

Department of Integrative Physiology University of North Texas Health Science Center

The Department: The core of the department's research focuses on the physiology and pathophysiology of the cardiovascular system. Research in the department is funded at over \$3 million per year by grants from the National Institutes of Health, the American Heart Association, the U.S. Department of Defense, and NASA. In addition, several faculty receive funding from private sources to support developmental research in biotechnology.

THE FACULTY

Steve W. Mifflin, Ph.D., *Chair and Professor* (Ph.D., Physiology and Biophysics, University of Texas Medical Branch, 1983). Research focuses on brainstem neurons that regulate blood pressure and respiration. Of particular interest is how these neurons adapt following chronic changes in physiological state (high blood pressure, low oxygen levels, sleep apnea, high salt intake). Studies are conducted over the spectrum from conscious, freely moving animals to single cell electrophysiology. The goal is to better understand if alterations in central nervous system function in pathophysiological states are protective or contribute to the pathophysiology. This knowledge can guide new therapeutic approaches.

Selected Recent Publications

Zhang W, **Mifflin SW**. Chronic sustained hypoxia enhances both evoked EPSCs and norepinephrine inhibition of glutamatergic afferent inputs in the nucleus of the solitary tract. *J Neurosci* 2009;29:3093-3102.

Zhang W, Carreño FR, Cunningham JT, **Mifflin SW**. Chronic sustained and intermittent hypoxia reduce function of ATP-sensitive potassium channels in nucleus of the solitary tract. *Am J Physiol Regul Integr Comp Physiol* 2008; 295:R1555-R1562.

de Paula, P., G. Tolstykh and **S.W. Mifflin**. Chronic intermittent hypoxia alters NMDA and AMPA-evoked currents in NTS neurons receiving carotid body chemoreceptor inputs. *Am J Physiol Regul Integr Comp Physiol* 2007; 292:2259-2265.

Tolstykh, G., P. de Paula, and **S.W. Mifflin**. Voltage-dependent calcium currents are enhanced in NTS neurons isolated from renal wrap hypertensive rats. *Hypertension*, 49:1163-1169, 2007.

James L. Caffrey, Ph.D., *Professor* (Ph.D., Physiology, University of Virginia, 1973). Laboratory studies the neuroendocrine regulation of the heart and circulation with specific emphasis on interactions between the autonomic neurotransmitters (acetylcholine and norepinephrine) and the endogenous opioids (endorphins, enkephalins, and dynorphins). Studies in this program include both molecular and intact organ system approaches in both human subjects and experimental animals. The laboratory emphasis includes the role of opioids in cardioprotection, cardiometabolic disease in general and diabetes in particular. A current laboratory focus is the identification of early markers of cardiometabolic disease in ethnic minorities and the development of strategic interventions to address those disparities. Our results suggest that determining the cardiac and neurovascular influences of endogenous opioids will help to develop new strategies for the treatment and prevention of the emerging world wide epidemic of cardiometabolic disease.

Selected Recent Publications

Deo SH, Barlow MA, Gonzalez L, Yoshishige D, **Caffrey JL**. Repeated arterial occlusion, delta-opioid receptor (DOR) plasticity and vagal transmission within the sinoatrial node of the anesthetized dog. *Exp Biol Med* 2009; 234:84-94.

Deo SH, Barlow MA, Gonzalez L, Yoshishige D, **Caffrey JL**. Cholinergic location of delta opioid receptors in canine atria and SA node. *Am J Physiol Heart Circ Physiol* 2008; 294:H829-H838.

Zatta AJ, Kin H, Yoshishige D, Jiang R, Wang N, Reeves JG, Mykytenko J, Guyton RA, Zhao ZQ, **Caffrey JL**, Vinten-Johansen J. Evidence that cardioprotection by postconditioning involves preservation of myocardial opioid content and selective opioid receptor activation. *Am J Physiol Heart Circ Physiol* 2008; 294:H1444-H1451.

Davis S, Deo S, Barlow M, Yoshishige D, Farias M, **Caffrey JL**. The monosialosyl ganglioside, GM-1 reduces the vagolytic efficacy of δ_2 -opioid receptor stimulation. *Am J Physiol Heart Circ Physiol* 2006; 291:H2318-H2326.

Flávia R Carreño, Ph.D., *Research Assistant Professor; Director Biochemical/Molecular Biology Core* (Ph.D., Cellular and Tissue Biology, University of Sao Paulo, Brazil, 2004). Primary goal is to identify molecular mechanisms associated with adaptations and/or neuroplasticity in animal models of chronic disease states such as inappropriate vasopressin release, hypertension and sleep apnea. Studies in this program include biochemical and molecular approaches to evaluate neurotrophins related signal transduction mechanisms; lipid raft-protein association; protein-protein interactions among signaling molecules and receptors; post-translational modifications with an emphasis on glycosylation, ubiquitination, lipidation and phosphorylation.

Selected Recent Publications

Carreño FR, Ji LL, Cunningham JT. Altered central TRPV4 expression and lipid raft association related to inappropriate vasopressin secretion in cirrhotic rats. *Am J Physiol Regul Int Comp Physiol* 2009; 296:R454-466.

Zhang W, **Carreño FR**, Cunningham JT, Mifflin SW. Chronic sustained hypoxia enhances both evoked EPSCs and norepinephrine inhibition of glutamatergic afferent inputs in the nucleus of the solitary tract. *J Neurosci.* 2009; 29:3093-3102.

Zhang W, **Carreño FR**, Cunningham JT, Mifflin SW. Chronic sustained and intermittent hypoxia reduce function of ATP-sensitive potassium channels in nucleus of the solitary tract. *Am J Physiol Regul Integr Comp Physiol* 2008; 295:R1555-R1562.

Carreño FR, Gofñi CN, Castro LM, Ferro ES. 14-3-3 epsilon modulates the stimulated secretion of endopeptidase 24.15. *J Neurochem* 2005; 93:10-25.

J. Thomas Cunningham, Ph.D., *Professor and Director of Cardiovascular Research Institute* (Ph.D., Biopsychology, University of Iowa, 1988). We investigate the role of the central nervous system in body fluid homeostasis and cardiovascular regulation. Current projects focus on the physiological regulation of vasopressin release by visceral afferents and the roles of hypothalamic TRP channels and brain derived neurotrophic factors in syndrome of inappropriate ADH (SIADH). We also study hypothalamic mechanisms that influence sympathetic outflow in animal models of hypertension.

Selected Recent Publications

Carreno FR, Ji LL, **Cunningham JT**. Altered central TRPV4 expression and lipid raft association related to inappropriate vasopressin secretion in cirrhotic rats. *Am J Physiol Regul Integ Comp Physiol* 2009; 296:R454-R466.

Shi P, Martinez MA, Calderon AS, Chen QH, **Cunningham JT**, Toney GM. Intra-carotid hyperosmotic stimulation increases Fos staining in forebrain organum vasculosum laminae terminalis neurones that project to the hypothalamic paraventricular nucleus. *J Physiol* 2008; 586:5231-5245.

Zhang WR, Carreno FR, **Cunningham, JT**, Mifflin, SW. Chronic sustained hypoxia enhances both evoked EPSCs and norepinephrine inhibition of glutamatergic afferent inputs in the nucleus of the solitary tract. *J Neurosci* 2009; 29:3093-3102.

Ma S, Mifflin SW, **Cunningham JT**, Morilak DA. Chronic intermittent hypoxia sensitizes acute hypothalamic-pituitary-adrenal stress reactivity and Fos induction in the rat locus coeruleus in response to subsequent immobilization stress. *Neuroscience* 2008; 154:1639-1647.

Dan Dimitrijevič, Ph.D., *Research Associate Professor* (Ph.D., Organic Synthesis, University of Bath, 1969). Cell-cell and cell-matrix interactions pertinent to wound healing, human tissue engineering strategies and *in vitro* generation of grafts for tissue replacement therapy. Development of 3-D *in vitro* models and studies of scar formation and prevention. Most recent tissue of interest is bone which regenerates without scar formation. Recent interest in targeted adult stem / progenitor cell isolation and delivery using tissue engineered grafts and the cellular and extracellular role of 14-3-3 proteins in development and homeostasis of human eye tissues. Patents obtained for engineering skin and cornea substitutes, rotating wall vessels for tissue engineering and a bioabsorbable anti-adhesion membrane.

Selected Recent Publications

US Patents 6,599,526 B2, 6,471,958, and 5,998,202.

Mootha VV, Kanoff JM, Shankardas J, Mootha VK, **Dimitrijevič SD**. Marked reduction of alcohol dehydrogenase gene expression in keratoconus corneal fibroblasts. *Mol Vision* 2009; in press.

Shankardas J, Senchyna M, **Dimitrijevič SD**. Presence and Distribution of 14-3-3 Proteins in the Human Ocular Surface Tissues. *Mol Vision* 2008; 14:2604-2615.

Bartosh TJ, Wang Z, Rosales AA, **Dimitrijevič SD**, Roque RS. 3D model of adult cardiac stem cells for investigations of cardiac differentiation and oxidative stress responses. *J Cell Biochem* 2008; 105: 612-623.

Flynn JM, **Dimitrijevič SD**, Younes M, Skliris G, Murphy LC, Cammarata PR. Role of wild-type estrogen receptor β in mitochondrial cytoprotection of cultured normal human male and female lens epithelial cells. *Am J Physiol Endocrinol Metab* 2008; 295:E637-E647.

H. Fred Downey, Ph.D., *Regents Professor and Vice Chair*, (Ph.D., Biophysics, University of Illinois, 1968). Research delineates mechanisms to protect the heart from ischemia. Investigations focus on mechanisms controlling the coronary circulation and myocardial metabolism and on interactions between the coronary circulation and cardiac function. Current emphasis is on right ventricular physiology and on effects of osteopathic manipulation on lymph flow and immune function.

Selected Recent Publications

Jung ME, Simpkins JW, Wilson AM, **Downey HF**, Mallet RT. Intermittent hypoxia conditioning prevents behavioral deficit and brain oxidative stress in ethanol-withdrawn rats. *J Appl Physiol* 2008; 105:510-517.

Downey HF, Durgam P, Williams AG Jr, Rajmane A, King HH, Stoll ST. Lymph flow in the thoracic duct of conscious dogs during lymphatic pump treatment, exercise, and expansion of extracellular fluid volume. *Lymphat Res Biol* 2008; 6:3-13.

Setty S, Zong P, Sun W, Tune JD, **Downey HF**. Hypoxia-induced vasodilation in the right coronary circulation of conscious dogs: role of adrenergic activation. *Auton Neurosci* 2008; 138:76-82.

Ryou MG, Sun J, Oguayo KN, Manukhina EB, **Downey HF**, Mallet RT. Hypoxic conditioning suppresses nitric oxide production upon myocardial reperfusion. *Exp Biol Med* 2008; 233:766-774.

Patricia A. Gwartz, Ph.D., Professor (Ph.D., Physiology, Thomas Jefferson University, 1978). The application of the core principle of "Respect of Persons" in ethical research is the concept of informed consent. Respect of persons in research implies consideration of and valuing the opinions and choices made by a subject who has adequate knowledge. This requires that the subject fully understand or comprehend the informed consent; otherwise their rights and respect are compromised. A major barrier to comprehension occurs when the informed consent must be translated. Current research is focusing on examining the effects of these linguistic problems and other contributing factors (e.g., education) on comprehension of the consent process.

Selected Recent Publications

Oglesby MW, Dubin BD, **Gwartz PA**, Martin MW, Putthoff SL, Papa FJ. An application-oriented curriculum: impact on medical student performance on national licensing boards. *Acad Med* (In Press)

Gwartz PA. Teaching the interrelationship between stress, emotions and cardiovascular risk using a classic paper by Walter Cannon. *Advan Physiol Educ* 2008; 32:18-22.

Gwartz PA, Dickey J, Vick D, Williams MA, Foresman B. Viscerosomatic interaction induced by myocardial ischemia in conscious dogs. *J Appl Physiol* 2007; 103:511-517.

Rong Ma, Ph.D., Assistant Professor (Ph.D., Physiology, University of Nebraska, 1999) Research focuses on Ca^{2+} -conductive channels (TRP channels) in kidney (glomerular mesangial cells and podocytes) and vascular smooth muscle cells. Major interests include regulation of TRP channels by protein kinases and reactive oxygen species, physiological relevance of TRP channels in kidney and blood vessels, and the association of TRP channel dysfunction with kidney and vascular diseases, such as diabetic nephropathy and vasculopathy.

Selected Recent Publications

Sours-Brothers S, **Ma R**, Koulen P. Ca^{2+} -sensitive transcriptional regulation: from kinase/phosphatase-mediated activity to direct DNA interaction. *Frontiers Biosci* 2009; 14:1851-1856.

Sours-Brothers S, Ding M, Graham S, **Ma R**. Interaction between TRPC1/TRPC4 assembly and STIM1 contributes to store-operated Ca^{2+} entry in mesangial cells. *Exp Biol Med* 2009; 234:673-682.

Wu Z, Xu Q, Zhang L, Kong D, **Ma R**, Wang L. Protective effect of resveratrol against kainic acid-induced temporal lobe epilepsy in rats. *Neurochem Res* 2009; 34:1393-1399.

Du J, Sours-Brothers S, Ding M, Graham S, **Ma R**. Mediation of angiotensin II-induced Ca^{2+} signaling by polycystin 2 in glomerular mesangial cells. *Am J Physiol Renal Physiol* 2008; 294:F909-F918.

Robert T. Mallet, Ph.D., Professor (Ph.D., Physiology, George Washington University, 1986). Research emphasizes development of novel strategies to protect heart and brain from ischemic and inflammatory injury by modifying metabolic fuel supply to these organs, or by hypoxia conditioning. Current studies are defining mechanisms responsible for protection of the heart and brain by pyruvate during cardiac arrest-resuscitation, cardiopulmonary bypass surgery and hemorrhagic shock, and robust preservation of ischemic heart muscle and brain by intermittent, normobaric hypoxia conditioning.

Selected Recent Publications

Jung ME, Simpkins JW, Wilson AM, Downey HF, **Mallet RT**. Intermittent hypoxia conditioning prevents behavioral deficit and brain oxidative stress in ethanol-withdrawn rats. *J Appl Physiol* 2008; 105:510-517.

Serebrovskaya TV, Manukhina EB, Smith ML, Downey HF, **Mallet RT**. Intermittent hypoxia: cause of or therapy for systemic hypertension? *Exp Biol Med* 2008; 233:627-650.

Ryou MG, Sun J, Oguayo KN, Manukhina EB, Downey HF, **Mallet RT**. Hypoxic conditioning suppresses nitric oxide production upon myocardial reperfusion. *Exp Biol Med* 2008; 233:766-774.

Sharma AB, Barlow MA, Yang SH, Simpkins JW, **Mallet RT**. Pyruvate enhances neurological recovery following cardiopulmonary arrest and resuscitation. *Resuscitation* 2008; 78:108-119.

Jeffrey T. Potts, Ph.D., Associate Professor (Ph.D., Physiology, University of North Texas Health Science Center, 1993). Research focuses on neuroplasticity in autonomic brainstem circuits controlling cardiovascular and respiratory function. Studies involve single cell-to-whole animal models employing electrophysiology, optical imaging, neuronal tracing and immunohistochemistry. The goal of my research is to understand the role of cardiorespiratory brainstem circuits in exercise and in disease states including hypertension, sudden infant death syndrome and sleep apnea.

Selected Recent Publications

Fong AY, **Potts JT**. Neurokinin-1 receptor activation in the Böttinger complex evokes bradypnea and is involved in mediating the Hering-Breuer reflex. *Adv Exp Med Biol* 2008; 605:366-370.

Fong AY, **Potts JT**. Neurokinin-1 receptors modulate the excitability of expiratory neurons in the ventral respiratory group. *J Neurophysiol*. 2008; 99:900-914.

Potts JT, Fong AY, Anguelov PI, Lee S, McGovern D, Grias I. Targeted deletion of NK1 receptor expressing NTS neurons precludes somatosensory depression of arterial-cardiac baroreflex. *Neuroscience* 2007; 468:1168-1181.

Potts JT, Paton JFR. Optical imaging of medullary ventral respiratory activity during eupnea and gasping *in situ*. *Eur J Neurosci*. 2006; 23:3025-3033. (Journal Cover)

Peter B. Raven, Ph.D., Professor (Ph.D., Scientific Basis of Physical Education, University of Oregon, 1969). Investigates cardiovascular regulation of the human during exercise and orthostasis. By using invasive and non-invasive procedures, integrative physiological mechanisms of cardiovascular regulation of the human are investigated during dynamic exercise and gravitational stress in both young and elderly individuals with varying levels of aerobic fitness.

Selected Recent Publications

Ogoh S, Fisher JP, Young CN, **Raven PB**, Fadel PJ. Transfer function characteristics of the neural and peripheral arterial baroreflex arcs at rest and during postexercise muscle ischemia in humans. *Am J Physiol Heart Circ Physiol* 2009; 296:H1416-H1424.

Hawkins MN, Barnes Q, Purkayastha S, Eubank W, Ogoh S, **Raven PB**. The effects of aerobic fitness and β_1 -adrenergic receptor blockade on cardiac work during dynamic exercise. *J Appl Physiol* 2009; 106:486-493.

Fisher JP, Ogoh S, Young CN, **Raven PB**, Fadel PJ. Regulation of middle cerebral artery blood velocity during dynamic exercise in humans: influence of aging. *J Appl Physiol* 2008; 105:266-273.

Ogoh S, Brothers RM, Eubank WL, **Raven PB**. Autonomic neural control of the cerebral vasculature: acute hypotension. *Stroke* 2008; 39:1979-1987.

Xiangrong Shi, Ph.D., Associate Professor (Ph.D., Environmental Physiology, Yale University, 1989). Research interests include body fluid and blood pressure regulation under various environmental stresses; cardiovascular adaptations to acute physical activity and/or chronic exercise training; and the interrelation of blood volume and blood pressure control and regulatory mechanisms with aging.

Selected Recent Publications

Liu Q, Liu R, Kashyap MV, Agarwal R, **Shi X**, Wang CC, Yang SH. Brainstem glioma progression in juvenile and adult rats. *J Neurosurg* 2008; 109:849-855.

Shi X, Schaller F, Tierney N, Chanthavong P, Chen S, Raven P, Smith M. Physically active lifestyle enhances vagal-cardiac function but not central autonomic neural interaction in elderly humans. *Exp Biol Med* 2008; 233:209-218.

Guo H, Tierney N, Schaller F, Raven P, Smith S, **Shi X**. Cerebral autoregulation is preserved during orthostatic stress superimposed with systemic hypotension. *J Appl Physiol* 2006; 100:1785-1792.

Formes KJ, Wray DW, O-Yurvati AH, Weiss MS, **Shi X**. Sympathetic cardiac influence and arterial blood pressure stability. *Autonom Neurosci* 2005; 118:116-124.

Michael L. Smith, Ph.D., Professor (Ph.D., Biology, University of North Texas, 1986). Research efforts focus on the neural control of cardiovascular function relating to mechanisms of sudden cardiac death, syncope, exercise training effects, and mechanisms of the association between obstructive sleep apnea and hypertension.

Selected Recent Publications

Serebrovskaya TV, Manukhina EB, **Smith ML**, Downey HF, Mallet RT. Intermittent hypoxia: cause of or therapy for systemic hypertension? *Exp Biol Med* 2008; 233:627-650.

Smith ML, Pacchia CF. Sleep apnea and hypertension: role of chemoreflexes in humans. *Exp Physiol* 2007; 92:45-50.

Segerson NM, Sharma N, **Smith ML**, Wasmund SL, Kowal RC, Abedin M, Macgregor JF, Pai PK, Freedman RA, Klein RC, Wall TS, Stoddard G, Hamdan MH. The effects of rate and irregularity on sympathetic nerve activity in human subjects. *Heart Rhythm* 2007; 4:20-26.

Thakre TP, **Smith ML**. Loss of lag-response curvilinearity of indices of heart rate variability in congestive heart failure. *BMC Cardiovasc Disord* 2006; 6:27.

Weirong Zhang, Ph.D., Research Assistant Professor (Ph.D., Physiological Sciences, University of Florida, 2004). Research efforts focus on neural control of cardiovascular and respiratory function. Studies involve various animal models, including chronic hypertension, chronic intermittent and sustained hypoxia. Current studies are investigating chronic hypoxia-induced neural plasticity in central nervous system.

Selected Recent Publications

Zhang W, Carreno FR, Cunningham JT, Mifflin SW. Chronic sustained hypoxia enhances both evoked EPSCs and norepinephrine inhibition of glutamatergic afferent inputs in the nucleus of solitary tract. *J Neurosci* 2009; 29:3093-3102.

Zhang W, Carreno FR, Cunningham JT, Mifflin SW. Chronic sustained and intermittent hypoxia reduce the function of ATP-sensitive potassium channels in the nucleus of solitary tract. *Am J Physiol Regul Integ Comp Physiol* 2008; 295:R1555-R1562.

Zhang W, Hayward LF, Davenport PW. Respiratory responses elicited by rostral versus caudal dorsal periaqueductal gray stimulation in rats. *Autonom Neurosci* 2007; 134:45-54.