Neurogenic Hypertension: Is the Enigma of Its Origin Near the Solution?

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Since the demonstration that the sympathetic nervous system exerts a fundamental role in the homeostatic control of blood pressure, the hypothesis has been advanced that abnormalities in the adrenergic regulation of either cardiac output or peripheral vascular resistance might represent the pathophysiological hallmarks of the essential hypertensive state of "neurogenic" nature. To date, the evidence supporting this hypothesis can be summarized as follows. First, the early stages of hypertension frequently display hyperkinetic circulation characterized by an increase in cardiac output coupled with an elevated heart rate (i.e., by hemodynamic abnormalities that have been shown to be triggered by a blunted parasympathetic and an enhanced sympathetic cardiovascular drive). Second, a meta-analysis of all published studies that have made use of plasma norepinephrine assay for evaluating adrenergic tone has provided evidence that, even accounting for some negative results, an indirect marker of the sympathetic function, such as plasma norepinephrine, is significantly elevated in essential hypertensive patients as compared with age-matched normotensive controls. Third, by using the technique based on the intravenous tracer infusion of small doses of radiolabeled norepinephrine, it has been possible to show that the rate of norepinephrine spillover from the sympathetic neuroeffector junctions is augmented in young subjects with borderline blood pressure elevation and that this enhanced release is particularly manifest in the kidney and in the heart (i.e., in two organs of key importance in the homeostatic process of blood pressure control). Fourth, hypertensive patients display at the $^{123}$I-metaiodobenzylguanidine cardiac imaging technique a lower uptake and a greater washout rate of the radiotracer when compared with normotensive subjects, thereby suggesting that adrenergic drive to the heart is enhanced when blood pressure levels are elevated long-term. Fifth, direct assessment of the efferent postganglionic sympathetic nerve traffic to the skeletal muscle vascular district has shown an increase in neuroadrenergic outflow in patients with essential hypertension, which (1) parallels for magnitude the severity of the high blood pressure state; (2) appears to be peculiar to the essential hypertensive condition, with no sympathetic overactivity being detectable in the secondary hypertensive states; (3) accompanies not only diastolic but also systolic blood pressure elevations, even when they occur in an "isolated" fashion like in the hypertensive state of the elderly; and (4) is potentiated when hypertension is combined with obesity, heart failure, or both the aforementioned conditions. Taken together, these findings therefore strongly support the notion that an increase in sympathetic cardiovascular drive participates at the development, maintenance, and progression of the hypertensive state and imply that sympathetic deactivation should represent a major goal of the antihypertensive pharmacologic treatment.

Despite years of investigation, the origin of the sympathetic activation characterizing the essential hypertensive state still remains largely unknown. This issue of Hypertension includes an article by Schlaich et al., in which a consistent fraction of the most credible hypotheses advanced throughout the years for explaining the hypertension-related neuroadrenergic hyperactivity has been thoughtfully tested by the authors. The study was founded on a number of technically demanding and unique methodological features, such as the concomitant use of microneurographic nerve traffic recording and radiotracer methodology, to directly quantify central neural outflow and regional norepinephrine kinetics, respectively, and the assessment of a variety of biochemical, neurobiological, and genetic variables, including norepinephrine metabolites, angiotensin II levels, and Gly478Ser mutation sequence.

Guided by the notion that arterial baroreceptors represent the major reflexogenic mechanism involved in the physiological modulation of sympathetic neural outflow, the authors have first tested the hypothesis that a reduction in the inhibitory influences exerted by carotid and aortic baroreceptors on adrenergic drive might represent the cause underlying the sympathetic overactivity. The results, however, have not allowed them to confirm the hypothesis, because no evidence of baroreflex dysfunction was detected. Although the method used to assess spontaneous baroreflex–sympathetic nerve traffic sensitivity was indirect (i.e., based on the computer-assisted plotting of diastolic blood pressure values versus sympathetic bursts), the data are virtually superimposable to those found by our group in a recent study. In our recent study, baroreflex function has been tested via a more direct and "classic" approach (i.e., the stepwise vasoactive drugs infusion technique). Indeed, when phenylephrine was infused to stimulate arterial baroreceptors, we found that the consequent sympathoinhibitory responses were similar for magnitude in essential hypertensives and in normotensive subjects, even when corrected for the greater baseline values. This was
also the case when the sympathoexcitatory responses triggered by the nitroprusside-induced arterial baroreceptor deactivation were taken into account. Because heart-rate responses (bradycardia and tachycardia, respectively) in both instances were less magnitude in hypertensive than in normotensive subjects, the conclusion was drawn that arterial baroreceptor control of the heart (which is predominantly vagal in nature) is impaired in hypertension and that no alteration occurs as far as the sympathetic component of the baroreflex is concerned. In contrast to the negative findings collected for the so-called reflex hypothesis of the sympathetic activation, Schlaich et al, by using the radiotracer methodology to assess the effects of hypertension on norepinephrine kinetics, have been able to identify a reduction in neuronal reuptake of the adrenergic neurotransmitter as cause of the increased norepinephrine spillover seen in the hypertensive population. These data, which point toward a peripheral origin of the hypertension-related adrenergic overactivity, differ from the findings reported by the same group of investigators in another condition also characterized by sympathetic activation, ie, the failing heart syndrome, in which norepinephrine release and reuptake have been shown to be markedly increased.12 This rules out the possibility that the reduced neuronal uptake of norepinephrine seen in the hypertensive state is a phenomenon specifically linked to an hyperadrenergic condition independently on its origin.

The results of the study by Schlaich et al11 provide two additional sets of data that should be interpreted with some caution. First, the authors have screened a subgroup of patients of the study population for the possible presence of a single nucleotide polymorphism related to the norepinephrine transporter gene without finding any hypertension-related genetic variation. As properly emphasized by the authors, the small sample size prevents a definitive conclusion to be drawn on this issue and calls for further larger-scale investigations. Second, the neurohumoral measurements performed in the study included the determination of arterial and coronary sinus plasma concentrations of angiotensin II, with the aim at determining whether the cardiac renin–angiotensin system contributes to the sympathoexcitative activity detected at myocardial level in the hypertensive state. The results in this case were also negative, showing no correlation between coronary angiotensin I or II levels and any indices of systemic or regional norepinephrine spillover. It should be stressed that these results cannot be taken as conclusive and indisputable evidence that no renin-angiotensin-sympathetic interaction does occur in normotensive or hypertensive subjects. It has been shown that in a variety of regional districts of the human cardiovascular system, such as the forearm and the coronary circulation, the local (ie, the tissue vascular) renin–angiotensin system can actively modulate regional sympathoexcitative neural outflow at normal and at high blood pressure values by facilitating norepinephrine release at presynaptic level and/or by potentiating the postsynaptic response to the adrenergic neurotransmitter.13,14 The interaction appears more easily detectable when the systems are activated. This finding may well explain the lack of any modulatory effect of the renin-angiotensin system on the adrenergic function reported by Schlaich et al in their study in which measurements were made in the control resting state but not during maneuvers known to activate the systems (ie, orthostatic stress, diuretics administration, low-salt diet, and so forth).11

Two final comments deserve to be made. First, the hypotheses tested by Schlaich et al in their study do not exclude other mechanistic possibilities. This is because it has been repeatedly shown that, at least in animal models of hypertension, an excessive hypothalamic drive may favor a “central” sympathoexcitation.10 It is also because a metabolic alteration frequently accompanying the high blood pressure state (ie, insulin resistance) has been shown to lead to hypersulinemia, which per se may increase sympathetic outflow and norepinephrine secretion by acting on the adrenergic nervous system both at central and peripheral levels.10,15 Second, the patients examined by Schlaich et al were middle-aged and displayed a stable blood pressure increase. This means that the sympathetic overactivity seen in the hypertensive state is not strictly confined to those with young age and/or borderline blood pressure elevation (as hypothesized some years ago), but rather it involves older patients displaying stable forms of hypertension as well.

References

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