HIGHLIGHTED TOPIC | Mechanisms of Sympathetic Regulation in Cardiovascular Disease

Be sympathetic to your nervous system

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THE INFLUENCE OF THE SYMPATHETIC nervous system in the regulation of cardiovascular function has been recognized since antiquity. Early reports of the so-called “vegetative nervous system” were based largely on anatomical observations (1). It is now well accepted that alterations in sympathetic and vagal outflow far beyond the norm can both initiate disease and contribute to the progress and severity of many disorders. The complexity of the autonomic nervous system grows with each study that focuses on the central and peripheral interactions between neurons, glia, and other components of this system. Many of the major anatomical pathways have been mapped. For instance, the major arterial baroreflex pathway is fairly well understood. Nonetheless, investigators now have concentrated on the regulation of neuronal discharge and the molecular mechanisms that are operative under normal conditions and in adverse states such as hypertension, heart failure, diabetes, and psychological stress. It is generally believed that chronic excessive sympathoexcitation at rest is detrimental to cardiovascular function, whereas increasing vagal outflow may be protective. If this is true, modulation of the autonomic nervous system has great potential for therapy in many disorders.

The reviews that appear in this Highlighted Topic originated from an American Physiological Society Conference on Autonomic Regulation of Cardiovascular Function in Health and Disease that took place in Omaha, Nebraska, in July 2012. Six reviews will be published, two in this issue and two each in the November and December issues, respectively. In the current issue, Gabor and Leenen (5) set the stage for a broad overview of neural regulation. They make the point that fast and slow issues, Gabor and Leenen (5) set the stage for a broad overview of neural regulation. They make the point that fast and slow signaling pathways subserve very different functions. Fast signaling events such as neuronal depolarization or hyperpolarization in response to neurotransmitter release are absolutely necessary for moment to moment control of blood pressure, blood flow, and other autonomic functions. On the other hand, slower responses that necessitate long-term alterations in membrane and intracellular proteins may contribute to cardiovascular disease. They use the example of the aldosterone-mineralocorticoid receptor (MR)-epithelial sodium channel (ENaC)-endogenous ouabain pathway as a potential contributor to the hypertensive process. In the spontaneous hypertensive rat and in the Dahl salt-sensitive rat, central aldosterone binding to the MR activates a transcriptional upregulation of ENaC, which in turn contributes to the production and release of endogenous ouabain, thus activating sympathoexcitatory areas in the hypothalamus. This process may be set in motion by either a sensing of high central sodium concentration or by increases in central ANG II. The end result of this process is an increase in sympathetic outflow and peripheral vasoconstriction leading to hypertension.

In the second review in this issue Prabhakhar et al. (8) focus on the contribution of the carotid chemoreflex in modulation of sympathetic function during intermittent hypoxia, a condition that simulates sleep apnea in humans and may importantly contribute to the development of cardiovascular disease. The data reviewed here provide a strong argument for the interplay of both molecular and neural signals during chronic intermittent hypoxia that modulate sympathoadrenal function. During chronic intermittent hypoxia, the balance between the hypoxia inducible factors, HIF-1α and HIF-2α, may determine the ratio of pro-oxidant and anti-oxidant enzymes, thus contributing at the level of the carotid body to the increased generation of reactive oxidant species (ROS). Increases in ROS together with other substances, such as endothelin-1, may contribute to an increase in carotid body chemoreceptor sensitivity and a decrease in carotid baroreflex sensitivity. This combination of effects leads to sympathoexcitation. In addition, increases in systemic ROS may lead to catecholamine release from the adrenal medulla.

Because of the current interest on neural modulation as a therapy for hypertension (7, 9), the review by Lohmeier and Iliescu (6) in the November issue of the Journal of Applied Physiology is particularly relevant. Carotid sinus nerve stimulation as a therapy for angina and for hypertension has been known for many years (3, 10). New technology and the realization that chronic baroreflex activation does not result in attenuation of the reflex over time has resurrected this idea. Lohmeier and Iliescu provide compelling data that chronic electrical stimulation of the carotid sinus adventitia in dogs results in a chronic reduction in arterial pressure, heart rate, and catecholamine release. Plasma renin activity does not increase despite the decrease in arterial pressure. These authors further point out that adjustment in renal sodium excretion is a contributing factor to the ability of baroreflex activation to lower blood pressure in hypertensive models subjected to long-term baroreceptor activation.

In humans, orthostatic intolerance (OI) is a malady that impacts quality of life and can result in fainting. Julian Stewart (12), in the November issue, reviews both the phenomenon and the potential neural and non-neural mechanisms that contribute to OI. He points out that the initial response to assumption of the upright posture from the recumbent position is a rapid cardiovascular adjustment coordinating changes in heart rate
and vascular tone. The maintenance of normal blood pressure and blood volume in the upright position is mediated by a combination of neural and physical factors. When these mechanisms are ineffective, OI, postural orthostatic tachycardia syndrome (POTS), and vasovagal syncope may result. Normal sympathetic vasoconstriction may be ineffective to make the appropriate adjustments in peripheral resistance and thus maladapted blood volume redistribution. At the molecular level, abnormalities in norepinephrine synthesis and transport may be important components contributing to OI. The Stewart review further discusses the relationships between respiratory and chemoreflex input on the genesis of OI.

Two important reviews will be published in the December issue. In the first, Samuel and Julie Chan (4) discuss molecular substrates that may contribute to the pathogenesis of hypertension by modulating sympathetic pathways at the level of the rostral ventrolateral medulla (RVLM) and nucleus tractus solitarii (NTS). The Chans provide evidence for the hypothesis that superoxide is mediated by an ANG II directed activation of NAPDH oxidase in the brain stem. This, in turn, leads to an inhibition of mitochondrial electron transport, resulting in additional superoxide. They point to the balance between superoxide and nitric oxide formation as a final arbiter of central sympathetic outflow.

The final review in this series by Diz et al. (2) focuses on important aspects of the central renin-ANG II system (RAS). By using transgenic rat models in which the glial renin-angiotensin system is disrupted by chronic expression of an antisense oligonucleotide to angiotensinogen, these investigators show that these animals exhibit blunted responses to activation of the central RAS. In addition to having lower sympathetic tone, these animals appear to have augmented parasympathetic tone. They provide evidence for a glia angiotensin-mediated activation of AT1 receptors, resulting in enhanced cardiovascular responses to stress. The interaction between central angiotensin peptides, particularly in response to psychosocial stress, is further discussed.

All inclusive, the review articles in this Highlighted Topic illustrate the importance of alterations in autonomic function on cardiovascular disease. Hans Selye (11) espoused the importance of sympathoadrenal activation in the general adaptation syndrome (11). However, our ability to utilize our understanding of autonomic function to prevent or reduce the progression and severity of cardiovascular disease is in its infancy. Understanding basic central mechanisms and pathways is integral to the development of new therapies. These reviews succinctly summarize some of the most recent and novel ideas in this area and hopefully will stimulate others to investigate basic mechanisms of autonomic function in health and disease.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES