

# IPS The Iowa Physiological Society



Annual Meeting 2009  
Saturday, May 2, 2009  
Program and Abstracts



**Location:** Drake University, Parents Hall, Olmsted Center, Des Moines, IA

**Board of The Iowa Physiological Society:**  
Ronald Torry, Des Moines, IA (President)  
Gina Schatteman, Iowa City, IA (Past President)  
Harald M. Stauss, Iowa City, IA (Secretary/Treasurer)

## Welcome!

Welcome to Drake University and the 14<sup>th</sup> Annual Iowa Physiological Society (IPS) meeting. IPS was established to help promote scientific exchange among physiologists in the region. We look forward to continuing this practice with this year's meeting and we hope you will enjoy your visit to Drake and the Des Moines metro area.

This year's program includes several highlights. First, we believe we have assembled an exceptional group of keynote speakers. **Dr. Andrew Holmes**, Section Chief, National Institute on Alcohol Abuse and Alcoholism, NIH will give the American Physiological Society keynote lecture. Dr. Holmes has a distinguished career in the molecular and genetic determinants of depression and anxiety.



**Dr. Robert Shumaker**, Research Director of the Great Ape Trust of Des Moines, will give the Iowa Physiological Society keynote lecture. Dr. Shumaker is internationally recognized for his work on great ape cognition, behavior and conservation.

We are pleased that **Dr. Andrew King**, Associate Research Investigator, Integrative Pharmacology, Abbott Laboratories will provide a lecture on utilizing state of the art instrumentation to assess hemodynamics in small animals. This lecture is *generously supported by Data Sciences International*. Attendees are encouraged to stop by the display at the back of the room and talk with Shannon Schirmer of DSI.

Finally, **Dr. Gina Schatteman**, past-president of IPS and current AAAS Science Technology Fellow in the Office of Science Education at NIH will provide a thought-provoking seminar on the state of science education in the United States and how researchers can/should help to improve K-12 science education.

In addition to these speakers, we have invited several local investigators to provide brief summaries of their work. The interesting topics cover behavioral, pharmaceutical, stem cell and clinical research programs so there is something for everyone.

Finally, ample time is available to view a variety of poster presentations by undergraduate students, graduate students and research associate/faculty members. I am particularly pleased to announce that the *American Physiological Society* has provided funds to allow cash awards for meritorious research in each of the student categories. The award presentations will conclude the meeting this afternoon.

We hope the schedule of the meeting will allow you to personally interact with colleagues from neighboring institutions and to build new friendships and collaborations. Thank you very much for coming to Des Moines and for helping to make this meeting a success. We look forward to seeing you at next year's meeting.

Ronald Torry  
President, IPS

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## Saturday Morning

**8:15-9:00** Breakfast, Registration, Poster Setup

**9:00-9:05** Opening Remarks and Introductions



**9:05-10:00 APS Keynote Lecture** (generously supported by

HOW RESEARCH ON MICE HELPS US UNDERSTAND THE GENETIC BASIS OF  
DEPRESSION AND ANXIETY

**Dr. Andrew Holmes**

*Section Chief, National Institute on Alcohol Abuse and Alcoholism, NIH*

**10:00-10:45 Investigator Presentations**

**10:00-10:20** ORGANIZATIONAL AND ACTIVATIONAL EFFECTS OF  
GENISTEIN ON WATER MAZE PERFORMANCE

**Dr. Craige Wrenn**

*College of Pharmacy & Health Sciences, Drake University*

**10:25-10:45** DIFFERENTIAL REGULATION OF DRUG METABOLIZING  
ENZYMES EXPRESSION BY OXYCODONE

**Dr. Alan Myers**

*College of Pharmacy & Health Sciences, Drake University*

**10:45-11:30** Break and Poster Viewing

**11:30-12:30 IPS Keynote Lecture**

UNDERSTANDING ORANGUTANS, THE NEGLECTED APE - PERSPECTIVES ON  
BEHAVIOR, COGNITION, AND CONSERVATION

**Dr. Robert Shumaker**

*Research Director, Great Ape Trust, Des Moines, IA*

**12:30-1:30** Lunch and Poster Viewing

## Saturday Afternoon



- 1:30-2:30 DSI Keynote Lecture** (generously supported by )  
 CHRONIC MEASUREMENT OF ARTERIAL PRESSURE IN SMALL LABORATORY ANIMALS  
**Dr. Andrew King**  
*Associate Research Investigator, Integrative Pharmacology, Abbott Laboratories*
- 2:30-3:15 Investigator Presentations**
- 2:30-2:50** AUTONOMIC RESPONSES TO THE COLD FACE TEST IN SPINAL CORD INJURY  
**Dr. Joseph Weir**  
*Physical Therapy/Exercise Physiology, Des Moines University*
- 2:55-3:15** MECHANISMS FOR TISSUE REPAIR USING BONE MARROW-DERIVED CELLS IN ISCHEMIC MURINE HIND LIMB  
**Eric Nau**  
*Research Associate, Department of Integrative Physiology, The University of Iowa*
- 3:15-4:00** Break with Snack, Poster Viewing and Award Scoring
- 4:00-4:30 Special Topic: Science Education**  
 SCIENTISTS IN SCIENCE EDUCATION: WHY WE SHOULD CARE ABOUT K-12 EDUCATION  
**Dr. Gina Schatteman**  
*AAAS Science & Technology Fellow, Office of Science Education, NIH*
- 4:30-4:45** Poster Award Presentations and Closing Remarks
- 4:45-5:00** IPS Business Meeting

# Business Meeting

1. Opening Remarks
2. Treasurer's Report
3. Vote for Dr. Julia Moffitt as new President
4. Nominations for President Elect
5. Location and Date for the Annual Meeting 2010
6. Relation to Iowa Academy of Science
7. Topics from The Floor
8. Closing Remarks

## Abstracts

**Disclaimer:** One of the abstracts contains fabricated data. Every participant of the meeting will receive a raffle ticket. Please write your name and the number of the poster with fabricated data on the raffle. We will draw a winner of the raffle at the end of the meeting.

## Undergraduate Student Competition

EFFECTS OF VAGUS NERVE STIMULATION (VNS) ON THE THRESHOLD AND  
INCIDENCE OF ACONITINE-INDUCED CARDIAC ARRHYTHMIAS IN THE  
ANESTHETIZED RAT

Rachel M. Firkins<sup>1</sup>, Pooja N. Patel<sup>1</sup>, Kathryn C. Welliver<sup>2</sup>,  
Julia A. Moffitt<sup>2</sup> (Mentor)

<sup>1</sup>Neuroscience, College of Arts and Sciences, Drake University and

<sup>2</sup>Physiology and Pharmacology, Des Moines University

Previous data indicate that VNS may induce anti-arrhythmic effects in animal models of ischemia. We hypothesized that VNS would increase the threshold and/or reduce the incidence of pharmacologically induced arrhythmias. Anesthetized, ventilated, male Sprague Dawley rats, were instrumented with femoral arterial and venous catheters for administration of drugs and measurement of arterial pressure and heart rate (HR), respectively. Subcutaneous electrocardiographic leads were placed in a lead II configuration for measurement of cardiac arrhythmic events. In the VNS group (n=6) a bipolar electrode was secured to the right vagus nerve, and electrical stimulation was delivered to achieve a stable 15-20 beat per minute decrease in HR, while control rats (n=5) underwent vagus isolation but received no VNS. VNS was delivered 10 min prior to, 10 min during and 10 min following infusion of the alkaloid drug aconitine at a rate of  $0.75\mu\text{g}/\text{kg}/\text{min}$  i.v. Our data indicate that VNS significantly delayed the onset of the first premature ventricular complex (VNS:  $338.61\pm 8.57$  vs. CON:  $228.84\pm 54.14$  sec) reduced the time spent in ventricular tachycardia (VT) (VNS:  $164.34\pm 8.08$  vs. CON:  $220.51\pm 19.62$  sec), and prolonged onset time to VT (VNS:  $376.87\pm 8.73$  vs. CON:  $337.64\pm 16.69$ ). There was a trend towards less time spent in ventricular fibrillation (VF) (VNS:  $15.37\pm 5.77$  vs. CON:  $21.65\pm 6.03$  sec) and increased time to onset of VF (VNS  $454.32\pm 30.23$  vs. CON:  $408.80\pm 49.95$  sec) during VNS. These data indicate that VNS may help increase the threshold for sustaining ventricular arrhythmias in the non-ischemic myocardium.

Poster No.: 1



DIFFERENTIAL EFFECT OF ANTIHYPERTENSIVE DRUGS ON HEMORRHAGIC  
STROKE IN STROKE-PRONE SPONTANEOUSLY HYPERTENSIVE RATS

Areeba Fatima, Robert C. Engel, Jonathan D. Alterie, Joshua R. Nelson,  
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Chronic renal failure and uremia as well as impaired cerebrovascular myogenic function have been identified as risk factors for hemorrhagic stroke. For example, patients on chronic hemodialysis have an impaired ability to autoregulate cerebral blood flow and also face a markedly elevated risk for hemorrhagic stroke. Because of the association between impaired cerebrovascular myogenic function and hemorrhagic stroke, antihypertensive drugs that do not affect myogenic vascular function may be more effective in preventing hemorrhagic stroke in hypertensive patients than drugs that reduce myogenic vascular function. Thus, the hypothesis of this study was that stroke-prone spontaneously hypertensive rats (SHR-SP) treated with calcium channel blockers, which inhibit myogenic vascular function, exhibit more severe cerebral hemorrhage than SHR-SP treated with  $\alpha_1$ -adrenergic receptor antagonists.

SHR-SP and stroke-resistant spontaneously hypertensive rats (SHR-SR) on high-salt diet (1% NaCl in drinking water) were treated with placebo (SHR-SR, n=7 and SHR-SP, n=7), the  $\text{Ca}^{++}$ -channel blocker nifedipine (SHR-SP only, n=7), or the  $\alpha_1$ -adrenergic receptor antagonist doxazosin (SHR-SP only, n=17) for a total observation period of 12 weeks. Blood pressure, body weight, and water intake were recorded weekly. Spectral analysis of systolic blood pressure was performed to assess very low frequency (VLF) blood pressure variability (BPV), which reflects myogenic vascular function and low frequency (LF) BPV, which reflects sympathetic modulation of vascular tone. At the end of the observation period, a blood sample was taken for determination of plasma urea concentration as indicator of renal function and the brain was harvested for histological assessment of cerebral hemorrhage.

During the 2<sup>nd</sup> half of the observation period, measures of water intake (normalized for body weight) and plasma urea concentration were higher in placebo-treated SHR-SP than in SHR-SR, indicating impaired renal function in SHR-SP. Treatment with either nifedipine or doxazosin prevented the increase in water intake and reduced plasma urea levels in SHR-SP. However, doxazosin reduced plasma urea levels to a lesser degree than nifedipine. During the 12-week observation period systolic blood pressure increased to  $\sim 200$  mmHg in placebo-treated SHR-SP but only to  $\sim 180$  mmHg in placebo-treated SHR-SR and nifedipine- or doxazosin-treated SHR-SP. VLF and LF BPV was significantly lower in nifedipine- and doxazosin-treated SHR-SP than in placebo-treated SHR-SP and SHR-SR, suggesting that both drugs reduced myogenic vascular function and sympathetic modulation of vascular tone. Nifedipine and doxazosin reduced the severity of hemorrhagic stroke compared to placebo-treated SHR-SP, but nifedipine-treatment was more effective in reducing severity of hemorrhagic stroke than doxazosin.

In conclusion, SHR-SP on high-salt diet develop impaired renal function as indicated by the elevated water intake and plasma urea levels. This reduction in renal function may promote impairment of cerebrovascular myogenic function and, subsequently, hemorrhagic stroke. Even though nifedipine and doxazosin impaired myogenic vascular function (estimated by VLF BPV), they reduced severity of hemorrhagic stroke

with a greater effect of nifedipine than of doxazosin. This effect may be mediated by a protective effect on the kidneys that is stronger for nifedipine than for doxazosin.  
*Supported by the American Heart Association*

Poster No.: 2



### BILE SALTS AND CANDIDA ALBICANS... HOW MUCH DO WE KNOW?

Bao Vu, Michael Essmann BS, Bryan Larsen PhD  
Microbiology and Immunology, Des Moines University

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*Objective:* The aim of this study was to use in vitro method to understand the effects of Sodium choleate on *Candida albicans* growth, induction of virulent phenotypes, and changes in azole drug susceptibility occasioned by bile exposure.

*Methods:* Yeast isolates (originally obtained from clinical sources) were tested by agar dilution to challenge the organisms against sodium choleate. Established microbial physiology methods were used to investigate the biological activities of sodium choleate on yeast morphology, virulence attributes and susceptibility to azole drugs. Pre-incubation of yeast in the presence of a range of sodium choleate concentrations was used to induce phenotypes examined in this study.

*Results:* Sodium choleate failed to inhibit growth of *Candida albicans*, even at the highest concentration tested (40 mg/ml). Consistent induction of CDR1p and biofilm was observed at lower concentrations of sodium choleate, but not at the higher concentrations. Despite the elevation of CDR1 at 5 mg/ml, cells were not protected against the azole drugs when the yeast was pre-treated with sodium choleate.

*Conclusion:* Sodium choleate does not have a fungistatic effect on *Candida albicans*. Although bile salt appears to augment the fitness of the organism in vitro, apparently, by upregulating some virulence factors, it sensitizes the organism toward azole treatment.

Poster No.: 3



AORTIC FLOW RESPONSES TO LEG LIFTING AND INSPIRATORY IMPEDANCE IN  
SPONTANEOUSLY BREATHING YOUNG ADULTS

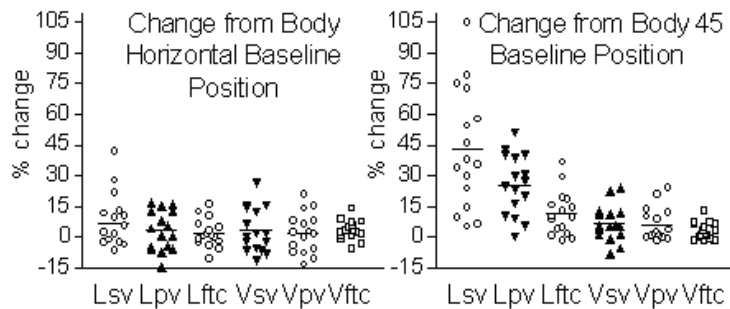
Jessica Wageman<sup>1</sup>, Betsy Litman<sup>1</sup>, Cathy Nguyen<sup>1</sup>, Charisse Buising<sup>1</sup> and  
Piper Wall<sup>2</sup>

<sup>1</sup>Biochemistry, Cell and Molecular Biology Program, College of Arts and Sciences,  
Drake University and <sup>2</sup>Department of Surgery Education and Trauma Research,  
Iowa Methodist Medical Center

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*Objective:* To examine aortic flow responses of healthy young adults to interventions of possible use for predicting fluid responsiveness of critically ill patients.

*Methods:* In 16 volunteers, aortic variables were monitored by transcutaneous continuous wave Doppler during 1) horizontal upper body with or without legs elevated 45 and horizontal whole body with or without use of an inspiratory impedance threshold device and 2) 135 angle of upper body to legs with either legs or upper body horizontal and with legs horizontal with or without inspiratory impedance.



*Results:* No consistent changes occurred with a horizontal whole body baseline position or with the addition of inspiratory impedance in either body position. Position change from upper body 45 elevated to legs 45 elevated increased ( $p > 0.01$ ) stroke volume (Lsv 5-105%),

peak velocity (Lpv 5-51%), and corrected flow time (Lftc-2-37%). (Inspiratory impedance valve variables: Vsv, Vpv, Vftc)

*Conclusions:* While horizontal, neither a 45 leg raise nor adding inspiratory impedance sufficiently enhances preload for stroke volume changes to indicate ventricular preload responsiveness in spontaneously breathing adults. A baseline upper body position of 45 may be preferable when using leg raising to assess preload responsiveness in spontaneously breathing patients.

*Funding:* IA Space Grant, Eagles, Drake U

Poster No.: 4



THE EFFECTS OF ACUTE COCAINE AND COCAINE WITHDRAWAL ON RATS'  
SHORT-TERM MEMORY PERFORMANCE DURING DELAYED MATCH TO SAMPLE  
TASKS IN Y-MAZE AND TWO-LEVER OPERANT PARADIGMS

Kate Long, Ankit Patel, Andrew Swisher and William D Klipec

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While an extensive literature exists on the effects of cocaine on many different behaviors, there has been little research on the effects of cocaine withdrawal in rats. Recently we have been developing delayed match to sample tasks (DMTS) in a Y-Maze paradigm and two-lever operant task pursuant to examining the effects of cocaine withdrawal on short term memory (STM). The absence of an observing response made the Y-maze task difficult to learn for many of the rats, and performance was highly variable. Nonetheless, rats that were able to master the task, showed a marginally significant decrease in STM performance during a week following 7 days of exposure to 45 mg/kg of cocaine per day over three hours compared to saline control conditions. Using a two lever DMTS task, we found consistently faster learning and less variability in performance with memory delays ranging from 3 to 8-sec. Using four pilot rats, we found a weak, transient decrease in DMTS performance compared to saline control conditions, during a week where 45 mg/kg of cocaine was administered after each daily training session, and after complete withdrawal from cocaine. Subsequently, we found that acute cocaine injections at 15 and 10 but not 5 mg/kg, prior to training sessions, disrupted DMTS performance. Although the two-lever DMTS task generates more accurate and less variable performance, it is more difficult to disrupt STM. Accordingly, we are modifying the training conditions to make STM more difficult, and therefore more sensitive to disruption.

Poster No.: 5



P300 EVENT RELATED POTENTIALS FROM RAT BRAIN TO CUES FOR  
REINFORCEMENT AND NON-REINFORCEMENT

Carly Bueltel, Heidi Woodland, Jill Swenson, Marissa Collins, Emily Flattery,  
Heather Price, Ankit Patel and William D Klipec (Mentor)  
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The P300 Event Related Potential (ERP) is a time locked, averaged EEG to task relevant stimuli. Previous research in our laboratory has shown that the P300 ERP in rats is a correlate of the brain's recognition of a conditioned reinforcer. More recently, we found that the P300 ERP to a tone that predicted reinforcement was indistinguishable from one that predicted non-reinforcement, linking the P300 ERP to the information in the cue even when the information was predicting the absence of a reinforcer. Here we compared the P300 ERP to the click of a food hopper under two conditions. In one condition (cued reinforcement) a tone signaled a click that was followed by food delivery. In the other condition, the absence of the tone signaled that the click would not be followed by food delivery (non-cued non reinforcement). We found that the P300 ERP to the non-cued non-reinforcement click rapidly disappeared suggesting that the absence of the tone was informative, predicting non-reinforcement and eliminating the response to the click. We are currently gathering data in a condition where the probability of food delivery following a click is 0.5, but there are no cues to provide information about the relevance of the click.

*Pending completion and analysis, these data will also be reported at DUCURS.*

Poster No.: 6



## Graduate Student Competition

### THE EFFECTS OF HOMOCYSTEINE ON CHICK EMBRYO CARDIAC NEURAL CREST CELLS

Mwakikunga, Anthony and Darrell Wiens

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Increased homocysteine (Hcys) levels during embryonic development are correlated with cardiovascular diseases and malformations related to neural crest cells (NCCs). Therefore, understanding how Hcys affects NCC formation, epithelial-to-mesenchymal transition (EMT) and migration is indispensable. Cells extend, adhere and contract to migrate, organizing their cytoskeleton locally using three (*Ras* GTPase enzymes) - *Rho*, *Rac* and *Cdc42*. When *Rho* is activated, cells bundle actin into stress fibers, and connect to focal contacts. *Rac* or *Cdc42* activation creates actin networks or new actin branch points, respectively in leading lamellae. We predicted that Hcys may tilt the balance of the *Ras* GTPase activities to favor *Rac* activity, allowing greater (but not excessive) adhesion and migration. We immunolocalized  $\alpha$ -actinin, vinculin, filamin, and LIM3 protein in migrating cardiac NCCs. Hcys caused significant differences in vinculin,  $\alpha$ -actinin and LIM3 expression, but not filamin. Hcys intensified vinculin expression in focal adhesions and lamellapodia and enhanced  $\alpha$ -actinin in focal adhesions, filapodia and around nuclei. LIM 3 was expressed mainly in nuclei and focal adhesions, and faintly throughout cytoplasm; Hcys elevated its expression. Whole embryo immunolocalization of LIM3 showed strong anterior head and heart staining. Filamin was more intense along cell periphery, caveolae and trans-Golgi vesicles with Hcys (although not significantly). Hcys-treated explants showed more spreading migrating NCCs than controls, but no significant difference regarding cell-cell attachment pattern. Our findings suggest that Hcys regulates the balance of organizing activity of the three *Ras* GTPases in NCCs to favor *Rac* activity allowing greater (but not excessive) adhesion and migration. Hcys also affects LIM3 expression in migrating cardiac NCCs, suggesting the modulation by Hcys of a signaling mechanism that adjusts actin-based cytoskeleton for enhanced migration. This could lead to mistimed and defective development of tissues that receive cardiac NCC contributions.

Poster No.: 7



THE EFFECTS OF ACUTE MYOCARDIAL INFARCTION ON HEART RATE  
VARIABILITY PARAMETERS RECORDED IN FREELY MOVING CONSCIOUS RATS

Kathryn C. Welliver<sup>1</sup>, Calvin G. Davis<sup>2</sup>, Terry G. Beltz<sup>3</sup>, Baojian Xue<sup>3</sup>,  
Alan Kim Johnson<sup>3,4,5,6</sup>, Julia A. Moffitt<sup>1,3</sup>

<sup>1</sup>Des Moines University, Physiology and Pharmacology; <sup>2</sup>Drake University;  
Biochemistry, Cell and Molecular Biology; Depts of <sup>3</sup>Psychology, <sup>4</sup>Pharmacology,  
<sup>5</sup>Integrative Physiology and the <sup>6</sup>Cardiovascular Center, University of Iowa

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Although the effects of myocardial infarction (MI) on heart rate variability (HRV) have previously been reported in rat models of MI, few studies have reported changes during the acute response to MI and over time, with animals serving as their own control. We hypothesized that acute MI would induce an increase in heart rate (HR), decrease in the standard deviation of the normal-to-normal interval (SDNN) and decrease in high frequency (HF) power of HRV. Radiotelemetry electrocardiographic probes were implanted subcutaneously in male, Sprague-Dawley rats 2 weeks prior to MI. Rats were anesthetized, intubated, and ventilated prior to induction of MI. Under aseptic conditions, the left anterior descending coronary artery was ligated between the pulmonary outflow tract and the left atrium. SHAM rats were treated in the same manner, but did not undergo coronary artery occlusion. Data were collected at 1,000 Hz for 5 minutes each hour, for a 6 day period; which included a 2 day baseline collection prior to the MI. Data for each day were averaged and the mean compared between groups. Both the SHAM (n=2) and MI (n=3) rats had a similar HR, SDNN, total power (TP), HF (0.195-0.8 Hz) power, and low frequency power (LF; 0.8-2.5 Hz) at baseline. Immediately following surgery HR increased in both groups and returned to normal in SHAM rats but remained elevated in MI rats. SDNN and TP immediately decreased in both groups and remained low in MI rats but returned to baseline in SHAM rats. HF power gradually decreased in MI rats but remained stable in SHAM rats. No differences in LF power were observed between groups over time. These preliminary data indicate that acute MI increases HR and predictably reduces time domain parameters of HRV, while changes in the frequency domain of HRV remain less clear.

Poster No.: 8



THERAPEUTIC POTENTIAL OF MESENCHYMAL STEM CELLS IN HEMORRHAGIC  
STROKE

Nick Leymaster<sup>1</sup>, Harald M. Stauss<sup>2</sup>, Warren Darling<sup>2</sup>, Gina C. Schatteman<sup>2</sup>

<sup>1</sup>Department of Biomedical Engineering and <sup>2</sup>Department of Integrative Physiology,  
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Stroke is the third leading cause of death in the United States. Thirteen percent of strokes are categorized as hemorrhagic and 44.6% of the patients of age 65 and older die within 30 days following the acute event. Mesenchymal stem cells (MSCs) are bone marrow-derived cells that promote healing after injury in a number of animal models including ischemic stroke. We tested the hypothesis that MSCs, as a therapeutic treatment, can reduce brain tissue damage and promote healing following hemorrhagic stroke.

MSCs were injected intravenously via the tail vein into salt loaded (1% NaCl in drinking water) spontaneously hypertensive stroke-prone (SHR/SP) rats. Water consumption and body mass were recorded. Tests of neurological function were performed along with behavioral observations to assess occurrence and severity of hemorrhagic stroke, which was confirmed by analysis of brain sections post-mortem. Rats that received the MSCs tended to have more severe strokes than controls ( $P \leq 0.05$ ) and tended to display a higher mortality rate than controls. Our findings suggest that MSCs may promote rather than prevent hemorrhagic stroke and could potentially decrease lifespan. Future studies may investigate the mechanisms of MSC induced angiogenesis in hemorrhagic stroke development.

Poster No.: 9



EFFECTS OF SELEGILINE IN NEUROPATHIC PAIN FROM  
PERIPHERAL NERVE INJURY

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Des Moines University, Des Moines, IA

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Reactive oxygen species (ROS) play mediatory roles in the development of neuropathic pain. If ROS mediate neuropathic pain states, antioxidants should ameliorate painful symptoms of peripheral neuropathies. For this series of studies, spinal nerve ligation surgery (SNL) was tested and induced peripheral neuropathy in Fischer 344 rats. After SNL, neuropathic rats developed lasting neuropathies confirmed by behavioral tests using von Frey filaments to detect mechanical sensitivity (allodynia). This study tests selegiline, a known MAO-B inhibitor that has neuroprotective effects in patients with Parkinson's disease via its ability to work as an antioxidant. The current study shows that selegiline (1.0 mg/kg i.p.) can be moderately efficacious in suppressing sensitivity to mechanical tests for allodynia after SNL. The present studies further test the usefulness of combination pharmacotherapy with selegiline and opiate analgesics in reversing neuropathic pain. Currently, morphine is the most powerful and efficacious analgesic used to treat clinical pain. However, sustained use of opiates lead to tolerance, a loss of effectiveness leading to increased dosage, and high doses of opiates can be hazardous or even fatal. In the current studies, administration of neither low dose morphine (3.0 mg/kg) nor selegiline (1.0 mg/kg) alone reversed neuropathic pain behavior and did not provide an analgesic affect. The final phase of these studies demonstrated the co-administration of low dose morphine with selegiline produced an additive effect with sustained reversal of allodynic symptoms following SNL induced neuropathic pain. These data suggest that selegiline has the ability to inhibit ROS related mechanisms leading to neuropathic pain. Further, co-administration of antioxidants and opiates completely reverse persistent pain following peripheral nerve injury.

Poster No.: 10



CONTRIBUTION OF WHOLE BODY AUTOREGULATION OF BLOOD FLOW AND  
BAROREFLEX FUNCTION TO BLOOD PRESSURE VARIABILITY

Richard J. Deklotz, Kevin R. Rarick, Don D. Sheriff, and Harald M. Stauss  
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Very low frequency (VLF, 0.02-0.2 Hz in rats) blood pressure variability (BPV) comprises more than 70% of overall BPV. However, its underlying mechanisms are not fully understood. Previously, we demonstrated that very low frequency (VLF) blood pressure variability (BPV) depends on voltage-gated L-type  $\text{Ca}^{++}$ -channels, suggesting that autoregulation of blood flow and/or myogenic vascular function significantly contributes to VLF BPV. To further substantiate this possibility, we tested the hypothesis that the frequency response characteristic of whole body autoregulation of blood flow is consistent with the frequency range of VLF BPV (0.02-0.2 Hz) in rats. Computer-regulated cardiac pacing was used to induce BPV at 8 different frequencies, ranging from 0.016 Hz (period=60 s) to 0.5 Hz (period=2 s) in anesthetized rats (n=11). Cardiac output (CO), blood pressure, and heart rate were recorded during control conditions (NaCl, 1ml/h i.v.) and during  $\alpha_1$ -adrenergic receptor stimulation (phenylephrine, 1mg/mL/h i.v), which has been reported to facilitate myogenic vascular function. Baroreceptor-heart rate reflex responses were elicited through bolus injections of phenylephrine and sodium nitroprusside to confirm a functional baroreflex despite anesthesia.

During control conditions, transfer function analyses between mean arterial pressure (MAP) and CO, and between MAP and total vascular conductance (CO/MAP), indicated autoregulation of blood flow at 0.016 Hz, passive vascular conductance between 0.033 Hz and 0.2 Hz, and vascular responses compatible with baroreflex-mediated mechanisms at 0.333 Hz and 0.5 Hz. Stimulation of  $\alpha_1$ -adrenergic receptors extended the frequency range of autoregulation of blood flow to frequencies up to 0.033 Hz.

In conclusion, depending on sympathetic vascular tone, whole body autoregulation of blood flow operates most effectively at frequencies below 0.05 Hz. This frequency range corresponds with the lower end of the frequency band of VLF BPV in rats (0.016-0.2 Hz). Baroreceptor reflex-like mechanisms contribute to LF (0.2-0.6 Hz) but not VLF BPV-induced vascular responses.

Poster No.: 11



## Faculty Presentations

### SHIFT OF AUTONOMIC BALANCE TOWARDS SYMPATHETIC DOMINANCE DURING 24 H-RECOVERY FROM EXERTIONAL VS. PASSIVE HEAT STRESS

Lauren E. Liaboe<sup>1</sup>, Lisa R. Leon<sup>2</sup>, Kevin C. Kregel<sup>1</sup>, and Harald M. Stauss<sup>1</sup>

<sup>1</sup>Department of Integrative Physiology, The University of Iowa and

<sup>2</sup>United State Army Research Institute of Environmental Medicine (USARIEM)

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Acute exposure to high ambient temperatures ( $T_a$ ), leading to increased core body temperature ( $T_c$ ), is associated with pronounced alterations in autonomic nervous system function. In this study we tested the hypothesis that the addition of exercise to heat stress (HS) exaggerates these alterations in autonomic function for a prolonged period of several hours into recovery.

Rats were exposed to an  $T_a$  of 39°C while resting (HS-C) or exercising on a running wheel (HS-EX). Once  $T_c$  reached 41.5°C, the exercise protocol was stopped in the HS-EX group and  $T_a$  was reduced to 25°C in both groups.  $T_c$  and blood pressure (BP) were recorded telemetrically throughout the protocol and the recovery period of 24 h.

$T_c$  increased to 41.5°C within 75 min in HS-EX and within ~165 min in HS-C. Mean BP and heart rate (HR) increased similarly in both groups to ~180 mmHg and ~425 bpm. During recovery,  $T_c$ , BP, and HR returned to baseline levels with no significant time-course difference. However, low frequency (LF) to high frequency (HF) ratio (LF/HF ratio) of HR variability remained higher in HS-EX than in HS-C for the first 15 h of recover, indicating that the addition of exercise to heat stress shifts autonomic balance towards sympathetic tone. Relative HF HR variability (expressed as % of total variability) was reduced in HS-EX for the complete recovery period of 24 h, further confirming a stronger relative contribution of sympathetic than parasympathetic activity to control of heart rate. Absolute LF BP variability remained elevated in HS-EX compared to HS-C for up to 8 h of recovery, indicating greater sympathetic modulation of vascular tone.

In conclusion, adding exercise to heat stress causes marked and sustained effects on autonomic function that last for several hours into the recovery period. These autonomic adjustments during recovery are characterized by a relative dominance of sympathetic over parasympathetic control of the heart and increased sympathetic modulation of vascular tone.

*Supported by USAMRMC; author views not official US Army or DoD policy*

Poster No.: 12



IMPORTANCE OF THE HYPOTHALAMIC NUCLEUS ORIENSIS FOR DEVELOPMENT  
OF HYPERTENSION IN SHR

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Astroglia cells within the newly discovered hypothalamic nucleus oriens (HNO) are thought to project to spinally-projecting parvocellular neurons in the hypothalamic paraventricular nucleus (PVN) that are known to contribute to regulation of peripheral sympathetic nerve activity and blood pressure (BP) control. Furthermore, recent evidence suggests that the neurotransmitter at the synapses between the dendrites of the HNO cells and cell bodies of the parvocellular PVN cells is cometine, a benzalacetophenone derivative. We tested the hypotheses that hypertension in spontaneously hypertensive rats (SHR) depends on a functional HNO and that hypertension in SHR can be prevented by inhibition of cometine.

Prehypertensive SHR (6 weeks of age) were randomly subjected to stereotactic lesioning of the HNO (n=7) or sham surgery (n=6). In two additional groups of SHR an antisense sequence of the cometine gene (n=6) or vehicle (n=5) were micro-infused into the HNO via subcutaneously implanted osmotic minipumps. Telemetric BP sensors were implanted in rats of all 4 groups and BP recorded weekly for an observation period of 12 weeks.

During the observation period of 12 weeks, BP increased continuously in sham operated and vehicle-treated SHR, reaching a final systolic BP of  $182 \pm 11$  mmHg and  $176 \pm 9$  mmHg, respectively. In contrast, BP in HNO-lesioned and cometine antisense-treated SHR remained normotensive.

In conclusion, our results demonstrate for the first time that hypertension in SHR depends on a functional HNO and that the neurotransmitter mediating the hypertensive action of the HNO is cometine.

Poster No.: 13



HYDROGEN PEROXIDE MEDIATES POST-EXCITATORY DEPRESSION OF  
BARORECEPTOR AFFERENT ACTIVITY IN VIVO

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Acute hypertension leads to 'post-excitatory depression' (PED) of baroreceptor (BR) activity after the period of elevated blood pressure (BP), a phenomenon that contributes to BR resetting. The molecular mechanism of PED is not fully understood. We recently demonstrated that electrical stimulation of isolated BR neurons in vitro generates reactive oxygen species that cause PED of action potential firing after the period of neuronal activation (*Hypertension* 43(6):1349, 2004). In the present study, we tested the hypothesis that the reactive oxygen species hydrogen peroxide ( $H_2O_2$ ) mediates BR PED in vivo. The left aortic depressor nerve (ADN) was draped over a recording/stimulating electrode and crushed centrally to prevent reflex changes in BP in anesthetized C57BL/6 mice. Afferent ADN (BR) activity was recorded before and after a brief period of ADN stimulation (3V, 2ms pulses at 20Hz for 10s). Afferent BR activity was markedly inhibited after the 10s period of electrical stimulation, averaging  $50\pm 5\%$  and  $80\pm 8\%$  of baseline levels 5 and 60s after the stimulation was terminated (n=7). This PED was abolished after administration of the membrane permeable  $H_2O_2$  scavenger PEG-catalase (4000 U, IV) with activity averaging  $100\pm 4\%$  and  $126\pm 7\%$  of baseline 5 and 60s after ADN stimulation (n=7). PED was unaffected by administration of the saline vehicle in a separate group of mice (n=6). We conclude that  $H_2O_2$  generated during activation of BR afferents causes PED. This autocrine-feedback inhibition of BR activity may contribute to rapid BR resetting in acute hypertension.

HL14388, VA

Poster No.: 14



AUTONOMIC DYSREGULATION IN A MOUSE MODEL OF MUSCULAR DYSTROPHY  
DESTINED TO DEVELOP DILATED CARDIOMYOPATHY

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Mutations in the dystrophin-glycoprotein complex cause muscular dystrophy and dilated cardiomyopathy (DCM) in animals and humans. Mice deficient in sarcoglycan delta (Sgcd), a component of this complex, develop muscular dystrophy at a young age (<10 wks) with later onset of DCM (*Cell* 98:465-474,1999). We hypothesized that autonomic dysregulation may occur early in the disease progression before development of DCM. We measured cardiac function (echocardiography); blood pressure (BP) and heart rate (HR) (telemetry); and indices of autonomic regulation including baroreflex sensitivity (BRS) and HR variability (HRV-SD) in 10-12 wk old Sgcd<sup>-/-</sup> and control C57BL/6 mice. Left ventricular ejection fraction (0.83±0.01 vs. 0.85±0.03) and end-diastolic volume (26±2 vs. 33±4 μl) were normal in Sgcd<sup>-/-</sup> mice. Histopathological features of muscular dystrophy were evident in skeletal muscle but not in the heart of Sgcd<sup>-/-</sup> mice. Compared with control mice, Sgcd<sup>-/-</sup> mice exhibited less locomotor activity (4±1 vs. 11±1 c/min), lower mean BP (100±2 vs.120±4 mmHg), and reductions in diurnal (night-day) variability, BRS and HRV-SD (see Table, \*P<0.05).

	Control (n=5)	Sgcd <sup>-/-</sup> (n=7)
Diurnal BP (ΔmmHg)	31±2	7±1 *
Diurnal HR (Δbpm)	114±19	25±4 *
Diurnal Activity (Δc/min)	21±4	4±1 *
BRS (ms/mmHg)	2.2±0.2	1.1±0.2 *
HRV-SD (ms)	5.0±1.0	3.0±0.2 *

We conclude that young Sgcd<sup>-/-</sup> mice exhibit decreased BP, loss of diurnal cardiovascular rhythms, and severe autonomic dysregulation prior to onset of cardiac dysfunction. We speculate that this early autonomic dysregulation may hasten the progression to DCM.

VA, HL14388

Poster No.: 15



REPEATED ADMINISTRATION OF OXYCODONE MODIFIES THE GENE  
EXPRESSION OF SEVERAL DRUG METABOLIZING ENZYMES IN THE HEPATIC  
TISSUE OF MALE SPRAGUE-DAWLEY RATS, INCLUDING GLUTATHIONE  
S-TRANSFERASE A-5 (RGSTA5) AND CYTOCHROME P450 3A2 (CYP3A2)  
Alan L. Myers, Hazem E. Hassan, Insong J. Lee, and Natalie D. Eddington Drake  
University, College of Pharmacy and Health Sciences, Des Moines, IA

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Pharmacotherapeutic use and illicit abuse of the potent opioid agonist oxycodone has dramatically increased over the past decade. Yet oxycodone remains one of the least studied opioids, particularly in regards to its potential physiological interactions with major drug metabolizing enzymes. The aim of this study was to examine possible physiological alterations in the gene expression of drug metabolizing enzymes in the liver tissue of male Sprague-Dawley rats chronically treated with oxycodone. Our initial approach to detect changes in RNA levels included microarray analysis that was validated by QRT-PCR. There was a strong correlation between the significant fold changes observed on microarray and QRT-PCR analyses. The expression of several drug metabolizing enzymes was modulated by oxycodone treatment, e.g. CYP2B2, CYP2C13, CYP17A1, EH-2, CES-2, FMO-1, GSTA5 and CYP3A2. Notably, the mRNA level of rat GSTA5 was up-regulated by ca. 6.5 fold and CYP3A2 was down-regulated by ca. 7.0 fold. Immunoblotting assays demonstrated a corresponding significant elevation of rGSTA5 protein and repression of CYP3A2 protein. The apparent cytosolic GST activity towards CDNB-SG conjugation and cumene hydroperoxide reduction was significantly higher in the liver of oxycodone treated rats than that of saline treated rats. In addition, liver microsomal samples from oxycodone treated rats exhibited a marked decrease in hydroxylase activity, measured via CYP3A2 specific  $6\beta$ -hydroxylation of testosterone. Our results are the first report, to our knowledge, that establish a significant up-regulation of rGSTA5 and concomitant down-regulation of CYP3A2 following repeated oxycodone administration. Further *in vivo* drug-drug interaction studies are clearly warranted to examine the likely clinical impact of our findings.

Poster No.: 16



MECHANISMS OF ENHANCED CAROTID BODY FUNCTION IN HEART FAILURE:  
A LINK TO VASCULAR ENDOTHELIAL FUNCTION

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Carotid body (CB) chemoreflex function is enhanced in congestive heart failure (CHF) and contributes to the elevation in sympathetic activity associated with the disease. We have undertaken studies to investigate the physiological and molecular mechanisms responsible for CB sensitization in CHF using a pacing-induced model of CHF in rabbits. Our studies demonstrate that moderate stable CHF (equivalent to a 40-50% reduction in left ventricular pump function) causes a decrease in voltage-gated  $K^+$  channel activity and an increase in  $Ca^{++}$  channel activity in CB glomus cells. These changes are consistent with the enhanced CB afferent discharge to hypoxia seen in the CHF rabbits. Studies confirm that these changes in afferent function result from a downregulation of NOS1 and NOS3, causing reduced NO activation of  $K^+$  channel activity and reduced NO-mediated inhibition of afferent discharge. In addition, endothelial angiotensin-converting enzyme 2 (ACE2) expression is inhibited, with reduced Ang 1-7 activation of NOS via the Mas receptor. Conversely, endothelial ACE expression is elevated in the CB in CHF, increasing angiotensin II-mediated superoxide anion production in glomus cells via AT1 receptor/NADPH oxidase activation. The enhanced superoxide signaling in glomus cells contributes to enhanced hypoxia inhibition of  $K^+$  currents and enhanced afferent discharge to hypoxia. Adenoviral transfer of either the nNOS or CuZn SOD gene expression to the CB reversed the enhanced afferent sensitivity of the CB seen in CHF. The role of CB blood flow was assessed in normal rabbits with inflatable occluders to effect a chronic reduction in carotid artery flow. A reduction in carotid arterial blood flow to the same extent as seen in CHF rabbits (30-40%) evoked changes in molecular expression of NOS and ACE enzymes and enhanced afferent discharge sensitivity of the CB similar to those seen in CHF animals. Endothelial Kruppel-Like Factor 2 (KLF2), the endothelial transcription factor activated by shear stress, was markedly reduced in the CB in CHF. Adenoviral transfer of KLF2 gene expression to the CB normalized afferent function in CHF animals. Similarly, daily exercise normalized KLF2 expression and afferent function in CHF rabbits. These results indicate that enhanced sensitivity of the CB in CHF results from downregulation of NO and upregulation of Ang II-superoxide signaling effects on ion channel function in CB glomus cells. Furthermore, a chronic reduction in CB blood flow in CHF may be responsible for these changes due to endothelial responses to reduced shear stress in the CB. Lastly, the beneficial effects of exercise to normalize CB function in CHF may be related to normalization of CB endothelial function due to regular periodic increases in blood flow.

Poster No.: 17



MECHANISMS FOR TISSUE REPAIR USING BONE MARROW-DERIVED CELLS IN  
ISCHEMIC MURINE HIND LIMBEric Nau, Chunhua Jiao, Josh Timpe, Chunlin Wang, Ola Awad<sup>1</sup>, and  
Gina C SchattemanIntegrative Physiology and Anatomy & Cell Biology<sup>1</sup>,  
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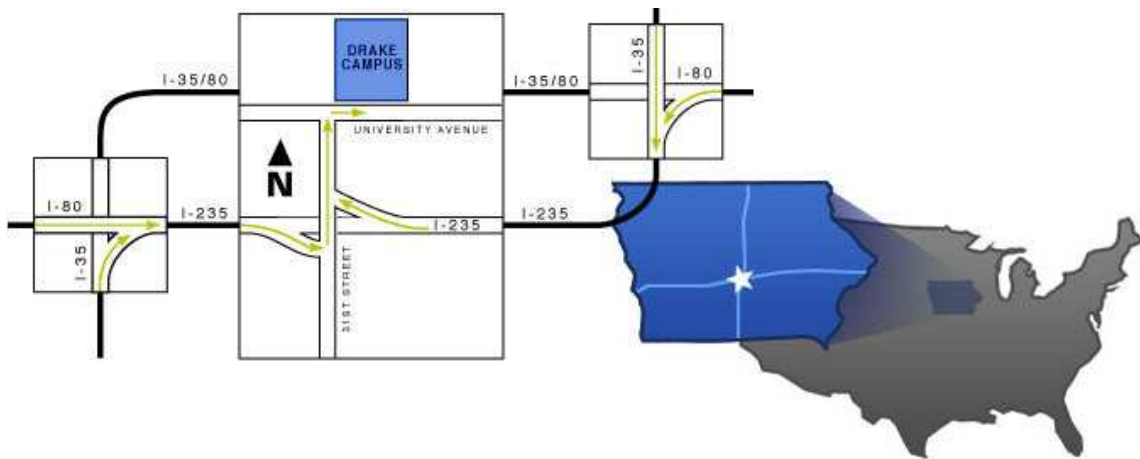
Numerous studies have documented the potential of exogenous bone marrow-derived cells (BMDCs) as therapeutic agents. Our data from a recent study using murine knockout for Monocyte Chemoattractant Protein-1 (MCP-1) provides evidence that MCP-1 is essential for BMDC mediated vascular growth and tissue healing. However, injection of recombinant MCP-1 directly into ischemic hind limb muscles failed to improve blood flow recovery. Based on this evidence, we hypothesize that the attenuated recovery of limb perfusion after arterial ligation is due to temporal deficits of expression of angiogenic growth factors. Hind limb ischemia was induced in diabetic (*lepr<sup>db</sup>*) mice via femoral artery ligation. Exogenous BMDCs were injected into the ischemic hind limb, and limbs were harvested 1, 3, and 5 days post-injection for ELISA and Luminex assays. The BMDCs injected into the limbs were from 3 different strains of mice: C57/Bl6 (control), *lepr<sup>db/db</sup>* (diabetic), and *MCP-1<sup>-/-</sup>*. The growth factors analyzed include placental growth factor (PIGF), fibroblast growth factor-2 (FGF-2), erythropoietin (Epo), stromal-derived factor-1 (SDF-1), and vascular endothelial growth factor A (VEGFA). Our current data show that PIGF, VEGF, and SDF-1 levels were higher one day post-injection compared to 5 days post-injection, while Epo and FGF-2 showed a mirrored profile. Interestingly, levels of PIGF 3 days post-injection were significantly decreased in hind limbs injected with BMDCs from *lepr<sup>db/db</sup>* and *MCP-1<sup>-/-</sup>* compared to BMDC from C57/Bl6 controls. No difference among treatments was observed with the other growth factors evaluated. Together our data suggest that the temporal balance of angiogenic growth factors, rather than the amounts of each factor influences the overall healing environment. Identification of mechanisms underlying growth factor activation and interactions will facilitate design of clinical protocols utilizing BMDCs.

Poster No.: 18



# Driving Directions

Drake University  
 Olmsted Center, Parents Hall  
 2507 University Ave.  
 Des Moines, IA



## From the East and North

At the northeast edge of Des Moines, I-80 and I-35 join and go west around the city while I-235 goes through Des Moines. Take I-235 west for about six miles to the 31st Street exit, which is past the downtown area. You will see a sign that says “Exit 6, Drake University”. Exit I-235 at the 31st Street exit and turn right (north). Travel approximately six blocks on 31st Street to the stoplight at University Avenue. At University Avenue, turn right and go one block and you will see the Olmsted Center parking lot on the left (north) side of University.

## From the West and South

At the southwest edge of Des Moines, I-80 and I-35 join and go east around the city while I-235 goes through Des Moines. Take I-235 east to the 31st Street exit in Des Moines. Be sure you have passed the 63rd Street exit. Exit at 31st Street and turn left (north). Travel approximately six blocks on 31st Street to the stoplight at University Avenue. At University Avenue, turn right and go one block and you will see the Olmsted Center parking lot on the left (north) side of University.

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