Journal of the American Society of Hypertension 10(5) (2016) 457–466

Review Article

Evidence for a critical role of the sympathetic nervous system in hypertension

Guido Grassi, MD[a,b,*] and Venkata S. Ram, MD[c,d]

[a]*Clinica Medica, Dipartimento di Medicina e Chirurgia, Universita' Milano-Bicocca, Milano, Italy;*
[b]*IRCCS Multimedica, Sesto San Giovanni Milano, Milano, Italy;*
[c]*Apollo Institute for Blood Pressure Clinics, Apollo Hospitals Hyderabad, Telangana, India; and*
[d]*Texas Blood Pressure Institute, University of Texas, Dallas, TX, USA*

Manuscript received February 2, 2016 and accepted February 25, 2016

Abstract

Autonomic cardiovascular control is impaired in hypertension, leading to a reduction in the parasympathetic tone and to an increase in the sympathetic influences to the heart and peripheral vessels. The sympathetic dysfunction depends on a variety of reflex and nonreflex mechanisms and participates at development and progression of the essential hypertensive state. This has been shown to be the case for borderline hypertension, for moderate and severe high blood pressure, and for resistant hypertension as well. In addition, the adrenergic overdrive participates at the pathophysiology of the complex cardiometabolic alterations, known as ''end-organ damage,'' detectable in the clinical course of hypertensive disease. In the present article, we will review the main features of the adrenergic abnormalities characterizing essential hypertension, the mechanisms potentially involved in this neural abnormality, and its consequences as well. We will also discuss the most recent information achieved in the field and the areas worthy of future investigations. J Am Soc Hypertens 2016;10(5):457–466.

Keywords: Cardiovascular risk; genetics; hypertension; sympathetic activity; target organ damage.

The sympathetic nervous system plays an important role in the pathogenesis of primary hypertension and in certain secondary forms of hypertension. Although hypertension is a disease of multifactorial etiology, the pathophysiological role of neuroadrenergic factors is well established, however. This has been confirmed by a relevant number of studies, which assessed adrenergic drive either indirectly, by measuring circulating blood levels of the adrenergic neurotransmitters epinephrine and norepinephrine or by evaluating via the power spectral approach vagal and sympathetic frequency components, or directly, by quantifying efferent postganglionic muscle sympathetic nerve traffic in peripheral nerves as well as regional norepinephrine release and reuptake by adrenergic nerves via the norepinephrine radiolabeled technique.[1,2] In recent years, such information has been expanded with collection of new data, allowing to confirm previous findings and in the meantime to generate new hypotheses.[1–3] The main purpose of the present article is to provide to the reader an update and critical overview of our knowledge on the behavior of the sympathetic cardiovascular function at normal and elevated blood pressure, focusing mainly on data collected in human studies and only briefly mentioning, for space-saving reasons, mechanisms, and therapeutic implications of the findings. The new concepts developed in the last few years and the areas of future research will be finally emphasized.

Conflict of interest: None.
Funding: None.

*Corresponding author: Guido Grassi, MD, Clinica Medica, Università Milano Bicocca, Ospedale San Gerardo dei Tintori, Via Pergolesi 33, 20052 Monza (Milano), Italy. Tel: +39-39-23336001; Fax: +39-39-2333357.
E-mail: guido.grassi@unimib.it

Sympathetic Influences in the Blood Pressure Regulation

Cardiac output and systemic vascular resistance are the major effector components of neural blood pressure regulation. The arteriolar tone is determined by the balance between vasoconstrictor and vasodilatory forces. The

1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2016.02.015

effects of the sympathetic nervous system on the vasomotor tone are conveyed by neurotransmitters (norepinephrine, epinephrine, and dopamine), and the sympathetic-blood pressure connection is expressed through adrenergic receptors and neurotransmitters.[4] Epinephrine is released from the adrenal medulla, whereas norepinephrine is released mainly from the nerve terminals where it is stored as subcellular granules.[4] In response to a stimulus, norepinephrine is released into the synaptic clefts where it exerts its vasoconstrictory effects (raising blood pressure).[4] Locally, norepinephrine is inactivated largely by reuptake by storage granules. The reminder of the neurotransmitter escapes into systemic circulation. Because only less than 20% of norepinephrine appears in the circulation, plasma levels are merely a rough indicator of sympathetic activity.[3]

Adrenergic and dopaminergic receptors are the main target sites through which neurotransmitters exert their vasomotor action. Various tissues differ in the density of α-, β-, and dopaminergic receptors. Activation of the α-receptors leads to vasoconstriction, whereas activation of the β-receptors increases cardiac output. The precise physiological activity of the dopaminergic receptors in blood pressure regulation is not completely understood. Animal models deficient of α_1-adrenergic receptors are resistant to vasopressor stimuli.[5] To some extent, cardiovascular hypertrophy is mediated by α_1-adrenergic receptors. In contrast to the α_1-adrenergic receptors, stimulation of α_2-adrenergic receptors leads to vasodilation. Both β_1- and β_2-adrenergic receptors have an influence on the heart rate and cardiac output, not so much on vascular resistance. Deficiency of β_1- and β_2-adrenergic receptors in animal models blunts the cardiac effects of adrenergic stimulation.[6,7] All the subtypes of dopamine receptors play a role in cardiovascular and renal function.[7] In addition to the incompletely understood cardiovascular actions, dopamine exerts important effects on hormonal signaling, renal sodium, and blood flow,[8,9] although the quantitative contribution of dopamine to blood pressure regulation remains poorly understood. Finally, a large body of evidence demonstrates that blood pressure and blood volume regulation closely depends on the interactions existing between the sympathetic nervous system, the renin-angiotensin system, and renal sodium excretion.[10,11] Indeed, in different animal models, electrical stimulation of renal sympathetic nerves increases renin release from juxtaglomerular cells not only via indirect mechanisms, that is, through changes in renal blood flow, but also directly through the stimulation of β-adrenergic receptors located in the juxtaglomerular cells.[10–12] A further evidence supporting the key role of the sympathetic nervous system in blood sodium homeostatic control is that renal sympathetic nerve stimulation exerts antinatriuretic effects by a direct action on tubular renal sodium reabsorption.[10]

Sympathetic Drive in the Short-Term and Long-Term Control of Blood Pressure

The earlier concept was that control of blood pressure by the central vasomotor center is restricted to short-term hemodynamic alterations.[13] However, it has now become clear that adrenergic drive is critical to long-term regulation of blood pressure.[14] Given the close relationships between neuroadrenergic drive and arterial baroreceptors (which provide a tonic restraint on sympathetic tone), it can be anticipated that also arterial baroreceptors play a critical role in long-term blood pressure control. It appears now well established that this is the case and that arterial baroreceptor contribute not only to short- but also long-term regulation of blood pressure levels.[15–17] The baroreceptors function and reset in time for the ''prevailing'' level of blood pressure. It is likely that the anteroventral region of the third ventricle (in hypothalamus) plays an important role in the long-term regulation of blood pressure, sympathetic activity, and fluid/volume homeostasis. This region of the brain is sensitive to circulating hormones, blood pressure, and fluid/volume changes. These pathways are synthesized and routed to the paraventricular nucleus of the hypothalamus which is the transmitter of excitatory and inhibitory signals for long-term blood pressure control.

Sympathetic Overdrive in the Development of Hypertension

Early stages of the hypertensive disease are characterized by the so-called hyperkinetic circulatory state, which is mediated both by increased adrenergic drive and reduced parasympathetic function.[1,3] Such reciprocal changes in autonomic cardiovascular modulation have been documented by several studies, whose results can be summarized as follows. In young borderline hypertensive subjects, intravenous administration of atropine (which blocks the effects of the parasympathetic neurotransmitter acetylcholine on muscarinic receptors) triggers an increase in heart rate and cardiac output of lesser magnitude than that documented in pure normotensive age-matched controls.[18] This alteration, which demonstrates the impairment in the vagal heart rate control occurring in hypertension, is not limited to the parasympathetic function, but affects sympathetic cardiovascular control as well. Manifold evidence supports this statement. In a meta-analysis of published studies, an indirect marker of sympathetic tone, such as plasma norepinephrine, has been shown to be significantly elevated in essential hypertensive patients as compared to age-matched normotensive subjects.[19] Furthermore, by using a technique based on the intravenous tracer infusion of small doses of radiolabeled norepinephrine, Australian investigators were able to show that the rate of norepinephrine spillover from the neuroeffector junctions is increased in young subjects with borderline