Centre for
Biomedical
Research

University
of Victoria

# CANADIAN PHYSIOLOGICAL SOCIETY

# LA SOCIÉTÉ CANADIENNE de PHYSIOLOGIE

*Winter Meeting – 2008*
*Lake Louise, Alberta*

## PROGRAM & ABSTRACTS


Faculty of Physical Education & Recreation

# In Appreciation:





**CANADIAN PHYSIOLOGICAL SOCIETY WINTER MEETING - JANUARY 23-26, 2008**
**CO-HOSTED BY THE UNVERSITY OF VICTORIA AND THE UNIVERSITY OF ALBERTA**

Note: All scientific sessions are held in Beehive/Lakeshore unless otherwise stated.

| Wed. Jan. 23/08 | Thurs. Jan. 24, 2008 | Fri. Jan. 25, 2008 | Sat. Jan. 26, 2008 |
|---|---|---|---|
| 4:00 - 8:00 pm Registration<br>Heritage Hall | 7:45-8:45 AM Registration & coffee<br>Trail Foyer | 8:00-8:30 AM Registration & Coffee<br>Trail Foyer | 7:45-8:45 Coffee<br>Trail Foyer |
| | 8:45 am - 10:00 am: Physiology I<br>Chair: Dr. Rui Wang<br>10:30 am -11:45 am: Physiology II<br>Chair: Dr. Cathy Chan<br>12:00pm - 3:30 pm<br><br>Free Time | 8:30am - 10 am Neuroscience I<br>Chair: Dr. Kelvin Jones<br>10:30am-12:00 pm: Neuroscience II<br>Chair: Dr. Patrick Whelan<br>12:00pm - 5:00 pm<br><br>Free Time | 8:45am - 10:00 am: Cardiovascular I<br>Chair: Dr. Doug Jones<br>10:30-12:00pm: Cardiovascular II<br>Chair: Dr. Quentin Pittman<br>12:00pm - 3:30 pm<br><br>Free Time |
| | 3:30pm - 6:00 pm<br>Symposium I - "Neurorehabilitation from physiology to physical therapy"<br>Chair Dr. David Collins | 5:00pm<br>Cash Bar<br><br>5:00pm - 5:30 pm<br>CPS AGM & Business Mtg.<br>Plain of Six Glaciers<br>5:30pm - 6:30 pm<br>Stevenson Award Lecture "How Chloride Gets Through theCFTR Channel" Dr. P. Linsdell | 3:30pm - 6:30 pm<br><br>Symposium II - "Information transfer in the microcirculation" Chair Dr. Will Cupples |
| 7:00pm - 10:00 pm<br>Reception hosted by ADInstruments<br>Heritage Hall | 7 PM -- CPS council meeting<br><br>Lefroy Room | | 7:00pm - 8:00 pm<br>Sarazzin Award Lecture "Some like it hot: an inflammatory view of physiology" Dr. Q. Pittman<br><br>8:00pm Onwards<br>CPS Banquet<br>Plain of Six/Saddleback |

*NOTE: Presenting authors are required to give their talks on flash drive to the session chairs 30 minutes prior to the beginning of each session. Each presentation is allocated 15 minutes in total (10 minutes with 5 additional minutes for questions).*

***ALL SESSIONS ARE HELD IN BEEHIVE/LAKESHORE***

## THURSDAY MORNING
## PHYSIOLOGY I:
## CHAIR DR. RUI WANG

**8:45 UNCOUPLING PROTEIN-2 MODIFIES NF-KAPPA-B PATHWAY ACTIVATION IN PANCREATIC BETA-CELLS**
Chan, Catherine B. and *Nino-Fong, Rodolpho. University of Alberta and University of Prince Edward Island.

**9:00 P450 AROMATASE GENE EXPRESSION IN GOLDFISH BRAIN AND GONAD** Bruce Mathieson, Biology and Physical Geography, UBC-Okanagan.

**9:15 CONTROLLED DYNAMIC STIMULATION OF *DROSOPHILA* OLFACTORY RECEPTORS**
Schuckel, Julia*, Meisner, Shannon*, Torkkeli, Päivi H., French, Andrew S.

**9:30 MODULATION OF BRAIN INFLAMMATION BY OVARIAN HORMONES** Mouihate A.* and Pittman Q.J. Department of Physiology and Biophysics University of Calgary

**9:45 EFFECTS OF H2S AND UVB-IRRADIATION ON THE GROWTH OF HUMAN KERATINOCYTES**
Machha Ajay[1], Guangdong Yang[2], and Rui Wang[1] [1]Department of Biology and [2]the School of Kinesiology, Lakehead University, Thunder Bay, Ontario, Canada

**10:00-10:30 Break**

## PHYSIOLOGY II:
## CHAIR DR. CATHY CHAN

**10:30 HYDROGEN SULFIDE MEDIATES THE ANTI-PROLIFERATIVE EFFECT OF BUTYRATE IN COLON CANCER CELLS**
Qiuhui Cao[1]*, Guangdong Yang[2]*, and Rui Wang[1] [1]Department of Biology, and [2]The School of Kinesiology, Lakehead University, Thunder Bay, Ontario, Canada

**10:45 SURVEY OF THE GLUT TRANSLOCATION PORE FOR SUBSTRATE SELECTIVITY DETERMINANTS; WHAT MAKES A GLUCOSE TRANSPORTER A FRUCTOSE TRANSPORTER?**
Witkowska Kate* and Cheeseman Chris, I., Department of Physiology, University of Alberta, Alberta, Canada

**11:00 CHOLECYSTOKININ SIGNALING IN THE DORSOMEDIAL HYPOTHALAMUS**
Crosby, Karen M., Bains, Jaideep S., and Pittman, Quentin J. Department of Physiology and Biophysics, University of Calgary

**11:15 MEMBRANE DEPOLARICATION AND THE EXCITATORY ACTION OF GABA AND MUSCIMOL IN SPIDER MECHANOSENSORY NEURONS**
Pfeiffer, Keram*, Höger, Ulli* French Andrew S. and Torkkeli Päivi H. Department of Physiology and Biophysics, Dalhousie University

**11:30 TRANSCRIPTION FACTOR EXPRESSION IN THE DEVELOPING DIAPHRAGM: SIGNIFICANCE FOR CONGENITAL DIAPHRAGMATIC HERNIA**
Robin D Clugston, Wei Zhang and John J Greer. Department of Physiology, University of Alberta

## THURSDAY AFTERNOON
## 3:30-6:00 PM

## SYMPOSIUM: "NEUROREHABILITATION FROM PHYSIOLOGY TO PHYSICAL THERAPY Chair—Dr. D.F. Collins

**CENTRAL AND PERIPHERAL CONTRIBUTIONS TO CONTRACTIONS EVOKED BY NEUROMUSCULAR ELECTRICAL STIMULATION**
Collins, David F., University of Alberta, Alberta Canada

**MEASUREMENT AND MODULATION OF BRAIN PLASTICITY IN HUMANS USING TRANSCRANIAL MAGNETIC STIMULATION.** Chen, Robert, Toronto Western Hospital

**MOTOR AND SENSORY AXON REGENERATION IN THE PERIPHERAL AND CENTRAL NERVOUS SYSTEMS: PROBLEMS AND SOLUTIONS.** Gordon, Tessa, University of Alberta

**REMODELING OF MUSCLE ACTIVATION PATTERNS WITH THERAPEUTIC EXERCISE FOLLOWING STROKE**
Garland S Jayne*, Gray Vicki L*, Ivanova Tanya D* University of Western Ontario

## FRIDAY MORNING

## NEUROSCIENCE I:
## CHAIR DR. KELVIN JONES

**8:30 FUNCTIONAL ELECTRICAL STIMULATION FOR FOOT DROP STRENGTHENS RESIDUAL CORTICO-SPINAL CONNECTIONS**
Stein, Richard B., Everaert, Dirk.G.*, Chong, Su Ling*, Thompson, Aiko K.*, University of Alberta

**8:45 EFFECT OF PERIPHERAL SENSORY INPUT ON EXCITABILITY IN THE HUMAN LEG MOTOR CORTEX**
Roy, Francois D* and Gorassini, Monica A Department of Biomedical Engineering and Centre for Neuroscience, University of Alberta

**9:00 HOFFMANN REFLEX MODULATION AND MUSCULAR STRENGTH GAINS ASSOCIATED WITH UNILATERAL RESISTANCE TRAINING**
Dragert, Katie L., Zehr, E. P. Rehabilitation Neuroscience Laboratory, UVic, Victoria BC, Canada International Collaboration on Repair Discoveries, Vancouver BC, Canada Centre for Biomedical Research, UVic, Victoria BC, Canada

**9:15 DOPAMINERGIC MODULATION OF SPINAL NEURONAL EXCITABILITY**
Han P, Nakanishi ST, Tran MA, Whelan PJ. Hotchkiss Brain Institute, University of Calgary

**9:30 DEVELOPMENTAL DIVERSIFICATION OF INTRINSIC MOTONEURON ELECTRICAL PROPERTIES IN EARLY POSTNATAL MICE**
Nakanishi Stan T and Whelan Patrick J Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada

**9:45 EVALUATING TWO MYELINATED AXON MODELS FOR EVALUATING ION CHANNEL DISORDERS IN HUMAN PERIPHERAL NERVES**
Jones, Kelvin E (University of Alberta)

**10:00-10:30 Break**

## NEUROSCIENCE II:
## CHAIR DR. PATRICK WHELAN

**10:30 SOLEUS H-REFLEX AMPLITUDE IS UNAFFECTED BY LOAD DURING ARM CYCLING**
Hundza, Sandra R, de Ruiter, Geoff C, Zehr E. Paul Rehabilitation Neuroscience Laboratory, Univ Victoria, Victoria, BC, Canada International Collaboration on Repair Discoveries, Vancouver, BC, Canada Centre for Biomedical Research, Univ Victoria, Victoria, BC, Canada

**10:45 NEUROMECHANICAL COMPARISON OF RHYTHMIC ARM LOCOMOTOR TASKS**
Klimstra, Marc[1] and E.Paul Zehr[1,2,3] [1]Rehabilitation Neuroscience Laboratory, University of Victoria. [2]Human Discovery Science, ICORD [3]Centre for Biomedical Research, University of Victoria.

**11:00 LOCOMOTOR EXPRESSION OF INTERACTIONS BETWEEN SPATIAL MEMORY, VESTIUBLAR RESPONSE AND PODOKINETIC AFTER ROTATIONS (PKAR)**
Melvill-Jones Geoffrey[1], Fletcher William E[1]*, Block Edward E[1]*, Horak Fay[2]*, Hu Bin[1]*. [1]Clinical Neurosciences, University of Calgary, [2]Oregon Health Sciences, Portland OR, USA

**11:15 MODULATION OF WINDUP AND FICTIVE LOCOMOTION IN THE ISOLATED MOUSE SPINAL CORD BY TRP CHANNELS**
MANDADI S and WHELAN PJ Hotchkiss Brain Inst., Univ. of Calgary, Calgary, AB, Canada

**11:30 PRE-LANDING STABILIZATION OF LINEAR AND ANGULAR SWING FOOT MOVEMENTS DURING CURVED LOCOMOTION**

Block Edward W[1]*, Fletcher William A[1]*, Melvill-Jones Geoffrey[1], Horak Fay[1]*, Hu Bin[2]*. [1]Department of Clinical Neurosciences University of Calgary, Canada and [2]Oregon Health Sciences, Portland OR, USA

**11:45 REFLECTIONS ON THE QUADRUPEDAL NATURE OF BIPEDAL LOCOMOTION**

E. Paul Zehr[1,2,3], Sandra Hundza[1], and Erin V. Vasudevan[4] [1]Rehabilitation Neuroscience Laboratory, University of Victoria, Victoria, BC, Canada [2]International Collaboration on Repair Discoveries (ICORD), Vancouver, BC, Canada [3]Centre for Biomedical Research, University of Victoria, [4]Johns Hopkins School of Medicine, Baltimore MD

## SATURDAY MORNING
## CARDIOVASCULAR PHYSIOLOGY I:
## CHAIR DR. DOUG JONES

**8:45 BROWN-NORWAY RATS SHOW ABERRANT NO-DEPENDENT MODULATION OF RENAL BLOOD FLOW DYNAMICS**

Cupples, Will A. & Wang, Xuemei. CFBR, Univ. Of Victoria & SMRG, Univ of Calgary

**9:00 CARDIAC ELECTROPHYSIOLOGY AND ARRHYTHMIA IN THE MOUSE**

Tuomi, Jari M.[1] and Jones Douglas L.[1,2,3] Physiology & Pharmacology[1] and Medicine[2], University of Western Ontario, London, Ontario, N6A 5C1, Cardiovascular Group[3], The Lawson Health Research Institute, London

**9:15 CALCIUM-DEPENDENT ACTIVATION OF CYSTATHIONINE GAMMA-LYASE IN SMOOTH MUSCLE CELLS**

Shengming Zhang[1]*, Guangdong Yang[2]*, and Rui Wang[1], [1]Department of Biology, and [2]The School of Kinesiology, Lakehead University, Thunder Bay, Ontario, Canada

**9:30 MICRORNA MIR-21 REPRESSES CYSTATHIONINE GAMMA-LYASE EXPRESSION IN SMOOTH MUSCLE CELLS**

Guangdong Yang[1]*, Lingyun Wu[2], and Rui Wang[3] [1]The School of Kinesiology, Lakehead University, Thunder Bay, Ontario, Canada, [2]Department of Pharmacology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada, [3]Department of Biology, Lakehead University, Thunder Bay, Ontario, Canada

**9:45 ROLE OF SOLUBLE EPOXIDE HYDROLASE (EPHX2) IN THE GENERATION AND MAINTENANCE OF HIGH BLOOD PRESSURE IN SPONTANEOUSLY HYPERTENSIVE RATS**

Koeners Maarten P.[1]*, Wesseling Sebastiaan [1]*, Sepúlveda1 Rocío López [1]*, Dijk Adele [1]*, Morisseau Christophe [3]*, Braam Branko [2]*, Hammock Bruce D. [3]* and Joles Jaap A.1*[1] [1]Nephrology and Hypertension, University Medical Center Utrecht, Netherlands [2]Nephrology and Immunology, University of Alberta, Edmonton, Canada [3]Department of Entomology and Cancer Research Center, UC Davis Cancer Center, Davis, CA

**10-10:30 Break**

## CARDIOVASCULAR PHYSIOLOGY II: DR. QUENTIN PITTMAN

**10:30 REAL-TIME VOLUME RESPONSES OF ASTROCYTES TO OSMOTIC AND ISCHEMIC STRESS IN VIVO AND IN CORTICAL SLICES REVEALED BY 2-PHOTON MICROSCOPY**
Andrew, R. David, Risher, W.Chris* and Kirov, Sergei A.* Centre for Neuroscience Studies, Kingston, ON, and Dept Neurosurgery, Medical College of Georgia, Augusta, GA

**10:45 WHOLE CELL RECORDING FROM PYRAMIDAL NEURONS HELP EXPLAIN ISCHEMIA PROTECTION BY A SODIUM CHANNEL BLOCKER**
White, Sean H. and Andrew, R. David, Centre for Neuroscience Studies, Queen's University, Kingston, ON, K7L 3N6

**11:00 EVIDENCE THAT THE HUMAN FACILITATIVE HEXOSE TRANSPORTER GLUT9 (SLC2A9) IS A HIGH CAPACITY URATE TRANSPORTER**
Cheeseman, Chris I [1], Patricia Monroe *[2], Mark Caulfield *[2], Farid Charchar *[2], Kelle Moley *[3], Kate Witkwoska *[1] & Deb O'Neill *[1].

**11:15 ACTIVATORS OF SKCA AND $IK_{CA}$ CHANNELS ENHANCE AGONIST-MEDIATED VASORELAXATION AND ENDOTHELIAL NO SYNTHESIS**
Braun, Andrew P, Sheng, JZ*, Ella, S*, Davis, MJ* and Hill, MA* Univ. Calgary (APB, JZS) and Univ. Missosuri (SE, MJD, MAH)

**11:30 SPLENIC NEURAL MODULATION OF MESENTERIC VASCULAR TONE**
Hamza, S.M. and Kaufman, S.E. University of Alberta

## SATURDAY AFTERNOON
**3:30-6:30 PM**

## SYMPOSIUM "INFORMATION TRANSFER IN THE MICROCIRCULATION": Chair—Dr. W. Cupples

Introduction: Branko Braam, University of Alberta

**The role of gap junctional proteins Cx37 and Cx40 in communication along the microvasculature during inflammation**
Tyml, Karel,[1,2,3], Rebecca McKinnon[2,3] and Michael Bolon[2,3], University of Western Ontario

**The spleen as a hemodynamic regulator: inter-organ communication in portal hypertension.**
Hamza, S.M. and Kaufman, S.E. University of Alberta

**Role of the erythrocyte in regulating oxygen supply in the microvasculature.**
Christopher Ellis, University of Western Ontario

**The Basis of Differential Communication in the Resistance Vasculature.**
Donald G. Welsh, Smooth Muscle Research Group and the Libin Cardiovascular Institute, The University of Calgary.

**Is there a role for T-type channels in intra- and intercellular calcium signaling in mesenteric arterioles?**
Niels-Henrik Holstein-Rathlou, Thomas Braunstein, and Lars Jørn Jensen.
Department of Biomedical Sciences, the University of Copenhagen, Denmark

# ABSTRACTS ORDERED ALPHABETICALLY BY FIRST AUTHOR

**REAL-TIME VOLUME RESPONSES OF ASTROCYTES TO OSMOTIC AND ISCHEMIC STRESS IN VIVO AND IN CORTICAL SLICES REVEALED BY 2-PHOTON MICROSCOPY**

Andrew, R. David, Risher, W.Chris* and Kirov, Sergei A.* Centre for Neuroscience Studies, Kingston, ON, and Dept Neurosurgery, Medical College of Georgia, Augusta, GA

Studies of how acute osmotic challenge affects the volume of single neurons and glia have necessarily been confined to isolated or cultured brain cells. Two-photon laser scanning microscopy (2PLSM) enables real-time visualization of functioning cells expressing Green Fluorescent Protein (GFP) deep (60-200 μm) within living neocortex in vivo and in brain slices. Using 2PLSM we recently showed that pyramidal somata, dendrites and spines steadfastly maintain their volume during osmotic stress, as do cerebellar axon terminals. However neurons dramatically swell and their processes bead during $O_2$/glucose deprivation (OGD) (Andrew et al. 2007, Cerebral Cortex 17, 787). Here we use 2PLSM to monitor changes in astrocytic volume in slices (400 μm) using mice of the FVB/N-Tg(GFAP-GFP)14Mes/J strain and in vivo using the FVB/N-Tg(GFAP-EGFP)GFEA-Fki strain whose founders were kindly provided by Dr. H. Kettenmann. Single astrocytic cell bodies, their processes and end-feet display GFP fluorescence (Zhuo et al. 1997). The volume of astrocytic cell bodies and their processes are measured in response to 20 min of overhydration (-40 mOsm) or dehydration (+40 or +80 mOsm) (n=17). Unlike pyramidal cells, astrocytes reversibly swell during overhydration and shrink during dehydration. Astrocytes also rapidly swell during briefly elevated $K^+$ or $O_2$/glucose deprivation (OGD) for 10 min, as do adjacent pyramidal neurons (ibid). Post-OGD, astrocytic volume recovers by 80-100% within 10 min (12 cells in 9 slices from 5 mice) whereas pyramidal neurons remain swollen with beaded dendrites (7 neurons in 7 slices from 6 mice). In vivo, cardiac arrest in the intact mouse likewise elicits astrocytic swelling within 3 minutes (n=11 cells in 4 mice). Arrest is simultaneously confirmed by imaging the cessation of blood flowing in adjacent capillaries. Moreover this swelling is replicated by a bolus injection of water intraperitoneally although the extent of the astrocytic arbor is unchanged (n=7 cells in 4 mice). We conclude that, in contrast to pyramidal neurons that do not express known aquaporins, astrocytic volume passively responds to acute osmotic stress, reflecting functional aquaporins in their plasma membrane. We have not detected astrocytic volume regulation in the face of acute osmotic challenge. Simulated ischemia induces an immediate and dramatic swelling of astrocytes and neurons upon onset of anoxic depolarization. However unlike swollen pyramidal neurons, astrocytes significantly recover, perhaps because their aquaporins allow water efflux post-stroke.

Source of Research Funds: National Institutes of Health / Heart & Stroke Foundation of Ontario

**PRE-LANDING STABILIZATION OF LINEAR AND ANGULAR SWING FOOT MOVEMENTS DURING CURVED LOCOMOTION**

Block Edward W[1]*, Fletcher William A[1]*, Melvill-Jones Geoffrey[1], Horak Fay[1]*, Hu Bin[2]*. [1]Department of Clinical Neurosciences University of Calgary, Canada and [2]Oregon Health Sciences, Portland OR, USA

Previously we reported a strong tendency for pre-landing stabilization of angular swing foot movement when stepping around on the spot. On walking forward round a curved trajectory linear movement is added to the angular one. Would pre-landing stabilization extend to this more complex pattern of combined movements? Using a new inertia-sensing system we recorded forward linear accelerations and horizontal angular velocities of trunk and one foot in subjects walking round a circle. Derived traces of velocity and position revealed (1) retention of the tendency for pre-landing stabilization in both linear and angular degrees of freedom, (2) close synchrony between linear and angular traces and (3) close synchrony of stabilization with the sharp transients of foot movement reversal re trunk which occur between swing and stance phases.

Source of Research Funds: CIHR Regenerative Medicine and Nanomedicine Team Grant, NIH #DC 04082

**ACTIVATORS OF SKCA AND $IK_{CA}$ CHANNELS ENHANCE AGONIST-MEDIATED VASORELAXATION AND ENDOTHELIAL NO SYNTHESIS**

Braun, Andrew P, Sheng, JZ*, Ella, S*, Davis, MJ* and Hill, MA* Univ. Calgary (APB, JZS) and Univ. Missosuri (SE, MJD, MAH)

Pharmacologic blockade of small- and intermediate conductance, calcium-activated $K^+$ channels ($SK_{Ca}$ and $IK_{Ca}$ channels, respectively) is known to interfere with agonist-evoked vasorelaxation via nitric oxide (NO) synthesis and the pathway involving an 'endothelium-derived hyperpolarizing factor' (EDHF). Given these important functional effects of vascular $SK_{Ca}$ and $IK_{Ca}$ channels, we examined the hypothesis that activation of these channels may augment the normal cellular pathway(s) underlying agonist-mediated vasorelaxation. In single human umbilical vein endothelial cells (HUVECs), the $SK_{Ca}/IK_{Ca}$ channel openers NS309 and DCEBIO in combination (1 μM each) enhanced ATP-evoked cytosolic $Ca^{2+}$ elevation and NO synthesis, as monitored by the intracellular fluorescent probes Fluo-3 and DAF-FM, respectively. NS309 and DCEBIO also enhanced ATP-induced membrane hyperpolarization. On their own, these channel openers produced significant membrane hyperpolarization and modest calcium elevations, but did not induce NO production. In rat cremaster arterioles pressurized to 70 mm Hg, NS309 and DCEBIO alone evoked a significant reduction of myogenic tone in a dose-dependent manner and further augmented agonist-induced dilation by producing a leftward shift of the acetylcholine (ACh) concentration-response curve. Removing the endothelium by passage of an air bubble through the vessel lumen significantly diminished the vasodilatory responses to either ACh or NS309 and DCEBIO, indicating a predominant endothelial site of action. These novel results demonstrate that augmenting endothelial $SK_{Ca}$ and $IK_{Ca}$ channel activities may be therapeutically relevant strategies in the treatment of vascular disorders associated with impaired NO synthesis.

Source of Research Funds: Supported by the CIHR and AHFMR

**HYDROGEN SULFIDE MEDIATES THE ANTI-PROLIFERATIVE EFFECT OF BUTYRATE IN COLON CANCER CELLS**

Cao, Qiuhui[1]*, Guangdong Yang[2]*, and Rui Wang[1] [1]Department of Biology, and [2]The School of Kinesiology, Lakehead University, Thunder Bay, Ontario, Canada

Butyrate, a short-chain fatty acid, is formed in the human colon by bacterial fermentation of carbohydrates, and putatively suppresses colorectal cancer. Hydrogen sulfide ($H_2S$) can also be produced as a bacterial metabolite in the lumen of the large intestine, affecting the viability of the colonic epithelium. Using human colon carcinoma epithelial WiDr cells, we studied the interaction of butyrate and $H_2S$ on WiDr cell viability. Cystathionine gamma-lyase (CSE), a $H_2S$ producing enzyme, is strongly expressed in WiDr cells. The expression level of cystathionine beta-synthase (CBS), another H2S producing enzyme, is about 1000-fold lower than that of CSE. Endogenous production of H2S (0.4 nmol/g/min) from WiDr cells was detected. Incubation of the cells with 5 mM butyrate for 24 hours significantly increased CSE expression. Furthermore, butyrate treatment (5 mM) for 24 hours decreased cell viability by 45%. Co-treatment of the cells with 1 mM DL-propargylglycine (PPG, an inhibitor of CSE) and butyrate only decreases cell viability by 29.2%. $H_2S$ at physiologically relevant concentrations (50-200 *f*ÝM) also significantly decreased cell viability when the cells were seeded in low density (1„e104 cells/well), but not in high density (1„e105 cells/well). $H_2S$ increased the activities of ERK and p38 mitogen-activated protein kinase (MAPK), but not c-Jun N-terminal kinase activity in WiDr cells. Our results showed that H2S is not only a bacterial metabolite in the intestines, but also endogenously produced by colon epithelial cells, and H2S may mediate the anti-cancer effect of butyrate by activating ERK and p38 MAPK. These findings may help design novel strategies based on H2S metabolism for abnormal cellular proliferation and apoptosis in colon cancer.

Source of Research Funds: NSERC and Gasotransmitter Research And Training (GREAT) Program.

**UNCOUPLING PROTEIN-2 MODIFIES NF-KAPPA-B PATHWAY ACTIVATION IN PANCREATIC BETA-CELLS**

Chan, Catherine B. and *Nino-Fong, Rodolpho. University of Alberta and University of Prince Edward Island.

Mutations in the UCP2 gene are linked to type-2 diabetes. Here, the mechanism by which lack of uncoupling protein-2 (UCP2) is cytoprotective in pancreatic beta-cells was investigated. Basal apoptosis was attenuated in UCP2-/- islet cells while the nuclear factor (NF)-kappaB pathway was constitutively activated. Nitric oxide
production was elevated in UCP2-/- islets and inhibition of its production strongly reduced NF-kappaB activation but not apoptosis. Proliferation (cyclin D2) and anti-apoptosis (A20) genes had increased mRNA expression in UCP2-/- islets whereas pro-apoptosis genes (jun, myc) were reduced. UCP2+/+ and UCP2-/- islets were treated with cytokines or palmitic acid for 24h. Cytokines did not increase NF-kappaB transactivation or apoptosis in UCP2-/- islets and A20 was more strongly induced in UCP2-/- islets. These novel data show that null expression of UCP2 induces constitutive activation of NF-kappaB in islets due to nitric oxide-dependent up-regulation of IKKbeta activity and that this results in altered expression of genes that enhance a pro-survival phenotype basally and when beta-cells are exposed to cytokines.

Source of Research Funds: CIHR

**EVIDENCE THAT THE HUMAN FACILITATIVE HEXOSE TRANSPORTER GLUT9 (SLC2A9) IS A HIGH CAPACITY URATE TRANSPORTER**

Cheeseman, Chris I [1], Patricia Monroe *[2], Mark Caulfield *[2], Farid Charchar *[2], Kelle Moley *[3], Kate Witkwoska *[1] & Deb O'Neill *[1].

Introduction: Several population studies have shown a strong correlation between hypertension and moderately elevated plasma urate levels (hyperuricaemia). Recent genomic analyses have found a very strong correlation between SNP's in the gene SLC2A9 and individuals with elevated plasma urate levels, on average ~ 20 μM higher than normal. GLUT9 the gene product of SLC2A9 is expressed primarily in the kidney and has two transcripts, GLUT9a and b which are differentially expressed in the basolateral and apical poles of the proximal convoluted tubule (PCT). This led us to investigate the possibility that human GLUT9 might be a facilitative urate transporter. Methods: Adult female Xenopus laevis oocytes were injected with 20 nl (1 ng/ nl) GLUT9a or GLUT9b synthetic mRNA transcript and incubated for 5 days at 16-18 ºC prior to functional uptake assays. Influx experiments were performed at 22 ºC using 10-12 oocytes for each condition and 14C labelled urate at a specific activity of 54 mCi/ mmole, 250 microCi/ ml. Efflux experiments were performed by injecting oocytes with 40 nl of 14C-urate just prior to the flux measurements. Eggs were then incubated in batches of 20 in 1 ml of medium for 20 minutes at 22 0C. 20 μl samples of incubation medium were taken every 2 minutes to measure the appearance of urate in the outside solution. The incubation volume was kept constant by sequential addition of medium after the removal of each sample. The activity remaining in the eggs at the end of the incubation was measured by solubilizing the oocytes in 1 ml 5% SDS overnight. Results: Urate uptake in oocytes expressing hGLUT9a was very rapid and saturable with Michaelis-Menten constants of a Km = 981 μM and a Vmax of 304 pmoles/ oocyte/ 20 min. In contrast, there was no detectable urate flux mediated by hGLUT1. GLUT9a & b have been characterized as high affinity, low capacity glucose and fructose transporters, therefore we tested the ability of these two hexoses to inhibit urate fluxes and conversely for urate to inhibit hexose uptake. Concentrations of glucose up to 1 mM had no effect on the uptake of 10 μM urate and urate concentrations of up to 2mM had no effect on the uptake of 50 μM D-glucose. The uricosemic drug probenecid (1mM) had a minimal effect on urate uptake, however, 100 μM

benzbromarone did significantly inhibit GLUT9a mediated urate uptake. Urate efflux could be described by a single exponential curve over a period of up to 20 minutes and the presence of 5 mM extracellular D-glucose greatly accelerated urate movement, while fructose (5 mM) was less effective (7 fold vs 3 fold respectively). Urate (2 mM) also accelerated the efflux of hot urate, while L-glucose had no effect. Discussion: These data indicate that hGLUT9a is a transporter which can mediate the transport of urate with a Km higher than normal plasma urate concentrations (250-500 μM). However, competition experiments indicate that hexoses and urate do not share the same substrate binding sites on the transporter but they can accelerate each other's movement by exchange. Thus, it is possible that hGLUT9a may provide a route for blood to cell fluxes of urate in the PCT BLM. Genetic defects in this transporter may then reduce renal secretion of urate into the urine leading to hyperuricaemia, which in turn is related to hypertension.

**TRANSCRIPTION FACTOR EXPRESSION IN THE DEVELOPING DIAPHRAGM: SIGNIFICANCE FOR CONGENITAL DIAPHRAGMATIC HERNIA**

Clugston, Robin D., Wei Zhang and John J Greer. Department of Physiology, University of Alberta

Congenital Diaphragmatic Hernia (CDH) is a severe birth defect causing life-threatening respiratory distress in the newborn. The etiology of CDH is poorly understood, though recent genetic studies have led to the identification of certain genes that may be involved in its development. CDH-associated genes have been identified from so-called "CDH-critical regions" and from syndromic forms of CDH, and notably include several transcription factors such as COUP-TFII, GATA4, FOG2 and WT1. The role that each of these transcription factors plays in normal and pathological diaphragm development is unknown. In order to learn more about how specific gene mutations can lead to the development of CDH we studied the expression of these transcription factors in the pleuro-peritoneal fold (PPF). This structure constitutes one of the earliest recognizable structures in diaphragm embryology and is malformed in multiple animal models of CDH. Initially, we used laser capture micro-dissection to isolate cells of the PPF which were then screened for specific gene transcripts. Subsequently, the pattern of protein expression in the PPF was determined by immunohistochemistry. Our results show that mRNA for COUP-TFII, GATA4, FOG2 and WT1 can be isolated from the PPF. Importantly, protein expression of these transcription factors was restricted to the non-muscular cells of the PPF. Further, our co-localisation experiments suggest that these proteins are co-expressed in the same cells. These findings are consistent with the hypothesis that it is the non-muscular cells of the PPF that are abnormal in CDH, even in cases with distinct genetic origins. This study is the first to provide a detailed examination of how genes associated with CDH are expressed in the developing diaphragm, and provides an important foundation for understanding how the deletion of specific genes may contribute to abnormal diaphragm formation.

Source of Research Funds: CIHR, March of Dimes, AHFMR

**CENTRAL AND PERIPHERAL CONTRIBUTIONS TO CONTRACTIONS EVOKED BY NEUROMUSCULAR ELECTRICAL STIMULATION**

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Neuromuscular electrical stimulation (NMES) is often used for rehabilitation to restore movement or reduce muscle atrophy after injury or disease. It is well accepted that the evoked contractions arise from the depolarization of motor axons beneath the stimulating electrodes. However, the stimulation also depolarizes sensory axons, but the extent to which the ensuing sensory volley recruits spinal neurons and contributes to the evoked contractions is rarely considered. By recording electromyographic activity during NMES we have found that motor units are recruited in three distinct ways. The peripheral mechanism involves the depolarization of motor axons and results in motor unit discharge at a fixed and short (~5ms) latency after each

stimulus pulse known as an M-wave. The central mechanism arises from the evoked sensory volley which recruits motor units in two different ways; 1) motor unit activity time-locked to each stimulus pulse as an H-reflex (~ 35 ms latency) and 2) motor unit activity not synchronized with each stimulus pulse, possibly maintained by plateau potentials in spinal neurons. This central contribution can be enhanced by delivering NMES using wide-pulse widths (1 ms) at high frequencies (up to 100Hz). Maximising this central contribution may be beneficial for rehabilitation as the synaptic recruitment of motor units follows Henneman's size principle, recruiting the most fatigue resistant

**CHOLECYSTOKININ SIGNALING IN THE DORSOMEDIAL HYPOTHALAMUS**

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Overwhelming evidence indicates that the hypothalamus plays a critical role in the control of energy homeostasis. Recently, the dorsomedial hypothalamus (DMH) has received increasing attention as a key regulator of food intake, metabolism and body weight, in part through its projections to the paraventricular hypothalamic nucleus (PVN). Several lines of evidence suggest that the DMH integrates central and peripheral signals involved in feeding. One such signal is cholecystokinin (CCK), a satiety hormone released upon ingestion that triggers cessation of eating via its actions in the DMH. However, the mechanism of this CCK-induced satiety signaling in the DMH has yet to be elucidated. We therefore investigated the effect of CCK on DMH neurons in rats using an electrophysiological approach. Using whole cell recordings, CCK was found to increase GABA release onto DMH neurons, an effect that was attenuated by application of the CCK1 receptor antagonist, lorglumide. CCK also enhanced a GABAergic response that was evoked synaptically in DMH neurons but had no effect on the paired pulse ratio, suggesting a postsynaptic mechanism of action. These results suggest that CCK enhances GABA drive to DMH neurons. This would in turn suppress excitatory drive from the DMH to PVN neurons and therefore decrease food intake (increasing excitatory drive to PVN neurons that receive input from the DMH has previously been shown to increase food intake). Overall, these data suggest a possible mechanism of CCK-induced satiety signaling in the DMH and contribute to our knowledge regarding the neuronal control of energy intake and expenditure.

**BROWN-NORWAY RATS SHOW ABERRANT NO-DEPENDENT MODULATION OF RENAL BLOOD FLOW DYNAMICS**

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We showed in several strains of rats that non-selective inhibition of NO synthase (NOS) by L-NAME augments myogenic autoregulation of renal blood flow (RBF) and profoundly reduces RBF. Augmentation is determined from the blood pressure - RBF transfer function by showing that the slope of gain reduction is steeper and the associated phase peak is higher. In Wistar rats the augmentation of autoregulation, but not the vasoconstriction is duplicated by the nNOS-selective inhibitor N5-(1-imino-3-butenyl)- L-ornithine (L-VNIO, ~1 μmol/L); inhibition of iNOS by N-[3-(aminomethyl)benzyl] acetamidine (1400W, ~5 μmol/L) had no effect on RBF or on RBF dynamics (AJP 290: R982). This was interpreted as information transfer from tubuloglomerular feedback to the afferent arteriole and requires that macula densa nNOS can sufficiently alter ambient [nitric oxide], i.e. that eNOS and iNOS do not substantively alter local [nitric oxide]. Because the Brown Norway (BN) rat often shows aberrant responses to NOS inhibition, and has abnormal renal autoregulation, we studied systemic and renal vascular responses in 3 experiments. The first showed dose-dependent, transient blood pressure reduction by bolus i.v. acetylcholine (0.01, 0.1, 1 μg/kg) that was substantially prolonged in BN vs Wistar rats. In both strains the depressor response decayed more rapidly after L-NAME (10 mg/kg, i.v.) and the difference between strains was lost, indicating a greater contribution of nitric oxide in BN rats. In BN rats (n=9), however, 5 μmol/L 1400W in RBF reduced RBF (-16 ± 7%) and

augmented myogenic autoregulation. Similarly 1 μmol/L L-VNIO in RBF reduced RBF (-25 ± 4 %) and modestly augmented myogenic autoregulation. Responses to intrarenal nNOS inhibition do not differ markedly between BN and Wistar rats. However, the significant response to intrarenal iNOS inhibition in BN rats, plus the markedly enhanced, and L-NAME sensitive, endothelial depressor response suggest that physiological signalling by nitric oxide within the kidney may be impaired in BN rats due to irrelevant or inappropriate input of nitric oxide by eNOS and iNOS.
Source of Research Funds: CIHR

**HOFFMANN REFLEX MODULATION AND MUSCULAR STRENGTH GAINS ASSOCIATED WITH UNILATERAL RESISTANCE TRAINING**

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In the early weeks of high-intensity resistance training increases in muscular strength are attributed to adaptation in the nervous system. Significant changes in H-reflex excitability have been observed in the soleus (SOL) muscle following such training. In addition to adaptations in the trained limb, neural adaptations associated with unilateral training have been found to cause crossed effects in the untrained limb. Recently it was observed that unilateral training of the SOL muscle caused increased H-reflex amplitude only in the trained limb, despite comparable bilateral changes in SOL strength (Lagerquist et al., 2006). It is unknown whether similar changes in H-reflex amplitude can be observed in other muscle groups, and in particular the functional agonist of the SOL, the tibialis anterior (TA) muscle. Also, following unilateral training it is unknown whether a reduced reflex response in the functional antagonist muscle contributes to strength increases in the untrained agonist muscle. The purpose of this study was to examine the effects of high-intensity unilateral dorsiflexion (TA) resistance training on agonist and antagonist (SOL) muscular strength and H-reflex response in the trained and untrained limbs. Dorsiflexion ankle torque as well as SOL and TA H-reflex responses were measured before and after a 5wk unilateral dorsiflexion training program, and compared to untrained controls. During data collection, subjects were seated in a chair while bilateral H-reflexes were evoked via stimulation delivered to either the tibial nerves (SOL) or common peroneal nerves (TA). Electromyographic (EMG) recordings were taken from the SOL and TA for H-reflex and M-wave amplitudes, and from vastus lateralis, posterior and anterior deltoid muscles to detect background EMG. Measurement parameters of H-reflex excitability were taken from recruitment curves and included modulation of 50% Hmax and Hmax. Following training, a crossed effect was found for TA force output which was significantly increased in both the trained and untrained limbs. TA H-reflex amplitude increased in the trained limb, but not in the untrained limb. In contrast, SOL (antagonist) H-reflex amplitudes tended to decrease after training. These data provide evidence for equal access to neural training adaptations between functional antagonists operating at the ankle.
Source of Research Funds: Michael Smith Foundation for Health Research, National Science and Engineering Research Canada

**ROLE OF THE ERYTHROCYTE IN REGULATING OXYGEN SUPPLY IN THE MICROVASCULATURE**

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The regulation of oxygen ($O_2$) supply to match the $O_2$ demands of a tissue is such a fundamental physiological process that it is often assumed that the mechanisms responsible are well understood. But how is the information that cells need more $O_2$ communicated to the arterioles that regulate the supply of $O_2$? This is not a simple question given the complexity of

microvascular $O_2$ transport where $O_2$ supply is determined not simply by the regulation of arteriolar tone but also by: i) the rheological properties of erythrocytes (RBCs) flowing through bifurcating networks, which influences local RBC flow distributions and ii) diffusional $O_2$ exchange among RBCs flowing through all levels of microvessels. We have been exploring the potential role of the RBC in regulating $O_2$ supply in addition to its well known role as the primary carrier of $O_2$ to the tissue. RBCs exposed to low $O_2$ levels have been shown to release adenosine 5'-triphosphate (ATP) in a hemoglobin $O_2$ saturation dependent manner. Our hypothesis is that as RBCs traverse arterioles, capillaries and venules, information on tissue oxygen needs are transferred to the RBCs via the local $O_2$ tension. If $O_2$ supply is not adequate, tissue $O_2$ tension falls as does the hemoglobin $O_2$ saturation in RBCs. This desaturation activates a signaling pathway in the RBC to release more ATP thus increasing vascular caliber, either directly in arterioles or via conducted signalling from capillaries and venules to arterioles. Our approach to unraveling the complexity of this regulatory system in vivo involves a systems biology approach in which experiments provide information that can be used in mathematical simulations to aid in understanding the experimental results and in predicting new factors or mechanisms that need to be tested experimentally. To develop an experimental protocol that tests the local $O_2$ regulatory system without triggering regulatory mechanisms associated with metabolism, a gas exchange chamber was built in the stage of an inverted intravital video microscope to alter the $O_2$ environment at the muscle surface (rat extensor digitorum longus) using computer controlled gas flowmeters. By altering the % $O_2$ in the chamber, the balance between $O_2$ supplied to the surface layers of tissue via the microvasculature or the chamber can be controlled, thus allowing us to explore the local regulation of $O_2$ supply. To provide quantitative experimental data for the computational model we use our functional imaging system to measure the changes in RBC $O_2$ saturation in surface capillaries and the regulatory response via changes in capillary RBC velocity, hematocrit and supply rate. We have found a time delay between the changes in $O_2$ environment and the regulatory response that likely corresponds to the conduction velocity along the vascular endothelium from capillaries to upstream arterioles. Our systems biology approach is enabling us to explore the integration of information needed to regulate tissue oxygenation. It will also help us determine how a loss of information (e.g. reported defect in RBCs of humans with type II diabetes) may impair tissue oxygenation.

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**REMODELING OF MUSCLE ACTIVATION PATTERNS WITH THERAPEUTIC EXERCISE FOLLOWING STROKE**

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Postural control is fundamental to mobility. There is a solid body of knowledge revealing impairment of muscle activation patterns during standing postural tasks after stroke. Although physiotherapy and therapeutic exercise play a large role in the rehabilitation of individuals following stroke, little is known about whether exercise promotes functional recovery through compensation or through the remodeling of the impaired muscle activation. The purpose of this research is to determine 1) whether muscle activation patterns can be retrained in patients following stroke and 2) whether the effects of specific therapeutic exercise transfer to postural control responses in standing. Given the evidence in the literature on use-dependent plasticity of the motor cortex following stroke, we hypothesized that exercise targeted specifically toward improving the timing, speed and pattern of muscle contraction would be able to evoke change in postural control following stroke. Subjects who were one month post-stroke were tested in two sessions. In the first session, electromyography from hamstrings, quadriceps, soleus, and tibialis anterior muscles bilaterally and force platform measures of postural sway for each leg were taken during two standing balance perturbation tasks (unilateral arm raise and load drop tasks). In the second session, subjects completed the same balance perturbation tasks before and after exercise

retraining. The exercise retraining involved 50 trials of fast squats and lunge steps that elicited triphasic muscle activation patterns in healthy subjects. The latency, slope and area of muscle bursts and force platform center of pressure excursions were analyzed. Results revealed an improvement in the timing and the amplitude of the muscle bursts in the balance perturbation tasks. This study demonstrated that a single session of therapeutic exercise was able to evoke the remodeling of muscle activation patterns associated with postural control in standing.
Source of Research Funds: Heart and Stroke Foundation of Ontario

**MOTOR AND SENSORY AXON REGENERATION IN THE PERIPHERAL AND CENTRAL NERVOUS SYSTEMS: PROBLEMS AND SOLUTIONS**

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The motor unit that comprises the motor axon and the muscle fibers which it supplies is the final common pathway of the nervous system since all neural processing ultimately results in movement. Injuries to both central and peripheral nerves disrupt this normal processing but it is only the regenerative capacity of nerves in the peripheral and not the central nervous system (PNS and CNS) that allows for some recovery of function. Even so, functional recovery after PNS nerve injuries is frequently poor because the long periods of axotomy of the neurons and the denervation of Schwann cells in the growth pathways concomitant with the slow rates of axonal regeneration, result in progressive decline in regenerative capacity. Axon outgrowth across a lesion site is actually much slower than previously appreciated with periods of a month or more required for axons to grow across a lesion site. Our investigations of this slow rate of axon outgrowth revealed that a low frequency short period of 1 hour electrical stimulation is effective in accelerating the outgrowth of both sensory and motor axons such that the regenerating axons reach their denervated targets more quickly in animals and human patients. We also demonstrated this stimulation induced accelerated axon outgrowth for sensory axons within the lesioned CNS. The stimulation-induced accelerated outgrowth occurs in association with upregulation of neurotrophic factors and their receptors and the elevation of cAMP that results in the upregulation of growth associated genes such as tubulin and actin for axon growth. Thus, electrical stimulation accelerates axon outgrowth which effectively translates into functional recovery. Since chronic axotomy and/or chronic denervation of Schwann cells progressively reduces regenerative capacity, it is essential to accelerate the outgrowth of axons *as well as* to continue to explore methods to reduce the deterioration of the growth state of the neurons and the growth supportive state of the glial cells for axon regeneration.

**THE SPLEEN AS A HEMODYNAMIC REGULATOR: INTER-ORGAN COMMUNICATION IN PORTAL HYPERTENSION**

Hamza, S.M. and Kaufman, S.E. University of Alberta

Portal hypertension is characterized by hemodynamic changes, which ultimately precipitate the development of a hyperdynamic circulation. However, the progression to a hyperdynamic state is not wholly understood. In addition to elevated portal venous pressure, splenic venous pressure is also increased in portal hypertension. This results in the initiation of neural and endocrine communication between the spleen and other vascular beds, effecting functional hemodynamic changes. In an acute rat model, we have demonstrated that selective elevation of splenic venous pressure results in increased splenic afferent nerve activity and a reflex increase in renal efferent nerve activity. This spleno-renal reflex caused a fall in renal blood flow and arterial conductance, a phenomenon which was abolished by splenic or renal denervation. Similarly, increased splenic venous pressure also resulted in a reflex increase in mesenteric efferent nerve activity. Portal venous flow and mesenteric vascular conductance were significantly reduced, effects also

abolished by splenic denervation. Preliminary data for intravital visualization of mesenteric microvessels shows arteriolar constriction upon elevation of splenic venous pressure, which is not present after splenic denervation. Interestingly, mesenteric denervation exacerbated rather than attenuated the drop in mesenteric conductance, suggesting a role for humoral mediators, such as vasopressin and angiotensin II, potentially released in response to splenic nerve activity. In fact, in addition to the spinal reflexes above, we have shown that elevated splenic venous pressure activates neurons in central cardiovascular centres, which is mediated through splenic and renal nerves. This central simulation could potentially lead to release of endocrine mediators such as vasopressin. We have also shown that the spleen itself is a source of a hypotensive factor which causes a dose-dependent diuresis and natriuresis upon i.v. injection in conscious rats. This factor was subsequently shown to increase glomerular filtration rate, likely having vasoactive effects on afferent and efferent glomerular arterioles. Given the hypotensive nature of this splenic factor, a potential role in mediating the vasodilatation characteristic of the hyperdynamic circulation is possible. Studies on the effects of the splenic factor on isolated vessels are in progress. We conclude that the spleen is integral in mediating both neural and humoral communication between organs in portal hypertension, which results in hemodynamic changes involving microvessels of the kidney and intestine. Although these pathways have been shown acutely, inter-organ communication initiated by the spleen may prospectively be involved in the long-term development of the hyperdynamic circulation in portal hypertension.

**SPLENIC NEURAL MODULATION OF MESENTERIC VASCULAR TONE**

Hamza, S.M. and Kaufman, S.E. University of Alberta

Portal hypertension impedes outflow from the splanchnic vascular beds. We hypothesized that the increase in splenic intravascular pressure may initiate a neural reflex to increase mesenteric arterial tone and reduce blood flow into the plethoric mesenteric vascular bed. Splenic venous pressure was selectively increased by partial splenic vein occlusion (6.9±0.5 to 22.5±0.3 mmHg, n=47). During the 3 minutes following occlusion, mesenteric vascular conductance fell (-0.01±0.002 = mmHg/mL•min$^{-1}$; $p<0.05$ n=7), an effect which was unchanged by renal denervation (-0.01±0.009 mmHg/mL•min$^{-1}$; n=6) and exacerbated by mesenteric denervation (-0.02±0.004 mmHg/mL•min$^{-1}$; $p<0.05$, n=7). The fall in conductance was abolished by splenic denervation (-0.002±0.002 mmHg/mL•min$^{-1}$; $p<0.05$ n=6). Similarly, the significant increase in mesenteric efferent nerve activity observed during splenic venous occlusion (22.2±2.8 to 27.9±3.8 spikes/sec, $p<0.05$ n=13) was absent after splenic denervation (32.4±2.4 to 31.2±1.6 spikes/sec, n=7). Although the spleen is thus integral to initiating the reflex, the accompanying increase in mesenteric nerve activity is not wholly responsible for increasing mesenteric arterial tone.

Source of Research Funds: HSFC, CIHR

**DOPAMINERGIC MODULATION OF SPINAL NEURONAL EXCITABILITY**

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It is well recognized that dopamine (DA) can modulate spinal networks and reflexes. DA fibres and receptors are present in the spinal cord and evidence for DA release within the spinal cord has been published. A critical gap is the lack of data regarding dopaminergic modulation of intrinsic and synaptic properties of motoneurons and ventral interneurons in the mammalian spinal cord. In this paper we address this issue by examining the cellular mechanisms underlying DA's excitatory effect on motor systems. We examine DA's effects on two classes of cells important for motor control, motoneurons and Hb9 interneurons located in lamina VIII. We show that DA can boost excitability in spinal motoneurons by decreasing the first spike latency and the afterhyperpolarization (mAHP). Collectively, this leads to an increase in the f-I slope likely due to modulation of IA and SKCa currents. We also demonstrate that DA increases

glutamatergic transmission onto motoneurons. Our data also suggest that DA stabilizes the rhythmic output of conditionally bursting interneurons. Collectively, these data indicate that DA has widespread actions on intrinsic and synaptic properties of ventral spinal neurons.
Source of Research Funds: CHIR, Christopher Reeve Foundation, HBI

**IS THERE A ROLE FOR T-TYPE CHANNELS IN INTRA- AND INTERCELLULAR CALCIUM SIGNALING IN MESENTERIC ARTERIOLES?**

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Voltage-dependent $Ca^{2+}$ channels are crucial for excitation-contraction coupling in muscle cells from heart, skeletal muscle and various types of smooth muscle including vascular smooth muscle cells (VSMC). These channels have been roughly divided into high-voltage activated (L-, P/Q-, N-, R-type) *vs.* low-voltage activated calcium channels (T-type), referring to the fact that the former requires larger depolarization for activation than the latter. In the majority of VSMC, excitation-contraction coupling is maintained by L-type $Ca^{2+}$ channels pharmacologically distinguished by their sensitivity to dihydropyridines such as nifedipine. However, evidence has recently emerged to suggest that in some microvascular resistance vessels other types of voltage-dependent $Ca^{2+}$ channels, in particular T-type channels, may have a significant role in the excitation-contraction coupling.

To investigate the possible role of T-type channels in mesenteric arterioles we have conducted a series of studies to determine: 1) by RT-PCR which voltage dependent calcium channels are present in mesenteric arterioles; 2) the cellular localization of T- and L-type channels by immunofluorescence; 3) the functional role of the different calcium channels by determining the effects of various T- and L-type channel blockers on intra- and intercellular calcium signaling.

The results show that T-type channels are expressed in mesenteric arterioles, and that they are present in both vascular and endothelial cells. Furthermore, T-type channels are involved in both the local and the conducted increase in intracellular calcium in response to depolarization, but does not appear to be necessary for conduction *per se*.

**SOLEUS H-REFLEX AMPLITUDE IS UNAFFECTED BY LOAD DURING ARM CYCLING**

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Suppression of soleus H-reflex amplitudes in stationary legs is seen during rhythmic arm cycling (Frigon et al, 2004). We examined specific arm cycling parameters to determine possible contributions to the signal responsible for this suppression. Suppression is graded with arm cycling frequency (Hundza and Zehr, 2006, SfN abstract), however it is not largely influenced by afferent feedback associated with phase of movement or crank length (Loadman and Zehr, 2006). Load is known to play an influential role in the control of rhythmic movement (Dietz and Duysens, 2000; Duysens et al, 2000, Dietz 1998), however the effect of the load on soleus H-reflex suppression during arm cycling has not been explicitly explored. Since limb loading significantly alters reflex excitability in the legs (Dietz and Duysens, 2000; Duysens et al, 2000), we hypothesized a significant effect of arm cycling load on H-reflex amplitudes in the leg. Soleus H-reflexes were evoked with tibial nerve stimulation during static control and rhythmic 1 Hz arm cycling trials across 6 different loads. A constant M-wave was maintained across all trials. Peak to peak amplitudes of the soleus H-reflexes were determined off line and normalized to the maximum M-wave determined from individual recruitment curves. Contrary to our hypothesis, H-reflex modulation was insensitive to changes in crank loads. Taken in conjunction with previous findings the current results suggest that centrally driven rhythm generation commands for arm cycling provide the primary signal responsible for the soleus H-reflex suppression while movement parameters have little effect. In addition, arm cycling load

significantly influenced EMG in leg muscles despite having no influence on soleus H-reflex amplitude. This result corroborates suppositions by Stephens and Yang, (1999) that EMG levels and CPG timing output are differentially modulated. The fact that crank load during arm movement is less influential than cycling frequency in engaging CPG-related interlimb neural pathways may be important to consider therapeutically when targeting certain neural pathways.
Source of Research Funds: MSFHR, NSERC, ICORD and HSF BC & Y

**EVALUATING TWO MYELINATED AXON MODELS FOR EVALUATING ION CHANNEL DISORDERS IN HUMAN PERIPHERAL NERVES**

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A new commercial electrodiagnostic device is being used to measure the excitability of human motor and sensory nerves in vivo. The excitability measurements include rheobase, chronaxie, recovery cycle, threshold electrotonus and an indirect current-voltage estimate. Clinical neurophysiologists are using these data to suggest possible ion channelopathies associated with various peripheral nerve disorders. In this study we illustrate how the use of mathematical models of myelinated axons can be used in computer simulations to augment interpretation of the excitability tests. Two mathematical models of a myelinated motor axon were subjected to a sensitivity analysis and the results were compared to control data collected from healthy human subjects. One of the mathematical models provided a good fit to the experimental data. We then used this model to test whether changes in excitability measures for diabetic polyneuropathy were congruent with hypothesized channelopathies. We conclude that the model provides an objective test of this new electrodiagnostic method and will help clinicians interpret there data.
Source of Research Funds: NSERC, AHFMR

**NEUROMECHANICAL COMPARISON OF RHYTHMIC ARM LOCOMOTOR TASKS**

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Evidence suggests that the neural control of rhythmic movement share common principles across many species and tasks. Neural and mechanical factors are inextricably linked and their influences are often difficult to differentiate. However less is known about the mechanical influences in the movement. During rhythmic movement, central motor drive activates the muscles while the mechanics of the musculoskeletal system can influence the neural pattern of activity to alter and sculpt motor output appropriately. Therefore, combined neural and mechanical measurement approaches are needed. For some time we have used a rhythmic arm cycling paradigm to study the neural control associated with rhythmic arm movements such as arm swing during walking. We have paid comparatively little attention to the neuromechanical linkages during the tasks of arm swing during walking and arm cycling. We hypothesize that both neural and mechanical features (such as shoulder kinematics and centre of pressure movement) are similar between rhythmic arm movement tasks. It was also anticipated that the pattern of muscle activity during arm swing and arm cycling reflect changes in the moment of inertia of the whole body. Subjects performed arm cycling and arm swing while standing stationary. Additionally, arm swing was also performed while walking on a treadmill while three dimensional kinematic measurements were collected using a VICON™ motion analysis system. Concurrently changes in force measures at the hand and foot were collected using ATI™ and Kistler™ force plates respectively. Muscle activity (EMG) data were collected continuously throughout all trials from the arms and trunk unilaterally. EMG, kinematic and kinetic data were appropriately segmented to allow comparison between and across conditions. Data from all tasks were normalized and averaged to a full 100% movement cycle based on shoulder excursion. Principal Components Analysis of 374 kinematic/kinetic and neural variables as well as cross-correlation of EMG signals were performed in order to determine common task features. Overall,

the results are consistent with common motor control mechanisms operational for arm swing and arm cycling but appropriately sculpted to unique task demands in each case.This type of neuromechanical analysis serves as a baseline of measurement for future studies in rhythmic movement motor control which will be implemented into the ongoing goal of developing rehabilitative interventions including arm swing for locomotor recovery after neurotrauma.
Source of Research Funds: Heart and Stroke Foundation. NSERC, ICORD

**ROLE OF SOLUBLE EPOXIDE HYDROLASE (EPHX2) IN THE GENERATION AND MAINTENANCE OF HIGH BLOOD PRESSURE IN SPONTANEOUSLY HYPERTENSIVE RATS**

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Epoxyeicosatrienoic acids (EETs) are potent vasodilator agents, which act as an endothelial-derived hyperpolarizing factor. They are also pronatriuretic. EET's are synthesized by cytochrome P450 mono-oxygenase 2C (Cyp2C). Soluble epoxide hydrolase (SEH; Ephx2) metabolizes EETs to less active dihydroxyeicosatrienoic acids (DHETEs). An orally active Ephx2 inhibitor, 12-(3-adamantan-1-yl-ureido)-dodecanoic acid (AUDA), was found to largely attenuate angiotensin II (Ang II) induced hypertension in mice and rats. Blood pressure in spontaneously hypertensive rats (SHR) is Ang II dependent. We hypothesized that a reduced Cyp2c and enhanced Ephx2 gene expression in the kidneys contributes to elevated blood pressure in SHR. Determined by quantitave PCR Cyp2c gene expression was decreased and Ephx2 gene expression was increases in SHR vs. WKY from birth to old age. AUDA did not lower blood pressure in adult male SHR. However, perinatal treatment with AUDA (administered orally to the dams 25mg/L drinking water) during the last two wks of gestation and the 4 wk lactation period persistently lowered blood pressure in female offspring followed up to 24 wks (171±4 vs. 185±3 mmHg, $P<0.01$) and in male offspring up to 16 wks (171±4 vs. 195±4 mmHg, $p<0.01$). At 24 wks there was no change in renal vascular resistance, but natriuresis was increased at 4wks in SHR perinatally treated with AUDA (6.0±0.3 vs. 4.5±0.9 (micromole.g bw-1.day-1, $p<0.05$), suggesting that an early reduction of extracellular volume may have contributed to this antihypertensive action. In conclusion, Ephx2 appears to have a specific pathogenic role in the generation but not in the maintenance of high BP in SHR.
Source of Research Funds: Dutch Kidney Fdn

**EFFECTS OF H2S AND UVB-IRRADIATION ON THE GROWTH OF HUMAN KERATINOCYTES**

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Hydrogen sulfide ($H_2S$) is known as a novel gasotransmitter in mammalian cells. $H_2S$ is involved in many physiological processes including regulation of cell growth (i.e. apoptosis). Exposure to ultraviolet (UV) B light is known to inhibit growth of epidermal keratinocytes. In the present study, the effects of $H_2S$ on the growth of epidermal keratinocytes in the presence or absence of UVB radiation were investigated using cultured normal human epidermal keratinocyte (NHEK) cells. Western blot analysis confirmed the expression of cystathionine gamma-lyase (CSE, a $H_2S$ producing enzyme) protein in NHEK cells. Treatment with DL-propargylglycine (PPG, a CSE inhibitor, $\geq 2$ mM) for 24 h inhibited the viability of NHEK cells in a dose-dependent manner as determined by MTT assay. Treatment for 24 h with an exogenous $H_2S$ donor sodium hydrosulfide (NaHS) at 50, 100, 250 and 500 μM did not alter viability of NHEK cells. However, continued exposure to NaHS at the given concentrations for

48 h inhibited the viability of NHEK cells in a dose-dependent manner. Exposure to single dose of UVB light (intensity = 20 W/$m^2$) inhibited viability of NHEK cells in a time-dependent manner with about 50 % of inhibition observed at 100 s (i.e. 2000 J/$m^2$). Treatment with PPG and/or NaHS for 3 h before and 24 h after UVB (2000 J/$m^2$) exposure failed to preserve viability of UVB-irradiated NHEK cells. UVB (2000 J/$m^2$)-irradiation reduced CSE protein expression in NHEK cells, detected 24 h after UVB exposure. These results suggest that endogenous production of $H_2S$ may contribute to the growth of epidermal keratinocytes, and exposure to UVB radiation reduces expression of CSE in epidermal keratinocytes. Further experiments are warranted to evaluate whether reduced bioavailability of $H_2S$ coupled to the reduction in the expression of CSE may contribute to the inhibition of epidermal keratinocyte growth by UVB radiation..

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**MODULATION OF WINDUP AND FICTIVE LOCOMOTION IN THE ISOLATED MOUSE SPINAL CORD BY TRP CHANNELS**

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Although chronic pain is common following spinal cord injuries, surprisingly little is known about the effects of nociceptive signals on spinal motor networks. This is important since rehabilitation therapies that aim to improve locomotor function following injury are often performed in the presence of drugs that decrease pain. Afferent stimulation is becoming a popular method for eliciting fictive locomotion in isolated spinal cord preparations. Yet the contribution and mechanisms by which specific subclasses of afferents provide the excitatory drive to activate locomotor pattern generators is unclear. Since trains of electrical stimuli produce a windup-like phenomenon, we decided to target nociceptive pathways and examine a role for Transient Receptor Potential (TRP) channels in the modulation of the windup response. The goals of this project are to delineate mechanisms that modulate windup and locomotion via one such TRP member, TRPM8. Afferent stimulation (4 Hz) of either lumbar dorsal roots was used to evoke motor activity in isolated spinal cord preparations. Agonists of TRPM8 receptors (menthol) inhibited windup and also modulated pattern generator function in a dose-dependent fashion. TRPM8 receptors are known to be expressed in subpopulations of C and A delta fibers suggesting that these classes of afferents are important for the expression of afferent evoked fictive locomotion. Current experiments are examining mechanisms of action.

**P450 AROMATASE GENE EXPRESSION IN GOLDFISH BRAIN AND GONAD**

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Estrogen is synthesized from testosterone in gonad and brain tissues by the enzyme Cytochrome P450 Aromatase. This enzyme is coded by the genes CYP19a and CYP19b; two isoforms expressed predominately in the ovary and brain, respectively. Regulation of CYP19 expression and aromatase activity are critical for reproductive maturation of vertebrates, as well as steroid-dependant development of sexually-dimorphic brain structures and reproductive behaviours. Experiments were conducted to measure changes in expression of these two genes in goldfish treated with injections of gonadotrophin releasing hormone (GnRH). Following hormonal treatment, RNA was extracted from gonads and brain, and gene expression was measured semi-quantitatively using CYP19a and CYP19b specific primer pairs. Results showed that both CYP19a & CYP19b are expressed in goldfish ovary, testis and brain. In testis, CYP19a predominates, whereas in ovary both isoforms are expressed equally. In brains of both males and females, CYP19b predominates, and is expressed mostly in the forebrain. Following 24-48hr hormonal stimulation with GnRH, gonad histology showed rapid maturation. In ovary, CYP19a increased dramatically over 48hrs. In brain, CYP19a was not affected by GnRH, whereas

CYP19b expression was strongly inhibited in both males and females. Because locally synthesized estrogen is influential in steroid-dependant CNS morphology and function, alterations in CYP19 expression and/or aromatase activity could have important behavioral consequences, especially for reproduction. These results support the need for further research into the effects of environmental exposure to endocrine disrupting chemicals on CYP19 expression in vertebrate CNS.
Source of Research Funds: UBCO Individual Research Grant

**LOCOMOTOR EXPRESSION OF INTERACTIONS BETWEEN SPATIAL MEMORY, VESTIUBLAR RESPONSE AND PODOKINETIC AFTER ROTATIONS (PKAR)**

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Exp I. Two blindfolded subjects successfully walked for 6 min round a previously memorised circle of 1m radius. Since the initial rotational vestibular signal would rapidly decay (T~15s), locomotor output was presumably derived from memory alone during the latter part of the trial. Exp II. The above task was repeated after installing PKAR, which unknowingly tends to reduce trajectory radius (R). Result: R first rapidly reduced from 1.0m to ~ 0.5m (T~15s) and then slowly increased back towards its initial value (T ~ 8.0 min). Conclusion: In Exp II PKAR was initially opposed by a memory-based expectation of the initial vestibular response. This then decayed along with the vestibular decay time constant of T ~ 15s. Thereafter the known time constant of PKAR decay (T~8min) allowed memory of the circle to restore trajectory radius toward its intended value of 1.0m.
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**MODULATION OF BRAIN INFLAMMATION BY OVARIAN HORMONES**

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Brain inflammation is a hallmark of many neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. This inflammation damages brain cells and exacerbates the disease outcome. Accumulated evidence suggested that ovarian hormones reduce innate immune responses and consequently could be useful tools for dampening brain inflammation. We thus asked whether ovarian hormones could dampen brain inflammation acutely induced by an immune challenge. By using a well-established model of brain inflammation which consists of either local or systemic application of the active component of gram negative bacteria (Lipopolysacharide or LPS), we assessed the potential beneficial role of ovarian hormones. In contrast to the commonly held view, estrogen (E2) administration to ovariectomised rats exacerbated brain inflammation induced by intra-parenchymal administration of LPS (500ng/2µl). Interestingly, when E2 was concomitantly administered with progesterone (Pr), brain inflammation was largely reduced as assessed by the levels of microglial activation. The most important mechanism by which LPS activates microglia is the local mobilization of pro-inflammatory cytokines, namely interleukins and tumor necrosis factor (TNF-alpha) and pro-inflammatory prostaglandins. Therefore we measured ovarian hormones effect on both brain TNF-alpha and the inducible prostaglandin producing enzyme (COX-2) levels. Combined E2 and Pr administration lowered brain levels of both TNF-alpha and COX-2. Because brain inflammation reduces neurogenesis, we tested whether ovarian hormones induced reduction in brain inflammation was associated with recovery of normally occurring neurogenesis. Indeed, neurogenesis was not drastically altered in ovariectomised rats subjected to brain inflammation and given combined E2 and Pr treatment. These data strongly suggest that combined E2 and Pr

regimen, and not that of E2 alone, dampens brain inflammation via an inhibitory effect on pro-inflammatory molecules such as TNF-alpha and COX-2. Importantly, the observed reduction in brain inflammation likely prevents alteration of neurogenesis.
Source of Research Funds: Canadian Institutes of Health Research

**DEVELOPMENTAL DIVERSIFICATION OF INTRINSIC MOTONEURON ELECTRICAL PROPERTIES IN EARLY POSTNATAL MICE**

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During early postnatal development, the motor behavior of young mice changes from relatively uncoordinated movements to weight-supporting, coordinated locomotion. The onset of weight-supporting is critical for survival, yet relatively little is known about the underlying mechanisms that contribute to this process. The changes that contribute to normal motor system development include changes in the intrinsic properties of alpha motoneurons which innervate skeletal muscles. The mouse is an ideal preparation to examine these changes since the onset of weight-bearing occurs relatively quickly around postnatal day 9. Here, we will present preliminary data showing the developmental diversification of intrinsic motoneuron electrical properties, particularly those properties that relate to excitability (rheobase current and input resistance) and the regulation of repetitive firing (after-hyperpolarization and persistent inward currents). Furthermore, these intrinsic motoneuron electrical properties may be modulated be descending monoaminergic transmitters such as serotonin (5-HT), and we will present some of these preliminary results also. Taken together, these studies describe the developmental diversification and serotonergic modulation of intrinsic motoneuron electrical properties in early postnatal mice. Future studies will test the hypothesis that postnatal motor activity is critical for correct differentiation of motoneuronal properties.
Source of Research Funds: AHFMR, CIHR, HBI

**MEMBRANE DEPOLARICATION AND THE EXCITATORY ACTION OF GABA AND MUSCIMOL IN SPIDER MECHANOSENSORY NEURONS**

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γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in a variety of animal species. Activation of $GABA_A$ receptors in the mechanosensory afferents entering the vertebrate spinal cord as well as the arthropod central ganglia induces primary afferent depolarization and an increase in membrane conductance (shunting), leading to inhibition. Mechanosensory neurons of the slit-sense organ (VS-3) in the patella of the tropical wandering spider *Cupiennius salei* are innervated by GABAergic efferents and they show similar responses (depolarization, shunting and inhibition) to application of GABA and muscimol, agonists of $GABA_A$ receptors. In the present study we show that when the VS-3 neurons were stimulated with a pseudorandom white-noise mechanical or electrical stimulation during muscimol application, the initial inhibitory response was followed by excitation, lasting for up to ten minutes. The VS-3 neuron spike rate, sensitivity and information capacity all increased during this period. Using intracellular current-clamp recordings, we investigated if membrane depolarization alone could induce similar excitatory effect as muscimol application. When VS-3 neurons were subjected to white noise stimulation while positive current was injected to produce 20-30 mV depolarization, a large increase in the neuron's spike rate, sensitivity and information capacity was observed. To learn if prevention of membrane depolarization during muscimol application would impede the excitatory effect, we used white-noise stimulation when the neurons were loosely voltage-clamped to their resting potential, thus suppressing slow changes in the membrane potential but allowing action potential transmission. Under these conditions muscimol elicited similar effects as under current-clamp conditions. These results suggest that membrane depolarization may

contribute to the muscimol induced excitatory effect, but it is possible that another, yet unknown, signaling pathway is also involved.
Source of Research Funds: CIHR, Nova Scotia Health Research Foundation

**EFFECT OF PERIPHERAL SENSORY INPUT ON EXCITABILITY IN THE HUMAN LEG MOTOR CORTEX**

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In the hand motor system, peripheral sensory inputs both facilitate and inhibit cortical networks in the primary motor cortex. The excitatory connections are thought to reinforce ongoing movements whereas the inhibitory connections are thought to prune unwanted activity in adjacent muscles in a manner equivalent to surround inhibition in the visual system. In this study, we characterized how afferent inputs modulate the excitability of the leg area of the primary motor cortex by examining how peripheral nerve stimulation modifies motor evoked potentials (MEPs) activated by transcranial magnetic stimulation (TMS). MEP responses in the soleus muscle were facilitated when the homonymous tibial nerve (TN) was stimulated 45-60 ms earlier whereas MEPs were inhibited when TN stimulation occurred 26-30 ms earlier ($p < 0.05$). Similar time-dependent modulation occurred in the tibialis anterior (TA) muscle in response to heteronymous activation of either the TN or posterior tibial nerve (PTN), a nerve that supplies the ventral surface of the foot. To determine the source (spinal or cortical) of this afferent-evoked facilitation and suppression of MEP responses, we compared the effects of PTN stimulation to muscle responses evoked at sub-cortical sites. In contrast to MEP facilitation, spinal H-reflexes and evoked responses from stimulation of the corticospinal tract at the level of the brainstem were unchanged or slightly depressed when preceded by a PTN stimulus 40 to 50 ms earlier and suggests that the observed MEP facilitation was cortical in origin. In contrast, H reflex and brainstem responses were suppressed at shorter interstimulus intervals where suppression of MEP responses were observed and suggests that unlike in the hand, short latency afferent inhibition in the leg motor cortex has a strong spinal component. We also used paired pulse TMS to identify the intracortical circuits that were affected by afferent inputs. At interstimulus intervals that produced MEP facilitation, afferent inputs suppressed short-interval intracortical inhibition (SICI) and tended to facilitate circuits involved in short-interval intracortical facilitation (ICF). In particular, the more indirect I2 and I3 facilitatory networks appear to be activated by afferent inputs.

**CONTROLLED DYNAMIC STIMULATION OF *DROSOPHILA* OLFACTORY RECEPTORS**

Schuckel, Julia*, Meisner, Shannon*, Torkkeli, Päivi H., French, Andrew S.

Perception of a large number of volatile chemicals, or odorants, allows animals from invertebrates to mammals to orient themselves in their chemical environments. The *Drosophila melanogaster* olfactory system provides an excellent model for studying mechanisms of olfactory perception because of the availability of a wide repertoire of experimental tools including genetics, behavior and electrophysiology. Time-dependent properties of chemical signals are probably crucially important to many animals, but relatively little is known about the dynamics of chemoreceptor neurons or the components that control their dynamic properties. Behavioral evidence of dynamic sensitivity has been found in several insect species. Male moth flight is controlled by the spatio-temporal structure of pheromone plumes from females. In mosquitoes, the fine time scale of the carbon dioxide plume leading to a host strongly influences the behavioral response of the animal. These natural odor plumes are shredded into discrete filaments of varying concentration because of variable wind directions and velocity fractions, producing complex, time dependent odor concentrations. Characterizing the dynamic properties of sensory receptors requires control and measurement of the stimulus over a frequency bandwidth that equals or exceeds the receptor response. Techniques for dynamic stimulation of

olfactory receptors have lagged behind other major sensory modalities because of difficulties in controlling and measuring the concentration of odorants at the receptor. We used a new servo-controlled laminar flow system, combined with photoionization detection of a surrogate tracer gas, to characterize the electroantennogram of *Drosophila* antennae during stimulation with four different fruit odorants and a pheromone. Frequency response functions and coherence functions measured with a bandwidth of 0-100 Hz were well characterized by first-order low-pass linear filter functions. Filter time constants varied over almost a ten-fold range, and was characteristic for each stimulant, indicating that several dynamically different chemotransduction mechanisms are present. Response amplitudes, and consequently signal-to-noise ratios, also varied consistently with different stimulants. Accurate dynamic characterization promises to provide important new information about chemotransduction and the resulting behavioral responses to time varying chemical signals.
Source of Research Funds: CIHR, Dalhousie Medical Research Foundation

**FUNCTIONAL ELECTRICAL STIMULATION FOR FOOT DROP STRENGTHENS RESIDUAL CORTICO-SPINAL CONNECTIONS**
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Sixty-five subjects with foot drop were studied before and after using a foot drop stimulator for up to 12 months to improve walking (functional electrical stimulation, FES) in a multi-centre study. Subjects were divided by diagnosis into generally progressive disorders such as multiple sclerosis and generally non-progressive disorders such as stroke and incomplete spinal cord injury. The same trends were seen in both groups for the first 3 months of FES use; walking speed increased 23% and 16% in the non-progressive and progressive groups respectively while wearing the device. Some divergence was seen at later times (26% and 12% increase at about 6 months and 42% and 9% at about a year in the two groups). After 3 months of using the FES device, walking speed without FES also increased and effort decreased, as measured by Physiological Cost Index (PCI), particularly in the non-progressive group. To determine the mechanisms involved that could lead to long-term, neuroplastic changes from using FES we also measured in a subgroup of 35 subjects in one centre: 1) maximum voluntary contraction (MVC) as mean rectified EMG in tibialis anterior (TA) muscles, 2) maximum M-wave ($M_{max}$) in this muscle and 3) motor evoked potentials (MEP) from transcranial magnetic stimulation of motor cortex. Increases in MVC (40%) and the MEP (25%) after at least 3 months of stimulation were highly significant. $M_{max}$ did not change significantly in the whole population, suggesting that the increases did not arise from increased muscle bulk. The large increases in MVC and MEP suggest that regular use of FES strengthens activation of motor cortex and its residual descending connections. The strengthening may also account for the previously observed carry-over effects that allow some subjects to walk faster even without FES. Our results suggest that subjects with both progressive and non-progressive disorders can benefit from FES, although the benefits may be superimposed on a decreasing level of function over time in progressive disorders.
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**CARDIAC ELECTROPHYSIOLOGY AND ARRHYTHMIA IN THE MOUSE**
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Background: With the advent of genetic manipulation of mice, they have become a major resource for investigating dysfunction of the cardiovascular system. A major limitation is the small size of the mouse, which hampers cardiac electrophysiological (EP) phenotype characterizations. We have uncovered technical issues resulting in uninterruptable EP data in the published literature. In most EP studies, body temperature was not monitored or maintained.

Also, by recording stable His bundle potentials during pacing, we have obtained precise measurements of atrial and AV nodal function.
Methods: We determined cardiac EP parameters in 1 and 6 month old C57BL/6 wild type (WT) mice at 37 $^{o}$C (normal) and *33.5* $^{o}$C (low) body temperatures. AH intervals, atrial, ventricular, and AV nodal effective refractory periods (AERP, VERP, AVNERP), Wenkebach cycle length (WCL), and AV nodal hysteresis curves (AHC) were determined from intracardiac electrograms in mice during programmed electrical stimulation at paced cycle lengths of 150 and 100 ms. Atrial burst pacing determined inducibility of atrial fibrillation (AF), while ventricular burst pacing determined the inducibility of AV nodal re-entrant tachycardia (AVNRT).
Results: Using His bundle recordings as a landmark of catheter position AERPs were lower in the mid-right atrium (MRA) ($A_M$ERP=21.6±1.6 ms) compared to the high right atrium (HRA) ($A_H$ERP=31.4±2.2 ms) at 37$^{o}$C (P<0.01) and were prolonged at *33.5* $^{o}$C (*29.3±2.9* ms vs *42.7 ± 3.7* ms, respectively, P<0.01). Also, at *33.5* $^{o}$C, $AH_{150}$ (21.7±0.6 vs *25.4±0.7* ms), WCL (85.4±1.2 vs *111.7±9.3* ms), and $AVNERP_{150}$ (60.4±1.9 vs 76.7±1.7 ms) were prolonged. AHCs were depressed at *33.5* $^{o}$C. We induced AF (>100 s) in 2 of 8, 6 month old mice without carbachol. AF was more inducible at normal body temperature, and with pacing in the MRA. Also, AVNRT (>15 s) was inducible in 5 of 8, 6 month old mice with ventricular burst pacing, but not with atrial pacing.
Conclusions: Most EP parameters were prolonged at *33.5* $^{o}$C. For comparison between studies, there is a need to provide EP parameters in the mouse at its normal body temperature. Using the His as a landmark is important for evaluating atrial and AV nodal properties. A novel finding was the inducibility of clinically relevant arrhythmia (AF and AVNRT) in the mouse. Thus, the mouse model is suitable to examine genetics and the effects of pharmacological and other interventions on electrophysiology and arrhythmia.
Source of Research Funds: HSFO and CIHR

**THE ROLE OF GAP JUNCTIONAL PROTEINS CX37 AND CX40 IN COMMUNICATION ALONG THE MICROVASCULATURE DURING INFLAMMATION**
Tyml, Karel[1,2,3], Rebecca McKinnon[2,3] and Michael Bolon[2,3]
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Although electrical coupling along the endothelium is central in arteriolar conducted response and in control of vascular resistance, little is known about the effect of inflammation on this coupling. We examined the effect lipopolysaccharide (LPS, an initiating factor in sepsis) on electrical coupling *in vitro*, in monolayers of microvascular endothelial cells derived from mouse hindlimb skeletal muscle. Coupling was assessed in terms of the spread of electrical current injected into the monolayer. LPS reduced coupling in cells from wild type (WT), $Cx37^{-/-}$, $Cx43^{G60S}$ (non-functional mutant), but not from $Cx40^{-/-}$ mice. In WT cells, LPS reduced coupling tyrosine-, ERK1/2-, PKA-, and PKC-dependently, via PKA-specific serine dephosphorylation of Cx40. Sepsis impairs capillary blood flow in skeletal muscle, leading to micro-regional hypoxia/reoxygenation (H/R). Thus, concurrent LPS+H/R could further reduce electrical coupling. Similar to LPS, H/R alone reduced coupling oxidant-, PKA- and Cx40-dependently. Significantly, LPS+H/R synergistically reduced coupling and enhanced PKA-specific serine dephosphorylation of Cx40. We also examined the effect of NO (a factor in advanced sepsis) on coupling. Sepsis (cecal ligation and perforation model) reduced arteriolar conducted response in the cremaster muscle *in vivo* in WT, $iNOS^{-/-}$, $eNOS^{-/-}$, but not in $nNOS^{-/-}$ mice, cGMP-independently. NO scavenger eliminated this reduction. In monolayers *in vitro*, exogenous NO rapidly (within minutes) and reversibly reduced coupling in WT, $Cx40^{-/-}$, $Cx43^{G60S}$, but not in $Cx37^{-/-}$ cells, also cGMP-independently. In WT cells, NO scavenger, but not superoxide or peroxynitrite scavenger, eliminated this reduction. We propose that sepsis reduces electrical coupling along the microvasculature in skeletal muscle by a complex

multistage process. In the early stage, LPS-induced signaling closes gap junctions via PKA-specific serine dephosphorylation of Cx40. H/R aggravates this effect oxidant-dependently. In the later stage associated with nNOS-derived NO overproduction, NO closes gap junctions by targeting Cx37 instead, via a cGMP- and oxidant-independent mechanism. (Support: CIHR and HSFO).

**THE BASIS OF DIFFERENTIAL COMMUNICATION IN THE RESISTANCE VASCULATURE**

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Electrical responses initiated in endothelial but not smooth muscle cells conduct robustly along resistance arteries. The origin of this dichotomy is uncertain and was consequently the focus of this investigation. Computational models based on physical and electrical properties of vascular cells provide two rationalizations for the inability of smooth muscle responses to conduct. First, given the differential orientation of vascular cells and the known variability in coupling resistance, it is conceivable that a resistance artery is inherently designed to limit the conduction of smooth muscle-initiated responses. This view is consistent with the inability of a high K+ solution, discretely applied to stimulate smooth muscle, to elicit a conducted response. Second, it is plausible given the passive nature of an artery's electrical properties that some smooth muscle agonists fail to elicit the local electrical response required for conduction. This second rationalization was confirmed experimentally by focally applying phenylephrine and monitoring vasomotor and electrical responses in resistance arteries. Further experimentation revealed no evidence the electrical feedback mechanisms in smooth muscle or endothelial cells play a measurable role in limiting the conduction of smooth muscle responses. In closing, our work highlights that by focusing on known biophysical properties, one can rationally explain the disparate ability of endothelial and smooth muscle responses to conduct. These findings are important to our understanding of blood flow control.

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**WHOLE CELL RECORDING FROM PYRAMIDAL NEURONS HELP EXPLAIN ISCHEMIA PROTECTION BY A SODIUM CHANNEL BLOCKER**

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The acute neuronal swelling and dendritic beading that occurs within minutes of stroke onset is a consequence of the anoxic depolarization (AD) that is abruptly triggered upon failure of the $Na^+/K^+$ATPase pump. The AD front is imaged as an increase in tissue translucency within 3-6 min of $O_2$/glucose deprivation (OGD) both in vivo and in live cortical brain slices. AD onset is delayed in slices pretreated with 1-100 μM dibucaine and related `caines` that block voltage-gated $Na^+$ channels, but it is unclear if this is the actual mechanism of AD inhibition. We examined if changes to single cell excitability could explain how dibucaine inhibits AD onset. We blind-patch recorded from CA1 somata in hippocampal slices during OGD exposure for 10 min at 33°C to examine dibucaine effects on intrinsic pyramidal cell properties and on AD onset. AD propagation was recorded as a sudden profound depolarization of the single neuron just as the wave front of elevated LT passed by the pipette tip. Bath pretreatment of slices with 1 or 10 μM dibucaine for 40 min had no effect upon resting membrane potential, action potential amplitude/duration or whole cell input resistance (n=15) compared to untreated slices (n=37). However 10 μM (but not 1) consistently raised spike threshold and increased the spike hyperpolarizing afterpotential (n=23), thereby reducing the neuron`s input/output relationship. Inclusion of 10 μM (n=15) or 100 μM (n=12) dibucaine within the patch pipette had similar and more immediate effects. These observations partly explain our previously observed effects of dibucaine on the evoked CA1 field potential which showed that dibucaine dramatically blunts orthodromic and antidromic population spikes. We are currently examining if dibucaine also

inhibits excitatory synaptic input and/or antidromic conduction to explain how particularly potent $Na^+$ channel blockers work to inhibit AD onset.
Source of Research Funds: Heart and Stroke Foundation of Ontario

**SURVEY OF THE GLUT TRANSLOCATION PORE FOR SUBSTRATE SELECTIVITY DETERMINANTS; WHAT MAKES A GLUCOSE TRANSPORTER A FRUCTOSE TRANSPORTER?**

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The recent expansion and characterization of the human facilitative hexose transporter family has revealed that at least 5 out of the 14 members are capable of both glucose (GLU) and fructose (FRU) transport. This raises the important question of how FRU can permeate some GLUTs but not others given the structural similarity between GLU and FRU molecules.

Extensive experiments using site-directed and cysteine-scanning mutagenesis in combination with hexose analogue inhibition studies, revealed several highly conserved motifs in the TMs forming the translocation pore. These motifs were identified as likely to interact with the substrate hexoses via hydrogen bonds (Mueckler and Makepeace, 2005). Seatter *et al.* (1998) has shown a motif distal to the binding site, which can alter the substrate specificity of GLUT3 to that of a GLUT2-like FRU transporter. Through comparative studies Manolescu *et al.* (2005) identified a single hydrophobic residue, which is part of the three-residue motif (NXV/I) close to the outer vestibule of the transporter, presumably affecting substrate selectivity by way of affecting its access.

The objective of this study is to characterize the potential roles of key motifs within TM 7 of the hGLUT1 and GLUT2 isoforms, through the use of site directed mutagenesis and the *Xenopus* oocyte expression system. Wildtype hGLUT1 transports FRU at a rate of 0.1% relative to GLU transport. Mutating Val of the NAV motif into an Ile increases FRU transport to approximately 0.9% (~ 2.5 pmols/oocyte/30 min, 100 uM substrate) relative to that of GLU. Mutating the molecular filter QLS in hGLUT1 into HVA also increases the relative rate of FRU transport (up to 0.5%) but to a lesser extent then the Val to Ile mutation, suggesting that substrate access is the main determinant of substrate selectivity. When hGLUT1 HVA_NAI mutant was made, we observed a relative FRU transport rate of 1.1 %. (~ 6 pmols/oocyte/30 min, 100 uM substrate). When the kinetic analysis was performed for the hGLUT1 HVA_NAI mutant, the $K_m$ for GLU was comparable to that of hGLUT1wt (1.5mM), while $K_m$ for FRU was comparable to that for hGLUT2 FRU transport.

These results point to presence of, at least two, selectivity filters within class I GLUTs. The first is the exofacial access filter (NAV/NAI) that was previously demonstrated for class II GLUTs. The second, QLS/HVA motif, seems to play a role in allowing FRU translocation beyond the substrate binding site without influencing its binding and/or translocation, further supporting its role in selectivity. Taken together, we have successfully introduced hGLUT2-like FRU kinetics into hGLUT1, without affecting the GLU transport of this isoform. References: Manolescu, A, Salas-Burgos AM, Fishbarg J, Cheeseman CI. *J Biol Chem*. 2005. 280(52):42978-83. Seatter MJ, De la Rue SA, Porter LM, Gould GW. *Biochem*. 1998. 37(5):1322-6.

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**MICRORNA MIR-21 REPRESSES CYSTATHIONINE GAMMA-LYASE EXPRESSION IN SMOOTH MUSCLE CELLS**

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We have previously found that the expression of cystathionine gamma-lyase (CSE), an important $H_2S$-produing enzyme in smooth muscle, was significantly reduced during the development of balloon injury-induced neointimal hyperplasia, and treatment with $H_2S$ reversed neointimal lesion formation by inhibiting smooth muscle cell (SMC) proliferation. The mechanisms underlying the alteration of CSE expression in this pathological condition, however, remain unknown. Recent discovery of microRNAs has revolutionized our understanding of the mechanisms that regulate gene expression. As an oncogenic miRNA, microRNA-21 (miR-21) exhibits anti-apoptotic activity in various carcinomas. By in silico analysis, we identified one potential target site in the 3' untranslational regions of CSE gene for miR-21, and the target site is highly conserved across rat, mouse, human, and chimpanzee. A remarkable overexpression of miR-21 was discovered in rat carotid artery after balloon injury compared with the uninjured arteries. The expression of miR-21 in rat thoracic aorta SMCs and human aorta SMCs (HASMCs) was demonstrated. Incubation of HASMCs with 50 nM anti-miR™ miR-21 inhibitor to knockdown miR-21 expression significantly augmented CSE expression and H2S production by 10.0 ± 0.8%, while overexpression of miR-21 by treating the cells with 50 nM pre-miR™ miR-21 precursor significantly inhibited CSE expression and $H_2S$ production by 18.4 ± 1.9%. Suppression of miR-21 expression inhibited HASMC proliferation, which was partly and significantly reversed by co-treatment with DL-propargylglycine (10 mM, a CSE inhibitor). On the other hand, overexpression of miR-21 stimulated HASMC proliferation. Our studies show that miR-21 acts as a novel repressor of CSE expression, which may be a new therapeutic target for proliferative vascular diseases such as atherosclerosis.
Source of Research Funds: NSERC

**REFLECTIONS ON THE QUADRUPEDAL NATURE OF BIPEDAL LOCOMOTION**

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In humans, neural circuits regulating movement can be probed indirectly by stimulating peripheral nerves and recording reflex changes in muscle activity. Differences in reflex modulation between rhythmic and non-rhythmic movement have been ascribed to the influence of spinal neural circuits contributing to locomotor control (e.g. CPGs). In the title of a Trends in Neurosciences article from 2002, Volker Dietz asked "Do human bipeds use quadrupedal coordination?" Arguments were advanced in this regard but several issues central to the question—namely the neural control of arm movement during locomotion and the neurological interaction of the arms and legs—were largely speculative. In the 5 years since this review was published, significant advances in our understanding of the neural regulation and linkage between arm and leg motion has been made. Human locomotion can be a very automated process with CPGs playing a role in the coordination of the arms and legs. Recent experimental evidence now suggests that both the arms and legs are regulated by CPGs and that interlimb coordination during gait is assisted by sensory feedback from the moving limbs. Interestingly the strength of coupling between the arms is weaker than that between the legs. Rhythmic arm movement contributes to the neural excitation of leg muscles during locomotion in a pattern reminiscent of the quadrupedal cat. These linkages subserve functional roles in coordinating arm and leg activity during walking. This neuronal coupling is also the predicted evolutionary holdover from a quadrupedal arboreal origin. The conservation of elements of quadrupedal neural circuitry during bipedal locomotion has fundamental implications for the restoration and recovery of motor impairment occurring after stroke and spinal cord injury. This inherent quadrupedal locomotor circuitry may be exploited in rehabilitation after neurotrauma to allow our arms to give our legs a helping hand during gait retraining.
Source of Research Funds: NSERC, Heart & Stroke Foundation of BC & Yukon, MSFHR

**CALCIUM-DEPENDENT ACTIVATION OF CYSTATHIONINE GAMMA-LYASE IN SMOOTH MUSCLE CELLS**

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Hydrogen sulfide ($H_2S$), a novel gasotransmitter, has been shown to relax smooth muscle by opening ATP-sensitive potassium channel. The $H_2S$-induced vasorelaxation is extracellular calcium entry dependent. However, the effect of calcium on the activation of cystathionine gamma-lyase (CSE) and $H_2S$ production in smooth muscle remains unclear. CSE, a major $H_2S$-producing enzyme, is expressed in rat smooth muscle cells (SMCs). Incubation of rat thoracic artery SMCs with calcium ionophore A23187 (1 μM) or KCl (50 mM) for 5 minutes significantly increases H2S content in cell culture media containing 1.8 mM calcium by 6.4 or 1.4 times, measured with a sulphide-sensitive electrode. Fifteen minutes after incubation, A23187 or KCl increased $H_2S$ contents in cell culture media by 6.6 or 3.3 times, respectively. More $H_2S$ contents were detected when the cells were incubated with A23187 (9.2 times) or KCl (3.9 times) for 30 minutes compared with the control. These results indicate that regulation of CSE activity and $H_2S$ production in SMCs may be calcium-dependent. Interactions of calcium and CSE may provide a novel regulatory mechanism for the functions of vascular smooth muscle cells.

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