BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
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NAME	POSITION TITLE
Paul J. Fadel	Assistant Professor
eRA COMMONS USER NAME	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Brooklyn College, Brooklyn, NY	B.S.	1992	Physical Education
Northeastern University, Boston, MA	M.S.	1995	Exercise Physiology
UNT Health Science Center, Fort Worth, TX	Ph.D.	2000	Integrative Physiology
UT Southwestern Medical Center, Dallas, TX	Fellow	2004	Neural Control-Hypertension

A. Positions and Honors

Positions/Employment

9/98-8/00 Graduate Research Assistant, University of North Texas Health Science Center, Fort Worth, TX
9/00-2/04 Postdoctoral Fellow, UT Southwestern Medical Center, Division of Hypertension, Dallas, TX
2/04-6/04 Assistant Instructor, UT Southwestern Medical Center, Dept. Health Care Sciences, Dallas, TX
6/04-8/05 Assistant Professor, UT Southwestern Medical Center, Dept. Health Care Sciences, Dallas, TX
8/05-present Assistant Professor, University of Missouri, Dept. of Medical Pharmacology & Physiology

Professional Memberships

Member, American Physiological Society
Member, American College of Sports Medicine

Honors

1999 National Research Fellowship, Copenhagen Muscle Research Center, Denmark
2000 Outstanding Graduate Student, Department of Integrative Physiology, UNT Health Science Center at Fort Worth
2000 American College of Sports Medicine, Student Research Award, Texas Chapter
2001 NIH, Institutional Training Fellowship, UT Southwestern Medical Center at Dallas, Department of Internal Medicine, Division of Cardiology
2001 NIH, Individual National Research Service Award
2002 American Physiological Society, Caroline tum Suden/Frances A. Hellebrandt Professional Opportunity Award
2002 American Physiological Society, Research Career Enhancement Award
2003 American Physiological Society, Michael J. Brody Young Investigator Award, Neural Control & Autonomic Regulation Section
2005 UT Southwestern Allied Health Sciences School, New Investigator Award
2008 University of Missouri School of Medicine Dorsett L. Spurgeon Distinguished Medical Research Award
2008 American Physiological Society, New Investigator Award, Neural Control & Autonomic Regulation Section

B. Selected Peer-Reviewed Publications (in chronological order)

Publications

Manuscripts

1. Schneider, D.A., P.J. McDonough, **P.J. Fadel,** and J.P. Berwick. Creatine Supplementation and the Total Work Performed during 15-s and 1-min bouts of Maximal Cycling. *The Australian Journal of Science and Medicine in Sport*, 29 (3): 65-68, 1997.
2. Smith, S.A., R.G. Querry, **P.J. Fadel,** R.M. Welch-O'Connor, A. Olivencia-Yurvati, X. Shi, and P.B. Raven. Differential baroreflex control of heart rate in sedentary and aerobically fit individuals. *Med Sci Sports Exerc*, 32(8): 1419-1430, 2000.
3. Fadel, P.J., S. Ogoh, D.E. Watenpaugh, W. Wasmund, A. Olivencia-Yurvati, M.L. Smith, and P.B. Raven. Carotid Baroreflex Regulation of Sympathetic Nerve Activity during Dynamic Exercise in Humans. *AJP: (Heart Circ Physiol)*, 280: H1383-H1390, 2001.
4. Fadel, P.J., M. Stromstad, J. Hansen, M. Sander, K. Horn, S. Ogoh, M.L. Smith, N.H. Secher, and P.B. Raven. Arterial Baroreflex Control of Sympathetic Nerve Activity during Acute Hypotension: Effect of Fitness. *AJP: (Heart Circ Physiol)*, 280: H2524-2532, 2001.
5. Gallagher, K.M., **P.J. Fadel,** S.A. Smith, K.H. Norton, R.G. Querry, A. Olivencia-Yurvati, and P.B. Raven. Increases in Intramuscular Pressure Raises Arterial Blood Pressure during Dynamic Exercise. *J Appl Physiol*, 91: 2351-2358, 2001.
6. Smith, S.A., R.G. Querry, **P.J. Fadel,** M.W. Weiss, A. Olivencia-Yurvati, X. Shi, and P.B. Raven. Comparison of aortic and carotid baroreflex stimulus-response characteristics in humans. *Auton Neurosci*, 88: 74-85, 2001.
7. Gallagher, K., **P.J. Fadel,** M. Stromstad, K. Ide, S. Smith, R. Querry, P. Raven and N. Secher. Effects of Exercise Pressor Reflex Activation on Carotid Baroreflex Function during Exercise in Humans. *J Physiol*, 533.3: 871-880, 2001.
8. Gallagher, K., **P.J. Fadel,** M. Stromstad, K. Ide, S. Smith, R. Querry, P. Raven and N Secher. Effects of Partial Neuromuscular Blockade on Carotid Baroreflex Function during Exercise in Humans. *J Physiol*, 533.3: 861-870, 2001.
9. Raven, P.B., **P.J. Fadel,** and S.A. Smith. The Influence of Central Command on Baroreflex Resetting during Exercise. *Exerc Sport Sci Rev*, 30 (1): 39-44, 2002.
10. Ogoh, S., **P.J. Fadel,** F. Montiero, W.L. Wasmund, and P.B. Raven. Haemodynamic Changes during Neck Pressure and Suction in Seated and Supine Positions. *J Physiol*, 540.2: 707-716, 2002.
11. Tuncel, M., Z. Wang, D. Arbique, **P.J. Fadel,** R.G. Victor, and W. Vongpatanasin. Mechanism of the Blood Pressure-Raising Effect of Cocaine in Humans. *Circulation*, 105: 1054-1059, 2002.
12. Fadel, P.J., D.W. Wray, M. Stromstad, S.A. Smith, P.B. Raven, and N.H. Secher. New insights into differential baroreflex control of heart rate in humans. *AJP (Heart Circ Physiol),* 284: H735-H743, 2003.
13. Fadel, P.J., W. Zhao, and G.D. Thomas. Impaired Vasomodulation is Associated with Reduced Neuronal Nitric Oxide Synthase in Skeletal Muscle of Ovariectomized Rats. *J Physiol*, 549: 243-253, 2003.
14. Fadel, P.J., Z. Wang, M. Tuncel, H. Watanabe, A. Abbas, D. Arbique, W. Vongpatanasin, R.W. Haley, R.G. Victor, G.D. Thomas. Reflex Sympathetic Activation during Static Exercise is Severely Impaired in Patients with Myophosphorylase Deficiency. *J Physiol*, 548: 983-993, 2003.
15. Fadel, P.J., S. Ogoh, D.M. Keller, and P.B. Raven. Recent Insights into Carotid Baroreflex Function in Humans Using the Variable Pressure Neck Chamber. *Exp Physiol*, 88.6: 671-680, 2003.
16. Fadel, P.J. Muscle Metaboreflex-Induced Increases in Stroke Volume: Commentary. *Med Sci Sports Exerc*, 35 (2): 229, 2003.
17. Keller, D.M., W.L. Wasmund, D.W. Wray, S. Ogoh, **P.J. Fadel,** M.L. Smith, and P.B. Raven. Carotid Baroreflex Control of Leg Vascular Conductance at Rest & during Exercise. *J Appl Physiol*, 94: 542-548, 2003.
18. Muenter Swift, N., M.J. Cutler, **P.J. Fadel,** W.L. Wasmund, S. Ogoh, D.M. Keller, P.B. Raven, M.L. Smith. Carotid baroreflex function during and following voluntary apnea in humans. *AJP (Heart Circ Physiol)*, 285: H2411-H2419, 2003.
19. Ogoh, S., **P.J. Fadel,** P. Nissen, O. Jans, C. Selmer, N.H. Secher, and P.B. Raven. Baroreflex-Mediated Changes in Cardiac Output and Vascular Conductance in Response to Alterations in Carotid Sinus Pressure during Exercise in Humans. *J Physiol*, 550.1: 317-324, 2003.
20. Smith, S.A., R.G. Querry, **P.J. Fadel,** K.M. Gallagher, M. Stromstad, K. Ide, P.B. Raven, and N.H. Secher. Partial Blockade of Skeletal Muscle Somatosensory Afferents Attenuates Baroreflex Resetting during Exercise in Humans. *J Physiol*, 551: 1013-1021, 2003.

21. Ogoh, S., **P.J. Fadel,** J.M. Hardisty, W.L. Wasmund, D.M. Keller, P.B. Raven, and M.L. Smith. Does Pulsatile and Sustained Neck Pressure or Neck Suction Produce Differential Cardiovascular and Sympathetic Responses in Humans? *Exp Physiol*, 88.5: 595-601, 2003.
22. Barman, S.M., **P.J. Fadel,** W. Vongpatanasin, R.G. Victor, G.L. Gebber. Basis for the Cardiac-Related Rhythm in Muscle Sympathetic Nerve Activity of Humans. *AJP (Heart Circ Physiol),* 284: H584-H597, 2003.
23. Fadel, P.J., S.M. Barman, S.W. Phillips, and G.L. Gebber. Fractal Fluctuations in Human Respiration. *J Appl Physiol*, 97: 2056-2064, 2004.
24. Fadel, P.J., D.M. Keller, H. Watanabe, P.B. Raven and G.D. Thomas. Noninvasive assessment of sympathetic vasoconstriction in human and rodent skeletal muscle using near infrared spectroscopy and Doppler ultrasound. *J Appl Physiol*, 96: 1323-1330, 2004.
25. Fadel, P.J., H.S. Orer, S.M. Barman, W. Vongpatanasin, R.G. Victor, and G.L. Gebber. Fractal Properties of Human Muscle Sympathetic Nerve Activity. *AJP (Heart Circ Physiol),* 286: H1076-H1087, 2004.
26. Wray, D.W., **P.J. Fadel,** M.L. Smith, P.B. Raven, and M. Sander. Inhibition of alpha adrenergic vasoconstriction in exercising human thigh muscles. *J Physiol*, 555.2: 545-563, 2004.
27. Keller, D.M., **P.J. Fadel,** S. Ogoh, R.M. Brothers, M. Hawkins, A. Olivencia-Yurvati, and P.B. Raven. Carotid Baroreflex Control of Leg Vasculature in Exercising and Non-Exercising Skeletal Muscle in Humans. *J Physiol*, 561.1: 283-293, 2004.
28. Wray, D.W., **P.J. Fadel,** D.M. Keller, S. Ogoh, M. Sander, P.B. Raven, and M.L. Smith. Dynamic Carotid Baroreflex Control of the Peripheral Circulation during Exercise. *J Physiol*, 559.2: 673-682, 2004.
29. Abbas, A., **P.J. Fadel,** Z. Wang, D. Arbique, I. Jialal, and W. Vongpatanasin. Contrasting Effects of Oral vs. Transdermal Estrogen on Serum Amyloid A (SAA) and HDL-SAA in Postmenopausal women. *Arterioscler Thromb Vasc Biol*, 24: 1-4, 2004.
30. Fadel, P.J., Z. Wang, H. Watanabe, D. Arbique, W. Vongpatanasin, and G.D. Thomas. Augmented Sympathetic Vasoconstriction in Exercising Forearms of Postmenopausal Women is Reversed by Oestrogen Therapy. *J Physiol*, 561.3: 893-901, 2004.
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32. Gallagher, K., **P.J Fadel,** S.A. Smith, M. Stromstad, K. Ide, N.H. Secher, and P.B. Raven. The interaction of central command and the exercise pressor reflex in mediating baroreflex resetting during exercise in humans. *Exp Physiol*, 91(1):79-87, 2006.
33. Davis, S.L., **P.J. Fadel,** J. Cui, G.D. Thomas, and C.G. Crandall. Skin blood flow influences near infrared spectroscopy derived measures of tissue oxygenation during heat stress. *J Appl Physiol*, 100(1):221-4, 2006.
34. Williamson, J.W., **P.J. Fadel,** and J.H. Mitchell. New insights into central cardiovascular control during exercise in humans: A central command update. *Exp Physiol*, 91(1):51-8, 2006.
35. Raven, P.B., **P.J. Fadel,** and S. Ogoh. Arterial baroreflex resetting during exercise: A current perspective. *Exp Physiol*, 91(1):37-49, 2006.
36. Fisher, J.P, S. Ogoh, E.A. Dawson, **P.J. Fadel,** N.H. Secher, P.B. Raven and M.J. White. Cardiac and vasomotor components of the carotid baroreflex control of arterial blood pressure during isometric exercise in humans. Journal of Physiology, 572.3: 869-880, 2006.
37. Ogoh S, JP Fisher, **PJ Fadel,** and PB Raven. Increases in central blood volume modulate carotid baroreflex resetting during dynamic exercise in humans. Journal of Physiology, 581.1: 405-18, 2007.
38. Fisher JP, S Ogoh, A Ahmed, MR Aro, D Gute, **PJ Fadel.** Influence of age on cardiac baroreflex function during dynamic exercise in humans. *AJP: (Heart Circ Physiol)*, 293: H777-H783, 2007.
39. Fisher JP, S Ogoh, CN Young, DM Keller, and **PJ Fadel.** Exercise intensity influences cardiac baroreflex function at the onset of isometric exercise in humans. *J Appl Physiol*, 103(3): 941-7, 2007.
40. Ogoh S, JP Fisher, S Purkayastha, EA Dawson, **PJ Fadel,** MJ White, R Zhang, NH Secher, and PB Raven. Regulation of middle cerebral artery blood velocity during recovery from dynamic exercise in humans. *J Appl Physiol*, 102:713-21, 2007.
41. Menon DV, Z Wang, **PJ Fadel,** D Arbique, D Leonard, J Li, RG Victor, and W Vongpatanasin. Central Sympatholysis as a Novel Countermeasure for Cocaine-Induced Sympathetic Activation and Vasoconstriction in Humans. *J Am Coll Cardiol* 50 (7):626-33, 2007.
42. Ogoh S, JP Fisher, PB Raven, and **PJ Fadel.** Arterial baroreflex control of muscle sympathetic nerve activity in the transition from rest to steady-state dynamic exercise in humans. *AJP (Heart Circ Physiol)*, 293:H2202-H2209, 2007.

43. Fadel PJ. Dynamic arterial baroreflex function during high intensity exercise in humans: Insights into sympathetic control. *J Physiol*, 586.11: 2667-2668, 2008.
44. Young CN, JP Fisher, and **PJ Fadel.** The ups and downs of assessing baroreflex function. *J Physiol*, 586.5: 1209-1211, 2008.
45. Fisher JP, CN Young, and **PJ Fadel.** Effect of Muscle Metaboreflex Activation on Carotid-Cardiac Baroreflex Function in Humans. *AJP (Heart Circ Physiol)*, 294:H2296-H2304, 2008.
46. Fisher JP, S Ogoh, CN Young, PB Raven, and **PJ Fadel.** Regulation of Middle Cerebral Artery Blood Velocity during Dynamic Exercise in Humans: Influence of Aging. *J Appl Physiol*, 105(1):266-73, 2008.
47. Fadel PJ. Arterial Baroreflex Control of the Peripheral Vasculature in Humans: Rest & Exercise. Med Sci Sports Exerc, (in press), 2008.

Book Chapter

1. Fadel, P.J., S.A. Smith, and K.M. Gallagher. Neural Mechanisms Influencing Baroreflex Resetting during Exercise. Recent Res. Devel. Physiol, 2: 413-448, 2004.

Selected Abstracts (out of 53)

1. Fadel, P.J., S Wasmund, P. McDonough, M. Smith, P.B. Raven. Sympathetic nerve activity and ventilation exhibit similar activation patterns during graded arm cycling. Faseb J., Abstract #474.3, 20(4): A767, 2006.
2. Fisher, J.P., C. Junor, A. Ahmed, K.M. Gallagher, **P.J. Fadel.** The influence of statin therapy on resting sympathetic nerve activity in patients with heart failure. Faseb J., Abstract #910.9, 21(6): A1268, 2007.
3. Young, C.N., J.P. Fisher, S. Ogoh, **P.J. Fadel.** Influence of exercise intensity on carotid-cardiac responses at the onset of static exercise in humans. Faseb J., Abstract #614.25, 21(5): A574, 2007.
4. Nelson, J., J.P. Fisher, **P.J. Fadel**. Cardiac baroreflex function at rest and during exercise: Influence of age. Faseb J., Abstract #614. 30, 21(5): A575, 2007.
5. Young, C.N., J.P. Fisher, K.M. Gallagher, **P.J. Fadel.** Pharmacological inhibition of nitric oxide synthase increases sympathetic nerve activity in healthy humans. Faseb J., Abstract # 740.13, 2008.
6. Fisher, J.P., C.N. Young, A.A. Alter, J.W. LeMaster, **P.J. Fadel.** Glycemic control and muscle metaboreflex-induced pressor responses in type 2 diabetes patients. Faseb J., Abstract # 740.12, 2008.

C. Research Support

Current Research Support

"Sympathetic Overactivity & Hypertension in ESRD: A role for ADMA"
Principal Investigator: Paul J. Fadel — NIH/NIDDK
Period: 7/01/07-6/30/09 — R21 DK076636-02
This project tests the hypothesis that an elevation in the endogenous nitric oxide synthase inhibitor, ADMA, is a primary contributor to the sympathetic overactivity and hypertension in patients with end stage renal disease.

"Aging, Sex, and Neural Cardiovascular Control during Dynamic Exercise"
Principal Investigator: Paul J. Fadel — NIH/NHLBI
Period: 08/01/08-07/30/13 — R01 HL-093167-01
The aims of this project are to test the hypotheses that: 1) aging-induced impairments in arterial baroreflex function contribute to an exaggerated increase in BP during dynamic exercise via unrestrained sympathoexcitation and 2) in women, postmenopausal decreases in endogenous estrogen further impair baroreflex function and potentiate the sympathetic and pressor responses to dynamic exercise with age.

Pending Research Support

"Sympathetic Control in Heart Failure: A Role of Statins"
Principal Investigator: Irving Zucker — NIH/NHLBI
Co-Investigator: Paul J. Fadel
Period: 4/01/09-3/30/13 — R01
The aims of this project are to test the global hypothesis that statins reduce sympathetic outflow in CHF by acting centrally on cellular Angiotensin II, nitric oxide and reactive oxygen species using human and animal experimental paradigms.

Shih-Chun Wang Young Investigator Award **Paul J. Fadel**

Description of Current and Future Research Program

My research program focuses on the investigation of neural cardiovascular control in health and disease with a specific emphasis on the sympathetic branch of the autonomic nervous system. Ongoing studies involve assessing sympathetic responses during various physiological manipulations including handgrip exercise, lower body negative pressure, and infusions of vasoactive substances in normal healthy subjects, patients with heart failure and end stage renal disease, as well as normotensive and hypertensive postmenopausal women. An invaluable methodological tool for my research is the technique of microneurography, whereby sympathetic neurograms are obtained from the placement of a tungsten microelectrode into the subject's peroneal nerve near the fibular head. By obtaining such a direct and continuous measure of sympathetic neural firing, one can assess moment-to-moment as well as long term changes in sympathetic nerve activity both in healthy subjects and disease populations. Also, with the application of partial autospectral and time series analyses to muscle sympathetic neurograms I am beginning to investigate the central origin(s) and pattern(s) of sympathetic discharge in humans. A primary research focus is examining the overactivity of the sympathetic nervous system present in patients with diseases characterized by excessive sympathetic activation such as end stage renal disease (ESRD) and heart failure. Although sympathetic overactivity has become a hallmark characteristic of these disease states, the underlying mechanisms remain poorly understood.

I have an R21 from the National Institutes of Health to examine the potential underlying mechanism(s) for the high prevalence of hypertension in patients with ESRD. Hypertension is present in up to 80% of patients with ESRD and is a major risk factor for the excessive cardiovascular morbidity and mortality among these patients. An additional risk factor present in ESRD is overactivity of the sympathetic nervous system, which may not only contribute to the hypertension but could also accelerate the progression of heart disease independent of the rise in blood pressure (BP). Thus, I believe the sympathetic nervous system constitutes a putative new drug target for arresting the progression of hypertensive heart disease in ESRD. However, to develop effective countermeasures, it is important to first identify the signal driving the sympathetic overactivity. I suggest that a potential signal involves the accumulation of the endogenous nitric oxide synthase (NOS) inhibitor asymmetric dimethylarginine (ADMA). Increasing functional evidence indicates that nitric oxide (NO) is not only an endothelium-dependent vasodilator but also a key signaling molecule involved in the tonic restraint of central sympathetic outflow. Since ADMA is in part cleared by the kidney, abnormally high levels accumulate in patients with ESRD. Thus, my central hypothesis is that accumulation of ADMA constitutes a major mechanism for the sympathetic overactivity and hypertension in patients with ESRD. To test this hypothesis, we have two aims. First, we are directly measuring muscle and skin sympathetic nerve activity (SNA) in healthy subjects with normal renal function to determine if experimental NOS inhibition increases SNA. Second, we are measuring muscle and skin SNA in ESRD patients to determine if NO deficiency produced by increases in the endogenous NOS inhibitor ADMA is a major mechanism mediating the sympathetic overactivity and hypertension in ESRD. Specifically, we are determining if restoration of NO production with the infusion of L-arginine reduces SNA and BP. These studies will provide novel information about the sympathoinhibitory role of centrally produced NO in humans and provide a conceptual

framework for clinical research to determine if the NO pathway constitutes an effective therapeutic target for the sympathetic overactivity and hypertension in patients with ESRD as well as other forms of disease with elevated plasma ADMA concentrations. Although elevated plasma ADMA has been shown to be a strong and independent predictor of overall mortality and cardiovascular outcome in ESRD patients, the cardiovascular effects of this systemic increase in ADMA remain unclear. Identifying a role for ADMA-induced NOS inhibition in increasing sympathetic outflow has major therapeutic implications to help reduce the extremely high prevalence of hypertension and cardiovascular morbidity in patients with ESRD.

Another current research project involves the examination of a potential role of statin therapy in reducing sympathetic overactivity in heart failure (HF) patients. An overactive sympathetic nervous system has become a hallmark characteristic of HF. Although initially beneficial to maintain cardiac output and blood pressure, prolonged sympathetic overactivity becomes deleterious contributing to the worsening of HF and sudden cardiac death. Despite aggressive medical management, including conventional anti-adrenergic strategies, sympathetic nerve activity (SNA) has been shown to remain abnormally high in HF patients and improvements in survival have been limited. Thus, it is clear that other treatment strategies that include reducing SNA and its deleterious consequences are warranted. Recent findings from studies in pacing-induced HF rabbits have indicated that treatment with 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) reduces the excessive sympathetic activation in the HF state. Interestingly, this effect of statins appears to be specific to HF as statin therapy had no effect on SNA in normal control rabbits. Thus, our current work is determining whether these findings in experimental HF can be translated to the clinical setting of human HF. Our central hypothesis is that statins reduce sympathetic overactivity in HF patients. To test this hypothesis we are directly measuring muscle SNA before and after one month of statin therapy in a placebo controlled crossover designed study. In addition, to begin to elucidate the mechanism(s) involved in the statin-induced reductions in SNA we are assessing baroreflex-dependent and baroreflex-independent (i.e., central) components of SNA. The preliminary studies for this work have been funded by a Research Board Grant from the University of Missouri and the findings are part of a collaborative R01 grant submission with Dr. Irving Zucker from the University of Nebraska.

Besides my interests in neural control mechanisms at rest, I am also interested in understanding neural cardiovascular control during exercise. I recently received an R01 from the National Institutes of Health to examine age-related alterations in the neural mechanisms that contribute to exercise-induced sympathoexcitation as well as the peripheral modulators of sympathetically-mediated vasoconstriction in contracting skeletal muscle. Previous studies have demonstrated that older subjects, particularly estrogen deficient postmenopausal women, have more pronounced increases in blood pressure (BP) during dynamic exercise. This exaggerated rise in BP during exercise is potentially dangerous because it can increase the occurrence of stroke and adverse cardiac events such as acute myocardial infarction, arrhythmia or cardiac arrest elevating the risk of performing physical activity as well as daily chores. Our work is focused on identifying the mechanism(s) driving the excessive rise in BP during physical exertion in the elderly. Given the importance of the arterial baroreflex (ABR) to neural cardiovascular control and responsiveness during exercise, we hypothesize that a potential mechanism is impaired ABR function. Because postmenopausal women demonstrate the greatest elevation in BP during dynamic exercise and therefore, are at the highest risk, we are performing studies to examine sex and ovarian hormone related differences. We are testing 3 related aims.

Aim 1 is designed to determine whether an impaired ability of the ABR to buffer exercise-induced sympathoexcitation contributes to the greater BP response to dynamic exercise in older men and women. Furthermore, since augmented sympathetically-mediated vasoconstriction would not only cause an elevation in BP but may also limit blood flow to active muscle, aim 2 is designed to examine whether exaggerated sympathetic vascular transduction contributes to a lower exercising muscle blood flow in older subjects during dynamic exercise. Finally, because decreases in ovarian hormones following menopause may alter neural cardiovascular and hemodynamic responses to exercise, aim 3 is considering how endogenous estrogen and progesterone concentrations alter ABR function and sympathetic control of the circulation during dynamic exercise in older and younger women. This important aspect of aging in women has been understudied in human studies of age-related alterations in cardiovascular responsiveness during exercise. The findings from the proposed work may lead to the development of novel therapeutic interventions targeted at improving cardiovascular and hemodynamic responses during physical activity in the elderly. Indeed, if as preliminary data suggest, impairments in the ABR are identified as the underlying mechanism for the exaggerated pressor response to dynamic exercise in older subjects we will then be able to pursue interventions that could improve baroreflex function and potentially offset the deleterious neural cardiovascular responsiveness that manifests with aging. In addition, identifying how alterations in ovarian hormones influence neural cardiovascular control and responsiveness has important clinical therapeutic implications for women's health and the selection and usage of hormone replacement.

Aside from these projects, I am also conducting preliminary studies to examine the potential influence of obesity and diabetes on neural cardiovascular control at rest and during exercise. The number of obese individuals and diabetic patients is on the rise and although previous studies have identified altered cardiovascular responses during exercise in these patient groups, the underlying mechanisms remain unclear. Identifying the potential mechanisms involved will be a primary emphasis of future studies. The initial findings from the studies in diabetic patients are being submitted to the upcoming Experimental Biology meeting. Another future research goal is to further develop collaborations that will foster the design and performance of studies to help extend findings from animal studies to humans and at the same time use animal models to address questions that cannot be answered with the human studies. In addition, I would also like to begin more translational studies taking advantage of known genetic polymorphisms. For example, we can identify individuals with particular genetic polymorphisms and then bring them into the laboratory to examine their responses to particular physiological manipulations to determine the actual functional consequences of the polymorphism. Considering the continually increasing number of research studies identifying gene-expression profiles, these types of studies should prove to be both scientifically and clinically relevant.

Arterial baroreflex control of heart rate and sympathetic nerve activity in patients with type II diabetes

Colin N. Young[1], Shekhar H. Deo[1], James P. Fisher[5], Joseph W. LeMaster[2], Abdullah Hanna-Moussa[3], Uzma Z. Khan[3] & Paul J. Fadel[1, 4]

[1]Department of Medical Pharmacology & Physiology, [2]Department of Family and Community Medicine, [3]Department of Internal Medicine, [4]Dalton Cardiovascular Research Center, University of Missouri, Columbia, MO; School of Sport and Exercise Sciences, [5]University of Birmingham, Birmingham, UK.

Previous studies have indicated that diabetes is associated with postural hypotension and greater arterial blood pressure (BP) reactivity to acute cardiovascular stressors. However, whether impairments in arterial baroreflex (ABR) function contribute to alterations in BP control in diabetes remains unclear. To begin to address this question, muscle sympathetic nerve activity (MSNA), heart rate, and BP were continuously recorded in 8 type II diabetic patients and 4 healthy age-matched control subjects during intravenous bolus injections of sodium nitroprusside followed 60s later by phenylephrine hydrochloride. The sensitivity (i.e., gain) of ABR-cardiac and ABR-MSNA control were identified from the linear relationships between RR-interval and systolic BP and total MSNA and diastolic BP, respectively. ABR-cardiac gain tended to be lower in diabetic patients compared to healthy controls [4.95±0.67 diabetics (n=8) vs. 9.25±3.90 controls, ms/mmHg; P=0.18]. In contrast, the ABR-MSNA gain was similar between the two groups [-8.32±3.03 diabetics (n=5) vs. -9.67±1.40 controls, units/beat/mmHg; P=0.72]. These preliminary data suggest that type II diabetic patients exhibit differential alterations in ABR function demonstrating ~46% reductions in ABR-cardiac control, whereas ABR-MSNA control appears to be better preserved (~14% reduction vs. controls).

The influence of age on carotid baroreflex mediated vasoconstriction in humans

James P. Fisher[1], Colin N. Young[2], Lauro C. Vianna[1], Areum Kim[2], Shehkar Deo[2] & Paul J. Fadel[2]

[1]School of Sport and Exercise Sciences, University of Birmingham, Birmingham, UK
[2]Department of Medical Pharmacology & Physiology, Dalton Cardiovascular Research Center, University of Missouri, Columbia, MO

The carotid baroreflex (CBR) plays a critical role in the beat-to-beat regulation of arterial blood pressure (BP) primarily via reflex modulation of sympathetic nerve activity and vascular conductance. Decreased sensitivity of peripheral alpha-adrenergic receptors has been reported in healthy older subjects however, it is unclear whether this may influence the CBR regulation of BP. To begin to address this question, mean BP, leg vascular conductance (LVC) and heart rate (HR) responses to simulated CBR hypotension were characterized in five young (22±2yr) and six older middle-aged (63±2yr) healthy subjects using 5s pulses of neck pressure (NP, +40 Torr). Mean BP responses to NP tended to be reduced in older (Δ +4±2 mmHg) compared to younger subjects (Δ +9±3 mmHg), although this apparent difference did not reach statistical significance (P=0.209). Interestingly, the LVC responses to hypotension were similar in both groups (-25±5% vs. -23±8%, older vs. younger, respectively; P=0.900). In contrast, HR responses were significantly attenuated in the older (Δ +2±1 bpm) compared with the younger group (Δ +10±3 bpm, P=0.039). In summary, these preliminary data suggest that the ability of the CBR to regulate BP in response to a hypotensive challenge appears to be attenuated in older individuals; however, alterations in sympathetically-mediated leg vasoconstriction do not appear to contribute.

Differential carotid baroreflex control of arterial blood pressure in young women and men at rest and during dynamic exercise

Areum Kim[1], Colin N. Young[1], Shekhar H. Deo[1], James P. Fisher[3], & Paul J. Fadel[1,2]

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Arterial baroreceptors play a pivotal role in the rapid reflex adjustments that accompany acute cardiovascular stressors. Previous studies have demonstrated that the arterial blood pressure (BP) response of young women to cardiovascular stressors, such as exercise, was reduced compared to men. However, whether alterations in arterial baroreflex function may contribute to sex differences in BP control remains unclear. To address this, five second pulses of neck suction (NS, -60 Torr) and neck pressure (NP, +40 Torr) were applied to selectively load and unload the carotid baroreflex (CBR), respectively at rest and during steady-state cycling at 50% heart rate reserve in nine young women (22±1 yr) and nine men (22±1 yr). At rest, mean BP responses to NS were significantly greater in women (Δ-16±1 women vs. Δ-11±2 men mmHg; P=0.03), whereas responses to NP were similar between groups. Interestingly, exercise eliminated the group differences in mean BP responses to NS (Δ-11±2 women vs. Δ-11±2 men mmHg; P=0.98) however; responses to NP were significantly greater in women during exercise. These preliminary findings suggest that sex differences in CBR control of BP exist at rest and during exercise. In comparison to men, young women appear to be better able to defend against hypertensive challenges at rest, whereas during exercise women exhibit augmented CBR-mediated BP responses to hypotension.

Shih-Chun Wang Young Investigator Award **Paul J. Fadel**

Current Research Support

"Aging, Sex, and Neural Cardiovascular Control during Dynamic Exercise"
Principal Investigator: Paul J. Fadel NIH/NHLBI
Period: 08/01/08-07/30/13 R01 HL-093167-01
The aims of this project are to test the hypotheses that: 1) aging-induced impairments in arterial baroreflex function contribute to an exaggerated increase in BP during dynamic exercise via unrestrained sympathoexcitation and 2) in women, postmenopausal decreases in endogenous estrogen further impair baroreflex function and potentiate the sympathetic and pressor responses to dynamic exercise with age.

"Sympathetic Overactivity & Hypertension in ESRD: A role for ADMA"
Principal Investigator: Paul J. Fadel NIH/NIDDK
Period: 7/01/07-6/30/09 R21 DK076636-02
The aim of this project is to test the hypothesis that an elevation in the endogenous nitric oxide synthase inhibitor, asymmetric dimethylarginine, is a primary contributor to the sympathetic overactivity and hypertension in patients with end stage renal disease.

"Sympathetic overactivity and hypertension in chronic kidney disease: A novel therapeutic target"
Principal Investigator: Colin Young University of Missouri Institute for Clinical & Translational Studies
Sponsor: Paul J. Fadel
Period: 08/01/08-7/30/09 Predoctoral Category
This is a University of Missouri Predoctoral award providing funding for a project proposed by Colin Young a doctoral student in my laboratory.

"Exercising Blood Pressure & Diabetes: Underlying Mechanisms"
Principal Investigator: Colin Young American College of Sports Medicine
Sponsor: Paul J. Fadel
Period: 08/01/07-12/30/08 Predoctoral Fellowship
This is an American College of Sports Medicine Predoctoral Fellowship providing initial funding for a project proposed by Colin Young a doctoral student in my laboratory.

Pending Research Support

"Sympathetic Control in Heart Failure: A Role of Statins"
Principal Investigator: Irving Zucker NIH/NHLBI
Co-Investigator: Paul J. Fadel
Period: 4/01/09-3/30/13 R01
The aims of this project are to test the global hypothesis that statins reduce sympathetic outflow in heart failure by acting centrally on cellular Angiotensin II, nitric oxide and reactive oxygen species using human and animal experimental paradigms.