The Sympathetic Neurobiology of Essential Hypertension: Disparate Influences of Obesity, Stress, and Noradrenaline Transporter Dysfunction?

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Although the importance of sympathetic nervous activation in the pathogenesis of essential hypertension is well documented, the exact pathophysiology of the sympathetic nervous dysfunction present remains to be delineated. This review details three relatively new findings of disturbed sympathetic neurobiology in hypertension.

Adrenaline cotransmission is present in the cardiac sympathetic nerves of patients with essential hypertension, as it is in patients with panic disorder, providing presumptive evidence of exposure to high levels of mental stress in hypertensive patients. In lean patients with hypertension there is also evidence of faulty noradrenaline reuptake into the sympathetic nerves of the heart, an abnormality amplifying the sympathetic neural signal by impairing removal of noradrenaline from the synaptic cleft. If both abnormalities are present in the sympathetic nerves of the kidneys also (which we did not test), there would most probably be a direct contribution to hypertension development. In the kidneys the causal chain between sympathetic overactivity and the development of hypertension is stronger than for the heart.

In obesity-related hypertension there is evidence that renal sympathetic tone is high, based on approximately a doubling of the measured rate of spillover of noradrenaline into the renal veins. This increase in sympathetic outflow to the kidneys appears to be a necessary but apparently not a sufficient cause for the development of clinical hypertension, commonly being present also in overweight people with blood pressure in the normotensive range. High renal sympathetic tone in the latter, of course, may well still contribute to elevation of their pressure level, although not on such a scale as to cause clinical hypertension.

Key Words: Heart, kidneys, panic disorder, high blood pressure, adrenaline.

Although sympathetic nervous activation in essential hypertension has been well documented, with analysis of regional sympathetic nervous system function demonstrating activation of the sympathetic nervous outflows to the heart, kidneys and skeletal, muscle vasculature, the exact pathophysiology of the sympathetic nervous dysfunction present remains to be delineated.

This report details relatively new findings of disturbed sympathetic neurobiology in human hypertension: specifically, activation of the renal sympathetic outflow that characterises obesity and obesity-related hypertension, evidence for adrenaline cotransmission in the sympathetic nerves of the heart in both lean and obese patients with essential hypertension, and phenotypic features of faulty neuronal reuptake of noradrenaline found in lean hypertensive individuals only.

Measurement of Sympathetic Nervous Function in Human Hypertension

Measurement of the excretion of the sympathetic nervous neurotransmitter, noradrenaline, in urine is now largely obsolete as a test of human sympathetic nervous activity; and assay of the plasma concentration of noradrenaline, still widely used, has two major limitations. The first is the dependence of plasma noradrenaline concentrations on rates of removal of the neurotransmitter from plasma, not...
just sympathetic tone and noradrenaline release. The second deficiency is that no information is provided on regional sympathetic nervous function; sympathetic nervous system responses typically show regional differentiation, which can be detected in clinical research only by techniques that assess organ-specific sympathetic function.

Methods for Assessing Regional Sympathetic Nervous System Function

Clinical measurements of rates of sympathetic nerve firing and of noradrenaline release to plasma provide the most secure basis for studying regional sympathetic nervous function in patients with hypertension.

Clinical Microneurography This technique provides a method for studying nerve firing rates in subcutaneous sympathetic nerves distributed to skin and skeletal muscle. The technique involves the insertion of fine tungsten electrodes through the skin, with positioning of the electrode tip usually in the sympathetic fibers of the common peroneal nerve. Multifiber recordings of “bursts” of nerve activity synchronous with the heartbeat and, more recently, single fiber traces are generated.

Noradrenaline Spillover Rate Measurements Neurotransmitter release can be studied clinically using radiotracer-derived measurements of the appearance rate of noradrenaline in plasma from individual organs.

\[ \text{NA spillover} = \left[ \left( \text{NA}_\text{ven} - \text{NA}_\text{art} \right) + \text{NA}_\text{art} \cdot E \right] \cdot \text{PF} \]

where NA represents noradrenaline, NA_ven and NA_art the arterial and regional venous plasma concentration of noradrenaline, E the fractional extraction of plasma tritiated noradrenaline in transit through the organ, and PF the regional plasma flow. Microneurographic methods do not give access to sympathetic nerves of internal organs, a limitation that is overcome by using regional noradrenaline spillover measurements. With infusion of tritiated noradrenaline and regional blood sampling from the coronary sinus and renal veins, neurotransmitter release from the heart and kidneys can be measured.

Sympathetic Neurobiology in Essential Hypertension

The available evidence does indicate that essential hypertension is commonly neurogenic, with documentation of high rates of spillover of noradrenaline from the heart and kidneys. The increased cardiac and renal spillover of noradrenaline is no doubt attributable, at least in part, to increased sympathetic nerve firing rates, although this cannot be measured directly. Clinical microneurographic measurements in hypertensive patients have documented activation of sympathetic efferents in another sympathetic outflow, ie, that to the skeletal muscle vasculature.

There are additional potential neural mechanisms, however, which could be contributing to high intrasynaptic concentrations of norepinephrine and increased noradrenaline spillover in essential hypertension as well as to the development and maintenance of neurogenic variants of hypertension (Fig. 1). That there might be an increase in the density of sympathetic innervation in human hypertension, such as that which is well documented in the spontaneously hypertensive rat, remains one such possibility. Facilitation of neuronal norepinephrine release by epinephrine released from sympathetic nerves as a cotransmitter and impairment of neuronal norepinephrine reuptake after its release from sympathetic nerves are others.

Phenotypic Evidence for Faulty Neuronal Noradrenaline Reuptake in Essential Hypertension

Previous reports do suggest that neuronal noradrenaline reuptake may be impaired in some patients with essential hypertension, perhaps because of dysfunction of the noradrenaline transporter, although the evidence is inconclusive. In these earlier studies, the half-time of the rapid disappearance phase of tritiated noradrenaline removal from plasma on termination of an intravenous infusion of the tracer, which is primarily dependent on neuronal noradrenaline uptake, was found to be prolonged in some patients with essential hypertension.

Recently we further tested the proposition that impairment of neuronal reuptake of noradrenaline might contribute to the development of essential hypertension, by applying more specific radiotracer methods and by focusing in particular on neuronal processing of tritiated noradrenaline by the heart (Fig. 2). As the disposition of noradrenaline after its release is more dependent on neuronal re-
uptake in the heart than in any other organ, incomplete grades of impairment of noradrenaline transporter function would be most likely to be phenotypically evident there. We were encouraged in this line of thinking by the recent description of a missense mutation of the noradrenaline transporter gene in a family kindred with the postural tachycardia syndrome, in which the exaggerated reflex increase in heart rate with standing (which is a cardinal feature of the disorder) was due to the noradrenaline transporter fault.

Spillover of noradrenaline from the heart, as calculated from equation 1, was increased in the lean hypertensive patients studied (33.4 ± 20.6 ng/min [mean ± SD] vs 16.1 ± 11.7 ng/min in lean normotensive subjects, \( P < .05 \)), but this could have resulted from high cardiac sympathetic nerve firing rates, faulty noradrenaline reuptake, or both. The fractional extraction of plasma tritiated noradrenaline in passage through the heart, determined by neuronal noradrenaline uptake, was reduced in hypertension, as was the overflow into the coronary sinus of the intraneuronal metabolite of noradrenaline, dihydroxyphenylglycol (DHPG). MAO = monoamine oxidase; \( ^*P < .05 \).

In obesity-related hypertension there was no phenotypic evidence of noradrenaline transporter dysfunction. Although faulty neuronal reuptake of noradrenaline has been proposed as a predisposing factor in the development of the hypertension in the obese, a genetic fault involving the noradrenaline transporter in obesity-related hypertension now appears to be excluded.

Recent population screening has led to the identification of 13 DNA sequence variants of the noradrenaline transporter gene, of which five were interpreted as missense substitutions. In a preliminary screening for these five missense substitutions in the noradrenaline transporter gene that we recently conducted in 40 hypertensive patients (not those patients reported here), none were present. The transporter gene mutation recently described in the postural tachycardia syndrome kindred differs from the five identified earlier and is associated with almost total absence of transporter activity.
hypertension patients incorporating neurochemical indices of the competency of noradrenaline neuronal reuptake such as those used in the present study, coupled with testing for coding region mutations in the transporter gene and functional assessment of any identified DNA sequence variants, is now overdue.

**Adrenaline Cotransmission in the Sympathetic Nerves of the Heart in Hypertension: Presumptive Evidence for a Role of Stress in Pathogenesis**

Adrenaline, the principal hormone of the adrenal medulla, is present also in low concentrations in extra-adrenal tissues, largely contained within sympathetic nerves. Adrenaline in extra-adrenal tissues appears to have been largely derived from hormone circulating in plasma, although synthesis in situ has also been documented. Adrenaline within sympathetic nerves may be released with noradrenaline as a cotransmitter, facilitating the release of the major transmitter through stimulation of presynaptic β-adrenoceptors on sympathetic nerves and increasing the amount of noradrenaline released per nerve impulse. One theory of the pathogenesis of essential hypertension, the so called “adrenaline hypothesis,” draws on these concepts, envisaging that stress is a major factor in hypertension pathogenesis, with stress-induced elevations in the plasma concentration of adrenaline enlarging the pool of adrenaline present in sympathetic nerves, leading to release of adrenaline as a cotransmitter, as well as to facilitation of noradrenaline release, cardiovascular stimulation, and development of arterial hypertension.

To investigate whether the adrenaline hypothesis remains tenable, we recently tested whether adrenaline is, in fact, released from regional sympathetic nerves in the heart in essential hypertension. Using dual isotope dilution methodology, adrenaline and noradrenaline plasma kinetics were measured for the whole body and in the heart in untreated patients with essential hypertension and in healthy volunteers. All research participants underwent cardiac catheterization under resting conditions. At rest there was negligible adrenaline release from the sympathetic nerves of the heart in healthy subjects (0.27 ± 1.62 ng/min). In contrast, in patients with essential hypertension, adrenaline was released from the heart at a rate (1.46 ± 1.73 ng/min) equivalent to approximately 5% of the associated cardiac noradrenaline spillover value (Fig. 3). Cardiac noradrenaline spillover was higher in hypertensive patients (24.9 ± 17.0 ng/min compared with 15.4 ± 11.7 ng/min in healthy volunteers, P < .05).

Among patients, rates of cardiac adrenaline and noradrenaline spillover correlated directly (r = 0.59, P < .05). This study, in demonstrating release of adrenaline from the heart in patients with essential hypertension, and in disclosing a correlation between rates of cardiac adrenaline and noradrenaline release, coupled with a prior report of adrenaline release from the renal sympathetic nerves in essential hypertension, provides perhaps the most direct evidence to date in support of the adrenaline hypothesis of essential hypertension.

Sympathetic nerve adrenaline cotransmission does remain uncertain as a primary cause of essential hypertension. This is well exemplified by the findings in patients...
with panic disorder (Fig. 4), who, during panic attacks, have recurrent stress responses sufficient to load their cardiac sympathetic nerves with adrenaline and to continually corelease adrenaline from the sympathetic nerves, but who usually do not have persistently elevated blood pressure. Although we find that adrenaline is released from the heart in essential hypertension, it remains problematic whether a presynaptic action of regionally released adrenaline contributes to the well-documented higher rates of release of noradrenaline from the heart and kidneys in patients with essential hypertension. This may possibly be the case, but there are alternative explanations for the higher rates of noradrenaline to plasma. Sympathetic nerve firing rates are commonly increased in the postganglionic sympathetic fibers passing to the skeletal muscle vasculature and, based on noradrenaline spillover measurements, there is also activation of the cardiac and renal sympathetic outflows. As indicated earlier, there is also evidence of faulty reuptake of noradrenaline released from sympathetic nerves in essential hypertension, which would also increase noradrenaline overflow to the circulation. Despite these caveats, however, the finding that adrenaline is released from the heart in hypertensive patients does provide presumptive evidence that they have been exposed to high levels of stress.

Although continuing uncertainty exists regarding the role of stress in the pathogenesis of human hypertension, clinical, epidemiological and laboratory research does provide increasingly strong support for the notion that behavioral and psychological factors are important in the pathogenesis of human hypertension. Of particular importance in this regard are long-term follow-up studies of human populations (such as cloistered nuns) living in secluded and unchanging environments, in whom blood pressure does not show the expected rise with age, and epidemiologically based observations made on human populations who demonstrate blood pressure elevation soon after migration. In the latter setting, weight gain and stress are thought to interact to elevate blood pressure, so it is perhaps noteworthy that we find adrenaline cotransmission to be present in obesity-related hypertension.

In short, although the concept that essential hypertension may arise in some patients through psychological mechanisms is not entirely proved, there is a wealth of supporting experimental and clinical evidence. Long-term neural effects of stress on renal function could possibly be the principal mechanism elevating blood pressure, but the causal significance of sympathetic nerve adrenaline cotransmission per se remains uncertain.

**Regional Sympathetic Nervous Activity in Obesity-Related Hypertension**

Patients with primary hypertension are commonly overweight. As obesity prevalence soars in industrialized countries and progressively increases in Third World countries with the appearance of altered patterns of nutrition and a reduction in work-related energy expenditure, obesity-related hypertension has truly become a global health issue. Despite the scale of the problem, the mechanisms of the blood pressure elevation accompanying overweight are poorly understood.

As positive energy balance initiates thermogenesis by stimulation of the sympathetic nervous system, the sympathetic activation seen in essential hypertension could...
perhaps represent an adaptive response to overeating.\textsuperscript{21} Selective activation of the sympathetic nerves to the kidneys and skeletal muscle vasculature is present in normotensive obese individuals, accompanied by reduced rates of noradrenaline spillover from the heart, which possibly represents reflex suppression of the cardiac sympathetic outflow.\textsuperscript{22} (Fig. 5). This is recent evidence that the sino-aortic and cardiopulmonary baroreflexes do have the capacity to \textit{chronically} suppress heart rate and, presumably, cardiac sympathetic outflow, which has previously been in dispute.\textsuperscript{23} The higher renal and lower cardiac noradrenaline spillover most likely represents differentiation of the CNS sympathetic outflow, with increased traffic in the renal sympathetic nerves and reduced cardiac sympathetic nerve firing.

What might be the basis for activation of the renal sympathetic nerves? Hyperinsulinemia and hyperleptinemia accompanying obesity are candidates; but, as yet, the evidence for both is inconclusive. The reduction in cardiac sympathetic activity in normotensive obese individuals also defies ready explanation. It is possible that cardiac sympathetic nervous activity is reflexly depressed in response to circulatory overloading brought on by enhanced renal sympathetic nervous activity and sodium retention. Cardiopulmonary blood volume, stroke volume and cardiac output are increased substantially in obese subjects.\textsuperscript{24} In patients with obesity-related hypertension there is elevation of renal noradrenaline spillover comparable to that in normotensive obese individuals, but without suppression of the cardiac sympathetic outflow, as in obese hypertensives cardiac noradrenaline spillover is more than double that of normotensive obese subjects and is 25\% higher than in healthy volunteers.\textsuperscript{22} (Fig. 5).

The possible importance of activation of the renal sympathetic outflow in the pathogenesis of obesity-related hypertension has been the subject of a comprehensive review.\textsuperscript{25} This increase in sympathetic outflow to the kidneys appears to be necessary, but apparently is not sufficient cause for the development of clinical hypertension, commonly being present also in overweight persons with blood pressure in the normotensive range. High renal sympathetic tone in the latter group, of course, may well have contributed to the level of their pressure, although not in sufficient degree to cause clinical hypertension.

**Neurogenic Hypertension: Diagnostic Dilemmas**

When associated with elevated blood pressure, the clinical features in some other disorders may suggest the presence of neurogenic essential hypertension. If blood pressure appears to be highly variable or if heart rate is high in hypertensive patients, neural mechanisms are often thought to be operating. Heightened blood pressure variability, in fact, is not a typical feature of syndromes of neurogenic essential hypertension, which have other phenotypic markers.

**Panic Disorder**

The symptomatology and blood pressure peaks of panic attacks can cause confusion. Sympathetic nervous activity, adrenaline secretion, heart rate and blood pressure do increase during panic attacks, but patients with panic disorder typically have both normal blood pressure and normal sympathetic nervous activity between attacks.\textsuperscript{17}
White Coat Hypertension

Another form of anxiety, the situational anxiety of “white coat hypertension,”26 may also masquerade as neural essential hypertension, especially if heart rates are high in the clinic. Such individuals who show an alerting response to medical examination, with accompanying blood pressure elevation, need to be differentiated from those with neural essential hypertension, in whom hypertension is sustained on 24-h ambulatory blood pressure monitoring.

Pheochromocytoma

Persistent tachycardia in patients with catecholamine-secreting tumors can also cause diagnostic uncertainty in the present context. The need to identify patients with possible pheochromocytoma and to confirm the diagnosis by measurement of urinary excretion of catecholamines and their metabolites is self-evident. It is unusual for the level of sympathetic activation in neural essential hypertension to be such that urinary noradrenaline values are so elevated as to create diagnostic difficulty, but this can sometimes be the case.

Labile Hypertension

Sometimes the term “labile hypertension” is equated with neurogenic hypertension. Labile hypertension, however, is a misnomer that is typically applied to patients with borderline blood pressure elevations.27 In borderline hypertension, blood pressure recorded in the clinic, while showing the usual degree of variability, creates an illusion of greater fluctuation or variability than normal by oscillating around the cutoff point for the diagnosis of established hypertension. Although the earlier suggestion was that spontaneous variability of arterial pressure was greater in borderline hypertension, 24-h ambulatory blood pressure monitoring has disclosed unremarkable pressure traces, with blood pressure fluctuation no greater than in healthy subjects.28

A Special Place For Antiadrenergic Therapies In Neurogenic Hypertension?

Given that sympathetic activation in hypertensive patients seems to contribute to clinical adverse events in hypertension, might it be appropriate to specifically recommend drugs that reduce sympathetic tone in hypertensive patients in whom sympathetic nervous activation is present? Using this reasoning, with essential hypertension in young adults and with obesity-related hypertension in particular, antiadrenergic agents might have a special place because the hypertension in both cases is, in part, neurogenic.29 Conversely, in variants of hypertension in which sympathetic nervous activity appears to be normal (such as essential hypertension in the elderly) or is reduced (such as in primary aldosteronism), antiadrenergic agents would have little to recommend them. Such a logical “tailoring” of antihypertensive drug therapy to the underlying hypertension pathophysiology might be expected to lead to greater efficacy in reducing arterial pressure and the cardiovascular complications of hypertension, with a lesser incidence of adverse drug effects. The current high level of interest shown by many pharmaceutical companies in “pharmacogenetics” illustrates the pervasive influence of ideas such as this.

This line of reasoning can also be extended to nonpharmacological therapies. The two nonpharmacological measures most commonly applied in the treatment of obesity-related hypertension, ie, dietary calorie restriction and an exercise program, are well known to suppress sympathetic nervous system activity. With negative energy balance from calorie restriction, sympathetic tone and blood pressure is lowered.30 Aerobic exercise training preferentially reduces renal sympathetic activity31 and might be especially efficacious in obesity-related hypertension because of this specific neurophysiological effect.

Matching of Anti hypertensive Therapy to Neural Pathophysiology: Theoretically Appealing but Premature

Given our present state of knowledge, however, matching of antihypertensive therapy to the pathophysiology of the hypertension in an individual patient (or, for that matter, pharmacogenetic information) cannot be the primary therapeutic principle at present—in part, because knowledge both of hypertension pathophysiology and of the precise mechanisms of drug action remain imperfect. Currently, overriding clinical considerations commonly dictate the choice of initial therapy, such as the presence of coexisting illnesses carrying particular pharmaceutical recommendations,32 the potential surgical cure of secondary hypertension, or the intolerance of elderly patients for postural hypotension in the face of pharmacological inhibition of neurocirculatory reflexes.

References


