 3. Statistics. **...**
The benefits as well as mechanisms of hypothermia in brain injuries are actively studied at the bench and in the clinic. However, methods used in controlling hypothermia vary among laboratories, and usually brain temperatures are not monitored directly in animals due to the need for an invasive procedure. Here we show a method, water immersion technique, which we developed recently to regulate body temperature in mice during hypothermia process. This method significantly reduced the temperature variation around target temperature. Importantly, this method demonstrated a parallel and consistent relationship between rectal temperature and brain temperature (the brain temperature was consistently 0.5 C higher than rectal temperature) throughout hypothermia maintenance. This technique may be well adapted to hypothermia studies in mice and other rodents, especially to the assessment and regulation of brain temperature during studies.

Transient hypercapnia reveals an underlying cerebrovascular pathology in a murine model for HIV-1 associated neuroinflammation: role of NO-cGMP signaling and normalization by inhibition of cyclic nucleotide phosphodiesterase-5

http://www.jneuroinflammation.com/content/9/1/253/abstract

Tuesday, November 20, 2012

Jharon Silva, **Oksana Polesskaya**, **Walter Knight**, **Johnny T Zheng**, **Megan Granger**, **Tenée Lopez**,**Fernando Ontiveros**, **Changyong Feng**, **Chen Yan**, **Karl A Kasischke** and **Stephen Dewhurst**

.. The oxygen saturation and heart rate (HR) were continuously monitored using MouseOx (Harvard Apparatus, Starr Life Science Corporation, Holliston, MA, USA). Body temperature was monitored with a rectal probe. Cerebrovascular response to hypercapnia. ...
Background
Cerebral blood flow (CBF) is known to be dysregulated in persons with human immunodeficiency virus 1 (HIV-1), for uncertain reasons. This is an important issue because impaired vasoreactivity has been associated with increased risk of ischemic stroke, elevated overall cardiovascular risk and cognitive impairment.

Methods
To test whether dysregulation of CBF might be due to virally-induced neuroinflammation, we used a well-defined animal model (GFAP-driven, doxycycline-inducible HIV-1 Tat transgenic (Tat-tg) mice). We then exposed the mice to a brief hypercapnic stimulus, and assessed cerebrovascular reactivity by measuring 1) changes in cerebral blood flow, using laser Doppler flowmetry and 2) changes in vascular dilation, using in vivo two-photon imaging.

Results
Exposure to brief hypercapnia revealed an underlying cerebrovascular pathology in Tat-tg mice. In control animals, brief hypercapnia induced a brisk increase in cortical flow (20.8% above baseline) and vascular dilation, as measured by laser Doppler flowmetry and in vivo two-photon microscopy. These responses were significantly attenuated in Tat-tg mice (11.6% above baseline), but cortical microvascular morphology and capillary density were unaltered, suggesting that the functional pathology was not secondary to vascular remodeling. To examine the mechanistic basis for the diminished cerebrovascular response to brief hypercapnia, Tat-tg mice were treated with 1) gisadenafil, a phosphodiesterase 5 (PDE5) inhibitor and 2) tetrahydrobiopterin (BH4). Gisadenafil largely restored the normal increase in cortical flow following hypercapnia in Tat-tg mice (17.5% above baseline), whereas BH4 had little effect. Gisadenafil also restored the dilation of small (<25 μm) arterioles following hypercapnia (19.1% versus 20.6% diameter increase in control and Tat-tg plus gisadenafil, respectively), although it failed to restore full dilation of larger (>25 μm) vessels.

Conclusions
Taken together, these data show that HIV-associated neuroinflammation can cause cerebrovascular pathology through effects on cyclic guanosine monophosphate (cGMP) metabolism and possibly on PDE5 metabolism.

Increased intracranial pressure after diffuse traumatic brain injury exacerbates neuronal somatic membrane poration but not axonal injury: evidence for primary intracranial pressure-induced neuronal perturbation

http://www.nature.com/jcbfm/journal/v32/n10/full/jcbfm201295a.html

Monday, October 1, 2012

Audrey D Lafrenaye, Melissa J McGinn and John T Povlishock

.. measurements. The ICP was measured intraventricularly as described above. Heart rate, respiratory rate, and blood oxygenation were monitored via a foot pulse oximetry sensor (STARR Life Sciences, Oakmont, PA, USA). A ...

Increased intracranial pressure (ICP) associated with traumatic brain injury (TBI) is linked to increased morbidity. Although our understanding of the pathobiology of TBI has expanded, questions remain regarding the specific neuronal somatic and axonal damaging consequences of elevated ICP, independent of its impact on cerebral perfusion pressure (CPP). To investigate this, Fischer rats were subjected to moderate TBI. Measurements of ICP revealed two distinct responses to injury. One population exhibited transient increases in ICP that returned to baseline levels acutely, while the other displayed persistent ICP elevation (>20 mm Hg). Utilizing these populations, the effect of elevated ICP on neuronal pathology associated with

diffuse TBI was analyzed at 6 hours after TBI. No difference in axonal injury was observed, however, rats exhibiting persistently elevated ICP postinjury revealed a doubling of neurons with chronic membrane poration compared with rats exhibiting only transient increases in ICP. Elevated postinjury ICP was not associated with a concurrent increase in DNA damage; however, traditional histological assessments did reveal increased neuronal damage, potentially associated with redistribution of cathepsin-B from the lysosomal compartment into the cytosol. These findings indicate that persistently increased ICP, without deleterious alteration of CPP, exacerbates neuronal plasmalemmal perturbation that could precipitate persistent neuronal impairment and ultimate neuronal death.

Traumatic Brain Injury Increased IGF-1B mRNA and Altered IGF-1 Exon 5 and Promoter Region Epigenetic Characteristics in the Rat Pup Hippocampus

http://online.liebertpub.com/doi/abs/10.1089/neu.2011.2276

Tuesday, July 31, 2012

Michelle E. Schober, Xingrao Ke, Bohan Xing, Benjamin P. Block, Daniela F. Requena, Robert McKnight, and Robert H. Lane

Abstract

Traumatic brain injury (TBI) is a major cause of acquired cognitive disability in childhood. Such disability may be blunted by enhancing the brain's endogenous neuroprotective response. An important endogenous neuroprotective response is the insulin-like growth factor-1 (IGF-1) mRNA variant, IGF-1B. IGF-1B mRNA, characterized by exon 5 inclusion, encodes the IGF-1 and Eb peptides. IGF-1A mRNA excludes exon 5 and encodes the IGF-1 and Ea peptides. A region in the human IGF-1B homologue acts as an exon-splicing enhancer (ESE) to increase IGF-1B mRNA. It is not known if TBI is associated with increased brain IGF-1B mRNA. Epigenetic modifications may underlie altered gene expression in the brain after TBI. We hypothesized that TBI would increase hippocampal IGF-1B mRNA in 17-day-old rats, associated with DNA methylation and/or histone modifications at the promoter site 1 (P1) or exon 5/ESE region. Hippocampi from rat pups after controlled cortical impact (CCI) were used to measure IGF-1B mRNA, DNA methylation, and histone modifications at the P1, P2, and exon5/ESE regions. In CCI hippocampi, IGF-1B mRNA peaked at post-injury day (PID) 2 (1700±320% sham), but normalized by PID 14. IGF-1A peaked at PID 3 (280±52% sham), and remained elevated at PID 14. Increased IGF-1B mRNA was associated with increased methylation at P1, and increased histone modifications associated with gene activation at P2 and exon5/ESE, together with differential methylation in the exon 5/ESE regions. We report for the first time that hippocampal IGF-1B mRNA increased after developmental TBI. We speculate that epigenetic modifications at the P2 and exon 5/ESE regions are important in the regulation of IGF-1B mRNA expression. The exon 5/ESE region may present a means for future therapies to target IGF-1B transcription after TBI.

Persistent astroglial swelling accompanies rapid reversible dendritic injury during stroke-induced spreading depolarizations

http://onlinelibrary.wiley.com/doi/10.1002/glia.22390/full

Friday, July 20, 2012

W. Christopher Risher, Deborah Croom, Sergei A. Kirov

... 2009, 2010, 2011). Mice were anesthetized with an intraperitoneal injection of urethane (1.5 mg/g body weight) with heart rate monitored (450–650 beats/min) using MouseOx® pulse oximeter (**STARR Life Sciences**). Depth of **...**

Spreading depolarizations are a key event in the pathophysiology of stroke, resulting in rapid dendritic beading, which represents acute damage to synaptic circuitry. The impact of spreading depolarizations on the real-time injury of astrocytes during ischemia is less clear. We used simultaneous in vivo 2-photon imaging and electrophysiological recordings in adult mouse somatosensory cortex to examine spreading depolarization-induced astroglial structural changes concurrently with signs of neuronal injury in the early periods of focal and global ischemia. Astrocytes in the metabolically compromised ischemic penumbra-like area showed a long lasting swelling response to spontaneous spreading depolarizations despite rapid dendritic recovery in a photothrombotic occlusion model of focal stroke. Astroglial swelling was often facilitated by recurrent depolarizations and the magnitude of swelling strongly correlated with the total duration of depolarization. In contrast, spreading depolarization-induced astroglial swelling was transient in normoxic healthy tissue. In a model of transient global ischemia, the occurrence of a single spreading depolarization elicited by a bilateral common carotid artery occlusion coincided with astroglial swelling alongside dendritic beading. With immediate reperfusion, dendritic beading subsides. Astroglial swelling was either transient during short ischemic periods distinguished by a short-lasting spreading depolarization, or persistent during severe ischemia characterized by a long-lasting depolarization with the ultraslow negative voltage component. We propose that persistent astroglial swelling is initiated and exacerbated during spreading depolarization in brain tissue with moderate to severe energy deficits, disrupting astroglial maintenance of normal homeostatic function thus contributing to the negative outcome of ischemic stroke as astrocytes fail to provide neuronal support.

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Friday, July 20, 2012

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MT5-MMP, ADAM-10, and N-Cadherin Act in Concert To Facilitate Synapse Reorganization after Traumatic Brain Injury

http://online.liebertpub.com/doi/abs/10.1089/neu.2012.2383

Monday, July 9, 2012

Kelly M. Warren, Thomas M. Reeves, and Linda L. Phillips

.. During surgical preparations, animals were monitored for heart rate (beats per minute, bpm), arterial oxygen saturation (% O2), breath rate (breath per minute, brpm), pulse distention (in µm), and breath distention (in µm) (MouseOx; Starr Life Sciences, Oakmont, PA). ...

Matrix metalloproteinases (MMPs) influence synaptic recovery following traumatic brain injury (TBI). Membrane type 5-matrix metalloproteinase (MT5-MMP) and a distintegrin and metalloproteinase-10 (ADAM-10) are membrane-bound MMPs that cleave N-cadherin, a protein critical to synapse stabilization. This study examined protein and mRNA expression of MT5-MMP, ADAM-10, and N-cadherin after TBI, contrasting adaptive and maladaptive synaptogenesis. The effect of MMP inhibition on MT5-MMP, ADAM-10, and N-cadherin was assessed during maladaptive plasticity and correlated with synaptic function. Rats were subjected to adaptive unilateral entorhinal cortical lesion (UEC) or maladaptive fluid percussion TBI+bilateral entorhinal cortical lesion (TBI+BEC). Hippocampal MT5-MMP and ADAM-10 protein was significantly elevated 2 and 7 days post-injury. At 15 days after UEC, each MMP returned to control level, while TBI+BEC ADAM-10 remained elevated. At 2 and 7 days, N-cadherin protein was below control. By the 15-day synapse stabilization phase, UEC N-cadherin rose above control, a shift not seen for TBI+BEC. At 7 days, increased TBI+BEC ADAM-10 transcript correlated with protein elevation. UEC ADAM-10 mRNA did not change, and no differences in MT5-MMP or N-cadherin mRNA were detected. Confocal imaging showed MT5-MMP, ADAM-10, and N-cadherin localization within reactive astrocytes. MMP inhibition attenuated ADAM-10 protein 15 days after TBI+BEC and increased N-cadherin. This inhibition partially restored long-term potentiation induction, but did not affect paired-pulse facilitation. Our results confirm time- and injury-dependent expression of MT5-MMP, ADAM-10, and N-cadherin during reactive synaptogenesis. Persistent ADAM-10 expression was correlated with attenuated N-cadherin level and reduced

functional recovery. MMP inhibition shifted ADAM-10 and N-cadherin toward adaptive expression and improved synaptic function.

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Distinctive Effects of T Cell Subsets in Neuronal Injury Induced by Cocultured Splenocytes In Vitro and by In Vivo Stroke in Mice

http://stroke.ahajournals.org/content/43/7/1941.short

Thursday, June 7, 2012

Lijuan Gu, MD; Xiaoxing Xiong, MD, Hongfei Zhang, MD, PhD; Baohui Xu, MD, PhD; Gary K. Steinberg, MD, PhD; Heng Zhao, PhD

.. 17 Rectal temperature was maintained at 37±0.5°C with a heating pad (Harvard Apparatus, Holliston, MA). Heart rate, oxygen saturation, and respiratory rate were monitored continuously (STARR Life Sciences Corp, Allison Park, PA). ...
Background and Purpose—T cells and their subsets modulate ischemic brain injury. We studied the effects of the absence of T cell subsets on brain infarction after in vivo stroke and then used an in vitro coculture system of splenocytes and neurons to further identify the roles of T cell subsets in neuronal death.

Methods—Stroke was induced by middle cerebral artery suture occlusion in mice and infarct sizes were measured 2 days poststroke. Splenocytes were cocultured with neurons, and neuronal survival was measured 3 days later.

Results—A deficiency of both T and B cells (severe combined immunodeficiency) and the paucity of CD4 or CD8 T cells equally resulted in smaller infarct sizes as measured 2 days poststroke. Although a functional deficiency of regulatory T cells had no effect, impaired Th1 immunity reduced infarction and impaired Th2 immunity aggravated brain injury, which may be due to an inhibited and enhanced inflammatory response in mice deficient in Th1 and Th2 immunity, respectively. In the in vitro coculture system, wild-type splenocytes resulted in dose-dependent neuronal death. The neurotoxicity of splenocytes from these immunodeficient mice was consistent with their effects on stroke in vivo, except for the mice with the paucity of CD4 or CD8 T cells, which did not alter the ratio of neuronal death.

Conclusion—T cell subsets play critical roles in brain injury induced by stroke. The detrimental versus beneficial effects of Th1 cells and Th2 cells both in vivo and in vitro reveal differential therapeutic target strategies for stroke treatment.

Extracellular Chromatin Is an Important Mediator of Ischemic Stroke in Mice

http://atvb.ahajournals.org/content/early/2012/05/24/ATVBAHA.112.250993.short

Thursday, May 24, 2012

Simon F. De Meyer, Georgette L. Suidan*, Tobias A. Fuchs*, Marc Monestier, Denisa D. Wagner

Objective—Recently, a growing number of studies have revealed a prothrombotic and cytotoxic role for extracellular chromatin. Cerebral ischemia/reperfusion injury is characterized by a significant amount of cell death and neutrophil activation, both of which may result in the release of chromatin. The goal of this study was to assess the effect of extracellular chromatin in ischemic stroke using a mouse model of transient middle cerebral artery occlusion.

Methods and Results—Similar to reports in stroke patients, we observed increased levels of circulating nucleosomes and DNA after ischemic stroke in mice. In addition, we observed that general hypoxia also augmented extracellular chromatin. We hypothesized that targeting extracellular chromatin components would be protective in ischemic stroke. Indeed, treatment with recombinant human DNase 1 significantly improved stroke outcome. Neutralization of histones using an antihistone antibody was also protective as evidenced by smaller infarct volumes, whereas increasing levels of extracellular histones via histone infusion exacerbated stroke outcome by increasing infarct size and worsening functional outcome.

Conclusion—Our results indicate that extracellular chromatin is generated and is detrimental during cerebral ischemia/reperfusion in mice. Targeting DNA and histones may be a new therapeutic strategy to limit injury resulting from ischemic stroke.

Modulation of bladder afferent signals in normal and spinal cord-injured rats by purinergic P2X3 and P2X2/3 receptors

http://onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2012.11189.x/full

Monday, April 30, 2012

Alvaro Munoz, George T. Somogyi,Timothy B. Boone, Anthony P. Ford,Christopher P. Smith

It is well known that urinary bladder sensation requires the activation by ATP of ionotropic purinergic P2X3/P2X2/3 receptors located in bladder afferent C-fibres. Furthermore, in rat models of neurogenic bladder hyperactivity the release of ATP from the bladder urothelium is greater than ATP release in neurally intact rats. Therefore, the activation of purinergic receptors in bladder sensory fibres seems to be a sentinel event for the development of bladder hyperactivity after spinal cord injury.

We found that inhibition of P2X3/P2X2/3 purinergic receptors decreased the frequency of sensory field potentials evoked by activation of bladder noxious pathways. At the same time, the pharmacological blockade of these receptors significantly decreased the frequency of non-voiding contractions in rats with neurogenic bladder hyperactivity. The present study uncovers sensory purinergic receptors as potential therapeutic targets to treat neurogenic bladder hyperactivity, especially when the release of ATP from the urothelium is elevated.

Spatiotemporal dynamics of diffusional kurtosis, mean diffusivity and perfusion changes in experimental stroke

http://www.sciencedirect.com/science/article/pii/S0006899312003502

Friday, April 27, 2012

Edward S. Hui, Fang Du, Shiliang Huang, Qiang Shen, Timothy Q. Duong

.. Rectal temperature was maintained at 37.0 °C ± 0.5 °C using a circulating warm-water pad throughout the experiments. Heart rate, respiratory rate and blood oxygen saturation level were monitored using MouseOx system (STARR Life Science, Oakmont, PA, USA). ...

Diffusional kurtosis imaging (DKI), which measures the non-Gaussianity of water diffusion, has been demonstrated to be a sensitive biomarker in many neuropathologies. The goal of this study was to longitudinally examine the spatiotemporal dynamics of DKI in cerebral ischemia in an animal model of permanent and transient (45 min) middle cerebral artery occlusion (MCAO) during the hyperacute, acute and chronic phases. Diffusional kurtosis showed different spatiotemporal dynamics. In particular, mean kurtosis (MK) was sensitive to hyperacute and acute stroke changes, and exhibited different contrast than mean

diffusivity (MD) and higher contrast than fractional anisotropy (FA) and T2. MK contrast persisted 1 to 7 days post-occlusion, whereas MD showed renormalization at day 1–2 and reversed contrast at day 7. The current study showed that DKI has the potential to complement existing stroke imaging techniques, particularly in the assessment of subacute to early chronic stroke evolution.

Fatal breathing dysfunction in a mouse model of Leigh syndrome

http://www.jci.org/articles/view/62923#sd

Wednesday, April 18, 2012

Albert Quintana, Sebastien Zanella, Henner Koch, Shane E. Kruse, Donghoon Lee, Jan M. Ramirez and Richard D. Palmiter

Leigh syndrome (LS) is a subacute necrotizing encephalomyelopathy with gliosis in several brain regions that usually results in infantile death. Loss of murine Ndufs4, which encodes NADH dehydrogenase (ubiquinone) iron-sulfur protein 4, results in compromised activity of mitochondrial complex I as well as progressive neurodegenerative and behavioral changes that resemble LS. Here, we report the development of breathing abnormalities in a murine model of LS. Magnetic resonance imaging revealed hyperintense bilateral lesions in the dorsal brain stem vestibular nucleus (VN) and cerebellum of severely affected mice. The mutant mice manifested a progressive increase in apnea and had aberrant responses to hypoxia. Electrophysiological recordings within the ventral brain stem pre-Bötzinger respiratory complex were also abnormal. Selective inactivation of Ndufs4 in the VN, one of the principle sites of gliosis, also led to breathing abnormalities and premature death. Conversely, Ndufs4 restoration in the VN corrected breathing deficits and prolonged the life span of knockout mice. These data demonstrate that mitochondrial dysfunction within the VN results in aberrant regulation of respiration and contributes to the lethality of Ndufs4-knockout mice.

Vitamin D Deficiency Exacerbates Experimental Stroke Injury and Dysregulates Ischemia-Induced Inflammation in Adult Rats

http://endo.endojournals.org/content/153/5/2420.short

Friday, March 9, 2012

Robyn Balden, Amutha Selvamani and Farida Sohrabji

Vitamin D deficiency (VDD) is widespread and considered a risk factor for cardiovascular disease and stroke. Low vitamin D levels are predictive for stroke and more fatal strokes in humans, whereas vitamin D supplements are associated with decreased risk of all-cause mortality. Because VDD occurs with other comorbid conditions that are also independent risk factors for stroke, this study examined the specific effect of VDD on stroke severity in rats. Adult female rats were fed control or VDD diet for 8 wk and were subject to middle cerebral artery occlusion thereafter. The VDD diet reduced circulating vitamin D levels to one fifth (22%) of that observed in rats fed control chow. Cortical and striatal infarct volumes in animals fed VDD diet were significantly larger, and sensorimotor behavioral testing indicated that VDD animals had more severe

poststroke behavioral impairment than controls. VDD animals were also found to have significantly lower levels of the neuroprotective hormone IGF-I in plasma and the ischemic hemisphere. Cytokine analysis indicated that VDD significantly reduced IL-1α, IL-1β, IL-2, IL-4, IFN-γ, and IL-10 expression in ischemic brain tissue. However, ischemia-induced IL-6 up-regulation was significantly higher in VDD animals. In a separate experiment, the therapeutic potential of acute vitamin D treatments was evaluated, where animals received vitamin D injections 4 h after stroke and every 24 h thereafter. Acute vitamin D treatment did not improve infarct volume or behavioral performance. Our data indicate that VDD exacerbates stroke severity, involving both a dysregulation of the inflammatory response as well as suppression of known neuroprotectants such as IGF-I.

An Antagomir to MicroRNA Let7f Promotes Neuroprotection in an Ischemic Stroke Model

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0032662

Wednesday, February 29, 2012

Amutha Selvamani, Pratheesh Sathyan, Rajesh C. Miranda, Farida Sohrabji

We previously showed that middle-aged female rats sustain a larger infarct following experimental stroke as compared to younger female rats, and paradoxically, estrogen treatment to the older group is neurotoxic. Plasma and brain insulin-like growth factor-1 (IGF-1) levels decrease with age. However, IGF-1 infusion following stroke, prevents estrogen neurotoxicity in middle-aged female rats. IGF1 is neuroprotective and well tolerated, but also has potentially undesirable side effects. We hypothesized that microRNAs (miRNAs) that target the IGF-1 signaling family for translation repression could be alternatively suppressed to promote IGF-1-like neuroprotection. Here, we report that two conserved IGF pathway regulatory microRNAs, Let7f and miR1, can be inhibited to mimic and even extend the neuroprotection afforded by IGF-1. Anti-mir1 treatment, as late as 4 hours following ischemia, significantly reduced cortical infarct volume in adult female rats, while anti-Let7 robustly reduced both cortical and striatal infarcts, and preserved sensorimotor function and interhemispheric neural integration. No neuroprotection was observed in animals treated with a brain specific miRNA unrelated to IGF-1 (anti-miR124). Remarkably, anti-Let7f was only effective in intact females but not males or ovariectomized females indicating that the gonadal steroid environment critically modifies miRNA action. Let7f is preferentially expressed in microglia in the ischemic hemisphere and confirmed in ex vivo cultures of microglia obtained from the cortex. While IGF-1 was undetectable in microglia harvested from the non-ischemic hemisphere, IGF-1 was expressed by microglia obtained from the ischemic cortex and was further elevated by anti-Let7f treatment. Collectively these data support a novel miRNA-based therapeutic strategy for neuroprotection following stroke.

Developmental traumatic brain injury decreased brain derived neurotrophic factor expression late after injury

http://www.springerlink.com/content/4167683584712657/

Wednesday, February 1, 2012

Michelle Elena Schober, Benjamin Block, Daniela F. Requena, Merica A. Hale and Robert H. Lane

Abstract

Pediatric traumatic brain injury (TBI) is a major cause of acquired cognitive dysfunction in children. Hippocampal Brain Derived Neurotrophic Factor (BDNF) is important for normal cognition. Little is known about the effects of TBI on BDNF levels in the developing hippocampus. We used controlled cortical impact (CCI) in the 17 day old rat pup to test the hypothesis that CCI would first increase rat hippocampal BDNF mRNA/protein levels relative to SHAM and Naïve rats by post injury day (PID) 2 and then decrease BDNF mRNA/protein by PID14. Relative to SHAM, CCI did not change BDNF mRNA/protein levels in the injured hippocampus in the first 2 days after injury but did decrease BDNF protein at PID14. Surprisingly, BDNF mRNA decreased at PID 1, 3, 7 and 14, and BDNF protein decreased at PID 2, in SHAM and CCI hippocampi relative to Naïve. In conclusion, TBI decreased BDNF protein in the injured rat pup hippocampus 14 days after injury. BDNF mRNA levels decreased in both CCI and SHAM hippocampi relative to Naïve, suggesting that certain aspects of the experimental paradigm (such as craniotomy, anesthesia, and/or maternal separation) may decrease the expression of BDNF in the developing hippocampus. While BDNF is important for normal cognition, no inferences can be made regarding the cognitive impact of any of these factors. Such findings, however, suggest that meticulous attention to the experimental paradigm, and possible inclusion of a Naïve group, is warranted in studies of BDNF expression in the developing brain after TBI.

Neuroimaging Assessment of Traumatic Brain Injury

http://www.springerlink.com/content/k5495841q7510001/#section=1072448&page=1

Sunday, January 1, 2012

Janna L. Harris and William M. Brooks

... Instruments Inc; CWE Inc). An MR-compatible pulse oximeter (eg, Starr Life Sciences)

can also be used to monitor blood oxygenation as well as heart rate and breathing

rate during scanning. Although in vivo neuroimaging ...

Postnatal morphine administration alters hippocampal development in rats

http://onlinelibrary.wiley.com/doi/10.1002/jnr.22750/full

Tuesday, October 4, 2011

Christopher M. Traudt, Ivan Tkac, Kathleen M. Ennis, Leah M. Sutton, Daniel M. Mammel, Raghavendra Rao

Abstract

Morphine is frequently used as an analgesic and sedative in preterm infants. Adult rats exposed to morphine have an altered hippocampal neurochemical profile and decreased neurogenesis in the dentate gyrus of the hippocampus. To evaluate whether neonatal rats are similarly affected, rat pups were injected twice daily with 2 mg/kg morphine or normal saline from postnatal days 3 to 7. On postnatal day 8, the hippocampal neurochemical profile was determined using in vivo 1H NMR spectroscopy. The mRNA and protein concentrations of specific analytes were measured in hippocampus, and cell division in dentate gyrus was assessed using bromodeoxyuridine. The concentrations of γ-aminobutyric acid (GABA), taurine, and myo-insotol were decreased, whereas concentrations of glutathione, phosphoethanolamine, and choline-containing compounds were increased in morphine-exposed rats relative to control rats. Morphine decreased glutamic acid decarboxylase enzyme levels and myelin basic protein mRNA expression in the hippocampus. Bromodeoxyuridine labeling in the dentate gyrus was decreased by 60–70% in morphine-exposed rats. These results suggest that recurrent morphine administration during brain development alters hippocampal structure.

Critically ill preterm infants are frequently treated with prolonged courses of opiates to decrease pain and stress (Anand et al.,2004). The efficacy of such treatment is debated, but the clinical practice persists (Franck et al.,2000; Simons et al.,2003; Carbajal et al.,2005; Cignacco et al.,2008), because the effects of untreated pain are well established (Anand,2000; Duric and McCarson,2006). There are increasing concerns that opiates may have detrimental effects on neurodevelopmental outcomes. Neonatal morphine treatment with and without stress is associated with short-term changes in gene expression and cellular composition in the hippocampus (Vien et al.,2009; Juul et al.,2011) and long-term neurobehavioral deficits in rodents (McPherson et al.,2007; Boasen et al.,2009).

In adult rats, the neurochemical profile of the hippocampus is altered during morphine administration (Corrigall,1983; Simonato,1996; Gao et al.,2007), and hippocampus-mediated learning is impaired (Spain and Newsom,1991; Bhutta et al.,2001), possibly because of decreased neurogenesis in the dentate gyrus of the hippocampus (Eisch et al.,2000; Lledo et al.,2006).

To evaluate the safety of morphine for sedation in the absence of pain, we used a neonatal rat model of morphine administration (McPherson et al.,2007). We hypothesized that neonatal morphine administration would alter the neurochemical profile of the developing hippocampus and decrease neurogenesis in the dentate gyrus. The metabolites indexing neuronal and glial integrity, energy substrates and energy sufficiency, phospholipid biosynthesis, and amino acids and neurotransmitters in the developing hippocampus were assessed using high-field in vivo 1H NMR spectroscopy, followed by evaluation of mRNA and protein expression of relevant analytes in the hippocampus. We assessed cell proliferation in the dentate gyrus using bromodeoxyuridine (BrdU) histochemistry and found that rat pups exposed to recurrent morphine administration had an altered neurochemical profile, decreased glutamic acid decarboxylase (GAD) and myelin basic protein (MBP) expressions in the hippocampus, and decreased incorporation of BrdU in the dentate gyrus.

Respiratory function following bilateral mid-cervical contusion injury in the adult rat

http://www.sciencedirect.com/science/article/pii/S0014488611003323

Wednesday, September 21, 2011

Michael A. Lanea, Kun-Ze Leeb, Krystal Salazara, Barbara E. O'Steena, David C. Bloomc, David D. Fullerb, Paul J. Reiera

Abstract

The consequences of spinal cord injury (SCI) are often viewed as the result of white matter damage. However, injuries occurring at any spinal level, especially in cervical and lumbar enlargement regions, also entail segmental neuronal loss. Yet, the contributions of gray matter injury and plasticity to functional outcomes are poorly understood. The present study addressed this issue by investigating changes in respiratory function following bilateral C3/C4 contusion injuries at the level of the phrenic motoneuron (PhMN) pool which in the adult rat extends from C3 to C5/6 and provides innervation to the diaphragm. Despite extensive white and gray matter pathology associated with two magnitudes of injury severity, ventilation was relatively unaffected during both quiet breathing and respiratory challenge (hypercapnia). On the other hand, bilateral diaphragm EMG recordings revealed that the ability to increase diaphragm activity during respiratory challenge was substantially, and chronically, impaired. This deficit has not been seen following predominantly white matter lesions at higher cervical levels. Thus, the impact of gray matter damage relative to PhMNs and/or interneurons becomes evident during conditions associated with increased respiratory drive. Unaltered ventilatory behavior, despite significant deficits in diaphragm function, suggests compensatory neuroplasticity involving recruitment of other spinal respiratory networks which may entail remodeling of connections. Transynaptic tracing, using pseudorabies virus (PRV), revealed changes in PhMN-related interneuronal labeling rostral to the site of injury, thus offering insight into the potential anatomical reorganization and spinal plasticity following cervical contusion.

Abbreviations

BDA, biotin dextran amine; C#, spinal cervical segment #; C2Hx, C2 lateral hemisection; CPP, crossed-phrenic phenomenon; diaEMG, diaphragm electromyography; f, breathing frequency; KD, kilodynes; PEF, peak expiratory flow; PhMN, phrenic motoneuron; PIF, peak inspiratory flow; PRV, pseudorabies virus; SpO2, blood oxygen saturation; E, minute ventilation; VRC, ventral respiratory column; VT, tidal volume

Keywords

Spinal cord injury; Respiration; Plasticity; Interneuron; Pseudorabies virus; Contusion

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MeCP2 Is Critical within HoxB1-Derived Tissues of Mice for Normal Lifespan

http://www.neuro.cjb.net/content/31/28/10359.short

Wednesday, July 13, 2011

Christopher S. Ward, E. Melissa Arvide, Teng-Wei Huang, Jong Yoo, Jeffrey L. Noebels and Jeffrey L. Neul

Abstract

Rett syndrome is a neurodevelopmental disorder caused by mutations in methyl-CpG-binding protein 2 (MECP2), a transcriptional regulator. In addition to cognitive, communication, and motor problems, affected individuals have abnormalities in autonomic function and respiratory control that may contribute to premature lethality. Mice lacking Mecp2 die early and recapitulate the autonomic and respiratory phenotypes seen in humans. The association of autonomic and respiratory deficits with premature death suggests that Mecp2 is critical within autonomic and respiratory control centers for survival. To test this, we compared the autonomic and respiratory phenotypes of mice with a null allele of Mecp2 to mice with Mecp2 removed from their brainstem and spinal cord. We found that MeCP2 is necessary within the brainstem and spinal cord for normal lifespan, normal control of heart rate, and respiratory response to hypoxia. Restoration of MeCP2 in a subset of the cells in this same region is sufficient to rescue abnormal heart rate and abnormal respiratory response to hypoxia. Furthermore, restoring MeCP2 function in neural centers critical for autonomic and respiratory function alleviates the lethality associated with loss of MeCP2 function, supporting the notion of targeted therapy toward treating Rett syndrome.

Perlecan domain V is neuroprotective and proangiogenic following ischemic stroke in rodents

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3148740/

Monday, July 11, 2011

Boyeon Lee, Douglas Clarke, Abraham Al Ahmad, Michael Kahle, Christi Parham, Lisa Auckland, Courtney Shaw, Mehmet Fidanboylu, Anthony Wayne Orr, Omolara Ogunshola, Andrzej Fertala, Sarah A. Thomas, and Gregory J. Bix

Abstract

Stroke is the leading cause of long-term disability and the third leading cause of death in the United States. While most research thus far has focused on acute stroke treatment and neuroprotection, the exploitation of endogenous brain self-repair mechanisms may also yield therapeutic strategies. Here, we describe a distinct type of stroke treatment, the naturally occurring extracellular matrix fragment of perlecan, domain V, which we found had neuroprotective properties and enhanced post-stroke angiogenesis, a key component of brain repair, in rodent models of stroke. In both rat and mouse models, Western blot analysis revealed elevated levels of perlecan domain V. When systemically administered 24 hours after stroke, domain V was well tolerated, reached infarct and peri-infarct brain vasculature, and restored stroke-affected motor function to baseline pre-stroke levels in these multiple stroke models in both mice and rats. Post-stroke domain V administration increased VEGF levels via a mechanism involving brain endothelial cell α5β1 integrin, and the subsequent neuroprotective and angiogenic actions of domain V were in turn mediated via VEGFR. These results suggest that perlecan domain V represents a promising approach for stroke treatment.

Early and Sustained Increase in the Expression of Hippocampal IGF-1, But Not EPO, in a Developmental Rodent Model of Traumatic Brain Injury

http://online.liebertpub.com/doi/abs/10.1089/neu.2009.1226

Thursday, November 18, 2010

Michelle E. Schober, Benjamin Block, Joanna C. Beachy, Kimberly D. Statler, Christopher C. Giza, and Robert H. Lane

Abstract

Pediatric traumatic brain injury (pTBI) is the leading cause of traumatic death and disability in children in the United States. Impaired learning and memory in these young survivors imposes a heavy toll on society. In adult TBI (aTBI) models, cognitive outcome improved after administration of erythropoietin (EPO) or insulin-like growth factor-1 (IGF-1). Little is known about the production of these agents in the hippocampus, a brain region critical for learning and memory, after pTBI. Our objective was to describe hippocampal expression of EPO and IGF-1, together with their receptors (EPOR and IGF-1R, respectively), over time after pTBI in 17-day-old rats. We used the controlled cortical impact (CCI) model and measured hippocampal mRNA levels of EPO, IGF-1, EPOR, IGF-1R, and markers of caspase-dependent apoptosis (bcl2, bax, and p53) at post-injury days (PID) 1, 2, 3, 7, and 14. CCI rats performed poorly on Morris water maze testing of spatial working memory, a hippocampally-based cognitive function. Apoptotic markers were present early and persisted for the duration of the study. EPO in our pTBI model increased much later (PID7) than in aTBI models (12 h), while EPOR and IGF -1 increased at PID1 and PID2, respectively, similar to data from aTBI models. Our data indicate that EPO expression showed a delayed upregulation post-pTBI, while EPOR increased early. We speculate that administration of EPO in the first 1–2 days after pTBI would increase hippocampal neuronal survival and function.

The pathobiology of blast injuries and blast-induced neurotrauma as identified using a new experimental model of injury in mice

http://www.sciencedirect.com/science/article/pii/S0969996110003682

Thursday, November 11, 2010

Ibolja Cernaka, Andrew C. Merklea, Vassilis E. Koliatsosb, Justin M. Bilika, Quang T. Luonga, Theresa M. Mahotaa, Leyan Xub, Nicole Slacka, David Windlea, Farid A. Ahmeda

Abstract

Current experimental models of blast injuries used to study blast-induced neurotrauma (BINT) vary widely, which makes the comparison of the experimental results extremely challenging. Most of the blast injury models replicate the ideal Friedländer type of blast wave, without the capability to generate blast signatures with multiple shock fronts and refraction waves as seen in real-life conditions; this significantly reduces their clinical and military relevance. Here, we describe the pathophysiological consequences of graded blast injuries and BINT generated by a newly developed, highly controlled, and reproducible model using a modular, multi-chamber shock tube capable of tailoring pressure wave signatures and reproducing complex shock wave signatures seen in theater. While functional deficits due to blast exposure represent the principal health problem for today's warfighters, the majority of available blast models induces tissue destruction rather

than mimic functional deficits. Thus, the main goal of our model is to reliably reproduce long-term neurological impairments caused by blast. Physiological parameters, functional (motor, cognitive, and behavioral) outcomes, and underlying molecular mechanisms involved in inflammation measured in the brain over the 30 day post-blast period showed this model is capable of reproducing major neurological changes of clinical BINT.

Astrocyte targeted overexpression of Hsp72 or SOD2 reduces neuronal vulnerability to forebrain ischemia

http://onlinelibrary.wiley.com/doi/10.1002/glia.20985/abstract

Tuesday, March 16, 2010

Lijun Xu, John F. Emery, Yi-Bing Ouyang, Ludmila A. Voloboueva, Rona G. Giffard

Abstract

Brief forebrain ischemia is a model of the delayed hippocampal neuronal loss seen in patients following cardiac arrest and resuscitation. Previous studies demonstrated that selective dysfunction of hippocampal CA1 subregion astrocytes occurs hours to days before delayed neuronal death. In this study we tested the strategy of directing protection to astrocytes to protect neighboring neurons from forebrain ischemia. Two well-studied protective proteins, heat shock protein 72 (Hsp72) or superoxide dismutase 2 (SOD2), were genetically targeted for expression in astrocytes using the astrocyte-specific human glial fibrillary acidic protein (GFAP) promoter. The expression constructs were injected stereotacticly immediately above the hippocampal CA1 region on one side of the rat brain two days prior to forebrain ischemia. Cell type specific expression was confirmed by double label immunohistochemistry. When the expression constructs were injected two days before transient forebrain ischemia, the loss of CA1 hippocampal neurons observed seven days later was significantly reduced on the injected side compared with controls. This neuroprotection was associated with significantly better preservation of astrocyte glutamate transporter-1 immunoreactivity at 5-h reperfusion and reduced oxidative stress. Improving the resistance of astrocytes to ischemic stress by targeting either the cytosolic or mitochondrial compartment was thus associated with preservation of CA1 neurons following forebrain ischemia. Targeting astrocytes is a promising strategy for neuronal preservation following cardiac arrest and resuscitation. © 2010 Wiley-Liss, Inc.

Recombinant Fv-Hsp70 Protein Mediates Neuroprotection After Focal Cerebral Ischemia in Rats

http://stroke.ahajournals.org/content/41/3/538.abstract

Thursday, January 14, 2010

Xinhua Zhan, MD, PhD; Bradley P. Ander, PhD; Isaac H. Liao, BS; James E. Hansen, MD; Chester Kim; Douglas Clements, BS; Richard H. Weisbart, MD; Robert N. Nishimura, MD; Frank R. Sharp, MD

Abstract

Background and Purpose— This study investigated the effects of intravenous recombinant Fv-Hsp70 protein on infarction volume and behavior after experimental ischemic stroke.

Methods— Focal cerebral ischemia was produced by occluding the middle cerebral artery using the intraluminal suture technique. Rats subjected to 2 hours of focal ischemia were allowed to survive 24 hours. At 2¼ hours and 3 hours after onset of ischemia, Fv-Hsp70 recombinant protein (0.5 mg/kg) or saline was injected through the tail vein. Sensorimotor function and infarction volume were assessed at 24 hours after ischemia.

Results— Administration of Fv-Hsp70 after focal cerebral ischemia significantly decreased infarct volume by 68% and significantly improved sensorimotor function compared with the saline-treated control group. Western blots showed Fv-Hsp70 in ischemic but not in control brain; and Fv-Hsp70 suppressed endogenous Hsp70.

Conclusion— Fv-Hsp70 protected the ischemic brain in this experimental stroke model.

Key Words:

Antibody, behavior, Fv, Hsp70, ischemic stroke, rat, recombinant protein

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Novel Model of Frontal Impact Closed Head Injury in the Rat

http://online.liebertpub.com/doi/abs/10.1089/neu.2009.0968

Wednesday, December 23, 2009

Michael Kilbourne, Reed Kuehn, Cigdem Tosun, John Caridi, Kaspar Keledjian, Grant Bochicchio, Thomas Scalea, Volodymyr Gerzanich, and J. Marc Simard

Abstract

Frontal impact, closed head trauma is a frequent cause of traumatic brain injury (TBI) in motor vehicle and sports accidents. Diffuse axonal injury (DAI) is common in humans and experimental animals, and results from shearing forces that develop within the anisotropic brain. Because the specific anisotropic properties of the brain are axis-dependent, the anatomical site where force is applied as well as the resultant acceleration, be it linear, rotational, or some combination, are important determinants of the resulting pattern of brain injury. Available rodent models of closed head injury do not reproduce the frontal impact commonly encountered in humans. Here we describe a new rat model of closed head injury that is a modification of the impact-acceleration model of Marmarou. In our model (the Maryland model), the impact force is applied to the anterior part of the cranium and produces TBI by causing anterior-posterior plus sagittal rotational acceleration of the brain inside the intact cranium. Skull fractures, prolonged apnea, and mortality were absent. The animals exhibited petechial hemorrhages, DAI marked by a bead-like pattern of β-amyloid precursor protein (β-APP) in damaged axons, and widespread upregulation of β-APP in neurons, with regions affected including the orbitofrontal cortex (coup), corpus callosum, caudate, putamen, thalamus, cerebellum,

and brainstem. Activated caspase-3 was prominent in hippocampal neurons and Purkinje cells at the grey-white matter junction of the cerebellum. Neurobehavioral dysfunction, manifesting as reduced spontaneous exploration, lasted more than 1 week. We conclude that the Maryland model produces diffuse injuries that may be relevant to human brain injury.

Biphasic direct current shift, haemoglobin desaturation and neurovascular uncoupling in cortical spreading depression

http://brain.oxfordjournals.org/content/133/4/996.abstract

Sunday, December 13, 2009

Joshua C. Chang, Lydia L. Shook, Jonathan Biag, Elaine N. Nguyen, Arthur W. Toga, Andrew C. Charles and Kevin C. Brennan

Summary

Cortical spreading depression is a propagating wave of depolarization that plays important roles in migraine, stroke, subarachnoid haemorrhage and brain injury. Cortical spreading depression is associated with profound vascular changes that may be a significant factor in the clinical response to cortical spreading depression events. We used a combination of optical intrinsic signal imaging, electro-physiology, potassium sensitive electrodes and spectroscopy to investigate neurovascular changes associated with cortical spreading depression in the mouse. We identified two distinct phases of altered neurovascular function, one during the propagating cortical spreading depression wave and a second much longer phase after passage of the wave. The direct current shift associated with the cortical spreading depression wave was accompanied by marked arterial constriction and desaturation of cortical haemoglobin. After recovery from the initial cortical spreading depression wave, we observed a second phase of prolonged, negative direct current shift, arterial constriction and haemoglobin desaturation, lasting at least an hour. Persistent disruption of neurovascular coupling was demonstrated by a loss of coherence between electro-physiological activity and perfusion. Extracellular potassium concentration increased during the cortical spreading depression wave, but recovered and remained at baseline after passage of the wave, consistent with different mechanisms underlying the first and second phases of neurovascular dysfunction. These findings indicate that cortical spreading depression is associated with a multiphasic alteration in neurovascular function, including a novel second direct current shift accompanied by arterial constriction and decrease in tissue oxygen supply, that is temporally and mechanistically distinct from the initial propagated cortical spreading depression wave. Vascular/metabolic uncoupling with cortical spreading depression may have important clinical consequences, and the different phases of dysfunction may represent separate therapeutic targets in the disorders where cortical spreading depression occurs.

Key words

spreading depression haemoglobin neurovascular coupling migraine stroke

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Nimodipine Prevents Memory Impairment Caused by Nitroglycerin-Induced Hypotension in Adult Mice

http://www.anesth-analg.net/content/109/6/1943.abstract

Tuesday, December 1, 2009

Alex Bekker, MD, PhD*, Michael Haile, MD*, Yong-Sheng Li, MD†, Samuel Galoyan, PhD*, Edwardo Garcia, BS, BE*, David Quartermain, PhD†, Angela Kamer, DDS, PhD‡ and Thomas Blanck, MD, PhD*

Abstract

BACKGROUND: Hypotension and a resultant decrease in cerebral blood flow have been implicated in the development of cognitive dysfunction. We tested the hypothesis that nimodipine (NIMO) administered at the onset of nitroglycerin (NTG)-induced hypotension would preserve long-term associative memory.

METHODS: The passive avoidance (PA) paradigm was used to assess memory retention. For PA training, latencies (seconds) were recorded for entry from a suspended platform into a Plexiglas tube where a shock was automatically delivered. Latencies were recorded 48 h later for a testing trial. Ninety-six Swiss-Webster mice (30–35 g, 6–8 wk), were randomized into 6 groups 1) saline (control), 2) NTG immediately after learning, 3) NTG 3 h after learning, 4) NTG and NIMO, 5) vehicle, and 6) NIMO alone. The extent of hypotension and changes in brain tissue oxygenation (PbtO2) and in cerebral blood flow were studied in a separate group of animals.

RESULTS: All groups exhibited similar training latencies (17.0 ± 4.6 s). Mice subjected to hypotensive episodes showed a significant decrease in latency time (178 ± 156 s) compared with those injected with saline, NTG + NIMO, or delayed NTG (580 ± 81 s, 557 ± 67 s, and 493 ± 146 s, respectively). A Kruskal-Wallis 1-way analysis of variance indicated a significant difference among the 4 treatment groups ($H = 15.34$; $P < 0.001$). In a separate group of mice not subjected to behavioral studies, the same dose of NTG ($n = 3$) and NTG + NIMO ($n = 3$) caused mean arterial blood pressure to decrease from 85.9 ± 3.8 mm Hg sem to 31.6 ± 0.8 mm Hg sem and from 86.2 ± 3.7 mm Hg sem to 32.6 ± 0.2 mm Hg sem, respectively. Mean arterial blood pressure in mice treated with NIMO alone decreased from 88.1 ± 3.8 mm Hg to 80.0 ± 2.9 mm Hg. The intergroup difference was statistically significant ($P < 0.05$). PbtO2 decreased from 51.7 ± 4.5 mm Hg sem to 33.8 ± 5.2 mm Hg sem in the NTG group and from 38.6 ± 6.1 mm Hg sem to 25.4 ± 2.0 mm Hg sem in the NTG + NIMO groups, respectively. There were no significant differences among groups.

CONCLUSION: In a PA retention paradigm, the injection of NTG immediately after learning produced a significant impairment of long-term associative memory in mice, whereas delayed induced hypotension had no effect. NIMO attenuated the disruption in consolidation of long-term memory caused by NTG but did not improve latency in the absence of hypotension. The observed effect of NIMO may have been attributable to the preservation of calcium homeostasis during hypotension, because there were no differences in the PbtO2 indices among groups.

Reversible Cyclosporin A-sensitive Mitochondrial Depolarization Occurs within Minutes of Stroke Onset in Mouse Somatosensory Cortex in Vivo A TWO-PHOTON IMAGING STUDY*

http://www.jbc.org/content/284/52/36109.short

Thursday, November 5, 2009

Ran R. Liu and Timothy H. Murphy

Abstract

Neuronal structure and function are rapidly damaged during global ischemia but can in part recover during reperfusion. Despite apparent recovery in the hours/days following an ischemic episode, delayed cell death can be initiated, making it important to understand how initial ischemic events affect potential mediators of apoptosis. Mitochondrial dysfunction and the opening of the mitochondrial permeability transition pore (mPTP) are proposed to link ischemic ionic imbalance to mitochondrially mediated cell death pathways. Using two-photon microscopy, we monitored mitochondrial transmembrane potential (Δψm) in vivo within the somatosensory cortex during ischemia and reperfusion in a mouse global ischemia model. Our results indicated a synchronous loss of Δψm within 1–3 min of ischemic onset that was linked to within seconds of plasma membrane potential (Δψp) depolarization. Δψm recovered rapidly upon reperfusion, and no delayed depolarization was observed over 2 h. Cyclosporin A treatment largely blocked Δψm collapse during ischemia, suggesting a role for the mPTP. Blocking Δψm depolarization did not affect structural damage to dendrites, indicating that the opening of the mPTP and damage to dendrites are separable pathways that are activated during Δψp depolarization. Our findings using in vivo imaging suggest that mitochondrial dysfunction and specifically the activation of the mPTP are early reversible events during brain ischemia that could trigger delayed cell death.

Postischemic Brain Injury Is Attenuated in Mice Lacking the β2-Adrenergic Receptor

http://www.anesth-analg.org/content/108/1/280.abstract

Thursday, January 1, 2009

Ru-Quan Han, MD, PhD*†, Yi-Bing Ouyang, PhD*, Lijun Xu, MD*, Rani Agrawal, PhD*, Andrew J. Patterson, MD, PhD* and Rona G. Giffard, MD, PhD*

Abstract
BACKGROUND: Several β-adrenergic receptor (βAR) antagonists have been shown to have neuroprotective effects against cerebral ischemia. However, clenbuterol, a β2AR agonist, was shown to have neuroprotective activity by increasing nerve growth factor expression. We used β2AR knockout mice and a β2selective antagonist to test the effect of loss of β2ARs on outcome from transient focal cerebral ischemia.
METHODS: Ischemia was induced by the intraluminal suture method, for 60 min of middle cerebral artery occlusion (MCAO) followed by 24 h reperfusion. Neurological score was determined at 24 h reperfusion and infarct size was determined by cresyl violet or 2,3,5-triphenyltetrazolium chloride staining. β2AR knockout mice and wild-type congenic FVB/N controls were studied, as well as 2 groups of wild type mice given either ICI 118,551 (0.2 mg/kg) or 0.9% saline intraperitoneally 30 min before MCAO (n = 10 per group). Changes in expression of heat shock protein (Hsp)72 after ischemia were examined by immunohistochemistry and western blots.
RESULTS: Compared with wild type littermates, infarct volume was decreased by 22.3% in β2AR knockout

mice (39.7 ± 10.7 mm3 vs 51.0 ± 11.4 mm3, *n* = 10/group, *P* = 0.034) after 60 min of MCAO followed by 24 h reperfusion. Pretreatment with a β2AR selective antagonist, ICI 118,551, also decreased infarct size significantly, by 25.1%, compared with the saline control (32.8 ± 11.9 mm3vs 43.8 ± 10.3 mm3, *n* = 10/group, *P* = 0.041). Neurological scores were also significantly improved in mice lacking the β2AR or pretreated with ICI 118,551. After cerebral ischemia, total levels of Hsp72 and the number of Hsp72 immunopositive cells were greater in mice lacking β2 AR.
CONCLUSION: Brain injury is reduced and neurological outcome improved after MCAO in mice lacking the β2AR, or in wild type mice pretreated with a selective β2AR antagonist. This is consistent with a shift away from prosurvival signaling to prodeath signaling in the presence of β2AR activation in cerebral ischemia. Protection is associated with higher levels of Hsp72, a known antideath protein. The effect of β2AR signaling in the setting of cerebral ischemia is complex and warrants further study.

IMPLICATIONS: Brain injury is reduced and neurological outcome improved after middle cerebral artery occlusion in mice lacking the β2AR or in wild type mice pretreated with a selective β2AR antagonist. This is consistent with a shift away from prosurvival signaling to prodeath signaling in the presence of β2AR activation in cerebral ischemia.

Reproductive age modulates the impact of focal ischemia on the forebrain as well as the effects of estrogen treatment in female rats

http://www.neurobiologyofaging.org/article/S0197-4580(08)00301-1/abstract

Wednesday, October 1, 2008

Amutha Selvamani, Farida Sohrabji

Abstract

While human observational studies and animal studies report a neuroprotective role for estrogen therapy in stroke, the multicenter placebo-controlled Women's Health Initiative (WHI) study concluded that hormone therapy increased the risk for stroke in postmenopausal women. The present study therefore tested the hypothesis that estrogen replacement would increase the severity of a stroke-like injury in females when this replacement occurs after a prolonged hypoestrogenic period, such as the menopause or reproductive senescence, but not when given to females that were normally cycling immediately prior to the hormone replacement. Two groups of female rats were used: multiparous females with normal but lengthened estrus cycles (mature adults), and older multiparous females currently in a persistent acyclic state (reproductive senescent). Animals were either used intact, or were bilaterally ovariectomized and immediately replaced with a 17β-estradiol pellet or control pellet. Animals were subject to a forelimb placing test (a test for sensorimotor deficit) and thereafter to middle cerebral artery occlusion (MCAo) by stereotaxic injection of the vasoconstrictive peptide endothelin-1, adjacent to the MCA. One week after stroke, behavioral tests were performed again. Cortical and striatal infarct volume, measured from brain slices, was significantly greater in intact reproductive senescent females as compared to intact mature adults. Furthermore, estrogen treatment to ovariectomized mature adult females significantly reduced the cortical infarct volume. Paradoxically, estrogen treatment to ovariectomized reproductive senescent females significantly increased cortical and striatal infarct volumes as compared to control pellet replaced senescent females. Significant post-stroke behavioral deficit was observed in all groups on the side contralateral to the lesion, while senescent females also exhibited

deficits on the ipsilateral side, in the cross-midline forelimb placement test. Using an animal model that approximates the natural ovarian aging process, these findings strongly support the hypothesis that the effectiveness of estrogen therapy in protecting brain health may depend critically on the time of initiation with respect to a female's reproductive status.

Keywords: 17β-Estradiol, Reproductive senescence, Endothelin-1, Middle cerebral artery occlusion, Stroke, Forelimb placing test

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Hardware and methodology for targeting single brain arterioles for photothrombotic stroke on an upright microscope

http://www.sciencedirect.com/science/article/pii/S0165027008000095

Friday, December 21, 2007

Albrecht Siglera, Alexander Goroshkovc, Timothy H. Murphya

Abstract
Investigators have begun to probe the role of individual surface arterioles in maintaining both the structure and function of cortical regions using vessel-specific clotting by *in vivo* photothrombosis after craniotomy in mice. To induce targeted strokes we describe a simple adaptation of a commercial upright Olympus BX51WI microscope, permitting light from a 532 nm laser to be directed into the back aperture of a high numerical aperture fluorescence objective. The system involves using a filter slot available on an Olympus BX series microscope to direct a collimated laser beam through the normal epifluorescence path to the objective back aperture resulting in focused photoactivation, with lateral and axial dimensions less than 3 and 5 μm, respectively. Existing fluorescence filters and dichroic mirrors are employed permitting one to safely target the green laser beam and view the clotting process based as red epifluorescence, either through the eye pieces or using a CCD camera. Interruption in blood flow can be confirmed using laser speckle microscopy. The positioning of the photothrombotic laser in this manner does not impede subsequent analysis of brain microcirculation using two-photon microscopy or other imaging methods. It is conceivable that this modification and laser system can also be used for other scenarios where targeted photoactivation or photobleaching would be required.

Keywords
Two-photon imaging: Stroke; *In vivo*; Photothrombosis; Dendrite; Neurovascular unit;Speckle imaging;Mouse; Imaging; Ischemia; Intrinisic signal imaging

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- *In vivo*;
- Photothrombosis;
- Dendrite;
- Neurovascular unit;
- Speckle imaging;
- Mouse;
- Imaging;
- Ischemia;
- Intrinisic signal imaging

Vital Signs Monitoring During Imaging

Variations in the temporal pattern of perforant pathway stimulation control the activity in the mesolimbic pathway

http://www.sciencedirect.com/science/article/pii/S1053811912008956
Tuesday, January 1, 2013

Cornelia Helbinga, Grit Wernera, Frank Angenstein

... During the entire stimulation/fMRI experiment, blood oxygen saturation, breathing and heart rate were continuously monitored using a MRI-compatible pulse oxymeter (MouseOx TM, Star Life Sciences Corp. Pittsburgh PA, USA). ...

Signal processing in the hippocampal formation and resultant signal propagation to cortical and subcortical structures during high frequency stimulation (i.e. 100 Hz) of the perforant pathway was studied in medetomidine anesthetized rats by functional magnetic resonance imaging (fMRI) and electrophysiological recordings. The perforant pathway was stimulated with bursts of 20 pulses, one burst per second, or with continuously applied pulses. The stimulation duration was adjusted to 8 s (short) or 30 s (long). In general, extending the stimulation duration only caused a local spreading of the fMRI response, but no changes in the magnitude of the fMRI response. This was in agreement with the electrophysiological responses, which also remained unchanged. In contrast, increasing the number of pulses in one stimulus train (i.e. changing from burst to continuous stimulation), caused both spreading and an increase in local fMRI responses that were accompanied by an altered neuronal response pattern. Continuous stimulation also triggered additional fMRI responses in the septum, nucleus accumbens, anterior cingulate cortex/medial prefrontal cortex, and ventral tegmental area/substantia nigra. The appearance of fMRI responses outside the hippocampal formation required at least 3 consecutive stimulation trains, characterized by region specific hemodynamic response functions. Thus, once triggered, continuous stimulation caused a sequential appearance in fMRI responses starting in the hippocampal formation, followed by signal changes in the ventral tegmental area/substantia nigra and anterior cingulate cortex/medial prefrontal cortex and eventually in the nucleus accumbens. These results indicate that high frequency stimulation of the hippocampal formation can activate the mesolimbic pathway, provided that repetitive stimulations are applied.

Blood flow and anatomical MRI in a mouse model of retinitis pigmentosa

http://onlinelibrary.wiley.com/doi/10.1002/mrm.24232/full
Tuesday, January 1, 2013

Eric R. Muir, Bryan De La Garza, Timothy Q. Duong

.. 37 ± 0.5°C via a circulating warm water pad. Respiration rate, heart rate, and oxygen saturation were continuously monitored (MouseOx, STARR Life Science Corp., Oakmont, PA). MRI. MRI studies were performed on a 7 T, 30 ...

This study tested the sensitivity of an arterial spin labeling MRI method to image changes in retinal and choroidal blood flow (BF) and anatomical thickness of the retina in the rd10 mouse model of retinitis pigmentosa. High-resolution (42 × 42 μm) MRI was performed on rd10 mice and age-matched controls at 25, 35, and 60 days of age (n = 6 each group) on a 7-T scanner. Anatomical MRI was acquired, and quantitative BF was imaged using arterial spin labeling MRI with a separate cardiac labeling coil. Histology was obtained to confirm thickness changes in the retina. In control mice, the retinal and choroidal vascular layers were quantitatively resolved. In rd10 mice, retinal BF decreased progressively over time, while choroidal BF was unchanged. The rd10 retina became progressively thinner at later time points compared with age-matched controls by anatomical MRI and histology ($P < 0.01$). BF and anatomical MRI were capable of detecting decreased BF and thickness in the rd10 mouse retina. Because BF is tightly coupled to metabolic function, BF MRI has the potential to noninvasively assess retinal diseases in which metabolism and function are perturbed and to evaluate novel treatments, complementing existing retinal imaging techniques. Magn Reson Med, 2013. © 2012 Wiley Periodicals, Inc.
Retinitis pigmentosa (RP) is a group of inherited retinal diseases which cause retinal degeneration and vision loss, affecting 1.5 million people worldwide (1). It is characterized initially by a progressive loss of photoreceptors, with secondary deterioration of vascular and other cell layers (2). Most RP patients undergo a preliminary loss of

peripheral vision and impaired night vision because rods are usually affected first. Secondary degeneration, usually including loss of cones, follows, resulting in the loss of central visual field, color vision, and potentially complete blindness (1). A large number of mutations in various genes which cause RP have been described, including the genes for rhodopsin, mertk, and phosphodiesterase ß (2–4).
The rd10 mouse is an established animal model of RP (5–7). rd10 mice have a mutation in the Pde6b gene, encoding a subunit of the rod phosphodiesterase (5, 6). Mutations in the gene for the ß subunit of the rod phosphodiesterase have been found in human autosomal recessive RP (3). The mutation in the Pde6b gene causes deficient activity of the rod phosphodiesterase, which results in the accumulation of cyclic GMP and death of rod cells (6). Based on histological data, retinal degeneration begins in rd10 mice about postnatal 16 days, and the outer nuclear layer and inner and outer segments completely degenerate by 60 days of age (6, 7). Degeneration of the outer retina begins first with loss of rods, with cone loss and remodeling of the inner retina occurring later (7).
Although the genetic aspects and thickness changes of RP are well studied, the lack of noninvasive, depth-resolved imaging techniques has limited the investigation of physiologic changes associated with retinal degeneration in vivo. Clinical examinations of RP include digital fundus photography using the seven stereo fields (8), full-field electroretinography (4), Goldmann visual field with V4e test object, and optical coherence tomography of the macula and optic disc and macular thickness (4). Many potential treatments (9), including vitamin A supplementation, intravitreal administration of growth factors (10), neuroprotective drugs (11), hyperoxia (12), gene therapy (13), and stem cell therapy (14), show potential to slow, halt, or reverse retinal degeneration. Noninvasive imaging technologies that can pinpoint layer-specific cellular and vascular changes may enable longitudinal staging of RP, objective measures of therapeutic interventions, and improved understanding of disease processes in vivo.
Vascular changes occur secondary to photoreceptor loss in RP (14–16), with atrophy of the retinal (14, 15) and choroidal (17) vasculature. Histological studies showed leakage in the retinal vessels in Royal College of Surgeons (a model of RP) rats by 2 months of age (18). In a cat model of RP, retinal blood flow (rBF) was compromised while choroidal blood flow (chBF) was not significantly affected (19). In RP patients, diameter, blood velocity, blood flow (BF) in retinal veins, and total rBF were found to be lower (20), subfoveal chBF was lower (17), and chBF was reduced in late, but not early, stages of the disease (21). These findings suggest that there are vascular-specific (retinal and choroidal) changes accompanying retinal degenerations. Improved understanding of the physiological changes accompanying retinal degeneration may enable better understanding of the pathophysiology. BF changes may occur before irreversible degeneration, which could provide a potential objective measure of therapeutic interventions.
The goal of this study was to test whether anatomical and BF MRI techniques could detect changes of retinal thickness and possible changes of retinal and choroidal BF at different stages of retinal degeneration in the rd10 mouse model. Anatomical MRI was acquired using a balanced steady state free precession (bSSFP) sequence for fast image acquisition with high signal-to-noise ratio. BF MRI used cardiac spin labeling MRI (22), which is based on the continuous arterial spin labeling technique with a separate cardiac coil to avoid saturation of the imaging signal in the retina due to the small size of mice.

Arterial input function of an optical tracer for dynamic contrast enhanced imaging can be determined from pulse oximetry oxygen saturation measurements

http://iopscience.iop.org/0031-9155/57/24/8285
Thursday, November 29, 2012

Jonathan T Elliott, Eric A Wright, Kenneth M Tichauer, Mamadou Diop, Laura B Morrison, Brian W Pogue, Ting-Yim Lee, and Keith St. Lawrence

.. Validation experiments were conducted in rabbits using a small animal oximetry device (MouseOx, STARR Life Sciences, Oakmont, PA), but the approach is translatable to the clinic, capitalizing on the ubiquity of pulse oximeters.

In many cases, kinetic modeling requires that the arterial input function (AIF)—the time-dependent arterial concentration of a tracer—be characterized. A straightforward method to measure the AIF of red and near-infrared optical dyes (e.g., indocyanine green) using a pulse oximeter is presented. The method is motivated by the ubiquity of pulse oximeters used in both preclinical and clinical applications, as well as the gap in currently available technologies to measure AIFs in small animals. The method is based on quantifying the interference that is observed in the derived arterial oxygen saturation (SaO2) following a bolus injection of a light-absorbing dye. In other words, the change in SaO2 can be converted into dye concentration knowing the chromophore-specific extinction coefficients, the true arterial oxygen saturation, and total hemoglobin concentration. A simple error analysis was

performed to highlight potential limitations of the approach, and a validation of the method was conducted in rabbits by comparing the pulse oximetry method with the AIF acquired using a pulse dye densitometer. Considering that determining the AIF is required for performing quantitative tracer kinetics, this method provides a flexible tool for measuring the arterial dye concentration that could be used in a variety of applications.

General scientific summary In dynamic contrast enhanced optical imaging, a targeted or untargeted optical dye is injected into the subject to recover functional information from a tissue region, such as blood flow, leakage, or molecular binding. The models used to recover the functional information often require that the arterial concentration of dye—also called the arterial input function (AIF)—be characterized. A specialized piece of equipment, known as a pulse dye densitometer (PDD) can be used to measure the AIF in adult humans; however, PDDs are expensive, uncommon and do not function properly in small animals or infants. We present a straightforward method of measuring the AIF using a standard pulse oximeter, which is ubiquitous in both clinical and preclinical settings. When an optical dye is injected, it causes interference in the oxygen saturation measurement. The AIF can be quantified from this interference. As proof-of-principle, we present numerical and experimental results.

Automated measurement of blood flow velocity and direction and hemoglobin oxygen saturation in the rat lung using intravital microscopy

http://ajplung.physiology.org/content/early/2012/11/13/ajplung.00178.201...
Friday, November 16, 2012

Gabi Hanna, Andrew Fontanella, Gregory Palmer, Siqing Shan, Daniel R. Radiloff, Yulin Zhao, David C. Irwin, Karyn L. Hamilton, Alina Boico, Claude A. Piantadosi, Gert Blueschke, Mark W. Dewhirst, Timothy J McMahon, and Thies Schroeder

... Vital signs were monitored using pulse 74 oximetry (MouseOx, **Starr Life Sciences**, Oakmont, PA), with blood oxygenation and heart rate recorded. 75 **...** pressure. The ventilator was connected in line with an OxyDial oxygen blender (**Starr Life Sciences**). 83 **...**
Intravital microscopy of the pulmonary microcirculation in research animals is of great scientific interest for its utility in identifying regional changes in pulmonary microcirculatory blood flow. Although feasibility studies have been reported, the pulmonary window can be further refined into a practical tool for pharmaceutical research and drug development. We have established a method to visualize and quantify dynamic changes in three key features of lung function: microvascular red blood cell velocity, flow direction and hemoglobin saturation. These physiologic parameters were measured in an acute closed-chest pulmonary window which allows real-time images to be captured by fluorescence and multispectral absorption microscopy; images were subsequently quantified using computerized analysis. We validated the model by quantifying changes in microcirculatory blood flow and hemoglobin saturation in two ways: 1) after changes in inspired oxygen content, and 2) after pharmacological reduction of pulmonary blood flow via treatment with the beta-1 adrenergic receptor blocker metoprolol. This robust and relatively simple system facilitates pulmonary intravital microscopy in laboratory rats for pharmacological and physiological research.

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http://ajplung.physiology.org/content/early/2012/11/13/ajplung.00178.2012.abstract
Friday, November 16, 2012

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Neural Progenitor Cells Regulate Capillary Blood Flow in the Postnatal Subventricular Zone

http://www.jneurosci.org/content/32/46/16435.short
Wednesday, November 14, 2012

Benjamin Lacar, Peter Herman, Jean-Claude Platel, Cathryn Kubera, Fahmeed Hyder and Angelique Bordey

... pia at 52.9/42.4° angle for rats/mice). The animal vital signs were monitored with a small animal plethysmograph on the footpad (MouseOx; **Starr Life Sciences**). Immediately following the experiments, the brains were removed **...**
In the postnatal subventricular zone (SVZ), S phase entry of neural progenitor cells (NPCs) correlates with a local increase in blood flow. However, the cellular mechanism controlling this hemodynamic response remains unknown. We show that a subpopulation of SVZ cells, astrocyte-like cells or B-cells, sends projections ensheathing pericytes on SVZ capillaries in young mice. We examined whether calcium increases in pericytes or B-cells led to a vascular response in acute slices using the P2Y2/4 receptor (P2Y2/4R) agonist UTP, electrical stimulation, or transgenic mice expressing exogenous Gq-coupled receptors (MrgA1) in B-cells. UTP increased calcium in pericytes leading to capillary constrictions. Electrical stimulation induced calcium propagation in SVZ cells followed by capillary constrictions involving purinergic receptors. In transgenic mice, selective calcium increases in B-cells induced P2Y2/4R-dependent capillary constrictions, suggesting that B-cells release ATP activating purinergic receptors on pericytes. Interestingly, in the presence of a P2Y2/4R blocker, dilation was observed. Intraventricular UTP injection transiently decreased blood flow monitored in vivo using laser Doppler flowmetry. Using neonatal electroporation, we expressed MrgA1 in slow cycling radial glia-derived B1 cells, i.e., NPCs. Intraventricular injection of an MrgA1 ligand increased blood flow in the SVZ. Thus, upon intracellular calcium increases B-cells/NPCs release ATP and vasodilating factors that activate purinergic receptors on pericytes triggering a vascular response and blood flow increase in vivo. Considering that NPCs receive signals from other SVZ cells, these findings further suggest that NPCs act as transducers of neurometabolic coupling in the SVZ.

MicroPET/CT Imaging of [18F]-FEPPA in the Nonhuman Primate: A Potential Biomarker of Pathogenic Processes Associated with Anesthetic-Induced Neurotoxicity

http://www.hindawi.com/isrn/anesthesiology/2012/261640/
Saturday, September 15, 2012

Xuan Zhang, Merle G. Paule, Glenn D. Newport, Fang Liu, Ralph Callicott, Shuliang Liu, Marc S. Berridge, Scott M. Apana, William Slikker Jr.,and Cheng Wang

... physiological parameters of the neonatal monkeys were monitored following procedures described previously [20, 21] Briefly, noninvasive pulse oximetry (N-395 Pulse Oximeter, Nellcor, Pleasanton, CA, USA; MouseO X Plus Vital Sign Monitor, Starr Life Sciences, Oakmont, PA ...

Background. The inhalation anesthetics nitrous oxide (N2O) and isoflurane (ISO) are used in surgical procedures for human infants. Injury to the central nervous system is often accompanied by localization of activated microglia or astrocytosis at the site of injury. The tracer that targets to the peripheral benzodiazepine receptor (PBR), [18F]N-2-(2-fluoroethoxy)benzyl)-N-(4-phenoxypyridin-3-yl)acetamide ([18F]-FEPPA), has been reported as a sensitive biomarker for the detection of neuronal damage/inflammation. Methods. On postnatal day (PND) 5 or 6 rhesus

monkey neonates were exposed to a mixture of N2O/oxygen and ISO for 8 hours and control monkeys were exposed to room air. MicroPET/CT images with [18F]-FEPPA were obtained for each monkey 1 day, one week, three weeks, and 6 months after the anesthetic exposure. Results. The radiotracer quickly distributed into the brains of both treated and control monkeys on all scan days. One day after anesthetic exposure, the uptake of [18F]-FEPPA was significantly increased in the temporal lobe. One week after exposure, the uptake of [18F]-FEPPA in the frontal lobe of treated animals was significantly greater than that in controls. Conclusions. These findings suggest that microPET imaging is capable of dynamic detection of inhaled anesthetic-induced brain damage in different brain regions of the nonhuman primate.

Photoacoustic tomography can detect cerebral hemodynamic alterations in a neonatal rodent model of hypoxia-ischemia

http://www.ez.ane.pl/pdf/7223.pdf
Wednesday, August 22, 2012

Craig B. Sussman, Candace Rossignol, Qizhi Zhang, Huabei Jiang, Tong Zheng, Dennis Steindler, Linda Young, and Michael D. Weiss

.. imaging process by MouseOx® Pulse Oximeter (STARR Life Sciences™ Corp, Oakmont, PA). Post-imaging, the pups fully recovered on a heating gel pad and were then returned to their mother to nurse. The subjects were monitored ...

Hypoxic-Ischemic Encephalopathy (HIE) is one of the most recognized causes of neurological deficits in children. Cerebral blood flow (CBF) reductions, as seen with HIE, resulting in neuronal injury have not been evaluated in real-time. Photoacoustic Tomography (PAT) is a form of optical imaging which can detect cerebral hemodynamic alterations in a non-invasive, non-ionizing fashion via changes in hemoglobin optical absorption. Further, this technology has the potential to capture cerebral blood volume (CBV) fluctuations and perhaps CBF changes in real-time. We hypothesized that PAT can detect a reduction in cerebral hemoglobin optical absorption, and therefore CBF, in a neonatal model of hypoxia-ischemia. To investigate, P7 rats underwent right carotid artery ligation and exposure to 8% oxygen for 60 minutes while imaged with PAT every 20 minutes. Cerebral hemodynamic alterations, as measured by mean optical absorption (MOA), were calculated as a change from baseline. Global and regional MOA was analyzed using a linear mixed model. Global MOA was reduced within the right hemisphere as compared to the left during hypoxia. Regional differences in MOA were detected between the left and right sides for the middle and posterior cortical regions. Injury was confirmed using immunohistochemistry. We conclude that a reduction in global and regional MOA, and hence CBF, could be identified by PAT in a neonatal rat model of HIE. This is the first study described in the literature utilizing a neonatal rat model of HIE to demonstrate in vivo alterations in cerebral hemodynamics in a non-invasive and near real-time fashion.

Amyloid-ß-dependent compromise of microvascular structure and function in a model of Alzheimer's disease

http://brain.oxfordjournals.org/content/135/10/3039.short
Friday, July 13, 2012

A Dorr, B Sahota, LV Chinta, ME Brown, AY Lai, K Ma…

... End-tidal respiratory pressure, temperature, oxygen saturation, breath and pulse distention and heart rate were recorded throughout surgery and imaging (Biopac MP150, Biopac Systems Inc.; MouseOx, **Starr Life Sciences** Corp.). Image acquisition. **...**
The majority of patients with Alzheimer's disease have cerebral amyloid angiopathy, thus showing deposition of amyloid-ß peptides in the walls of leptomeningeal and cortical arterioles. These deposits are believed to result from impaired clearance of parenchymal amyloid-ß peptides. In the current work, we examined the changes in cortical microvascular structure and function in situ in TgCRND8, a transgenic mouse model of Alzheimer's disease. In contrast to venules, cortical arterioles were shown to increase in tortuosity and decrease in calibre with amyloid-ß peptide accumulation. These structural changes were accompanied by progressive functional compromise, reflected in higher dispersion of microvascular network transit times, elongation of the transit times, and impaired microvascular reactivity to hypercapnia in the transgenic mice. Moreover, inhibition of amyloid-ß peptide

oligomerization and fibrillization via post-weaning administration of scyllo-inositol, a naturally occurring stereoisomer of myo-inositol, rescued both structural and functional impairment of the cortical microvasculature in this Alzheimer's disease model. These results demonstrate that microvascular impairment is directly correlated with amyloid-ß accumulation and highlight the importance of targeting cerebrovascular amyloid angiopathy clearance for effective diagnosis, monitoring of disease progression and treatment of Alzheimer's disease.

A Polished and Reinforced Thinned-skull Window for Long-term Imaging of the Mouse Brain

http://www.jove.com/video/3742/a-polished-reinforced-thinned-skull-window-for-long-term-imaging
Wednesday, March 7, 2012

Shih, A. Y., Mateo, C., Drew, P. J., Tsai, P. S., Kleinfeld, D. A

In vivo imaging of cortical function requires optical access to the brain without disruption of the intracranial environment. We present a method to form a polished and reinforced thinned skull (PoRTS) window in the mouse skull that spans several millimeters in diameter and is stable for months. The skull is thinned to 10 to 15 µm in thickness with a hand held drill to achieve optical clarity, and is then overlaid with cyanoacrylate glue and a cover glass to: 1) provide rigidity, 2) inhibit bone regrowth and 3) reduce light scattering from irregularities on the bone surface. Since the skull is not breached, any inflammation that could affect the process being studied is greatly reduced. Imaging depths of up to 250 µm below the cortical surface can be achieved using two-photon laser scanning microscopy. This window is well suited to study cerebral blood flow and cellular function in both anesthetized and awake preparations. It further offers the opportunity to manipulate cell activity using optogenetics or to disrupt blood flow in targeted vessels by irradiation of circulating photosensitizers.

In Vivo MR Imaging of Pulmonary Perfusion and Gas Exchange in Rats via Continuous Extracorporeal Infusion of Hyperpolarized 129Xe

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0031306
Tuesday, February 21, 2012

Zackary I. Cleveland, Harald E. Möller, Laurence W. Hedlund, John C. Nouls, Matthew S. Freeman, Yi Qi, Bastiaan Driehuys

Background

Hyperpolarized (HP) 129Xe magnetic resonance imaging (MRI) permits high resolution, regional visualization of pulmonary ventilation. Additionally, its reasonably high solubility (>10%) and large chemical shift range (>200 ppm) in tissues allow HP 129Xe to serve as a regional probe of pulmonary perfusion and gas transport, when introduced directly into the vasculature. In earlier work, vascular delivery was accomplished in rats by first dissolving HP 129Xe in a biologically compatible carrier solution, injecting the solution into the vasculature, and then detecting HP 129Xe as it emerged into the alveolar airspaces. Although easily implemented, this approach was constrained by the tolerable injection volume and the duration of the HP 129Xe signal.

Methods and Principal Findings

Here, we overcome the volume and temporal constraints imposed by injection, by using hydrophobic, microporous, gas-exchange membranes to directly and continuously infuse 129Xe into the arterial blood of live rats with an extracorporeal (EC) circuit. The resulting gas-phase 129Xe signal is sufficient to generate diffusive gas exchange- and pulmonary perfusion-dependent, 3D MR images with a nominal resolution of 2×2×2 mm3. We also show that the 129Xe signal dynamics during EC infusion are well described by an analytical model that incorporates both mass transport into the blood and longitudinal relaxation.

Conclusions

Extracorporeal infusion of HP 129Xe enables rapid, 3D MR imaging of rat lungs and, when combined with ventilation imaging, will permit spatially resolved studies of the ventilation-perfusion ratio in small animals. Moreover, EC infusion should allow 129Xe to be delivered elsewhere in the body and make possible functional and molecular imaging approaches that are currently not feasible using inhaled HP 129Xe.

Two-photon microscopy as a tool to study blood flow and neurovascular coupling in the rodent brain

http://www.ncbi.nlm.nih.gov/pubmed/22293983
Wednesday, February 1, 2012

Shih AY, Driscoll JD, Drew PJ, Nishimura N, Schaffer CB, Kleinfeld D.

Abstract

The cerebral vascular system services the constant demand for energy during neuronal activity in the brain. Attempts to delineate the logic of neurovascular coupling have been greatly aided by the advent of two-photon laser scanning microscopy to image both blood flow and the activity of individual cells below the surface of the brain. Here we provide a technical guide to imaging cerebral blood flow in rodents. We describe in detail the surgical procedures required to generate cranial windows for optical access to the cortex of both rats and mice and the use of two-photon microscopy to accurately measure blood flow in individual cortical vessels concurrent with local cellular activity. We further provide examples on how these techniques can be applied to the study of local blood flow regulation and vascular pathologies such as small-scale stroke.

Neuroimaging Assessment of Traumatic Brain Injury

http://www.springerlink.com/content/k5495841q7510001/#section=1072448&page=1
Sunday, January 1, 2012

Janna L. Harris and William M. Brooks

... Instruments Inc; CWE Inc). An MR-compatible pulse oximeter (eg, Starr Life Sciences) can also be used to monitor blood oxygenation as well as heart rate and breathing rate during scanning. Although in vivo neuroimaging ...

Pretreatment with a novel aquaporin 4 inhibitor, TGN-020, significantly reduces ischemic cerebral edema

http://www.springerlink.com/content/yv85t2l62k0mqm11/?MUD=MP
Tuesday, November 1, 2011

Hironaka Igarashi, Vincent J. Huber, Mika Tsujita and Tsutomu Nakada

We investigated the in vivo effects of a novel aquaporin 4 (AQP4) inhibitor 2-(nicotinamide)-1,3,4-thiadiazole, TGN-020, in a mouse model of focal cerebral ischemia using 7.0-T magnetic resonance imaging (MRI). Pretreatment with TGN-020 significantly reduced brain edema associated with brain ischemia, as reflected by percentage of brain swelling volume (%BSV), 12.1 ± 6.3% in the treated group, compared to (20.8 ± 5.9%) in the control group ($p < 0.05$), and in the size of cortical infarction as reflected by the percentage of hemispheric lesion volume (%HLV), 20.0 ± 7.6% in the treated group, compared to 30.0 ± 9.1% in the control group ($p < 0.05$). The study indicated the potential pharmacological use of AQP4 inhibition in reducing brain edema associated with focal ischemia.

Keywords Aquaporin 4 – Brain ischemia – Brain edema – Magnetic resonance imaging

Intravital Two-Photon Microscopy of Immune Cell Dynamics in Corneal Lymphatic Vessels

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0026253
Thursday, October 20, 2011

Philipp Steven, Felix Bock, Gereon Hüttmann, Claus Cursiefen

Background
The role of lymphatic vessels in tissue and organ transplantation as well as in tumor growth and metastasis has drawn great attention in recent years.

Methodology/Principal Findings
We now developed a novel method using non-invasive two-photon microscopy to simultaneously visualize and track specifically stained lymphatic vessels and autofluorescent adjacent tissues such as collagen fibrils, blood vessels and immune cells in the mouse model of corneal neovascularization in vivo. The mouse cornea serves as an ideal tissue for this technique due to its easy accessibility and its inducible and modifiable state of pathological hem- and lymphvascularization.
Neovascularization was induced by suture placement in corneas of Balb/C mice. Two weeks after treatment, lymphatic vessels were stained intravital by intrastromal injection of a fluorescently labeled LYVE-1 antibody and the corneas were evaluated in vivo by two-photon microscopy (TPM). Intravital TPM was performed at 710 nm and 826 nm excitation wavelengths to detect immunofluorescence and tissue autofluorescence using a custom made animal holder. Corneas were then harvested, fixed and analyzed by histology.
Time lapse imaging demonstrated the first in vivo evidence of immune cell migration into lymphatic vessels and luminal transport of individual cells. Cells immigrated within 1–5.5 min into the vessel lumen. Mean velocities of intrastromal corneal immune cells were around 9 μm/min and therefore comparable to those of T-cells and macrophages in other mucosal surfaces.

Conclusions
To our knowledge we here demonstrate for the first time the intravital real-time transmigration of immune cells into lymphatic vessels. Overall this study demonstrates the valuable use of intravital autofluorescence two-photon microscopy in the model of suture-induced corneal vascularizations to study interactions of immune and subsequently tumor cells with lymphatic vessels under close as possible physiological conditions.

Molecular Magnetic Resonance Imaging Allows the Detection of Activated Platelets in a New Mouse Model of Coronary Artery Thrombosis

http://journals.lww.com/investigativeradiology/Abstract/2011/10000/Molecular_Magnetic_Resonance_Imaging_Allows_the.3.aspx
Saturday, October 1, 2011

Duerschmied, Daniel MD*; Meissner, Mirko Dipl Phys†; Peter, Karlheinz MD‡; Neudorfer, Irene BSc*; Roming, Freya BSc*; Zirlik, Andreas MD*; Bode, Christoph MD*; von Elverfeldt, Dominik PhD†; von zur Muhlen, Constantin MD*

Objective: The final event leading to myocardial infarction is adhesion and activation of platelets after rupture of an atherosclerotic plaque, ending in thrombotic occlusion of the coronary artery. Imaging of imminent vessel occlusion may improve patient care. The feasibility of molecular magnetic resonance imaging (MRI) for the detection of coronary artery thrombosis in mice was examined.

Materials and Methods: The left anterior descending coronary artery was exposed by lateral thoracotomy and incubated with ferric chloride to induce nonocclusive thrombosis in C57Bl/6 mice. A single chain antibody targeting ligand-induced binding sites (LIBS) of the activated glycoprotein IIb/IIIa or control antibody was conjugated to 1 μm-sized microparticles of iron oxide (MPIOs), resulting in LIBS-MPIO or control-MPIO MRI contrast agent, and injected intravenously. Hearts were subjected to histology and ex vivo MRI at 9.4 Tesla.

Results: Thrombus size was comparable in mice injected with control-MPIO and LIBS-MPIO in histology. Significant binding of MPIOs to thrombi was observed in LIBS-MPIO-injected animals while no binding was observed in control animals ($P < 0.05$). In MRI, LIBS-MPIO binding to thrombi of the left anterior descending coronary artery resulted in significant MPIO-induced signal void compared with controls ($P < 0.05$). MRI signal void and the amount of bound contrast agent particles in histology showed a significant positive linear correlation ($r = 0.939$, $P < 0.001$).

Conclusions: We established a new mouse model of nonocclusive coronary artery thrombosis. LIBS-MPIO contrast agent binds to activated platelets in this model, allowing molecular MRI of coronary thrombosis. This could have important implications on the timely noninvasive detection of arterial thrombosis, helping to initiate early therapeutic interventions.

Somatic calcium level reports integrated spiking activity of cerebellar interneurons in vitro and in vivo

http://jn.physiology.org/content/106/4/1793.short
Wednesday, July 6, 2011

Romain Franconville, Gaëlle Revet, Guadalupe Astorga, Beat Schwaller, and Isabel Llano

We examined the relationship between somatic Ca2+ signals and spiking activity of cerebellar molecular layer interneurons (MLIs) in adult mice. Using two-photon microscopy in conjunction with cell-attached recordings in slices, we show that in tonically firing MLIs loaded with high-affinity Ca2+ probes, Ca2+-dependent fluorescence transients are absent. Spike-triggered averages of fluorescence traces for MLIs spiking at low rates revealed that the fluorescence change associated with an action potential is small (1% of the basal fluorescence). To uncover the relationship between intracellular Ca2+ concentration ([Ca2+]i) and firing rates, spikes were transiently silenced with puffs of the GABAA receptor agonist muscimol. [Ca2+]i relaxed toward basal levels following a single exponential whose amplitude correlated to the preceding spike frequency. The relaxation time constant was slow (2.5 s) and independent of the probe concentration. Data from parvalbumin (PV)−/− animals indicate that PV controls the amplitude and decay time of spike-triggered averages as well as the time course of [Ca2+]i relaxations following spike silencing. The [Ca2+]i signals were sensitive to the L-type Ca2+ channel blocker nimodipine and insensitive to ryanodine. In anesthetized mice, as in slices, fluorescence traces from most MLIs did not show spontaneous transients. They nonetheless responded to muscimol iontophoresis with relaxations similar to those obtained in vitro, suggesting a state of tonic firing with estimated spiking rates ranging from 2 to 30 Hz. Altogether, the [Ca2+]i signal appears to reflect the integral of the spiking activity in MLIs. We propose that the muscimol silencing strategy can be extended to other tonically spiking neurons with similar [Ca2+]i homeostasis.

Occlusion of cortical ascending venules causes blood flow decreases, reversals in flow direction, and vessel dilation in upstream capillaries

http://www.nature.com/jcbfm/journal/v31/n11/full/jcbfm201195a.html?WT.ec_id=JCBFM-201111
Wednesday, June 29, 2011

John Nguyen, Nozomi Nishimura, Robert N Fetcho, Costantino Iadecola and Chris B Schaffer

The accumulation of small strokes has been linked to cognitive dysfunction. Although most animal models have focused on the impact of arteriole occlusions, clinical evidence indicates that venule occlusions may also be important. We used two-photon excited fluorescence microscopy to quantify changes in blood flow and vessel diameter in capillaries after occlusion of single ascending or surface cortical venules as a function of the connectivity between the measured capillary and the occluded venule. Clotting was induced by injuring the target vessel wall with femtosecond laser pulses. After an ascending venule (AV) occlusion, upstream capillaries showed decreases in blood flow speed, high rates of reversal in flow direction, and increases in vessel diameter. Surface venule occlusions produced similar effects, unless a collateral venule provided a new drain. Finally, we showed that AVs and penetrating arterioles have different nearest-neighbor spacing but capillaries branching from them have similar topology, which together predicted the severity and spatial extent of blood flow reduction after occlusion of either one. These results provide detailed insights into the widespread hemodynamic changes produced by cortical venule occlusions and may help elucidate the role of venule occlusions in the development of cognitive disorders and other brain diseases.

Keywords:
collateral flow; hemodynamics; nonlinear microscopy; stroke; vasoregulation

Two-Photon Intravital Multicolour Imaging to Study Metastatic Behaviour of Cancer Cells In Vivo

http://www.springerlink.com/content/uh54253158lv5485/#section=922625&page=1
Saturday, January 1, 2011

Sylvia E. Le Dévédec, Wies van Roosmalen, Chantal Pont, Reshma Lalai, Hans de Bont and Bob van de Water

9. 339 22 Two-Photon Intravital Multicolour Imaging to Study Metastatic Behaviour… quality due to numerous artefacts. The monitoring can be done visually, or by using the **MouseOx** pulse oximetry sys- tem (**Starr life Sciences** Corp) as done in other laboratories. **...**

Two-Photon Intravital Multicolour Imaging to Study Metastatic Behaviour of Cancer Cells In Vivo

http://www.springerlink.com/content/uh54253158lv5485/#section=922625&page=1&locus=5
Saturday, January 1, 2011

Sylvia E. Le Dévédec, Wies van Roosmalen, Chantal Pont, Reshma Lalai, Hans de Bont and Bob van de Water

... Page 9. 339 22 Two-Photon Intravital Multicolour Imaging to Study Metastatic Behaviour… quality

due to numerous artefacts. The monitoring can be done visually, or by using the MouseOx pulse

oximetry sys- tem (Starr life Sciences Corp) as done in other laboratories. ...

A Novel Technique for the In Vivo Imaging of Autoimmune Diabetes Development in the Pancreas by Two-Photon Microscopy

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3009738/
Thursday, December 23, 2010

Ken Coppieters, Marianne M. Martinic, William B. Kiosses, Natalie Amirian, and Matthias von Herrath,

Type 1 diabetes (T1D) is characterized by the immune-mediated destruction of beta cells in the pancreas. Little is known about the in vivo dynamic interactions between T cells and beta cells or the kinetic behavior of other immune cell subsets in the pancreatic islets. Utilizing multiphoton microscopy we have designed a technique that allows for the real-time visualization of diabetogenic T cells and dendritic cells in pancreatic islets in a live animal, including their interplay with beta cells and the vasculature. Using a custom designed stage, the pancreas was surgically exposed under live conditions so that imaging of islets under intact blood pressure and oxygen supply became possible. We demonstrate here that this approach allows for the tracking of diabetogenic leukocytes as well as vascularization phenotype of islets and accumulation of dendritic cells in islets during diabetes pathogenesis. This technique should be useful in mapping crucial kinetic events in T1D pathogenesis and in testing the impact of immune based interventions on T cell migration, extravasation and islet destruction.

Pretreatment with a novel aquaporin 4 inhibitor, TGN-020, significantly reduces ischemic cerebral edema

http://www.springerlink.com/content/yv85t2l62k0mqm11/
Wednesday, October 6, 2010

Hironaka Igarashi, Vincent J. Huber, Mika Tsujita and Tsutomu Nakada

We investigated the in vivo effects of a novel aquaporin 4 (AQP4) inhibitor 2-(nicotinamide)-1,3,4-thiadiazole, TGN-020, in a mouse model of focal cerebral ischemia using 7.0-T magnetic resonance imaging (MRI). Pretreatment with TGN-020 significantly reduced brain edema associated with brain ischemia, as reflected by percentage of brain swelling volume (%BSV), 12.1 ± 6.3% in the treated group, compared to (20.8 ± 5.9%) in the control group ($p < 0.05$), and in the size of cortical infarction as reflected by the percentage of hemispheric lesion volume (%HLV), 20.0 ± 7.6% in the treated group, compared to 30.0 ± 9.1% in the control group ($p < 0.05$). The study indicated the potential pharmacological use of AQP4 inhibition in reducing brain edema associated with focal ischemia.

Imaging retinal blood flow with laser speckle flowmetry

http://www2.neuroscience.umn.edu/eanwebsite/PDF%20EAN%20pubs/Front%20Neu...
Wednesday, September 15, 2010

Anja I. Srienc, Zeb L. Kurth-Nelson and Eric A. Newman

Laser speckle flowmetry (LSF) was initially developed to measure blood flow in the retina. More recently, its primary application has been to image baseline blood flow and activity-dependent changes in blood flow in the brain. We now describe experiments in the rat retina in which LSF was used in conjunction with confocal microscopy to monitor light-evoked changes in blood flow in retinal vessels. This dual imaging technique permitted us to stimulate retinal photoreceptors and measure vessel diameter with confocal microscopy while simultaneously monitoring blood flow with LSF. We found that a flickering light dilated retinal arterioles and evoked increases in retinal blood velocity with similar time courses. In addition, focal light stimulation evoked local increases in blood velocity. The spatial distribution of these increases depended on the location of the stimulus relative to retinal arterioles and venules. The results suggest that capillaries are largely unresponsive to local neuronal activity and that hemodynamic responses are mediated primarily by arterioles. The use of LSF to image retinal blood flow holds promise in elucidating the mechanisms mediating functional hyperemia in the retina and in characterizing changes in blood flow that occur during retinal pathology.

Keywords: retina, choroid, blood flow, arterioles, capillaries, functional hyperemia, laser speckle flowmetry

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Probabilistic independent component analysis for laser speckle contrast images reveals in vivo multi - component vascular responses to forepaw stimulation

http://ieeexplore.ieee.org/xpl/login.jsp?reload=true&tp=&arnumber=5627526&url=http%3A%2F%2Fieeexplore.ieee.org%2Fxpls%2Fabs_all.jsp%3Farnumber%3D5627526
Saturday, September 4, 2010

Nan Li

Biomed. Eng. Dept., Johns Hopkins Univ., Baltimore, MD, USA

Brain's functional response can be studied by observing the spatiotemporal dynamics of functional and structural changes in cerebral vasculature. However, very few studies explore detailed changes at the level of individual microvessels while revealing the simultaneous wide field view of microcirculation responses to functional stimulation. Here we use a high spatiotemporal resolution laser speckle contrast imaging method, in combination with probabilistic independent component analysis to reveal the changes of cerebral blood flow pattern in response to electrical forepaw stimulation in an anesthetized rat model. The proposed method is able to pick up the response of a single vessel down to ~20μm diameter in a 4mm × 4mm field of view, and automatically extract response from multiple vascular components. Two main vascular components, arteriolar and capillary responses respectively, show significantly different temporal dynamics. Overall, the experimental results from five rats reveal that the specific arteriole branch proximal to the activation sites dilate prior consistently to the increase of blood flow in the capillaries with a latency time 0.91±0.05s. The presented results provide novel microscopic scale evidence of the contribution of different vascular compartments in the hemodynamic response to neuronal activation.

Mild Sensory Stimulation Completely Protects the Adult Rodent Cortex from Ischemic Stroke

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0011270
Wednesday, June 23, 2010

Christopher C. Lay, Melissa F. Davis, Cynthia H. Chen-Bee, Ron D. Frostig

Despite progress in reducing ischemic stroke damage, complete protection remains elusive. Here we demonstrate that, after permanent occlusion of a major cortical artery (middle cerebral artery; MCA), single whisker stimulation can induce complete protection of the adult rat cortex, but only if administered within a critical time window.

Animals that receive early treatment are histologically and behaviorally equivalent to healthy controls and have normal neuronal function. Protection of the cortex clearly requires reperfusion to the ischemic area despite permanent occlusion. Using blood flow imaging and other techniques we found evidence of reversed blood flow into MCA branches from an alternate arterial source via collateral vessels (inter-arterial connections), a potential mechanism for reperfusion. These findings suggest that the cortex is capable of extensive blood flow reorganization and more importantly that mild sensory stimulation can provide complete protection from impending stroke given early intervention. Such non-invasive, non-pharmacological intervention has clear translational potential.

Laser speckle contrast imaging of collateral blood flow during acute ischemic stroke

http://www.nature.com/jcbfm/journal/v30/n8/full/jcbfm201073a.html
Wednesday, June 2, 2010

Glenn A Armitage, Kathryn G Todd, Ashfaq Shuaiband Ian R Winship

Collateral vasculature may provide an alternative route for blood flow to reach the ischemic tissue and partially maintain oxygen and nutrient support during ischemic stroke. However, much about the dynamics of stroke-induced collateralization remains unknown. In this study, we used laser speckle contrast imaging to map dynamic changes in collateral blood flow after middle cerebral artery occlusion in rats. We identified extensive anastomatic connections between the anterior and middle cerebral arteries that develop after vessel occlusion and persist for 24 hours. Augmenting blood flow through these persistent yet dynamic anastomatic connections may be an important but relatively unexplored avenue in stroke therapy.

The current functional state of local neuronal circuits controls the magnitude of a BOLD response to incoming stimuli

http://www.sciencedirect.com/science/article/pii/S1053811910000923
Saturday, May 1, 2010

Frank Angensteina, Karla Krautwalda, Henning Scheichc

Abstract
The purpose of this study was to determine how the history-dependent activation state of neuronal networks controls fMRI signals to incoming stimuli. Simultaneous electrophysiological and blood oxygen level-dependent (BOLD) responses were monitored during stimulation of the perforant pathway with low, high, and again low intensity but, otherwise identical pulse trains. Under three different anesthetics (α-chloralose, medetomidine, isoflurane) consecutive low intensity stimulation trains, set just below the threshold for population spike generation to single pulses, yielded a stable BOLD response, although at different magnitudes. The first high intensity train increased the BOLD response under all anesthetics and generated population spikes, with varying amplitudes and latencies (α-chloralose, metedomidine) or in a regular pattern (isoflurane). Concurrent to the second high intensity train, the BOLD response became minimal, then slowly increasing with subsequent trains (α-chloralose, metedomidine), or immediately rising to a stable level (isoflurane). Second train population spikes became regularized, but at low amplitudes and long latencies that were slowly reversed across trains (α-chloralose, medetomidine); while under isoflurane, amplitude and latencies became stabilized with the second train. In comparison to initial stimulation, the final low intensity stimulation trains failed to produce BOLD responses (α-chloralose, medetomidine), or left the response unchanged (isoflurane), only reaching stable potentiation of population spikes when under isoflurane. Therefore, the fate of BOLD responses depends on whether a new stable functional state of the intrinsic network can be reached after high intensity stimulation.

Blood oxygenation level-dependent (BOLD) functional MRI of visual stimulation in the rat retina at 11.7 T

http://ric.uthscsa.edu/duong/2010Jun_NBMvisualstim.pdf
Wednesday, April 28, 2010

Bryan H. De La Garzaa, Eric R. Muira,b, Guang Lia,c, Yen-Yu I. Shiha

and Timothy Q. Duonga–g,*

Although optically based imaging techniques provide valuable functional and physiological information of the retina, they are mostly limited to the probing of the retinal surface and require an unobstructed light path. MRI, in contrast, could offer physiological and functional data without depth limitation. Blood oxygenation level-dependent functional MRI (BOLD fMRI) of the thin rat retina is, however, challenging because of the need for high spatial resolution, and the
potential presence of eye movement and susceptibility artifacts. This study reports a novel application of highresolution
(111T111T1000 mm3) BOLD fMRI of visual stimulation in the anesthetized rat retina at 11.7 T. A high-field MRI scanner was utilized to improve the signal-to-noise ratio, spatial resolution and BOLD sensitivity. Visual stimuli (8 Hz diffuse achromatic light) robustly increased BOLD responses in the retina [5.0W0.8% from activated pixels and 3.1W1.1% from the whole-retina region of interest (meanWSD), n¼12 trials on six rats, p<0.05 compared with baseline]. Some activated pixels were detected surrounding the pupil and ciliary muscle because of accommodation reflex to visual stimuli, and were reduced with atropine and phenylephrine eye drops. BOLD fMRI scans without visual stimulations showed no significantly activated pixels (whole-retina BOLD changes were 0.08W0.34%, n¼6 trials on five rats, not statistically different from baseline, p > 0.05). BOLD fMRI of visual stimulation has the potential to provide clinically relevant data to probe hemodynamic neurovascular coupling and dysfunction of the retina with depth resolution. Copyright 2010 John Wiley & Sons, Ltd.

Keywords: laminar specificity; high magnetic field; high-resolution fMRI; choroid; dark and light adaptation; blood flow

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Micro-CT imaging assessment of dobutamine-induced cardiac stress in rats

http://www.sciencedirect.com/science/article/pii/S105687191000050X
Friday, April 16, 2010

Cristian T. Badeaa, Laurence W. Hedlunda, James Cooka, Brian R. Berridgeb, G. Allan Johnsona,

Abstract

Introduction

Dobutamine (DOB) stress in animal models of heart disease has been imaged so far using echocardiography and magnetic resonance imaging. The purpose of this study was to assess normal response to DOB stress in rats using anatomical and functional data using micro-computed tomography (CT).

Methods

Ten normal adult male rats were first injected with a liposomal-based blood pool contrast agent and next infused with DOB via a tail vein catheter. Using prospective gating, 5 pairs of systole/diastole micro-CT images were acquired (a) pre-infusion baseline; (b) at heart rate plateau during infusion of 10 μg/kg/min DOB; (c) at post-DOB infusion baseline; (d) at heart rate plateau during infusion of 30 μg/kg/min DOB; and (e) after post-infusion return to baseline. Heart rate, peripheral and breathing distensions were monitored by oximetry. Micro-CT images with 88-μm isotropic voxels were segmented to obtain cardiac function based on volumetric measurements of the left ventricle.

Results

DOB stress increased heart rate and cardiac output with both doses. Ejection fraction increased above baseline by an average of 35.9% with the first DOB dose and 18.4% with the second dose. No change was observed in the relative peripheral arterial pressures associated with the significant increases in cardiac output.

Discussion

Micro-CT proved to be a robust imaging method able to provide isotropic data on cardiac morphology and function. Micro-CT has the advantage of being faster and more cost-effective than MR and is able to provide higher accuracy

than echocardiography. The impact of such an enabling technology can be enormous in evaluating cardiotoxic effects of various test drugs.

Keywords

Cardiac; Small animal imaging; Lung; Micro-CT; Stress; Dobutamine

Cooperative regulation of neurotransmitter release by Rab3a and synapsin II

http://www.sciencedirect.com/science/article/pii/S1044743110000618
Tuesday, March 23, 2010

William L. Colemanb, Maria Bykhovskaiaa,

Abstract

To understand how the presynaptic proteins synapsin and Rab3a may interact in the regulation of the synaptic vesicle cycle and the release process, we derived a double knockout (DKO) mouse lacking both synapsin II and Rab3a. We found that Rab3a deletion rescued epileptic-like seizures typical for synapsin II gene deleted animals (Syn II(−)). Furthermore, action potential evoked release was drastically reduced in DKO synapses, although spontaneous release remained normal. At low Ca2+ conditions, quantal content was equally reduced in Rab3a(−) and DKO synapses, but as Ca2+ concentration increased, the increase in quantal content was more prominent in Rab3a(−). Electron microscopy analysis revealed that DKO synapses have a combined phenotype, with docked vesicles being reduced similar to Rab3a(−), and intraterminal vesicles being depleted similar to Syn II(−). Consistently, both Syn II(−) and DKO terminals had increased synaptic depression and incomplete recovery. Taken together, our results suggest that synapsin II and Rab3a have separate roles in maintaining the total store of synaptic vesicles and cooperate in promoting the latest steps of neuronal secretion.

Keywords

Quantal content; Electron microscopy; EPSP; Epilepsy

Preparation of Mice for Long-Term Intravital Imaging of the Mammary Gland

http://cshprotocols.cshlp.org/content/2011/2/pdb.prot5562.short
Friday, January 1, 2010

Andrew J. Ewald, Zena Werb and Mikala Egeblad

Genetic studies and tumor biopsies have shown the importance of stromal components for cancer progression, but much remains to be learned about the dynamic interactions among the distinct tumor components within live animals. One challenge of studying cell behavior in progressively developing tumors has been the difficulty of maintaining live mice on the microscope stage. To prepare mice for long-term intravital imaging, auxiliary equipment is necessary to enable and to control anesthesia (such as the anesthesia gas mixer itself, a gas humidifier, indwelling lines for saline, and heat blanket). The other important component is to gain optical access to the mammary gland. This protocol describes a surgical technique that creates a skin flap with the mammary gland. The method is relatively easily taught, does not compromise the peritoneal cavity or any major blood vessels, and is generally well tolerated by the mice. There is minimal inflammatory response to the surgery itself if the solutions and tools are sterile, the surgical work area is clean, and aseptic techniques are used. This protocol works well for a single long-term image session, but does not enable repeated imaging sessions. For such approaches, methods for implanting imaging windows over the inguinal mammary gland should be used instead.

Real-time imaging of de novo arteriovenous malformation in a mouse model of hereditary hemorrhagic telangiectasia

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2769195/
Thursday, October 1, 2009

Sung Ok Park,Mamta Wankhede,Young Jae Lee,Eun-Jung Choi,Naime Fliess, Se-Woon Choe, Seh-Hoon Oh,Glenn Walter,Mohan K. Raizada, Brian S. Sorg, and S. Paul Oh

Arteriovenous malformations (AVMs) are vascular anomalies where arteries and veins are directly connected through a complex, tangled web of abnormal arteries and veins instead of a normal capillary network. AVMs in the brain, lung, and visceral organs, including the liver and gastrointestinal tract, result in considerable morbidity and mortality. AVMs are the underlying cause of three major clinical symptoms of a genetic vascular dysplasia termed hereditary hemorrhagic telangiectasia (HHT), which is characterized by recurrent nosebleeds, mucocutaneous telangiectases, and visceral AVMs and caused by mutations in one of several genes, including activin receptor–like kinase 1 (ALK1). It remains unknown why and how selective blood vessels form AVMs, and there have been technical limitations to observing the initial stages of AVM formation. Here we present in vivo evidence that physiological or environmental factors such as wounds in addition to the genetic ablation are required for Alk1-deficient vessels to develop to AVMs in adult mice. Using the dorsal skinfold window chamber system, we have demonstrated for what we believe to be the first time the entire course of AVM formation in subdermal blood vessels by using intravital bright-field images, hyperspectral imaging, fluorescence recordings of direct arterial flow through the AV shunts, and vascular casting techniques. We believe our data provide novel insights into the pathogenetic mechanisms of HHT and potential therapeutic approaches.

New Method to Quantify Angiogenesis in vivo Using Multi-photon Imaging

http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=6828756
Tuesday, September 1, 2009

B. J. Herrona, J. S. Smitha and R. W. Colea

Efforts to understand the basic mechanisms of angiogenesis, that is, the formation of new blood vessels from existing vasculature, have been limited by the methods that are currently used to measure vessel growth. Although in vivo assays provide the best environment in which to track angiogenesis, inherent difficulties in obtaining reproducible data limit the power of this approach. Limitations include: environmental variations between experimental animals, induction of inflammatory responses by surgical methods, and labor-intensive blood vessel quantification procedures. A better assay would measure vessel growth in one animal at multiple time points and would focus on minimization of artifacts induced by experimental manipulation.

Quantitative two-photon imaging of blood flow in cortex

http://www.physics.ucsd.edu/~a2shih/papers/Driscoll%20J%20CSHL%202009.pdf
Monday, July 27, 2009

Jonathan D. Driscoll, Andy Y. Shih, Patrick J. Drew, Ilya Valmianski andDavid Kleinfeld

Abstract

Cerebral blood flow plays a central role in maintaining homeostasis in the brain, and its dysfunction leads pathological conditions such as stroke. Moreover, understanding the dynamics of blood flow is central to the interpretation of data from imaging modalities, such as intrinsic optical signaling and functional magnetic resonance imaging, that rely on changes in cerebral blood flow and oxygen level to infer changes in the underlying neural activity. Recent advances in imaging techniques have allowed detailed studies of blood flow in vivo at high spatial and temporal resolutions. We discuss techniques to accurately measure cerebral blood flow at the level of individual blood vessels using two-photon laserscanning microscopy. By directing the scanning laser along a user-defined path, it is possible to measure red blood cell velocity, as well as vessel diameter, across multiple vessels near simultaneously. The combination of these measurements allows accurate assessment of total flux with

sufficient time resolution to measure fast modulations in flux, such as those caused by heart-beat, as well as slower signals caused by vasomotion and hemodynamic responses to stimulus.

A Novel Method to Quantify Angiogenesis in vivo Using Multi-photon Imaging

http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=5908400
Wednesday, July 1, 2009
R Cole, J Smith and B Herron

... Vital signs were monitored with the MouseOx system, Starr Life Science Corp. (Oakmount PA) throughout all procedures. Animals were given a tail vein injection of 70kD FITC conjugated dextran (Sigma Aldrich, St, Louis MO) before each imaging session. ...

Dendra2 Photoswitching through the Mammary Imaging Window

http://www.jove.com/video/1278/dendra2-photoswitching-through-the-mammary-imaging-window?ID=1278
Friday, June 5, 2009

Gligorijevic , B., Kedrin, D., Segall, J. E., Condeelis, J., van Rheenen

In the last decade, intravital microscopy of breast tumors in mice and rats at single-cell resolution1-4 has resulted in important insights into mechanisms of metastatic behavior such as migration, invasion and intravasation of tumor cells5, 6, angiogenesis3 and immune cells response7-9. We have recently reported a technique to image orthotopic mammary carcinomas over multiple intravital imaging sessions in living mice10. For this, we have developed a Mammary Imaging Window (MIW) and optimized imaging parameters for Dendra211 photoswitching and imaging in vivo. Here, we describe the protocol for the manufacturing of MIW, insertion of the MIW on top of a tumor and imaging of the Dendra2- labeled tumor cells using a custom built imaging box. This protocol can be used to image the metastatic behavior of tumor cells in distinct microenvironments in tumors and allows for long term imaging of blood vessels, tumor cells and host cells.

Two-Photon Imaging during Prolonged Middle Cerebral Artery Occlusion in Mice Reveals Recovery of Dendritic Structure after Reperfusion

http://www.jneurosci.org/content/28/46/11970.abstract
Wednesday, November 12, 2008

Ping Li and Timothy H. Murphy

Abstract

Filament occlusion of the middle cerebral artery (MCA) is a well accepted animal model of focal ischemia. Advantages of the model are relatively long occlusion times and a large penumbra region that simulates aspects of human stroke. Here, we use two-photon and confocal microscopy in combination with regional measurement of blood flow using laser speckle to assess the spatial relationship between the borders of the MCA ischemic territory and loss of dendrite structure, as well as the effect of reperfusion on dendritic damage in adult YFP (yellow fluorescent protein) and GFP (green fluorescent protein) C57BL/6 transgenic mice with fluorescent (predominantly layer 5) neurons. By examining the spatial extent of dendritic damage, we determined that 60 min of MCA occlusion produced a core with severe structural damage that did not recover after reperfusion (begins ~3.8 mm lateral to midline), a reversibly damaged area up to 0.6 mm medial to the core that recovered after reperfusion (penumbra), and a relatively structurally intact area (~1 mm wide; medial penumbra) with hypoperfusion. Loss of structure was preceded by a single ischemic depolarization 122.1 ± 10.2 s after occlusion onset. Reperfusion of animals after 60 min of ischemia was not associated with exacerbation of damage (reperfusion injury) and resulted in a significant restoration of blebbed dendritic structure, but only within ~0.6 mm lateral of the dendritic damage structural border. In summary, we find that recovery of dendritic structure can occur after reperfusion after even 60 min of ischemia, but is likely restricted to a relatively small penumbra region with partial blood flow or oxygenation.

Chemical calcium indicators

http://www.sciencedirect.com/science/article/pii/S104620230800159X
Thursday, October 16, 2008

R. Madelaine Paredes, Julie C. Etzler, Lora Talley Watts, Wei Zheng, James D. Lechleiter

Our understanding of the underlying mechanisms of Ca2+ signaling as well as our appreciation for its ubiquitous role in cellular processes has been rapidly advanced, in large part, due to the development of fluorescent Ca2+ indicators. In this chapter, we discuss some of the most common chemical Ca2+ indicators that are widely used for the investigation of intracellular Ca2+ signaling. Advantages, limitations and relevant procedures will be presented for each dye including their spectral qualities, dissociation constants, chemical forms, loading methods and equipment for optimal imaging. Chemical indicators now available allow for intracellular Ca2+ detection over a very large range (<50 nM to >50 μM). High affinity indicators can be used to quantify Ca2+ levels in the cytosol while lower affinity indicators can be optimized for measuring Ca2+ in subcellular compartments with higher concentrations. Indicators can be classified into either single wavelength or ratiometric dyes. Both classes require specific lasers, filters, and/or detection methods that are dependent upon their spectral properties and both classes have advantages and limitations. Single wavelength indicators are generally very bright and optimal for Ca2+ detection when more than one fluorophore is being imaged. Ratiometric indicators can be calibrated very precisely and they minimize the most common problems associated with chemical Ca2+ indicators including uneven dye loading, leakage, photobleaching, and changes in cell volume. Recent technical advances that permit *in vivo* Ca2+measurements will also be discussed.

Molecular Imaging in Oncology

http://books.google.com/books?hl=en&lr=&id=OMoKGGG25aEC&oi=fnd&pg=PA377&dq=+%22starr+life%22&ots=jJHas6WfY4&sig=_4UHOicwPWJ6Atj-FczbMBTn9eg
Monday, October 13, 2008

Martin G. Pomper

With molecular imaging becoming one the fastest growing topics in medical schools, Informa Healthcare presents Molecular Imaging in Oncology, the first comprehensive reference on molecular imaging in oncology. Filled with over 500 high-resolution color images exhibiting diagnostic and therapeutic capabilities of molecular imaging in cancer, this text outlines all procedures for the radiologists, radiology physicists, and oncologists in a concise single source guide.

Visualizing stromal cell dynamics in different tumor microenvironments by spinning disk confocal microscopy

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2562195/
Thursday, September 18, 2008

Mikala Egeblad,Andrew J. Ewald,Hanne A. Askautrud,Morgan L. Truitt, Bryan E. Welm,Emma Bainbridge, George Peeters, Matthew F. Krummel, and Zena Werb

The tumor microenvironment consists of stromal cells and extracellular factors that evolve in parallel with carcinoma cells. To gain insights into the activities of stromal cell populations, we developed and applied multicolor imaging techniques to analyze the behavior of these cells within different tumor microenvironments in the same live mouse. We found that regulatory T-lymphocytes (Tregs) migrated in proximity to blood vessels. Dendritic-like cells, myeloid cells and carcinoma-associated fibroblasts all exhibited higher motility in the microenvironment at the tumor periphery than within the tumor mass. Since oxygen levels differ between tumor microenvironments, we tested if acute hypoxia could account for the differences in cell migration. Direct visualization revealed that Tregs ceased migration under acute systemic hypoxia, whereas myeloid cells continued migrating. In the same mouse and microenvironment, we experimentally subdivided the myeloid cell population and revealed that uptake of fluorescent dextran defined a low-motility subpopulation expressing markers of tumor-promoting, alternatively

activated macrophages. In contrast, fluorescent anti-Gr1 antibodies marked myeloid cells patrolling inside tumor vessels and in the stroma. Our techniques allow real-time combinatorial analysis of cell populations based on spatial location, gene expression, behavior and cell surface molecules within intact tumors. The techniques are not limited to investigations in cancer, but could give new insights into cell behavior more broadly in development and disease.

Two-Photon Imaging of Stroke Onset In Vivo Reveals That NMDA-Receptor Independent Ischemic Depolarization Is the Major Cause of Rapid Reversible Damage to Dendrites and Spines

http://neuro.cjb.net/content/28/7/1756.abstract
Wednesday, February 13, 2008

Timothy H. Murphy, Ping Li, Kellen Betts, and Richard Liu

Abstract
We adapt a mouse global ischemia model to permit rapid induction of ischemia and reperfusion in conjunction with two-photon imaging to monitor the initial ionic, structural, and functional implications of brief interruptions of blood flow (6–8 min) *in vivo*. After only 2–3 min of global ischemia, a wide spread loss of mouse somatosensory cortex apical dendritic structure is initiated during the passage of a propagating wave (3.3 mm/min) of ischemic depolarization. Increases in intracellular calcium levels occurred during the wave of ischemic depolarization and were coincident with the loss of dendritic structure, but were not triggered by reperfusion. To assess the role of NMDA receptors, we locally applied the antagonist MK-801 [(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5,10-imine maleate] at concentrations sufficient to fully block local NMDA agonist-evoked changes in intracellular calcium levels *in vivo*. Changes in dendritic structure and intracellular calcium levels were independent of NMDA receptor activation. Local application of the non-NMDA glutamate receptor antagonist CNQX also failed to block ischemic depolarization or rapid changes in dendrite structure. Within 3–5 min of reperfusion, damage ceased and restoration of synaptic structure occurred over 10–60 min. In contrast to a reperfusion promoting damage, over this time scale, the majority of spines and dendrites regained their original structure during reperfusion. Intrinsic optical signal imaging of sensory evoked maps indicated that reversible alteration in dendritic structure during reperfusion was accompanied by restored functional maps. Our results identify glutamate receptor-independent ischemic depolarization as the major ionic event associated with disruption of synaptic structure during the first few minutes of ischemia *in vivo*.

Characterization And Feasibility Study Of A Near Infrared CCD Imager For Monitoring Tumor Hemodynamics

https://dspace.uta.edu/handle/10106/425
Thursday, August 23, 2007

Goel, Manan

Prostate cancer is one of the most common types of cancers diagnosed among North American men. Chemotherapy is generally used to target advanced metastatic prostate cancer. Near infrared spectroscopy (NIRS) has been previously investigated to monitor the hemodynamic changes in rat prostate tumors; however, the previous study with NIRS is limited by its spatial resolution. The goal of this study is to characterize an NIR, CCD imager and to explore the feasibility of using the CCD imager to non-invasively monitor hemodynamic changes in rat prostate tumors during gas intervention. Firstly, studies were conducted to characterize the CCD imager and understand the propagation of photons through simulated tissue phantoms. These results aid our understanding of light propagation through a uniform medium and detection of photons by the NIR, CCD imager. Secondly, experiments were performed to study the feasibility of the imager to monitor hemodynamic changes in rat prostate tumors during gas intervention. Adult male Copenhagen rats implanted with prostate carcinoma on the fore back were used in this study. Cyclophosphamide, a chemotherapeutic agent, was administered to treat the rat prostate tumors, and pure oxygen was used as gas intervention to introduce hemodynamic perturbation in the tumors during the measurements. After the CCD images were taken at multiple NIR wavelengths, for comparison with the previous records, the images were processed and integrated to provide global temporal files of various hemodynamic parameters for three different groups of rats. A few topographic hemodynamic maps were also obtained, showing spatial heterogeneity within the tumors. The animal experimental results also support the efficacy of cyclophosphamide to be effective in inhibiting

the growth of prostate carcinoma. Furthermore, the animal data reveals possible experimental sources causing instability of the measured NIR signals. Overall, this initial study basically demonstrates the feasibility of using a multi-wavelength NIR CCD imager for non-invasively monitoring tumor regional hemodynamics.

Imaging the Impact of Cortical Microcirculation on Synaptic Structure and Sensory-Evoked Hemodynamic Responses In Vivo

http://www.plosbiology.org/article/info:doi/10.1371/journal.pbio.0050119
Tuesday, May 1, 2007

Shengxiang Zhang and Timothy H. Murphy

In vivo two-photon microscopy was used to image in real time dendrites and their spines in a mouse photothrombotic stroke model that reduced somatosensory cortex blood flow in discrete regions of cortical functional maps. This approach allowed us to define relationships between blood flow, cortical structure, and function on scales not previously achieved with macroscopic imaging techniques. Acute ischemic damage to dendrites was triggered within 30 min when blood flow over >0.2 mm2 of cortical surface was blocked. Rapid damage was not attributed to a subset of clotted or even leaking vessels (extravasation) alone. Assessment of stroke borders revealed a remarkably sharp transition between intact and damaged synaptic circuitry that occurred over tens of μm and was defined by a transition between flowing and blocked vessels. Although dendritic spines were normally ~13 μm from small flowing vessels, we show that intact dendritic structure can be maintained (in areas without flowing vessels) by blood flow from vessels that are on average 80 μm away. Functional imaging of intrinsic optical signals associated with activity-evoked hemodynamic responses in somatosensory cortex indicated that sensory-induced changes in signal were blocked in areas with damaged dendrites, but were present ~400 μm away from the border of dendritic damage. These results define the range of influence that blood flow can have on local cortical fine structure and function, as well as to demonstrate that peri-infarct tissues can be functional within the first few hours after stroke and well positioned to aid in poststroke recovery.

Vital Signs Monitoring During Surgery & Experiments Requiring Anesthesia

Non-stationarity and power spectral shifts in EMG activity reflect motor unit recruitment in rat diaphragm muscle

http://www.sciencedirect.com/science/article/pii/S1569904812002492
Tuesday, January 15, 2013

Yasin B. Sevena, Carlos B. Mantillaa, b, Wen-Zhi Zhana, Gary C. Sieck

... In addition to DIAm EMG recordings, respiratory rate and blood O 2 levels were also measured using a pulse oximeter (MouseOX, Starr Life Sciences Corp., Oakmont, PA). A return to baseline respiratory rate and normoxic levels ...

We hypothesized that a shift in diaphragm muscle (DIAm) EMG power spectral density (PSD) to higher frequencies reflects recruitment of more fatigable fast-twitch motor units and motor unit recruitment is reflected by EMG non-stationarity. DIAm EMG was recorded in anesthetized rats during eupnea, hypoxia-hypercapnia (10% O2–5% CO2), airway occlusion, and sneezing (maximal DIAm force). Although power in all frequency bands increased progressively across motor behaviors, PSD centroid frequency increased only during sneezing ($p < 0.05$). The non-stationary period at the onset of EMG activity ranged from ~80 ms during airway occlusion to ~150 ms during eupnea. Within the initial non-stationary period of EMG activity 80–95% of motor units were recruited during different motor behaviors. Motor units augmented their discharge frequencies progressively beyond the non-stationary period; yet, EMG signal became stationary. In conclusion, non-stationarity of DIAm EMG reflects the period of motor unit recruitment, while a shift in the PSD towards higher frequencies reflects recruitment of more fatigable fast-twitch motor units.

Automated measurement of blood flow velocity and direction and hemoglobin oxygen saturation in the rat lung using intravital microscopy

http://ajplung.physiology.org/content/early/2012/11/13/ajplung.00178.201...
Friday, November 16, 2012

Gabi Hanna, Andrew Fontanella, Gregory Palmer, Siqing Shan, Daniel R. Radiloff, Yulin Zhao, David C. Irwin, Karyn L. Hamilton, Alina Boico, Claude A. Piantadosi, Gert Blueschke, Mark W. Dewhirst, Timothy J McMahon, and Thies Schroeder

... Vital signs were monitored using pulse 74 oximetry (MouseOx, **Starr Life Sciences**, Oakmont, PA), with blood oxygenation and heart rate recorded. 75 **...** pressure. The ventilator was connected in line with an OxyDial oxygen blender (**Starr Life Sciences**). 83 **...**
Intravital microscopy of the pulmonary microcirculation in research animals is of great scientific interest for its utility in identifying regional changes in pulmonary microcirculatory blood flow. Although feasibility studies have been reported, the pulmonary window can be further refined into a practical tool for pharmaceutical research and drug development. We have established a method to visualize and quantify dynamic changes in three key features of lung function: microvascular red blood cell velocity, flow direction and hemoglobin saturation. These physiologic parameters were measured in an acute closed-chest pulmonary window which allows real-time images to be captured by fluorescence and multispectral absorption microscopy; images were subsequently quantified using computerized analysis. We validated the model by quantifying changes in microcirculatory blood flow and hemoglobin saturation in two ways: 1) after changes in inspired oxygen content, and 2) after pharmacological reduction of pulmonary blood flow via treatment with the beta-1 adrenergic receptor blocker metoprolol. This robust and relatively simple system facilitates pulmonary intravital microscopy in laboratory rats for pharmacological and physiological research.

Embolic middle cerebral artery occlusion model using thrombin and fibrinogen composed clots in rat

http://www.sciencedirect.com/science/article/pii/S0165027012003780
Thursday, November 15, 2012

Ming Ren, Zi-Jing Lin, Hai Qian, Gourav Roy Choudhury, Ran Liu, Hanli Liu, Shao-Hua Yang

... The breath rate, heart rate and oxygen saturation was monitored (MouseOx, Starr Life Science Corp, Oakmont, PA, USA) and be kept in the range of 45-65 bpm, 300-400 bpm, and >90% during the surgery, respectively (Table 3). With the aid of an operating microscope, the left ...

Ischemic stroke accounts for over 80% in total human stroke which mostly affect middle cerebral artery (MCA) territory. Embolic stroke models induced by injection of homologous clots into the internal carotid artery and MCA closely mimic human stroke and have been commonly used in stroke research. Studies indicate that the size and composition of clots are critical for the reproducibility of the stroke model. In the present study, we modified the homologous clots formation by addition of thrombin and fibrinogen which produced even distribution of fibrin with tight cross linkage of red blood cells. We optimized the embolic MCA occlusion model in rats using different size of the mixed clots. A precise lodgment of the clots at the MCA bifurcation and highly reproducible ischemic lesion in the MCA territory were demonstrated in the embolic MCA occlusion model induced by injection of 10 pieces of 1-mm long mixed clots made in PE-60 catheter. We further tested the effect of recombinant tissue plasminogen activator (rtPA) in this embolic MCA occlusion model. rtPA induced thrombolysis, improved neurological outcome, and significantly reduced ischemic lesion volume when administered at 1 h after embolism as compared with control. In summary, we have established a reproducible embolic MCA occlusion model using clots made of homologous blood, thrombin and fibrinogen. The mixed clots enable precise lodgment at the MCA bifurcation which is responsive to thrombolytic therapy of rtPA.

Systemic Injection of Kainic Acid Differently Affects LTP Magnitude Depending on its Epileptogenic Efficiency

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0048128
Wednesday, October 31, 2012

Luz M. Suárez, Elena Cid, Beatriz Gal, Marion Inostroza, Jorge R. Brotons-Mas, Daniel Gómez-Domínguez, Liset Menéndez de la Prida, José M. Solís

... resistant and n = 6 epileptic. For electrode implantation, animals were anesthetized with isofluorane (1.5–2%) in oxygen (30%) and continuously monitored with an oximeter (MouseOX, Starr Life Sci). Local field potential recordings ...

Seizures have profound impact on synaptic function and plasticity. While kainic acid is a popular method to induce seizures and to potentially affect synaptic plasticity, it can also produce physiological-like oscillations and trigger some forms of long-term potentiation (LTP). Here, we examine whether induction of LTP is altered in hippocampal slices prepared from rats with different sensitivity to develop status epilepticus (SE) by systemic injection of kainic acid. Rats were treated with multiple low doses of kainic acid (5 mg/kg; i.p.) to develop SE in a majority of animals (72–85% rats). A group of rats were resistant to develop SE (15–28%) after several accumulated doses. Animals were subsequently tested using chronic recordings and object recognition tasks before brain slices were prepared for histological studies and to examine basic features of hippocampal synaptic function and plasticity, including input/output curves, paired-pulse facilitation and theta-burst induced LTP. Consistent with previous reports in kindling and pilocapine models, LTP was reduced in rats that developed SE after kainic acid injection. These animals exhibited signs of hippocampal sclerosis and developed spontaneous seizures. In contrast, resistant rats did not become epileptic and had no signs of cell loss and mossy fiber sprouting. In slices from resistant rats, theta-burst stimulation induced LTP of higher magnitude when compared with control and epileptic rats. Variations on LTP magnitude correlate with animals' performance in a hippocampal-dependent spatial memory task. Our results suggest dissociable long-term effects of treatment with kainic acid on synaptic function and plasticity depending on its epileptogenic efficiency.

Methylene Blue as a Cerebral Metabolic and Hemodynamic Enhancer

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0046585
Tuesday, October 9, 2012

Ai-Ling Lin, Ethan Poteet, Fang Du, Roy C. Gourav, Ran Liu, Yi Wen, Andrew Bresnen, Shiliang Huang, Peter T. Fox, Shao-Hua Yang, Timothy Q. Duong

.. We continuously monitored respiration rate (90–130 bpm) and rectal temperature (37°C ±0.5°C). We recorded heart rate and blood oxygen saturation level (SaO 2) with a MouseOx system (STARR Life Science, Oakmont, PA) and maintained these parameters within reference ...

By restoring mitochondrial function, methylene blue (MB) is an effective neuroprotectant in many neurological disorders (e.g., Parkinson's and Alzheimer's diseases). MB has also been proposed as a brain metabolic enhancer because of its action on mitochondrial cytochrome c oxidase. We used in vitro and in vivo approaches to determine how MB affects brain metabolism and hemodynamics. For in vitro, we evaluated the effect of MB on brain mitochondrial function, oxygen consumption, and glucose uptake. For in vivo, we applied neuroimaging and intravenous measurements to determine MB's effect on glucose uptake, cerebral blood flow (CBF), and cerebral metabolic rate of oxygen (CMRO2) under normoxic and hypoxic conditions in rats. MB significantly increases mitochondrial complex I–III activity in isolated mitochondria and enhances oxygen consumption and glucose uptake in HT-22 cells. Using positron emission tomography and magnetic resonance imaging (MRI), we observed significant increases in brain glucose uptake, CBF, and CMRO2 under both normoxic and hypoxic conditions. Further, MRI revealed that MB dramatically increased CBF in the hippocampus and in the cingulate, motor, and frontoparietal cortices, areas of the brain affected by Alzheimer's and Parkinson's diseases. Our results suggest that MB can enhance brain metabolism and hemodynamics, and multimetric neuroimaging systems offer a noninvasive, nondestructive way to evaluate treatment efficacy.

Adenosine increases nasal mucociliary clearance rate in mice through A2A and A2B adenosine receptors†

http://onlinelibrary.wiley.com/doi/10.1002/lary.23586/abstract?deniedAccessCustomisedMessage=&userIsAuthenticated=false
Monday, September 10, 2012

Xiaoyang Hua MD, Warren C. Naselsky BS, William D. Bennett PhD, Catherine Ledent PhD, Brent A. Senior MD, Stephen L. Tilley MD

... Mouse body temperature was maintained by using a heating pad. Oxygen saturation and heart rate of tested mice were monitored during the experiments using the MouseOx™ pulse oximeter (STARR Life Sciences, Oakmont, PA). ...
Objectives/Hypothesis:
Mucociliary clearance (MCC) is an important mechanism of host defense in the upper and lower respiratory tract. Impaired MCC plays a critical role in the development and perpetuation of chronic rhinosinusitis (CRS). The aim of this investigation was to determine the influence of adenosine on nasal MCC, and to determine the receptors mediating this physiology in vivo.

Study Design:
Prospective study using an animal model.

Methods:
Nasal MCC was measured by whole-nose scintigraphic acquisition in vivo. The effects of both endogenous and exogenous adenosine were investigated in wild-type and adenosine receptor knockout (A, A, AA, and A A) mice.

Results:
Exogenous adenosine aerosol robustly enhanced nasal MCC. The augmentation of MCC by adenosine was abolished in mice lacking both A2A and A2B receptors, but remained robust in mice lacking either A2A or A2B. Likewise, basal nasal MCC was reduced in mice lacking both the A2A and A2B receptors, but was statistically identical among wild-type mice and mice lacking either A2A or A2B.

Conclusions:
These findings indicate that activation of both Gs-coupled adenosine receptors can accelerate nasal MCC. Targeting these receptors may represent a novel therapeutic approach for enhancing MCC in CRS. Laryngoscope, 2012

Acid-sensing ion channels contribute to chemosensitivity of breathing-related neurons of the nucleus of the solitary tract

http://onlinelibrary.wiley.com/doi/10.1113/jphysiol.2012.232470/abstract?deniedAccessCustomisedMessage=&userIsAuthenticated=false
Friday, September 7, 2012

Rafiq Huda, Sarah L. Pollema-Mays, Zheng Chang, George F. Alheid, Donald R. McCrimmon, Marco Martina

... Rectal temperature was monitored and maintained at 36.5–38.5°C by means of a thermistor-controlled heating pad and heat lamp. Oxygen saturation and heart rate were monitored throughout surgery via a pulse oximeter (Mouse Ox, Starr Life Sciences Oakmont, PA, USA). ...

Cellular mechanisms of central pH chemosensitivity remain largely unknown. The nucleus of the solitary tract (NTS) integrates peripheral afferents with central pathways controlling breathing; NTS neurons function as central chemosensors, but only limited information exists concerning the ionic mechanisms involved. Acid-sensing ion channels (ASICs) mediate chemosensitivity in nociceptive terminals, where pH values ~6.5 are not uncommon in inflammation, but are also abundantly expressed throughout the brain where pH is tightly regulated and their role is less clear. Here we test the hypothesis that ASICs are expressed in NTS neurons and contribute to intrinsic chemosensitivity and control of breathing. In electrophysiological recordings from acute rat NTS slices, ~40% of NTS neurons responded to physiological acidification (pH 7.0) with a transient depolarization. This response was also present in dissociated neurons suggesting an intrinsic mechanism. In voltage clamp recordings in slices, a pH drop from 7.4 to 7.0 induced ASIC-like inward currents (blocked by 100 μm amiloride) in ~40% of NTS neurons, while at pH ≤ 6.5 these currents were detected in all neurons tested; RT-PCR revealed expression of ASIC1 and, less abundantly, ASIC2 in the NTS. Anatomical analysis of dye-filled neurons showed that ASIC-dependent chemosensitive cells (cells responding to pH 7.0) cluster dorsally in the NTS. Using in vivo retrograde labelling from the ventral respiratory column, 90% (9/10) of the labelled neurons showed an ASIC-like response to pH 7.0, suggesting that ASIC currents contribute to control of breathing. Accordingly, amiloride injection into the NTS reduced phrenic nerve activity of anaesthetized rats with an elevated arterial .

Introduction of a Rabbit Carotid Artery Model for Sonothrombolysis Research

http://link.springer.com/article/10.1007%2Fs12975-012-0194-5?LI=true
Saturday, September 1, 2012

Thilo Hölscher, David J. Fisher, Golnaz Ahadi, Arne Voie

.. For the surgical procedure, the animals were placed in supine position into a custom- ized, MRI-compatible rabbit holder and connected to a monitoring device (MouseOx™, STARR Lifesciences Corp., Oakmont, PA, USA) to control the vital signs during the procedure (Fig. ...

The goal of this study was to develop an in vivo sonothrombolysis model for stroke research. The rabbit carotid artery has average vessel diameters similar to human M1/M2 segments and allows generation of a thrombotic occlusion using various kinds of thrombus material as well as thrombus placement under visual control. It further allows real-time monitoring of flow and clot mechanics during the sonothrombolysis procedure using high-frequency diagnostic ultrasound. In the present study, the model will be introduced and first results to show feasibility using diagnostic as well as high-intensity focused ultrasound will be presented

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Reduced Ocular Blood Flow as an Early Indicator of Diabetic Retinopathy in a Mouse Model of Diabetes

http://www.iovs.org/content/53/10/6488.short
Tuesday, August 21, 2012

Eric R. Muir, René C. Rentería and Timothy Q. Duong

... Respiration rate, heart rate, and oxygen saturation were monitored (MouseOx; STARR Life Science Corp., Oakmont, PA) and maintained by adjusting the isoflurane level. MRI was performed on a 7-T, 30-cm horizontal magnet with a 1500-mT/m gradient (Bruker, Billerica, MA). ...

Purpose. To investigate ocular blood flow and visual function in the Ins2Akita diabetic retinopathy mouse model at early and late time points after onset of hyperglycemia.

Methods. Mice heterozygous for the Ins2Akita mutation, which become hyperglycemic at approximately 4 weeks old, were studied at 2.5 and 7.5 months of age, with age-matched wild-type littermates used as controls. Retinal and choroidal blood flows were noninvasively imaged at 42 × 42 × 400 μm using magnetic resonance imaging. Visual function was measured using optokinetic tracking to determine spatial frequency and contrast thresholds from the same mice.

Results. At 2.5 months, choroidal blood flow was significantly reduced ($P < 0.01$) by 20% in Ins2Akita mice ($n = 13$) compared with age-matched controls ($n = 16$), whereas retinal blood flow and visual function were not significantly affected ($P > 0.05$). At 7.5 months, both choroidal and retinal blood flow were significantly reduced ($P < 0.05$) by 27% and 28%, respectively, in Ins2Akita mice ($n = 11$) compared with age-matched controls ($n = 15$). Visual functions were also significantly worse ($P < 0.05$) in Ins2Akita mice at 7.5 months, as indicated by a 19% decreased spatial frequency threshold and 135% increased contrast threshold compared with age-matched controls. The magnitudes of the blood flow and vision deficits, however, were not correlated.

Conclusions. Although both choroidal and retinal blood flow and vision were altered after prolonged diabetes in the Ins2Akita mouse, choroidal blood flow was reduced even in young diabetic animals, suggesting ocular blood flow deficit could be an early pathological change in diabetic retinopathy.

In Vivo Alterations in Calcium Buffering Capacity in Transgenic Mouse Model of Synucleinopathy

http://www.jneurosci.org/content/32/29/9992.short
Wednesday, July 18, 2012

Lidia Reznichenko, Qun Cheng, Krystal Nizar, Sergey L. Gratiy, Payam A. Saisan, Edward M. Rockenstein, Tanya González, Christina Patrick, Brian Spencer, Paula Desplats, Anders M. Dale, Anna Devor, and Eliezer Masliah1

.. Expired CO 2 (CI240, Columbus instruments), heart rate, and blood O 2 saturation (Mouse OX, STARR), blood pressure (BP1, WPI), and body temperature (Homeothermic blanket, Harvard Apparatus) were monitored continuously. ...

Abnormal accumulation of α-synuclein is centrally involved in the pathogenesis of many disorders with Parkinsonism and dementia. Previous in vitro studies suggest that α-synuclein dysregulates intracellular calcium. However, it is unclear whether these alterations occur in vivo. For this reason, we investigated calcium dynamics in transgenic mice expressing human WT α-synuclein using two-photon microscopy. We imaged spontaneous and stimulus-induced neuronal activity in the barrel cortex. Transgenic mice exhibited augmented, long-lasting calcium transients characterized by considerable deviation from the exponential decay. The most evident pathology was observed in response to a repetitive stimulation in which subsequent stimuli were presented before relaxation of calcium signal to the baseline. These alterations were detected in the absence of significant increase in neuronal spiking response compared with age-matched controls, supporting the possibility that α-synuclein promoted alterations in calcium dynamics via interference with intracellular buffering mechanisms. The characteristic shape of calcium decay and augmented response during repetitive stimulation can serve as in vivo imaging biomarkers in this model of neurodegeneration, to monitor progression of the disease and screen candidate treatment strategies.

Amyloid-ß-dependent compromise of microvascular structure and function in a model of Alzheimer's disease

http://brain.oxfordjournals.org/content/135/10/3039.short
Friday, July 13, 2012

A Dorr, B Sahota, LV Chinta, ME Brown, AY Lai, K Ma…

... End-tidal respiratory pressure, temperature, oxygen saturation, breath and pulse distention and heart rate were recorded throughout surgery and imaging (Biopac MP150, Biopac Systems Inc.; MouseOx, **Starr Life Sciences** Corp.). Image acquisition. ...

The majority of patients with Alzheimer's disease have cerebral amyloid angiopathy, thus showing deposition of amyloid-ß peptides in the walls of leptomeningeal and cortical arterioles. These deposits are believed to result from impaired clearance of parenchymal amyloid-ß peptides. In the current work, we examined the changes in cortical microvascular structure and function in situ in TgCRND8, a transgenic mouse model of Alzheimer's disease. In contrast to venules, cortical arterioles were shown to increase in tortuosity and decrease in calibre with amyloid-ß peptide accumulation. These structural changes were accompanied by progressive functional compromise, reflected in higher dispersion of microvascular network transit times, elongation of the transit times, and impaired microvascular reactivity to hypercapnia in the transgenic mice. Moreover, inhibition of amyloid-ß peptide oligomerization and fibrillization via post-weaning administration of scyllo-inositol, a naturally occurring stereoisomer of myo-inositol, rescued both structural and functional impairment of the cortical microvasculature in this Alzheimer's disease model. These results demonstrate that microvascular impairment is directly correlated with amyloid-ß accumulation and highlight the importance of targeting cerebrovascular amyloid angiopathy clearance for effective diagnosis, monitoring of disease progression and treatment of Alzheimer's disease.

Commensal Bacteria Calibrate the Activation Threshold of Innate Antiviral Immunity

http://www.cell.com/immunity/retrieve/pii/S1074761312002373
Thursday, June 14, 2012

Michael C. Abt, Lisa C. Osborne, Laurel A. Monticelli, Travis A. Doering, Theresa Alenghat, Gregory F. Sonnenberg, Michael A. Paley, Marcelo Antenus, Katie L. Williams, Jan Erikson, E. John Wherry, David Artis

Signals from commensal bacteria can influence immune cell development and susceptibility to infectious or inflammatory diseases. However, the mechanisms by which commensal bacteria regulate protective immunity after exposure to systemic pathogens remain poorly understood. Here, we demonstrate that antibiotic-treated (ABX) mice exhibit impaired innate and adaptive antiviral immune responses and substantially delayed viral clearance after exposure to systemic LCMV or mucosal influenza virus. Furthermore, ABX mice exhibited severe bronchiole epithelial degeneration and increased host mortality after influenza virus infection. Genome-wide transcriptional profiling of macrophages isolated from ABX mice revealed decreased expression of genes associated with antiviral immunity. Moreover, macrophages from ABX mice exhibited defective responses to type I and type II IFNs and impaired capacity to limit viral replication. Collectively, these data indicate that commensal-derived signals provide tonic immune stimulation that establishes the activation threshold of the innate immune system required for optimal antiviral immunity.

Tumor Blood Flow Differs between Mouse Strains: Consequences for Vasoresponse to Photodynamic Therapy

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0037322
Friday, May 18, 2012

Mesquita RC, Han SW, Miller J, Schenkel SS, Pole A, et al.

Fluctuations in tumor blood flow are common and attributed to factors such as vasomotion or local vascular structure, yet, because vessel structure and physiology are host-derived, animal strain of tumor propagation may further determine blood flow characteristics. In the present report, baseline and stress-altered tumor hemodynamics as a function of murine strain were studied using radiation-induced fibrosacomas (RIF) grown in C3H or nude mice. Fluctuations in tumor blood flow during one hour of baseline monitoring or during vascular stress induced by photodynamic therapy (PDT) were measured by diffuse correlation spectroscopy. Baseline monitoring revealed fluctuating tumor blood flow highly correlated with heart rate and with similar median periods (i.e., ~9 and 14 min in C3H and nudes, respectively). However, tumor blood flow in C3H animals was more sensitive to physiologic or stress-induced perturbations. Specifically, PDT-induced vascular insults produced greater decreases in blood flow in the tumors of C3H versus nude mice; similarly, during baseline monitoring, fluctuations in blood flow were more regular and more prevalent within the tumors of C3H mice versus nude mice; finally, the vasoconstrictor L-NNA reduced tumor blood flow in C3H mice but did not affect tumor blood flow in nudes. Underlying differences in vascular structure, such as smaller tumor blood vessels in C3H versus nude animals, may contribute to strain-dependent variation in vascular function. These data thus identify clear effects of mouse strain on tumor hemodynamics with consequences to PDT and potentially other vascular-mediated therapies.

Extracellular DNA traps are associated with the pathogenesis of TRALI in humans and mice

http://bloodjournal.hematologylibrary.org/content/119/26/6335.short
Thursday, May 17, 2012

Grace M. Thomas, Carla Carbo, Brian R. Curtis, Kimberly Martinod Irina B. Mazo, Daphne Schatzberg, Stephen M. Cifuni, Tobias A. Fuchs, Ulrich H. von Andrian, John H. Hartwig Richard H. Aster, and Denisa D. Wagner

... Rectal temperatures were measured as an indicator of shock-like condition 2 hours after anti–H-2K d infusion using a rectal temperature probe (MouseOx Plus system; STARR Life Sciences) connected to a PowerLab data acquisition system (ADInstruments). ...

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related death. The biologic processes contributing to TRALI are poorly understood. All blood products can cause TRALI, and no specific treatment is available. A “2-event model” has been proposed as the trigger. The first event may include surgery, trauma, or infection; the second involves the transfusion of antileukocyte antibodies or bioactive lipids within the blood product. Together, these events induce neutrophil activation in the lungs, causing endothelial damage and capillary leakage. Neutrophils, in response to pathogens or under stress, can release their chromatin coated with granule contents, thus forming neutrophil extracellular traps (NETs). Although protective against infection, these NETs are injurious to tissue. Here we show that NET biomarkers are present in TRALI patients' blood and that NETs are produced in vitro by primed human neutrophils when challenged with anti–HNA-3a antibodies previously implicated in TRALI. NETs are found in alveoli of mice experiencing antibody-mediated TRALI. DNase 1 inhalation prevents their alveolar accumulation and improves arterial oxygen saturation even when administered 90 minutes after TRALI onset. We suggest that NETs form in the lungs during TRALI, contribute to the disease process, and thus could be targeted to prevent or treat TRALI.

SUB-SURFACE, FEMTOSECOND LASER INCISIONS AS A THERAPY FOR PARTIAL EPILEPSY

http://courses2.cit.cornell.edu/schafferlab/wp-content/uploads/Fetcho-Robert-Honors-Thesis.pdf
Tuesday, May 1, 2012

Robert N. Fetcho

... Heart rate and arterial oxygen saturation were monitored at all times using a pulse oximeter (MouseOx; Starr Life Sciences Corp., Oakmont, PA, USA). Subcutaneous injections of 5% glucose in saline (1mL/kg) were administered hourly for to maintain hydration of the animal. ...

Diet-induced obesity severely impairs myelinated aortic baroreceptor reflex responses

http://ajpheart.physiology.org/content/302/10/H2083.short
Wednesday, March 7, 2012

Belinda H. McCully, Virginia L. Brooks, and Michael C. Andresen

Abstract

Diet-induced obesity (DIO) attenuates the arterial cardiac baroreceptor reflex, but the mechanisms and sites of action are unknown. This study tested the hypothesis that DIO impairs central aortic baroreceptor pathways. Normal chow control (CON) and high-fat-chow obesity-resistant (OR) and obesity-prone (OP) rats were anesthetized (inactin, 120 mg/kg) and underwent sinoaortic denervation. The central end of the aortic depressor nerve (ADN) was electrically stimulated to generate frequency-dependent baroreflex curves (5–100 Hz) during selective activation of myelinated (A-fiber) or combined (A- and C-fiber) ADN baroreceptors. A mild stimulus (1 V) that activates only A-fiber ADN baroreceptors induced robust, frequency-dependent depressor and bradycardic responses in CON and OR rats, but these responses were completely abolished in OP rats. Maximal activation of A fibers (3 V) elicited frequency-dependent reflexes in all groups, but a dramatic deficit was still present in OP rats. Activation of all ADN

baroreceptors (20 V) evoked even larger reflex responses. Depressor responses were nearly identical among groups, but OP rats still exhibited attenuated bradycardia. In separate groups of rats, the reduced heart rate (HR) response to maximal activation of ADN A fibers (3 V) persisted in OP rats following pharmacological blockade of ß1-adrenergic or muscarinic receptors, suggesting deficits in both parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) reflex pathways. However, the bradycardic responses to direct efferent vagal stimulation were similar among groups. Taken together, our data suggest that DIO severely impairs the central processing of myelinated aortic baroreceptor control of HR, including both PNS and SNS components.

S Phase Entry of Neural Progenitor Cells Correlates with Increased Blood Flow in the Young Subventricular Zone

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0031960
Thursday, February 16, 2012

Lacar B, Herman P, Hartman NW, Hyder F, Bordey A

The postnatal subventricular zone (SVZ) contains proliferating neural progenitor cells in close proximity to blood vessels. Insults and drug treatments acutely stimulate cell proliferation in the SVZ, which was assessed by labeling cells entering S phase. Although G1-to-S progression is metabolically demanding on a minute-to-hour time scale, it remains unknown whether increased SVZ cell proliferation is accompanied by a local hemodynamic response. This neurovascular coupling provides energy substrates to active neuronal assemblies. Transcardial dye perfusion revealed the presence of capillaries throughout the SVZ that constrict upon applications of the thromboxane A2 receptor agonist U-46119 in acute brain slice preparations. We then monitored in vivo blood flow using laser Doppler flowmetry via a microprobe located either in the SVZ or a mature network. U-46119 injections into the lateral ventricle decreased blood flow in the SVZ and the striatum, which are near the ventricle. A 1-hour ventricular injection of epidermal and basic fibroblast growth factor (EGF and bFGF) significantly increased the percentage of Sox2 transcription factor-positive cells in S phase 1.5 hours post-injection. This increase was accompanied by a sustained rise in blood flow in the SVZ but not in the striatum. Direct growth factor injections into the cortex did not alter local blood flow, ruling out direct effects on capillaries. These findings suggest that an acute increase in the number of G1-to-S cycling SVZ cells is accompanied by neurometabolic-vascular coupling, which may provide energy and nutrient for cell cycle progression.

Staphylococcus aureus α-Hemolysin Mediates Virulence in a Murine Model of Severe Pneumonia Through Activation of the NLRP3 Inflammasome

http://jid.oxfordjournals.org/content/205/5/807.short
Wednesday, January 25, 2012

Chahnaz Kebaier, Robin R. Chamberland, Irving C. Allen, Xi Gao, Peter M. Broglie, Joshua D. Hall, Corey Jania, Claire M. Doerschuk, Stephen L. Tilley and Joseph A. Duncan

Abstract

Staphylococcus aureus is a dangerous pathogen that can cause necrotizing infections characterized by massive inflammatory responses and tissue destruction. Staphylococcal α-hemolysin is an essential virulence factor in severe S. aureus pneumonia. It activates the nucleotide-binding domain and leucine-rich repeat containing gene family, pyrin domain containing 3 (NLRP3) inflammasome to induce production of interleukin-1ß and programmed necrotic cell death. We sought to determine the role of α-hemolysin–mediated activation of NLRP3 in the pathogenesis of S. aureus pneumonia. We show that α-hemolysin activates the NLRP3 inflammasome during S. aureus pneumonia, inducing necrotic pulmonary injury. Moreover, Nlrp3−/− mice have less-severe pneumonia. Pulmonary injury induced by isolated α-hemolysin or live S. aureus is independent of interleukin-1ß signaling, implicating NLRP3-induced necrosis in the pathogenesis of severe infection. This work demonstrates the exploitation of host inflammatory signaling by S. aureus and suggests the NLRP3 inflammasome as a potential target for pharmacologic interventions in severe S. aureus infections.

α4* Nicotinic Acetylcholine Receptors Modulate Experience-Based Cortical Depression in the Adult Mouse Somatosensory Cortex

http://www.neuro.cjb.net/content/32/4/1207.short
Wednesday, January 25, 2012

Craig E. Brown, Danielle Sweetnam, Maddie Beange, Patrick C. Nahirney, and Raad Nashmi

The molecular mechanisms that mediate experience-based changes in the function of the cerebral cortex, particularly in the adult animal, are poorly understood. Here we show using in vivo voltage-sensitive dye imaging, that whisker trimming leads to depression of whisker-evoked sensory responses in primary, secondary and associative somatosensory cortical regions. Given the importance of cholinergic neurotransmission in cognitive and sensory functions, we examined whether α4-containing (α4*) nicotinic acetylcholine receptors (nAChRs) mediate cortical depression. Using knock-in mice that express YFP-tagged α4 nAChRs subunits, we show that whisker trimming selectively increased the number α4*-YFP nAChRs in layer 4 of deprived barrel columns within 24 h, which persisted until whiskers regrew. Confocal and electron microscopy revealed that these receptors were preferentially increased on the cell bodies of GABAergic neurons. To directly link these receptors with functional cortical depression, we show that depression could be induced in normal mice by topical application or micro-injection of α4* nAChR agonist in the somatosensory cortex. Furthermore, cortical depression could be blocked after whisker trimming with chronic infusions of an α4* nAChR antagonist. Collectively, these results uncover a new role for α4* nAChRs in regulating rapid changes in the functional responsiveness of the adult somatosensory cortex.

Hemodynamic Responses Evoked by Neuronal Stimulation via Channelrhodopsin-2 Can Be Independent of Intracortical Glutamatergic Synaptic Transmission

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0029859
Tuesday, January 10, 2012

Nadia A. Scott, Timothy H. Murphy

Maintenance of neuronal function depends on the delivery of oxygen and glucose through changes in blood flow that are linked to the level of ongoing neuronal and glial activity, yet the underlying mechanisms remain unclear. Using transgenic mice expressing the light-activated cation channel channelrhodopsin-2 in deep layer pyramidal neurons, we report that changes in intrinsic optical signals and blood flow can be evoked by activation of a subset of channelrhodopsin-2-expressing neurons in the sensorimotor cortex. We have combined imaging and pharmacology to examine the importance of glutamatergic synaptic transmission in this form of neurovascular coupling. Blockade of ionotropic glutamate receptors with the antagonists CNQX and MK801 significantly reduced forepaw-evoked hemodynamic responses, yet resulted in no significant reduction of channelrhodopsin-evoked hemodynamic responses, suggesting that stimulus-dependent coupling of neuronal activity to blood flow can be independent of local excitatory synaptic transmission. Together, these results indicate that channelrhodopsin-2 activation of sensorimotor excitatory neurons produces changes in intrinsic optical signals and blood flow that can occur under conditions where synaptic activation of neurons or other cells through ionotropic glutamate receptors would be blocked.

Assessment of Glial Function in the In Vivo Retina

http://www.springerlink.com/content/k651u8745384h27u/#section=999840&pag...
Sunday, January 1, 2012

Anja I. Srienc, Tess E. Kornfield, Anusha Mishra, Michael A. Burian and Eric A. Newman

... 3. End-tidal CO 2 monitor (microCapStar, CWE). 4. Ventilator (CWE SAR-830-P). 5. Blood gas

analyzer (Radiometer, ABL 800 Flex). 6. Pulse oximeter (MouseOx, Starr Life Sciences Corp.).

7. Thermostatically controlled heater (TC-1000 Temperature Controller, CWE). ...

Tandem insults of prenatal ischemia plus postnatal raised intrathoracic pressure in a novel rat model of encephalopathy of prematurity

http://thejns.org/doi/abs/10.3171/2011.9.PEDS11174
Thursday, December 1, 2011

Michael T. Koltz, M.D., Cigdem Tosun, B.S., David B. Kurland, B.A., Turhan Coksaygan, D.V.M., Ph.D., Rudolph J. Castellani, M.D., Svetlana Ivanova, Ph.D., Volodymyr Gerzanich, M.D., Ph.D., and J. Marc Simard, M.D., Ph.D.

Abstract

OBJECT

Encephalopathy of prematurity (EP) is common in preterm, low birth weight infants who require postnatal mechanical ventilation. The worst types of EP are the hemorrhagic forms, including choroid plexus, germinal matrix, periventricular, and intraventricular hemorrhages. Survivors exhibit life-long cognitive, behavioral, and motor abnormalities. Available preclinical models do not fully recapitulate the salient features of hemorrhagic EP encountered in humans. In this study, the authors evaluated a novel model using rats that featured tandem insults of transient prenatal intrauterine ischemia (IUI) plus transient postnatal raised intrathoracic pressure (RIP).

METHODS

Timed-pregnant Wistar rats were anesthetized and underwent laparotomy on embryonic Day 19. Intrauterine ischemia was induced by clamping the uterine and ovarian vasculature for 20 minutes. Natural birth occurred on embryonic Day 22. Six hours after birth, the pups were subjected to an episode of RIP, induced by injecting glycerol (50%, 13 µl/g intraperitoneally). Control groups included naive, sham surgery, and IUI alone. Pathological, histological, and behavioral analyses were performed on pups up to postnatal Day 52.

RESULTS

Compared with controls, pups subjected to IUI+RIP exhibited significant increases in postnatal mortality and hemorrhages in the choroid plexus, germinal matrix, and periventricular tissues as well as intraventricularly. On postnatal Days 35–52, they exhibited significant abnormalities involving complex vestibulomotor function and rapid spatial learning. On postnatal Day 52, the brain and body mass were significantly reduced.

CONCLUSIONS

Tandem insults of IUI plus postnatal RIP recapitulate many features of the hemorrhagic forms of EP found in humans, suggesting that these insults in combination may play important roles in pathogenesis.

Cathepsin G and neutrophil elastase play critical and non-redundant roles in lung protective immunity against Streptococcus pneumoniae in mice

http://iai.asm.org/content/early/2011/09/12/IAI.05593-11.abstract
Monday, September 12, 2011

Ines Hahn, Anna Klaus, Ann-Kathrin Janze, Kathrin Steinwede, Nadine Ding, Jennifer Bohling, Christina Brumshagen, Hélène Serrano, Francis Gauthier, James C. Paton, Tobias Welte and Ulrich A. Maus

ABSTRACT

Neutrophil serine proteases cathepsin G (CG), neutrophil elastase (NE) and proteinase-3 (PR3) have recently been shown to contribute to killing of Streptococcus pneumoniae in vitro. However, their relevance in lung protective immunity against different serotypes of S. pneumoniae in vivo has not been determined so far. Here, we examined the effect of CG and CG/NE deficiency on the lung host defense against S. pneumoniae in mice. Despite similar neutrophil recruitment, both CG KO mice and CG/NE double KO mice infected with focal pneumonia-inducing serotype 19 S. pneumoniae demonstrated a severely impaired bacterial clearance, which was accompanied by lack of CG and NE but not PR3 proteolytic activity in recruited neutrophils, as determined using fluorescence resonance energy transfer (FRET) substrates. Moreover, both CG and CG/NE KO mice but not wild-type mice responded with increased lung permeability to infection with S. pneumoniae, resulting in severe respiratory distress and progressive mortality. Both neutrophil depletion and ablation of hematopoietic CG/NE in bone marrow chimeras abolished intra-

alveolar CG and NE immunoreactivity and led to bacterial outgrowth in the lungs of mice, thereby identifying recruited neutrophils as the primary cellular source of intra-alveolar CG and NE. This is the first study showing a contribution of neutrophil-derived neutral serine proteases CG and NE to lung protective immunity against focal pneumonia-inducing serotype 19 S. pneumoniae in mice. These data may be important for the development of novel intervention strategies to improve lung protective immune mechanisms in critically ill patients suffering from severe pneumococcal pneumonia.

Lumbosacral sensory neuronal activity is enhanced by activation of urothelial purinergic receptors

http://www.sciencedirect.com/science/article/pii/S036192301100267X
Thursday, September 8, 2011

Alvaro Munoz,George T. Somogyi,Timothy B. Boone, Christopher P. Smith

Abstract

Urothelial purinergic receptors are important for the regulation of afferent sensory pathways in bladder pain and overactivity. Using in vivo electrophysiological recordings we evaluated the activity of spinal dorsal horn neurons in female rats at the L6/S1 level when urinary bladder pressure was abruptly increased. Intravesical infusion of ATP and systemic application of suramin allowed us to evaluate the contribution of urothelial purinergic receptors. Rats were anesthetized with isofluorane. Suprapubic, venous and tracheal catheters were implanted. Laminectomy was performed at the L6–S1 spinal levels. The cervical spinal cord was transected, and rats were mechanically pithed. Anesthesia was stopped, rats were ventilated, and a muscle relaxant was administered. The frequency of spinal neural activity was recorded via tungsten electrodes inserted into the dorsal horn at the L6–S1 level. The signal was amplified, filtered and recorded with a data acquisition system at 10 kHz sampling rate. Vital signs as well as bladder pressure were monitored in real time. We evaluated field potentials during intravesical pressure steps ranging from 0 to 60 cm H2O in (A) control (saline in the bladder), (B) after stimulation of urothelial purinergic receptors (1 mM vesical ATP), and (C) after the intravenous application of the non-specific purinergic antagonist suramin (100 mg/kg). Pressure steps were maintained for 1 min followed by 3 min for recovery. Only neurons that showed an increased activity during bladder distention were evaluated. Under control conditions, the generation of field potentials increased concomitantly with bladder pressure steps, showing an activity change threshold between 20 and 40 cm H2O. Intravesical application of 1 mM ATP produced an increase in baseline activity, indicative of noxious stimulation, and spinal neuronal activity markedly increased above 40 cm H2O pressure. Systemic suramin prevented the increase in neural activity in response to pressure changes, even after intravesical ATP. These results suggest that urothelial purinergic receptors are important modulators of lumbosacral dorsal spinal neuronal activity. The inhibitory effects of suramin imply that enhanced lumbosacral neuronal signals result from activation of C-fibers during noxious bladder stimulation.

A micro-advancer device for vitreal injection and retinal recording and stimulation

http://www.sciencedirect.com/science/article/pii/S0014483511002466
Friday, August 26, 2011

Dave Hultman, Eric A. Newman

Abstract

A micro-advancer device that positions a narrow-gauge needle within the vitreous humor of the rat eye is described. The device is compact, simple and inexpensive to manufacture. It consists of an outer guard needle and an inner injection needle that is advanced through the guard needle. With the rat held in a stereotaxic holder and the globe fixed to a stabilizing ring, the outer 25-gauge guard needle is advanced through the sclera using a standard micromanipulator. The inner 31-gauge injection needle is then advanced through the guard needle with a manually controlled leadscrew and carriage mechanism. The inner injection needle is attached to a Hamilton syringe and can be positioned to within microns of the retinal surface under visual observation through a microscope. The injection needle is fixed to the device by a quick-release clamp on the carriage and can be rapidly exchanged while the guard needle remains in place in the vitreous. This permits different solutions to be injected sequentially into the vitreous

humor. Recording electrodes, stimulating electrodes, and optical fibers can also be advanced through the guard needle and positioned accurately near the retinal surface or within the retina.

Degeneration of cortical function in the Royal College of Surgeons rat

http://www.sciencedirect.com/science/article/pii/S0042698911003014
Thursday, August 18, 2011

Carlos Gias, Anthony Vugler , Jean Lawrence , Amanda Jayne Carr , Li Li Chen , Ahmed Ahmado , Ma'ayan Semo , Peter J. Coffey

Abstract

The purpose of the current study was to determine the progress of cortical functional degeneration in the Royal College of Surgeons (RCS) rat. Cortical responses were measured with optical imaging of intrinsic signals using gratings of various spatial frequencies. Subsequently, electrophysiological recordings were also taken across cortical layers in response to a pulse of broad-spectrum light. We found significant degeneration in the cortical processing of visual information as early as 4 weeks of age. These results show that degeneration in the cortical response of the RCS rat starts before development has been properly completed.

Developmental Changes in Short-Term Plasticity at the Rat Calyx of Held Synapse

http://www.jneurosci.org/content/31/32/11706.short
Wednesday, August 10, 2011

Tom T. H. Crins, Silviu I. Rusu, Adrian Rodríguez-Contreras, and J. Gerard G. Borst

Abstract

The calyx of Held synapse of the medial nucleus of the trapezoid body functions as a relay synapse in the auditory brainstem. In vivo recordings have shown that this synapse displays low release probability and that the average size of synaptic potentials does not depend on recent history. We used a ventral approach to make in vivo extracellular recordings from the calyx of Held synapse in rats aged postnatal day 4 (P4) to P29 to study the developmental changes that allow this synapse to function as a relay. Between P4 and P8, we observed evidence for the presence of large short-term depression, which was counteracted by short-term facilitation at short intervals. Major changes occurred in the last few days before the onset of hearing for air-borne sounds, which happened at P13. The bursting pattern changed into a primary-like pattern, the amount of depression and facilitation decreased strongly, and the decay of facilitation became much faster. Whereas short-term plasticity was the most important cause of variability in the size of the synaptic potentials in immature animals, its role became minor around hearing onset and afterward. Similar developmental changes were observed during stimulation experiments both in brain slices and in vivo following cochlear ablation. Our data suggest that the strong reduction in release probability and the speedup of the decay of synaptic facilitation that happen just before hearing onset are important events in the transformation of the calyx of Held synapse into an auditory relay synapse.

Dibucaine Mitigates Spreading Depolarization in Human Neocortical Slices and Prevents Acute Dendritic Injury in the Ischemic Rodent Neocortex

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0022351
Friday, July 15, 2011

W. Christopher Risher, Mark R. Lee, Ioulia V. Fomitcheva, David C. Hess, Sergei A. Kirov

Background

Spreading depolarizations that occur in patients with malignant stroke, subarachnoid/intracranial hemorrhage, and traumatic brain injury are known to facilitate neuronal damage in metabolically compromised brain tissue. The dramatic failure of brain ion homeostasis caused by propagating spreading depolarizations results in neuronal and astroglial swelling. In essence, swelling is the initial response and a sign of the acute neuronal injury that follows if energy deprivation is maintained. Choosing spreading depolarizations as a target for therapeutic intervention, we

have used human brain slices and in vivo real-time two-photon laser scanning microscopy in the mouse neocortex to study potentially useful therapeutics against spreading depolarization-induced injury.

Methodology/Principal Findings

We have shown that anoxic or terminal depolarization, a spreading depolarization wave ignited in the ischemic core where neurons cannot repolarize, can be evoked in human slices from pediatric brains during simulated ischemia induced by oxygen/glucose deprivation or by exposure to ouabain. Changes in light transmittance (LT) tracked terminal depolarization in time and space. Though spreading depolarizations are notoriously difficult to block, terminal depolarization onset was delayed by dibucaine, a local amide anesthetic and sodium channel blocker. Remarkably, the occurrence of ouabain-induced terminal depolarization was delayed at a concentration of 1 μM that preserves synaptic function. Moreover, in vivo two-photon imaging in the penumbra revealed that, though spreading depolarizations did still occur, spreading depolarization-induced dendritic injury was inhibited by dibucaine administered intravenously at 2.5 mg/kg in a mouse stroke model.

Conclusions/Significance

Dibucaine mitigated the effects of spreading depolarization at a concentration that could be well-tolerated therapeutically. Hence, dibucaine is a promising candidate to protect the brain from ischemic injury with an approach that does not rely on the complete abolishment of spreading depolarizations.

Caudal nuclei of the rat nucleus of the solitary tract differentially innervate respiratory compartments within the ventrolateral medulla

http://www.sciencedirect.com/science/article/pii/S0306452211006646
Sunday, June 12, 2011

G.F. Alheid, W. Jiao, D.R. McCrimmon

Abstract

A substantial array of respiratory, cardiovascular, visceral and somatic afferents are relayed via the nucleus of the solitary tract (NTS) to the brainstem (and forebrain). Despite some degree of overlap within the NTS, specificity is maintained in central respiratory reflexes driven by second order afferent relay neurons in the NTS. While the topographic arrangement of respiratory-related afferents targeting the NTS has been extensively investigated, their higher order brainstem targets beyond the NTS has only rarely been defined with any precision. Nonetheless, the various brainstem circuits serving blood gas homeostasis and airway protective reflexes must clearly receive a differential innervation from the NTS in order to evoke stimulus appropriate behavioral responses. Accordingly, we have examined the question of which specific NTS nuclei project to particular compartments within the ventral respiratory column (VRC) of the ventrolateral medulla. Our analyses of NTS labeling after retrograde tracer injections in the VRC and the nearby neuronal groups controlling autonomic function indicate a significant distinction between projections to the Bötzinger complex and preBötzinger complex compared to the remainder of the VRC. Specifically, the caudomedial NTS, including caudal portions of the medial solitary nucleus and the commissural division of NTS project relatively densely to the region of the retrotrapezoid nucleus and rostral ventrolateral medullary nucleus as well as to the rostral ventral respiratory group while avoiding the intervening Bötzinger and preBötzinger complexes. Area postrema appears to demonstrate a pattern of projections similar to that of caudal medial and commissural NTS nuclei. Other, less pronounced differential projections of lateral NTS nuclei to the various VRC compartments are additionally noted.

Brain-derived neurotrophic factor modulates antiretroviral-induced mechanical allodynia in the mouse

http://onlinelibrary.wiley.com/doi/10.1002/jnr.22685/full
Monday, June 6, 2011

Cynthia L. Renn, Carmen C. Leitch, Sherrie Lessans, Peter Rhee, W. Cameron McGuire, Barbara A. Smith1, Rihard J. Traub, Susan G. Dorsey

Abstract

Nucleoside reverse transcriptase inhibitors (NRTIs) are key components of HIV/AIDS treatment to reduce viral load. However, these drugs can induce chronic neuropathic pain, leading to increased morbidity in HIV patients. This study examines the role of brain-derived neurotrophic factor (BDNF) in the spinal dorsal horn (SDH) in development of mechanical allodynia in male C57BL/6J mice treated with the NRTI stavudine (d4T). After d4T administration, mice developed increased neuronal activity and BDNF expression in the SDH and hind paw mechanical allodynia that was exacerbated by intrathecal BDNF administration. Intrathecal BDNF alone also increased neuronal activity and caused mechanical allodynia. Because excess BDNF amplified d4T-induced mechanical allodynia and neuronal activity, the impact of decreasing BDNF in the SDH was investigated. After d4T, BDNF heterozygous mice were less allodynic than wild-type littermates, which was negated by intrathecal BDNF administration. Finally, pretreatment with intrathecal trkB-Fc chimera prior to d4T or administration of the tyrosine kinase inhibitor K252a 3 days after d4T blocked BDNF-mediated signaling, significantly attenuated the development of mechanical allodynia (trkB-Fc), and decreased neuronal activity (trkB-Fc and K252a). Taken together, these findings provide evidence that BDNF in the SDH contributes to the development of NRTI-induced painful peripheral neuropathy and may represent a new therapeutic opportunity.

Multimodal assessment of painful peripheral neuropathy induced by chronic oxaliplatin-based chemotherapy in mice

http://www.molecularpain.com/content/7/1/29/
Tuesday, April 26, 2011

Cynthia L Renn, Valentina A Carozzi, Peter Rhee, Danisha Gallop, Susan G Dorsey and Guido Cavaletti

Abstract

Background

A major clinical issue affecting 10-40% of cancer patients treated with oxaliplatin is severe peripheral neuropathy with symptoms including cold sensitivity and neuropathic pain. Rat models have been used to describe the pathological features of oxaliplatin-induced peripheral neuropathy; however, they are inadequate for parallel studies of oxaliplatin's antineoplastic activity and neurotoxicity because most cancer models are developed in mice. Thus, we characterized the effects of chronic, bi-weekly administration of oxaliplatin in BALB/c mice. We first studied oxaliplatin's effects on the peripheral nervous system by measuring caudal and digital nerve conduction velocities (NCV) followed by ultrastructural and morphometric analyses of dorsal root ganglia (DRG) and sciatic nerves. To further characterize the model, we examined nocifensive behavior and central nervous system excitability by in vivo electrophysiological recording of spinal dorsal horn (SDH) wide dynamic range neurons in oxaliplatin-treated mice

Results

We found significantly decreased NCV and action potential amplitude after oxaliplatin treatment along with neuronal atrophy and multinucleolated DRG neurons that have eccentric nucleoli. Oxaliplatin also induced significant mechanical allodynia and cold hyperalgesia, starting from the first week of treatment, and a significant increase in the activity of wide dynamic range neurons in the SDH.

Conclusions

Our findings demonstrate that chronic treatment with oxaliplatin produces neurotoxic changes in BALB/c mice, confirming that this model is a suitable tool to conduct further mechanistic studies of oxaliplatin-related antineoplastic activity, peripheral neurotoxicity and pain. Further, this model can be used for the preclinical discovery of new neuroprotective and analgesic compounds.

Keywords: Oxaliplatin; peripheral neuropathy; cold hyperalgesia; mechanical allodynia; dorsal root ganglia; spinal dorsal horn; electrophysiology

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Keywords: Oxaliplatin; peripheral neuropathy; cold hyperalgesia; mechanical allodynia; dorsal root ganglia; spinal dorsal horn; electrophysiology

Chronic assessment of diaphragm muscle EMG activity across motor behaviors

http://www.sciencedirect.com/science/article/pii/S1569904811000930
Tuesday, March 15, 2011

Carlos B. Mantillaa, Yasin B. Sevena, Juan N. Hurtado-Palominoa, Wen-Zhi Zhana, Gary C. Siecka

Abstract

The diaphragm muscle is the main inspiratory muscle in mammals. Quantitative analyses documenting the reliability of chronic diaphragm EMG recordings are lacking. Assessment of ventilatory and non-ventilatory motor behaviors may facilitate evaluating diaphragm EMG activity over time. We hypothesized that normalization of diaphragm EMG amplitude across behaviors provides stable and reliable parameters for longitudinal assessments of diaphragm activity. We found that diaphragm EMG activity shows substantial intra-animal variability over 6 weeks, with coefficient of variation (CV) for different behaviors ~29–42%. Normalization of diaphragm EMG activity to near maximal behaviors (e.g., deep breathing) reduced intra-animal variability over time (CV ~ 22–29%). Plethysmographic measurements of eupneic ventilation were also stable over 6 weeks (CV ~ 13% for minute ventilation). Thus, stable and reliable measurements of diaphragm EMG activity can be obtained longitudinally using chronically implanted electrodes by examining multiple motor behaviors. By quantitatively determining the reliability of longitudinal diaphragm EMG analyses, we provide an important tool for evaluating the progression of diseases or injuries that impair ventilation.

Highlights

► Diaphragm EMG activity shows substantial variability within animals over time. ► Chronically implanted electrodes allow longitudinal assessment of diaphragm activity. ► Stable and reliable measurements can be obtained by examining multiple motor behaviors.

Keywords

Respiration; Motor unit recruitment; Ventilation; Hypoxia; Hypercapnia; Neuromotor control

State-specific Effects of Sevoflurane Anesthesia on Sleep Homeostasis: Selective Recovery of Slow Wave but Not Rapid Eye Movement Sleep

http://journals.lww.com/anesthesiology/Fulltext/2011/02000/State_specific_Effects_of_Sevoflurane_Anesthesia.18.aspx
Tuesday, February 1, 2011

Pal, Dinesh Ph.D.*; Lipinski, William J. M.S.†; Walker, Amanda J. B.S.‡; Turner, Ashley M. B.S.‡; Mashour, George A. M.D,. Ph.D.

Background: Prolonged propofol administration does not result in signs of sleep deprivation, and propofol anesthesia appears to satisfy the homeostatic need for both rapid eye movement (REM) and non-REM (NREM) sleep. In the current study, the effects of sevoflurane on recovery from total sleep deprivation were investigated.

Methods: Ten male rats were instrumented for electrophysiologic recordings under three conditions: (1) 36-h ad libitum sleep; (2) 12-h sleep deprivation followed by 24-h ad libitum sleep; and (3) 12-h sleep deprivation, followed by 6-h sevoflurane exposure, followed by 18-h ad libitum sleep. The percentage of waking, NREM sleep, and REM sleep, as well as NREM sleep δ power, were calculated and compared for all three conditions.

Results: Total sleep deprivation resulted in significantly increased NREM and REM sleep for 12-h postdeprivation. Sevoflurane exposure after deprivation eliminated the homeostatic increase in NREM sleep and produced a significant decrease in the NREM sleep δ power during the postanesthetic period, indicating a complete recovery from the effects of deprivation. However, sevoflurane did not affect the time course of REM sleep recovery, which required 12 h after deprivation and anesthetic exposure.

Conclusion: Unlike propofol, sevoflurane anesthesia has differential effects on NREM and REM sleep homeostasis. These data confirm the previous hypothesis that inhalational agents do not satisfy the homeostatic need for REM sleep, and that the relationship between sleep and anesthesia is likely to be agent and state specific.

Anesthetic Considerations for the Study of Murine Tumor Models

http://www.springerlink.com/content/p3k300676018w12t/
Saturday, January 1, 2011

Thies Schroeder, Siqing Shan and Mark W. Dewhirst

This chapter is to provide researchers with an overview over the requirements, challenges, and current solutions of rodent anesthesia in preclinical cancer research. Since the overwhelming majority of research is currently done in mouse models, rather than rats or other rodents, the review will focus predominantly on mouse strains. We will provide a range of hands-on protocols and suggestions on the application of the most commonly used rodent anesthesia procedures.

A Novel Technique for the In Vivo Imaging of Autoimmune Diabetes Development in the Pancreas by Two-Photon Microscopy

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3009738/
Thursday, December 23, 2010

Ken Coppieters, Marianne M. Martinic, William B. Kiosses, Natalie Amirian, and Matthias von Herrath,

Type 1 diabetes (T1D) is characterized by the immune-mediated destruction of beta cells in the pancreas. Little is known about the in vivo dynamic interactions between T cells and beta cells or the kinetic behavior of other immune cell subsets in the pancreatic islets. Utilizing multiphoton microscopy we have designed a technique that allows for the real-time visualization of diabetogenic T cells and dendritic cells in pancreatic islets in a live animal, including their interplay with beta cells and the vasculature. Using a custom designed stage, the pancreas was surgically

exposed under live conditions so that imaging of islets under intact blood pressure and oxygen supply became possible. We demonstrate here that this approach allows for the tracking of diabetogenic leukocytes as well as vascularization phenotype of islets and accumulation of dendritic cells in islets during diabetes pathogenesis. This technique should be useful in mapping crucial kinetic events in T1D pathogenesis and in testing the impact of immune based interventions on T cell migration, extravasation and islet destruction.

Purinergic Receptor Stimulation Reduces Cytotoxic Edema and Brain Infarcts in Mouse Induced by Photothrombosis by Energizing Glial Mitochondria

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0014401
Wednesday, December 22, 2010

Wei Zheng, Lora Talley Watts, Deborah M. Holstein, Suresh I. Prajapati, Charles Keller, Eileen H. Grass, Christi A. Walter, James D. Lechleiter

Treatments to improve the neurological outcome of edema and cerebral ischemic stroke are severely limited. Here, we present the first in vivo single cell images of cortical mouse astrocytes documenting the impact of single vessel photothrombosis on cytotoxic edema and cerebral infarcts. The volume of astrocytes expressing green fluorescent protein (GFP) increased by over 600% within 3 hours of ischemia. The subsequent growth of cerebral infarcts was easily followed as the loss of GFP fluorescence as astrocytes lysed. Cytotoxic edema and the magnitude of ischemic lesions were significantly reduced by treatment with the purinergic ligand 2-methylthioladenosine 5′ diphosphate (2-MeSADP), an agonist with high specificity for the purinergic receptor type 1 isoform (P2Y1R). At 24 hours, cytotoxic edema in astrocytes was still apparent at the penumbra and preceded the cell lysis that defined the infarct. Delayed 2MeSADP treatment, 24 hours after the initial thrombosis, also significantly reduced cytotoxic edema and the continued growth of the brain infarction. Pharmacological and genetic evidence are presented indicating that 2MeSADP protection is mediated by enhanced astrocyte mitochondrial metabolism via increased inositol trisphosphate (IP3)-dependent Ca2+ release. We suggest that mitochondria play a critical role in astrocyte energy metabolism in the penumbra of ischemic lesions, where low ATP levels are widely accepted to be responsible for cytotoxic edema. Enhancement of this energy source could have similar protective benefits for a wide range of brain injuries.

Glutamate transporter type 3 knockout reduces brain tolerance to focal brain ischemia in mice

http://www.nature.com/jcbfm/journal/v31/n5/full/jcbfm2010222a.html
Wednesday, December 8, 2010

Liaoliao Li and Zhiyi Zuo

Excitatory amino-acid transporters (EAATs) transport glutamate into cells under physiologic conditions. Excitatory amino-acid transporter type 3 (EAAT3) is the major neuronal EAAT and also uptakes cysteine, the rate-limiting substrate for synthesis of glutathione. Thus, we hypothesize that EAAT3 contributes to providing brain ischemic tolerance. Male 8-week-old EAAT3 knockout mice on CD-1 mouse gene background and wild-type CD-1 mice were subjected to right middle cerebral artery occlusion for 90 minutes. Their brain infarct volumes, neurologic functions, and brain levels of glutathione, nitrotyrosine, and 4-hydroxy-2-nonenal (HNE) were evaluated. The EAAT3 knockout mice had bigger brain infarct volumes and worse neurologic deficit scores and motor coordination functions than did wild-type mice, no matter whether these neurologic outcome parameters were evaluated at 24 hours or at 4 weeks after brain ischemia. The EAAT3 knockout mice contained higher levels of HNE in the ischemic penumbral cortex and in the nonischemic cerebral cortex than did wild-type mice. Glutathione levels in the ischemic and nonischemic cortices of EAAT3 knockout mice tended to be lower than those of wild-type mice. Our results suggest that EAAT3 is important in limiting ischemic brain injury after focal brain ischemia. This effect may involve attenuating brain oxidative stress.

Keywords: focal brain ischemia; glutamate transporter; ischemic tolerance; mouse; oxidative stress

Effects of d-3-hydroxybutyrate treatment on hypoglycemic coma in rat pups

http://www.sciencedirect.com/science/article/pii/S0014488610003985

Friday, November 5, 2010

Peter W. Schutza, Peter K.H. Wonga, John O'Kuskyb, Sheila M. Innisd, Sylvia Stocklera

d-3-Hydroxybutyrate (3OHB) is an alternative energy substrate for the brain during hypoglycemia, especially in infancy. Knowledge of the capacity and limits of 3OHB to compensate for cerebral glucose depletion during hypoglycemia in developing brain is important for its potential clinical use, but is scarce. We studied the effect of 3OHB treatment during insulin-induced hypoglycemia in 13-day-old rat pups. 3OHB treatment resulted in increased 3OHB plasma levels in hypoglycemic animals (3–4 mM vs. 0.5–1 mM untreated), and delayed the onset of clinical coma by 70 min and of burst-suppression coma by 90 min. 3OHB treated animals did not survive after resuscitation with glucose, compared to 80% survival of untreated hypoglycemic pups. Cleaved-caspase-3 immunohistochemistry and double labeling studies demonstrated a 20-fold increase of apoptotic mature oligodendrocytes in white matter of 3OHB treated animals. 3OHB treatment delays the onset of clinical and burst-suppression coma during hypoglycemia, but the prolonged duration of hypoglycemia is associated with increased mortality after resuscitation and cellular white matter injury.

Striatal and cortical BOLD, blood flow, blood volume, oxygen consumption, and glucose consumption changes in noxious forepaw electrical stimulation

http://www.nature.com/jcbfm/journal/v31/n3/full/jcbfm2010173a.html
Wednesday, October 13, 2010

Yen-Yu I Shih, Hsiao-Ying Wey, Bryan H De La Garza and Timothy Q Duong

Recent reports showed noxious forepaw stimulation in rats evoked an unexpected sustained decrease in cerebral blood volume (CBV) in the bilateral striatum, whereas increases in spike activity and Fos-immunoreactive cells were observed. This study aimed to further evaluate the hemodynamic and metabolic needs in this model and the sources of negative functional magnetic resonance imaging (fMRI) signals by measuring blood oxygenation-level-dependent (BOLD), cerebral-blood-flow (CBF), CBV, and oxygen-consumption (i.e., cerebral metabolic rate of oxygen (CMRO2)) changes using an 11.7-T MRI scanner, and glucose-consumption (i.e., cerebral metabolic rate of glucose (CMRglc)) changes using micro-positron emission tomography. In the contralateral somatosensory cortex, BOLD, CBF, CBV, CMRO2 ($n=7$, $P<0.05$), and CMRglc ($n=5$, $P<0.05$) increased. In contrast, in the bilateral striatum, BOLD, CBF, and CBV decreased ($P<0.05$), CMRO2 decreased slightly, although not significantly from baseline, and CMRglc was not statistically significant from baseline ($P>0.05$). These multimodal functional imaging findings corroborate the unexpected negative hemodynamic changes in the striatum during noxious forepaw stimulation, and support the hypothesis that striatal hemodynamic response is dominated by neurotransmitter-mediated vasoconstriction, overriding the stimulus-evoked fMRI signal increases commonly accompany elevated neuronal activity. Multimodal functional imaging approach offers a means to probe the unique attributes of the striatum, providing novel insights into the neurovascular coupling in the striatum. These findings may have strong implications in fMRI studies of pain.

Keywords: CBF; CBV; CMRglc; CMRO2; high-field fMRI; striatum

Lactate levels in the brain are elevated upon exposure to volatile anesthetics: A microdialysis study

http://www.sciencedirect.com/science/article/pii/S0197018610003049
Thursday, October 7, 2010

Tobias Horn, Jochen Klein

Abstract

Anesthetic agents have well-defined pharmacological targets but their effects on energy metabolism in the brain are poorly understood. In this study, we examined the effects of different anesthetics on extracellular lactate and glucose levels in blood, CSF and brain of the mouse. In vivo-microdialysis was used to monitor extracellular energy metabolites in the brain of awake mice and during anesthesia with seven different anesthetic drugs. In separate groups, lactate and glucose concentrations in blood and CSF were measured for each anesthetic. We found that anesthesia with isoflurane caused a large increase of extracellular lactate levels in mouse striatum and hippocampus (300–400%). Pyruvate levels also increased while glucose and glutamate levels were unchanged. This effect was dose-

dependent and was mimicked by other gaseous anesthetics such as halothane and sevoflurane but not by intravenous anesthetics. Ketamine/xylazine and chloral hydrate caused 2-fold increases of glucose levels in mouse blood and brain while lactate levels were only moderately increased. Propofol caused a minor increase of extracellular glucose levels while pentobarbital had no effect on either lactate or glucose. Volatile anesthetics also increased lactate levels in blood and CSF by 2–3-fold but had no effect on plasma glucose. Further experiments demonstrated that lactate formation by isoflurane in mouse brain was independent of neuronal impulse flow and did not involve ATP-dependent potassium channels. We conclude that volatile anesthetics, but not intravenous anesthetics, cause a specific, dose-dependent increase in extracellular lactate levels in mouse brain. This effect occurs in the absence of ischemia, is independent of peripheral actions and is reflected in strongly increased CSF lactate levels.

Limitations of collateral flow after occlusion of a single cortical penetrating arteriole

http://www.nature.com/jcbfm/journal/v30/n12/full/jcbfm2010157a.html
Wednesday, September 15, 2010

Nozomi Nishimura, Nathanael L Rosidi, Costantino Iadecola and Chris B Schaffer

Occlusions of penetrating arterioles, which plunge into cortex and feed capillary beds, cause severe decreases in blood flow and are potential causes of ischemic microlesions. However, surrounding arterioles and capillary beds remain flowing and might provide collateral flow around the occlusion. We used femtosecond laser ablation to trigger clotting in single penetrating arterioles in rat cortex and two-photon microscopy to measure changes in microvessel diameter and red blood cell speed after the clot. We found that after occlusion of a single penetrating arteriole, nearby penetrating and surface arterioles did not dilate, suggesting that alternate blood flow routes are not actively recruited. In contrast, capillaries showed two types of reactions. Capillaries directly downstream from the occluded arteriole dilated after the clot, but other capillaries in the same vicinity did not dilate. This heterogeneity in capillary response suggests that signals for vasodilation are vascular rather than parenchymal in origin. Although both neighboring arterioles and capillaries dilated in response to topically applied acetylcholine after the occlusion, the flow in the territory of the occluded arteriole did not improve. Collateral flow from neighboring penetrating arterioles is neither actively recruited nor effective in improving blood flow after the occlusion of a single penetrating arteriole.

Keywords: collateral flow; imaging; stroke; two-photon microscopy; vasodilation; vasoregulation

Duration of Anesthesia Affects Intraocular Pressure, But Not Outflow Facility in Mice Read More: http://informahealthcare.com/doi/abs/10.3109/02713683.2010.494241

http://informahealthcare.com/doi/abs/10.3109/02713683.2010.494241
Wednesday, September 1, 2010

Lucinda J. Camras, Kari E. Sufficool, Carl B. Camras, Shan Fan, Hong Liu, Carol B. Toris

Purpose: The study of aqueous humor dynamics (AHD) in mice is becoming more prevalent as more strains with elevated intraocular pressure (IOP) are developed. High IOP is usually associated with reduced outflow facility making this one of the more important AHD parameters to evaluate. Ocular measurements in mice require anesthesia that has profound effects on IOP but unknown effects on outflow facility. This study evaluates the effects of anesthesia duration and latanoprost treatment on outflow facility and IOP in BALB/c mice.

Methods: IOPs were measured in conscious and anesthetized mice by tonometry. Outflow facility was evaluated in 15-min intervals at three pressure levels over two 45-min periods. Comparisons were made between latanoprost-treated eyes and untreated contralateral eyes. To determine the effect of anesthesia duration on IOP, a microneedle method was used to follow IOP for 120 min in separate mice.

Results: IOP was 9.7 ± 0.3 mmHg (mean ± SEM) in conscious mice and 7.1 ± 0.02 within 10 min of anesthesia initiation ($p < 0.01$). IOP changed significantly between but not within assessment periods. IOP at 75 min was significantly ($p = 0.004$) reduced compared to IOP at 15 min after initial anesthesia. In control eyes, outflow facility did not change

between the two 45-min assessment periods during the 120 min test ($p = 0.80$). In latanoprost-treated eyes, outflow facility increased compared with control eyes during both assessment periods ($p = 0.03$). A test of filters in series with known resistance found that the method was sensitive enough to detect a change in outflow facility of 0.001 µl/min/mmHg.

Conclusions: Administration of ketamine/xylazine anesthesia for 120 min did not alter outflow facility or lessen the effect of latanoprost on outflow facility in mice as determined by a new analysis system. Accurate IOP measurements must be made within minutes of anesthesia administration but outflow facility measurements can be made with less haste.

Pulvinar Projections to the Striatum and Amygdala in the Tree Shrew

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2991220/
Tuesday, August 10, 2010

Jonathan D. Day-Brown, Haiyang Wei, Ranida D. Chomsung, Heywood M. Petry, and Martha E. Bickford

Visually guided movement is possible in the absence of conscious visual perception, a phenomenon referred to as "blindsight." Similarly, fearful images can elicit emotional responses in the absence of their conscious perception. Both capabilities are thought to be mediated by pathways from the retina through the superior colliculus (SC) and pulvinar nucleus. To define potential pathways that underlie behavioral responses to unperceived visual stimuli, we examined the projections from the pulvinar nucleus to the striatum and amygdala in the tree shrew (Tupaia belangeri), a species considered to be a prototypical primate. The tree shrew brain has a large pulvinar nucleus that contains two SC-recipient subdivisions; the dorsal (Pd) and central (Pc) pulvinar both receive topographic ("specific") projections from SC, and Pd receives an additional non-topographic ("diffuse") projection from SC (Chomsung et al., 2008). Anterograde and retrograde tract tracing revealed that both Pd and Pc project to the caudate and putamen, and Pd, but not Pc, additionally projects to the lateral amygdala. Using immunocytochemical staining for substance P (SP) and parvalbumin (PV) to reveal the patch/matrix organization of tree shrew striatum, we found that SP-rich/PV-poor patches interlock with a PV-rich/SP-poor matrix. Confocal microscopy revealed that tracer-labeled pulvino-striatal terminals preferentially innervate the matrix. Electron microscopy revealed that the postsynaptic targets of tracer-labeled pulvino-striatal and pulvino-amygdala terminals are spines, demonstrating that the pulvinar nucleus projects to the spiny output cells of the striatum matrix and the lateral amygdala, potentially relaying: (1) topographic visual information from SC to striatum to aid in guiding precise movements, and (2) non-topographic visual information from SC to the amygdala alerting the animal to potentially dangerous visual images.

Keywords: blindsight, superior colliculus, striosome, matrix, synapse

The Neurotoxic Effects of Estrogen on Ischemic Stroke in Older Female Rats Is Associated with Age-Dependent Loss of Insulin-Like Growth Factor-1

http://www.jneurosci.org/content/30/20/6852.short
Friday, January 1, 2010

Amutha Selvamani and Farida Sohrabji

Hormone therapy to postmenopausal females increases the risk and severity of ischemic stroke. Our previous work using an animal model of menopause (reproductive senescence) shows that middle cerebral artery occlusion (MCAo) causes a larger cortical–striatal infarct in this older acyclic group compared with younger females. Moreover, although estrogen treatment is neuroprotective in younger females, estrogen paradoxically increases infarct volume in acyclic females. We hypothesized that the neurotoxic effects of estrogen in older females occurs because of decreased availability of IGF-1, a neuroprotectant that decreases with advancing age and is downregulated by estrogen treatment. Our data show that plasma IGF-1 levels are significantly reduced in reproductive senescent females and further reduced by estrogen at all ages. The neuroprotective effect of estrogen on MCAo-induced cortical infarct volume in mature adult female is reversed by intracerebroventricular injections of IGF-1 receptor antagonist JB-1. Similarly, estrogens neurotoxic effects on cortical infarct volume in senescent females is attenuated by concurrent IGF-1 treatment, and reversed when IGF-1 is infused 4 h after the onset of ischemia (delayed IGF-1 treatment). Delayed IGF-1/estrogen treatment also suppressed ischemia-induced ERK1 phosphorylation, reduced protein oxidation, and stimulated an early increase in prostaglandin E2 at the infarct site. IGF-1 treatment was only

protective in senescent females that received estrogen, indicating that the neuroprotective actions of this peptide require interaction with the steroid hormone receptor. These data support the hypothesis that stroke severity in older females is associated with decreased IGF-1 and further indicate that short-term postischemic IGF-1 therapy may be beneficial for stroke.

Synaptic Organization of Connections between the Temporal Cortex and Pulvinar Nucleus of the Tree Shrew

http://cercor.oxfordjournals.org/content/early/2009/09/25/cercor.bhp162.abstract
Friday, August 14, 2009

Ranida D. Chomsung, Haiyang Wei, Jonathan D. Day-Brown1Heywood M. Petry and Martha E. Bickford

We examined the synaptic organization of reciprocal connections between the temporal cortex and the dorsal (Pd) and central (Pc) subdivisions of the tree shrew pulvinar nucleus, regions innervated by the medial and lateral superior colliculus, respectively. Both Pd and Pc subdivisions project topographically to 2 separate regions of the temporal cortex; small injections of anterograde tracers placed in either Pd or Pc labeled 2 foci of terminals in the temporal cortex. Pulvinocortical pathways innervated layers I–IV, with beaded axons oriented perpendicular to the cortical surface, where they synapsed with spines that did not contain gamma amino butyric acid (GABA), likely located on the apical dendrites of pyramidal cells. Projections from the temporal cortex to the Pd and Pc originate from layer VI cells, and form small terminals that contact small caliber non-GABAergic dendrites. These results suggest that cortical terminals are located distal to tectopulvinar terminals on the dendritic arbors of Pd and Pc projection cells, which subsequently contact pyramidal cells in the temporal cortex. This circuitry could provide a mechanism for the pulvinar nucleus to activate subcortical visuomotor circuits and modulate the activity of other visual cortical areas. The potential relation to primate tecto-pulvino-cortical pathways is discussed.

Injury Modality, Survival Interval and Sample Region are Critical Determinants of qRT-PCR Reference Gene Selection during Long-Term Recovery from Brain Trauma

http://online.liebertpub.com/doi/abs/10.1089/neu.2009-0875
Monday, June 8, 2009

Dr. Janna L Harris, Dr. Thomas Reeves Ph.D.Dr. Linda Phillips Ph.D

In the present study we examined expression of four real-time quantitative RT-PCR reference genes commonly applied to rodent models of brain injury. Transcripts for ß-actin, cyclophilin A, GAPDH, and 18S rRNA were assessed at 2-15 d postinjury, focusing on the period of synaptic recovery. Diffuse moderate central fluid percussion injury (FPI) was contrasted with unilateral entorhinal cortex lesion (UEC), a model of targeted deafferentation. Expression in UEC hippocampus, as well as in FPI hippocampus and parietotemporal cortex was analyzed by qRT-PCR. Within-group variability of gene expression was assessed and change in expression relative to paired controls determined. None of the four common reference genes tested was invariant across brain region, survival time and type of injury. Cyclophilin A appeared appropriate as a reference gene in UEC hippocampus, while ß-actin was most stable for the hippocampus subjected to FPI. However, each gene may fail as a suitable reference with certain test genes whose RNA expression is targeted for measurement. In FPI cortex, all reference genes were significantly altered over time, compromising their utility for time course studies. Despite such temporal variability, certain genes may be appropriate references if limited to single survival times. These data provide an extended baseline for identification of appropriate reference genes in rodent studies of recovery from brain injury. In this context, we outline additional considerations for selecting a qRT-PCR normalization strategy in such studies. As previously concluded for acute postinjury intervals, we stress the importance of reference gene validation for each brain injury paradigm and each set of experimental conditions.

Keywords: traumatic brain injury, genomics, molecular biological approaches, neuroplasticity, synaptic loss and deafferentation

Laboratory Animal Anaesthesia (BOOK)

http://books.google.com/books?hl=en&lr=&id=gBkFcYUpV5wC&oi=fnd&pg=PR7&dq=mouseox+OR+%22starr+life%22&ots=ie0Tx5px82&sig=38FFWfYyCqwH-CqQ8qYfMNAGekI#v=onepage&q=mouseox%20OR%20%22starr%20life%22&f=false
Thursday, January 1, 2009

Paul Flecknell

... Figure 2.23 Duration of anaesthesia and sleep times in rats with different anaesthetics CHAPTER

3 Figure 3.1 Methods of protecting an animal's eyes during anaesthesia Figure 3.2 Respiratory

monitor using a pressure sensor Figure 3.3 The 'Mouseox' pulse oximeter in use ...

Overexpression of mitochondrial Hsp70/Hsp75 in rat brain protects mitochondria, reduces oxidative stress, and protects from focal ischemia

http://www.nature.com/jcbfm/journal/v29/n2/full/jcbfm2008125a.html
Wednesday, November 5, 2008

Lijun Xu, Ludmila A Voloboueva, YiBing Ouyang, John F Emery and Rona G Giffard

Mitochondria are known to be central to the cell's response to ischemia, because of their role in energy generation, in free radical generation, and in the regulation of apoptosis. Heat shock protein 75 (Hsp75/Grp75/mortalin/TRAP1) is a member of the HSP70 chaperone family, which is targeted to mitochondria. Overexpression of Hsp75 was achieved in rat brain by DNA transfection, and expression was observed in both astrocytes and neurons. Rats were subjected to 100 mins middle cerebral artery occlusion followed by assessment of infarct volume, neurological score, mitochondrial function, and levels of oxidative stress at 24 h reperfusion. Overexpression of Hsp75 reduced infarct area from 44.6%±21.1% to 25.7%±12.1% and improved neurological outcome significantly. This was associated with improved mitochondrial function as shown by protection of complex IV activity, marked reduction of free radical generation detected by hydroethidine fluorescence, reduction of lipid peroxidation detected by 4-hydroxy-2-nonenol immunoreactivity, and increased preservation of ATP levels. This suggests that targeting mitochondria for protection may be a useful strategy to reduce ischemic brain injury.

Keywords: Grp75, mitochondria, mortalin, oxidative stress, stroke, TRAP1

Anesthesia with Isoflurane Increases Amyloid Pathology in Mice Models of Alzheimer'S Disease

http://iospress.metapress.com/content/n65807g2506m0216/
Tuesday, January 1, 2008

J Perucho, I Rubio, MJ Casarejos, A Gomez, JA

Anesthesia with Isoflurane Increases Amyloid Pathology

in Mice Models of Alzheimer's Disease Juan Peruchoa, Isabel Rubiob ...