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Sympathetic Activation in the Pathogenesis of Hypertension and Progression of Organ Damage

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Abstract—Although animal models of hypertension have clearly shown that high blood pressure is associated with and is probably caused by an increase in sympathetic cardiovascular influences, a similar demonstration in humans has been more difficult to obtain for methodological reasons. There is now evidence, however, of increased sympathetic activity in essential hypertension. This article will review this evidence by examining data showing that plasma norepinephrine is increased in essential hypertension and that this is also the case for systemic and regional norepinephrine spillover, as well as for the sympathetic nerve firing rate in the skeletal muscle nerve district. Evidence will also be provided that sympathetic activation is a peculiar feature of essential hypertension, particularly in its early stages, with secondary forms of high blood pressure not usually characterized by an increased central sympathetic outflow. Humoral, metabolic, reflex, and central mechanisms are likely to be the factors responsible for the adrenergic activation characterizing hypertension, which may also promote the development and progression of the cardiac and vascular alterations that lead to hypertension-related morbidity and mortality, independent of blood pressure values. This represents the rationale for considering sympathetic deactivation one of the major goals of antihypertensive treatment. **(*Hypertension*. 1999;34[part 2]:724-728.)**

Key Words: nervous system, sympathetic ■ hypertension, essential ■ hypertension, secondary ■ pressoreceptors ■ hypertrophy ■ norepinephrine

Neural adrenergic factors have long been hypothesized to be important in the initiation and maintenance of high blood pressure (BP). For a long time, however, the evidence supporting this hypothesis was largely limited to the results of studies performed in different animal models of hypertension (HT), in which an enhanced sympathetic drive to the heart and peripheral circulation was shown either to trigger a persistent BP elevation or to maintain the BP elevation originally induced by nonadrenergic mechanisms.[1–4] This picture has changed in the past 20 years or so because a variety of techniques that allow indirect or direct quantification of adrenergic cardiovascular influences have all provided evidence of an activation of the sympathetic nervous system (SNS) in human HT as well. This article will review the evidence that sympathetic activity is increased in essential HT and that this increase may have a pathogenetic role. It will also discuss 2 other issues, ie, (1) the mechanisms that lead to sympathetic hyperactivity in essential HT and (2) the role exerted by this hyperactivity in the progression of the cardiovascular alterations that may complicate the hypertensive state.

Evidence for Sympathetic Activation

In the past 30 years, several techniques designed to quantify sympathetic cardiovascular influences in humans have shown them to be increased in essential HT. More than 25 years ago, for example, Julius and coworkers[5] showed that the elevated resting heart rate values of borderline-hypertensive subjects were reduced by the intravenous administration of a β-blocking drug (propranolol) to a more marked degree than the lower heart rate of normotensive controls, suggesting that in the early hypertensive stage, cardiac sympathetic drive is enhanced. They further showed that after the subsequent intravenous injection of a muscarinic receptor antagonist (atropine), the increase in heart rate was less in borderline-hypertensive than in normotensive individuals, supporting the concept that at the cardiac level, an enhanced sympathetic drive combines with a reduced parasympathetic one to make the abnormality of neural cardiac control of borderline hypertensives a composite one.

Further important information has then come from techniques that assay in a sensitive fashion plasma levels of the adrenergic neurotransmitter norepinephrine (NE), because of the demonstration that these levels are low during sleep, increase progressively from the supine to the upright position, and increase from mild to moderate and severe exercise, thereby correlating with behaviorally induced changes in neural sympathetic drive in the cardiovascular system as a whole.[6] Although a number of early comparisons between normotensive and hypertensive individuals led to negative

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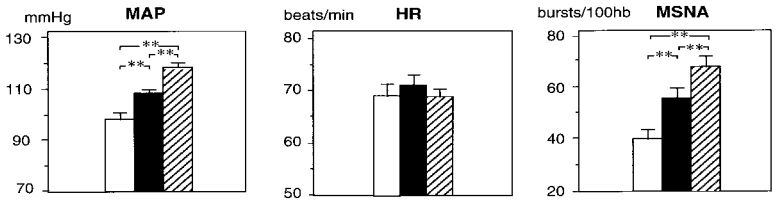

Figure 1. Values of mean arterial pressure (MAP), heart rate (HR), and muscle sympathetic nerve activity (MSNA) in normotensive subjects (n=15, open histograms), in moderate essential hypertensives (n=14, closed histograms), and in age-matched more severe essential hypertensives (n=14, dashed histograms). Data are shown as mean±SEM. $^{**}P<0.01$, statistically significant between groups. Modified from Reference 15, with permission.

results, a meta-analysis of all published data did show that essential-hypertensive patients displayed plasma NE values greater than those of normotensive individuals.[7] This finding has since been confirmed in several large-scale studies, including 1 from our group,[8] in which essential-hypertensive subjects were found to have an average plasma NE level significantly greater than that in normotensive individuals, although with a large overlap between the 2 groups.

Sophisticated biochemical and neurophysiological approaches, such as the NE radiolabeled technique[9] and the microneurographic recording of efferent postganglionic sympathetic nerve traffic from peroneal or brachial nerves,[10] have provided the evidence of sympathetic overactivity in human HT that is even more solid. The NE radiolabeled approach is based on intravenous infusion of small amounts of tritiated NE, which allows tissue clearance of this substance to be subtracted from plasma NE values and to make the remainder a marker of the neurotransmitter "spillover" from the neuroeffector junctions. This "spillover" (which, though not identical to it, mirrors in steady-state conditions the secretion of NE from the sympathetic nerve terminals) was shown to be greater in the general circulation of young hypertensive subjects compared with age-matched normotensive individuals.[9] It was also shown that in subjects with HT, NE spillover is greater even when separately determined in the brain, heart, and kidney, thereby pointing toward the existence of specific overactivity in the organs of key importance for cardiovascular modulation and performance.[9–11]

The results obtained by employing the microneurographic approach, which allows sympathetic nerve traffic to be recorded only in superficial nerves of the skin and/or muscle district,[10] can be summarized as follows. One, in normotensive subjects with a family history of HT, sympathetic nerve traffic may be increased.[12] Two, subjects with borderline HT display a number of sympathetic bursts over time (or corrected for heart rate values) that is greater than that found in normotensive controls.[3,13,14] Three, sympathetic nerve traffic increases progressively from the normotensive to the moderately and more severe essential-hypertensive state (Figure 1).[15] Four, an increased number of sympathetic bursts characterizes isolated systolic HT and pregnancy-induced HT.[16,17] The fifth point, confirming previous findings of an increase in urinary or plasma NE values,[18,19] is that the same phenomenon can be observed not only in obese hypertensive but also in obese normotensive subjects.[20,21] Thus, sympathetic overactivity can be detected in hypertensive patients with different degrees of BP elevation and of different ages. The very initial hypertensive stages are by no means an exception, which suggests that this phenomenon may have a role in both the maintenance and the initiation of this condition.

Two further issues deserve to be mentioned. First, secondary forms of HT are not necessarily characterized by an increased central sympathetic outflow. In primary aldosteronism,[22] adrenal pheochromocytoma, or renovascular HT,[15] for example, sympathetic nerve traffic has been found to be similar to that of age-matched normotensive controls. Furthermore, evidence has been provided that this traffic is increased after surgical removal of pheochromocytoma[23] or after successful renal angioplasty,[24] which may even imply that some secondary forms of HT are accompanied by an active central sympathoinhibition. This does not mean, however, that sympathetic cardiovascular influences are all invariably decreased. In renovascular HT, for example, an active central sympathoinhibition may coexist with a stimulation of NE secretion and an amplification of the adrenergic receptor responsiveness to the elevated levels of angiotensin II,[25] making the overall autonomic cardiovascular modulation more rather than less active. Second, the sympathetic overactivity characterizing essential HT may not be generalized to the whole cardiovascular system, as exemplified by the evidence that both in mild and more severe essential-hypertensive patients, the number of sympathetic bursts is increased in fibers innervating skeletal muscle tissue but not in fibers innervating the skin.[21] This heterogeneous behavior (which is also typical of obesity and heart failure[21]) may originate from the peculiarity of the mechanisms that govern skin vasomotor tone. This tone has been shown to exquisitely depend on autonomic modulation, in response, however, not from the baroreflex (as is muscle sympathetic tone[4,8]) but from thermoregulatory centers located in the hypothalamus.[26] It is possible that this modulation is more effectively preserved in disease because of the vital influence of temperature control for body homeostasis.

Mechanisms Responsible for Sympathetic Overactivity

The mechanisms responsible for the sympathetic activation occurring in essential HT have not been conclusively determined. Several possibilities can be discussed, however. One possibility is that activation of the SNS depends on the circulating angiotensin II concentrations, because angiotensin II has repeatedly been documented to exert excitatory effects on sympathetic outflow, to facilitate NE release from adrenergic nerve endings, and to amplify adrenergic receptor responsiveness to stimuli.[25] This may occur not only in individuals with high renin and angiotensin II levels (about one fourth of the hypertensive population) but also in low-renin patients, as the sympathetic enhancement of angiotensin II has been described in both normal and low-renin conditions, possibly because tissue production of this substance is

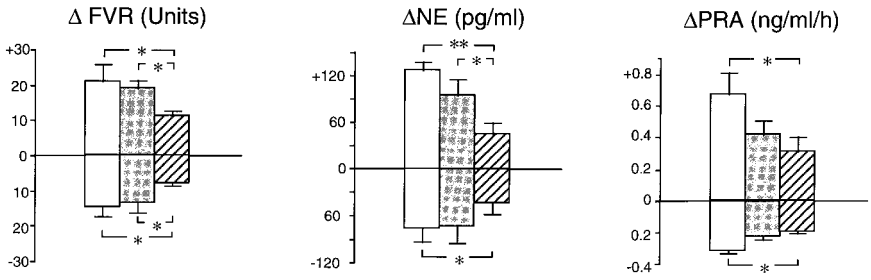

Figure 2. Changes in forearm vascular resistance (ΔFVR), plasma norepinephrine (ΔNE), and plasma renin activity (ΔPRA) induced by nonhypotensive lower-body negative pressure and passive leg raising in normotensive subjects (n=10, open histograms) and in essential-hypertensive patients without (n=10, closed histograms) and with (n=10, dashed histograms) echocardiographically detected left ventricular hypertrophy. Data are shown as mean±SEM. *$P<0.05$, **$P<0.01$ statistically significant between groups. Modified from Reference 36, with permission.

involved. Another possibility is that the cause of sympathetic hyperactivity in HT is insulin resistance because this frequent concomitant of a high-BP state leads to hyperinsulinemia, which is known to either increase sympathetic nerve traffic or to stimulate NE secretion from the sympathetic nerve endings, all effects being greater in subjects with HT.[27,28] It should be emphasized, however, that sympathetic activation has in turn been shown to cause insulin resistance,[29,30] so that it is still uncertain which of the 2 alterations precedes and determines the other. In a recent longitudinal study by Japanese investigators, an increase in plasma NE was seen years before the increase in plasma insulin levels also became manifest,[31] suggesting the derangement in glucose metabolism to follow rather than precede the sympathetic derangement.

Two additional possibilities also need to be briefly mentioned. The first 1 maintains that activation of the SNS has a central nature; ie, it depends on an excessive hypothalamic drive due to excessive environmental stimuli and/or an inherent subcortical hyperresponsiveness to an otherwise "normal" environment.[1,4] However, in essential-hypertensive subjects, heart rate, BP, and vascular responses to laboratory stressors have more often been shown to be normal than abnormal, both in the established and in the initial or even prehypertensive stage.[32] Furthermore, the studies that have tried to determine whether an initial hyperresponsiveness to stress more frequently leads to permanent HT (possibly through a period of an increased BP variability) have been in all instances retrospective and uncontrolled. Finally, it has been more and more widely seen that quantification of tissue responsiveness to stress is encumbered with methodological difficulties because (1) the hemodynamic responses to laboratory stressors have a limited reproducibility,[32] (2) an excessive pressor and tachycardic response to a given stress may not reflect an excessive response to all stressful stimuli,[33] and (3) cardiovascular reactivity to laboratory stressors bear only a limited relationship with BP variability as measured in daily life conditions.[33] Thus, although verified in animal models of HT and appealing to both investigators and patients, the possibility of a central and stress-related origin of essential HT must be regarded as unproven.

The second possibility maintains that the activation of the SNS accompanying HT is due to impairment of a reflex that restrains sympathetic tone to an important degree, ie, the arterial baroreflex.[34] This hypothesis has received support from animal and human studies that have shown that when BP is chronically elevated, the baroreceptor ability to modulate vagal tone undergoes early impairment,[34] which becomes progressively more evident as HT becomes more severe. However, carotid baroreceptor modulation of BP had in 1978 been shown to be similar in normotensive, mild hypertensive, and more severe essential-hypertensive subjects, who all showed similar depressor and pressor responses to carotid baroreceptor stimulation and deactivation obtained via a neck chamber device, ie, by increasing and reducing baroreceptor activity above and below the existing level of activity by increasing and reducing carotid transmural pressure.[35] Furthermore, recent data have clearly documented that when BP is progressively increased or reduced by stepwise intravenous infusions of nitroprusside or phenylephrine, the degree of reflex sympathoexcitation and inhibition is superimposable in normotensive, mild hypertensive, and more severe essential-hypertensive individuals, findings that are at variance with the concomitant reflex changes in heart rate, which have been shown to be markedly reduced in the latter 2 groups.[15]

This finding should not be interpreted, however, to imply that the adrenergic activation of HT has no relationship with reflex sympathetic modulation whatsoever. Essential HT is characterized by a resetting of the arterial baroreflex modulation of BP and sympathetic nerve traffic toward the elevated BP values (ie, by a displacement to the right from normotension to hypertension of the curve relating BP and sympathetic nerve traffic), a phenomenon that operates to maintain, rather than reduce, the BP increase.[15,34,35] In addition, the tonic inhibitory restraint exerted by cardiac volume receptors on sympathetic drive to skeletal muscle vessels, NE and renin release can be impaired in HT.[35] This was documented by our group in a study[36] in which rapid changes in forearm vascular resistance, plasma NE, and plasma renin activity to cardiac receptor stimulation (induced by an increase in central venous pressure due to passive leg raising) and deactivation (induced by a reduction in central venous pressure due to nonhypotensive lower-body negative pressure) were evaluated in normotensive and essential-hypertensive subjects without and with echocardiographic evidence of left ventricular hypertrophy. As shown in Figure 2, compared with normotensive controls, all responses were slightly reduced in hypertensive subjects without left ventricular hypertrophy but were markedly impaired in patients in whom the high-BP state was accompanied by an increased thickness of cardiac walls. It thus appears that reflex mechanisms may participate in the sympathetic activation of essential HT, although so far as the cardiogenic reflex is concerned, its role may be a later rather than an earlier one, with implications that thus deal more with

the maintenance than with the initiation of HT. In this context, it should be mentioned that the cardiogenic reflex participation in the later phases of HT may be nonspecifically related to cardiac hypertrophy rather than to HT "per se," because a similar impairment of reflex responses to cardiac receptor stimulation and deactivation has been observed in normotensive athletes with a marked "physiological" cardiac hypertrophy.[37]

Sympathetic Activation and Organ Damage

Studies performed both in animal models of HT and in essential human HT have shown that sympathetic factors are also involved in the progression of the cardiovascular structural alterations accompanying high BP.[1,4] For example, it has been shown that addition of adrenergic agonists to the perfusing medium stimulates the in vitro growth of myocytes as well as the replication of vascular smooth muscle cells, both phenomena being blocked by the simultaneous administration of adrenergic antagonists.[38,39] Furthermore, the progression and regression of left ventricular hypertrophy have been shown to depend not only on BP (and cardiac load) levels but also on the increase, in the former case, and the reduction, in the latter case, of cardiac sympathetic drive.[40,41] Finally, the arteriolar remodeling that characterizes HT and makes the elevation of total peripheral resistance partly dependent on structural factors, ie, an increased wall-to-lumen ratio, has been found to be much less marked in vessels subjected to sympathetic denervation than in normally innervated ones.[39,42] The mechanisms through which this is produced are likely to be multifold. Clearly, a direct influence of the SNS on the volume of myocytes, the replication of smooth muscle cells, and collagen synthesis are involved.[1–4,42–44] In facilitating the above-mentioned structural alterations, however, the SNS may also operate indirectly. That is, it may favor cardiac hypertrophy and vascular remodelling beyond an effect on BP, by increasing, for example, BP variability throughout the 24-hour cycle, given the evidence that BP variability depends on sympathetically mediated behavioral influences on the heart and peripheral circulation.[43] Additionally, it may increase cardiac and renal load by increasing blood viscosity.[44] This has long been shown to be a typical "sympathetic" effect, because under conditions of increased sympathetic drive, hematocrit is increased.[44]

Two final points deserve to be discussed. One, by promoting vascular smooth muscle cell replication, activation of the SNS can favor the atherogenic process because smooth muscle cell replication precedes their migration to the intima and transformation to macrophages, thereby representing a key element in the cascade of events leading to the established atherosclerotic plaque.[45] Two, we have shown in rats that carotid and femoral artery distensibility is increased by sympathectomy.[46] We have shown that this is also the case in humans in whom radial artery and femoral artery distensibilities were found to increase markedly after removal of adrenergic tone by anesthesia of the brachial plexus and the spinal cord, respectively.[47] This is presumably due to a sympathetically mediated contraction of vascular smooth muscle, because contracted muscle tissue is less prone to distension for intravascular pressure than is muscle tissue in a relaxed state.[39] Additionally, it may be due to the viscoelastic properties of the arterial wall that give its distensibility considerable inertia. This effect operates to stiffen the arteries even when heart rate increases, as occurs when the SNS is activated.[48]

Conclusions

The studies reviewed in this article provide evidence that the SNS is activated in essential HT and that this activation occurs early in the clinical course of this disease. The mechanisms responsible for sympathetic activation remain to be established, although stimulation by humoral factors and alterations in reflexes restraining sympathetic tone should be seriously considered. Finally, evidence is also available that adrenergic activation may be involved in the progression of the structural cardiovascular alterations characterizing HT, including atherosclerosis. These findings explain why sympathetic deactivation continues to represent one of the major goals of antihypertensive treatment.

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