

REVIEW

Sympathetic nerve activity and neurotransmitter release in humans: translation from pathophysiology into clinical practice

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Abstract

Aim: There has been a revolution in cardiovascular neuroscience in recent years with, in some cases, translation into clinical practice of the knowledge of pathophysiology gained through application of sympathetic nerve recording and catecholamine isotope dilution methodology.

Obesity-related hypertension: An earlier hypothesis, based on findings in most models, was that weight gain in obesity is due in part to sympathetic nervous underactivity reducing thermogenesis. Microneurography and regional noradrenaline spillover measurements in human obesity have disproven this hypothesis, weakening the case for the use of β_3 -adrenergic agonists to stimulate thermogenesis. Sympathetic nerve firing rates in post-ganglionic fibres directed to the skeletal muscle vasculature are increased, as is renal sympathetic tone, with a doubling of the spillover rate of noradrenaline from the kidneys. Given these findings, antiadrenergic antihypertensive drugs may be the preferred agents for obesity-related hypertension, but this has not been adequately tested.

Essential hypertension: Whether stress causes high blood pressure, previously hotly debated, has been under recent review by an Australian Government body, the Specialist Medical Review Council. Despite medicolegal implications, the ruling was that stress is one proven cause of hypertension. The judgment was reached after consideration of the epidemiological evidence, but in particular the described neural pathophysiology of essential hypertension: (a) persistent sympathetic nervous stimulation is commonly present, (b) suprabulbar projections of noradrenergic brainstem neurones are activated and (c) adrenaline is released as a cotransmitter in sympathetic nerves. These were taken to be biological markers of stress.

Cardiac failure: At one time, the failing heart was thought to be sympathetically denervated. Longterm administration of inotropic adrenergic agonists, to provide the cardiac catecholamine stimulation thought to be lacking, increased mortality. Noradrenaline isotope dilution methodology subsequently demonstrated that the sympathetic outflow to the heart was preferentially activated, cardiac noradrenaline spillover being increased as much as 50-fold. The level of stimulation of the cardiac sympathetic nerves was the most powerful predictor of death. These observations provide the theoretical foundation for the very successful introduction of β -adrenergic blockers for treatment of heart failure.

Keywords autonomic failure, heart failure, hypertension, noradrenaline, obesity.

After many years as a ‘Cinderella’ of internal medicine, the sympathetic nervous system has moved towards centre stage, particularly in cardiovascular medicine. Where previously the clinical application of research on the sympathetic nervous system and catecholamines was confined largely to the diagnosis of syndromes of autonomic nervous failure and phaeochromocytoma, more recently the impact has been wide-ranging. In some cases, there has been direct translation into clinical practice of the knowledge of pathophysiology gained through application of sympathetic nerve recording and catecholamine isotope dilution methodology, the use of β -adrenergic blockers for treatment of heart failure being the best known example.

This paper will detail what is known of the neural pathophysiology of obesity and obesity-related hypertension, essential hypertension, cardiac failure and syndromes of sympathetic nervous system failure, and review the extent to which these findings have provided the basis for improved clinical management.

Methods for studying regional sympathetic activity in humans

Current concepts of the participation of the sympathetic nervous system in disease development, progression and complications were dependent on the development of methods for studying regional sympathetic activity in the sympathetic outflows to different organs (Fig. 1). These techniques are clinical microneurography, which measures post-ganglionic sympathetic fibre firing rates in the nerves passing to the skeletal muscle vasculature (Hagbarth & Vallbo 1968, Sundlof & Wallin 1977), the isotope dilution technique for measurement of regional noradrenaline spillover (Esler *et al.* 1984a,b) and radio-scanning methodology for studying sympathetic innervation and function, applicable in particular to the heart (Goldstein *et al.* 1990, 1997, Allman *et al.* 1993).

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 in sympathetic fibres of, most commonly, the common peroneal nerve. Multifibre recordings of ‘bursts’ of nerve activity synchronous with the heart beat (Hagbarth & Vallbo 1968, Sundlof & Wallin 1977), and more recently single-fibre traces (Macefield *et al.* 1994), 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 (Esler *et al.* 1984a,b). Microneurographic methods do not give access to sympathetic nerves of internal organs, a limitation which is overcome by using regional noradrenaline spillover measurements. The relationship which holds, in general, between the sympathetic nerve firing rate in an organ and the rate of overflow of noradrenaline into its venous effluent provides the experimental justification for using regional noradrenaline spillover as a surrogate for nerve traffic 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.

Refinements of the noradrenaline isotope dilution methodology can provide additional information on sympathetic innervation and neuronal function. Uptake of tritiated noradrenaline from plasma during transit through an organ can be used to quantify neuronal noradrenaline uptake (Esler *et al.* 1991), and has allowed demonstration of impairment of noradrenaline transporter function in essential hypertension (Rumantir *et al.* 2000a). Quantifying the processing inside sympathetic nerves of tritiated noradrenaline to its intraneuronal metabolite, tritiated dihydroxyphenylglycol (DHPG), coupled with measurement of the specific activity of DHPG in coronary sinus plasma, has been used to estimate noradrenaline stores in the human heart (Eisenhofer *et al.* 1996, Brunner-La Rocca *et al.* 2002).

Radio-scanning methodologies

Imaging methodologies of several types, utilizing both positron emission tomography and single photon emission computed tomography scanning, can be used to demonstrate the anatomy of sympathetic innervation of an organ. The scanning agents most widely used are [^{123}I]meta-iodobenzylguanidine (MIBG), 6- ^{18}F fluorodopamine, and [^{11}C]hydroxyephedrine (Goldstein *et al.* 1990, 1997, Allman *et al.* 1993). Sympathetic denervation can be readily demonstrated with imaging techniques in patients with pure autonomic failure in whom post-ganglionic fibres are absent, and after the sympathetic nerve section and degeneration that accompanies cardiac transplantation.

Use of these agents to estimate sympathetic ‘activity’ (nerve firing and noradrenaline turnover) is more problematic. MIBG and [^{11}C]hydroxyephedrine, unlike noradrenaline, are not stored in the neurotransmitter vesicles and are not subject to electrically coupled vesicular release. 6- ^{18}F fluorodopamine is more satisfactory

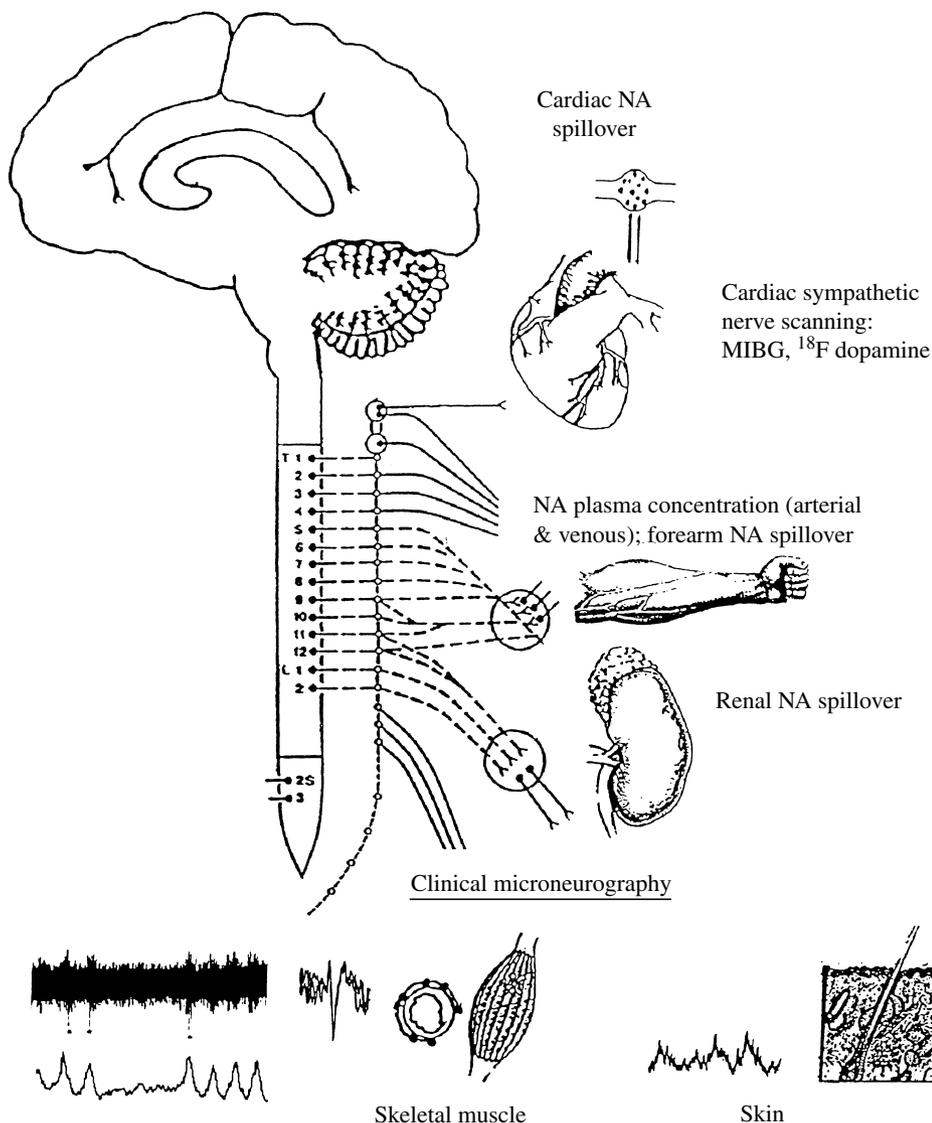


Figure 1 Methods for measuring regional sympathetic nervous system activity in humans. Nerve firing can be measured in post-ganglionic sympathetic fibres distributed to skin and the skeletal muscle vasculature using clinical microneurography. Single-fibre and multiunit recording is possible. Isotope dilution methodology can be used to measure the rates of spillover of noradrenaline to plasma from individual organs, providing a means of quantifying regional sympathetic activity in the limbs and viscera. Cardiac sympathetic nerve scans allow visualization of the anatomy of the sympathetic innervation of the heart.

in this regard, as the tracer is converted to 6- ^{18}F fluoronoradrenaline after it is taken up into sympathetic nerves. This probe has been successfully used, for example, in studying the various syndromes causing postural hypotension and has allowed differentiation of the diverse forms of underlying autonomic failure (Goldstein *et al.* 1997).

Clinical sympathetic nervous pathophysiology: translation into clinical management

There have been major recent advances in the understanding of the neural pathophysiology of obesity,

essential hypertension, cardiac failure and syndromes of autonomic nervous system failure, which in some cases have provided the basis for new and improved clinical management.

Obesity

As obesity prevalence soars in industrialized countries, and progressively increases in the third world with the appearance of altered patterns of nutrition and a reduction in work-related energy expenditure, obesity-related hypertension has become a truly global health issue. Despite the scale of the problem, the biological

basis of the differing predisposition to weight gain between individual members of the population, and of the mechanism of the blood pressure elevation accompanying overweight are not well understood.

An earlier hypothesis, based on the findings in many animal models, was that obesity is characterized by sympathetic nervous underactivity, which reduces thermogenesis and contributes to weight gain. Microneurography and regional noradrenaline spillover measurements in human obesity have disproven this hypothesis. Sympathetic nerve firing rates in post-ganglionic fibres directed to the skeletal muscle vasculature are increased (Grassi *et al.* 1998), as is renal sympathetic tone, with a doubling of the spillover rate of noradrenaline from the kidneys (Rumantir *et al.* 1999).

The selective activation of the sympathetic nerves to the kidneys and skeletal muscle vasculature present in normotensive human obesity is accompanied by suppression of the cardiac sympathetic outflow (Rumantir *et al.* 1999). The higher renal, and lower cardiac noradrenaline spillover most likely represents differentiation of the central nervous system (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? Hyperinsulinaemia and hyperleptinaemia accompanying obesity are candidates, but as yet the evidence for both is inconclusive. The reduction in cardiac sympathetic activity in the normotensive obese also defies ready explanation. It is probable 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 the obese (Messerli *et al.* 1983).

In patients with obesity-related hypertension, there is a comparable elevation of renal noradrenaline spillover to that present in the normotensive obese, but without suppression of cardiac sympathetics, as in them cardiac noradrenaline spillover is more than double that of normotensive obese and 25% higher than in healthy volunteers (Rumantir *et al.* 1999).

Relevance of the neural pathophysiology of obesity to clinical management. The demonstration that the suppressed sympathetic tone which characterizes many experimental models of obesity does not exist in human obesity has weakened the case for the use of β_3 -adrenergic agonists as thermogenic agents to facilitate weight loss. Although the neurobiology of obesity-related hypertension is now better understood, direct application in antihypertensive therapeutic strat-

egies has not yet occurred. Increased renal sympathetic activity is present in human obesity, predisposing to hypertension development. Calorie restriction and an exercise programme, both clinically applied as first-line measures in obesity-related hypertension, do inhibit the sympathetic nervous system, with aerobic exercise training preferentially inhibiting the renal sympathetic outflow (Meredith *et al.* 1991a). Whether antiadrenergic antihypertensive drugs are the preferred agents for blood pressure reduction have not been adequately tested.

Essential hypertension

Measurement of nerve firing in post-ganglionic sympathetic efferents directed to the skeletal muscle vasculature with microneurography and regional rates of noradrenaline spillover utilizing isotope dilution techniques demonstrates that activation of the sympathetic nerves of the heart, kidneys and skeletal muscle vasculature is commonly present in lean patients with essential hypertension (Esler *et al.* 1988, Grassi *et al.* 1998). The increase in sympathetic activity is thought to both initiate and to sustain the blood pressure elevation. The high renal sympathetic tone contributes to hypertension development by stimulating renin secretion and through promoting renal tubular reabsorption of sodium. Sympathetic overactivity seems to particularly influence systolic pressure (Esler *et al.* 1977) by increasing the rate of left ventricular ejection, by reducing aortic compliance through increasing neural arterial tone, and via arteriolar vasoconstriction, by promoting rebound of the reflected arterial pressure wave from the periphery (Esler 2002). The central nervous mechanism operating to increase sympathetic nerve firing is not entirely clear, but seems to involve sympathoexcitatory noradrenergic projections from the brainstem to suprabulbar subcortical regions (Ferrier *et al.* 1993, Lambert *et al.* 1994), perhaps chronically activated as part of an ongoing mental stress response.

Mental stress as a causal factor? The notion that mental stress can cause hypertension was an idea in the past often banished to the realm of medical folklore. Although some uncertainty still exists concerning the role of stress in the pathogenesis of human hypertension, clinical, epidemiological and laboratory research does provide increasingly strong support for the notion that behavioural and psychological factors are of importance in the pathogenesis of human hypertension (Timio *et al.* 1988, Poulter *et al.* 1990). 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 (Timio *et al.* 1988) and epidemiologically based observations made on human populations who demonstrate blood pressure elevation soon after migration (Poulter *et al.* 1990). 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 (Rumantir *et al.* 2000b).

An Australian Governmental body, the Specialist Medical Review Council has just ruled that stress, including occupational stress, is one proven cause of hypertension (Specialist Medical Review Council 2002). This determination will apply, in the first instance, in the area of Veterans Affairs. In their ruling, this body was mindful of the epidemiological evidence, but was influenced primarily by the neural pathophysiology of essential hypertension, mentioning in particular three findings: (i) the presence of sympathetic nervous system activation (Esler *et al.* 1988, Grassi *et al.* 1998), (ii) adrenaline cotransmission in sympathetic nerves (Rumantir *et al.* 2000b) and (iii) activation of suprabulbar subcortical projections of brainstem noradrenergic neurones (Ferrier *et al.* 1993, Lambert *et al.* 1994). These, in concert, were taken to provide biological evidence of ongoing mental stress.

Contributing abnormalities in the sympathetic varicosity? Although the importance of sympathetic nervous activation in the pathogenesis of essential hypertension seems clear, the exact pathophysiology of the sympathetic nervous dysfunction present remains to be delineated. There are several possible explanations of the increased spillover of noradrenaline from the kidneys and heart to plasma, a key piece of evidence supporting the neurogenic basis of essential hypertension, in addition to the obvious one of an increased rate of sympathetic nerve firing.

The hypothesis that there might be an increase in the density of sympathetic innervation in human hypertension, well documented in the spontaneously hypertensive rat (Cassis *et al.* 1985), is currently under investigation by us. Adrenaline cotransmission is present in the cardiac sympathetic nerves of patients with essential hypertension (Rumantir *et al.* 2000b), a possible basis for the observed increase in cardiac noradrenaline spillover, through pre-synaptic augmentation of noradrenaline release. Phenotypic evidence exists also of faulty noradrenaline reuptake into the sympathetic nerves of the heart in essential hypertension (Rumantir *et al.* 2000a), an abnormality which would amplify the sympathetic neural signal by impairing removal of noradrenaline from the synaptic cleft.

Sympathetic hyperinnervation? It remains an open possibility that there might be an increase in the density of sympathetic innervation in human hypertension, well documented in the spontaneously hypertensive rat (Cassis *et al.* 1985). In the spontaneously hypertensive rat, the increased sympathetic nerve density appears to result from increased neurotrophic stimulation because of overexpression of nerve growth factor (NGF) (Cassis *et al.* 1985). Sympathetic hyperinnervation, if present in patients with essential hypertension, would be expected to lead to increased interstitial concentration of noradrenaline in tissues and increased spillover of noradrenaline into the venous drainage of individual organs even at normal rates of nerve firing.

Adrenaline sympathetic cotransmission and pre-synaptic neuromodulation? One theory of the pathogenesis of essential hypertension, the so called 'adrenaline hypothesis' (Majewski *et al.* 1981) envisages 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, facilitation of noradrenaline release, cardiovascular stimulation and development of arterial hypertension. Adrenaline cotransmission in sympathetic nerves has been documented in essential hypertension (Rumantir *et al.* 2000b).

Sympathetic nerve adrenaline cotransmission, however, does remain uncertain as a primary causal mechanism in essential hypertension. It remains problematic whether a pre-synaptic action of regionally released adrenaline contributes to the well documented higher rates of spillover of noradrenaline from the heart and kidneys in patients with essential hypertension. This is well exemplified by findings in patients with panic disorder (Wilkinson *et al.* 1998) who during panic attacks have recurrent stress responses sufficient to load their cardiac sympathetic nerves with adrenaline, but typically do not have persistently increased cardiac noradrenaline spillover or elevated blood pressure (Wilkinson *et al.* 1998). Despite these caveats, 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.

Dysfunction of the neuronal noradrenaline transporter? The proposition that impairment of neuronal reuptake of noradrenaline might contribute to the development of essential hypertension has recently been tested by applying radiotracer methods focusing on neuronal processing of tritiated noradrenaline by the heart. As the disposition of noradrenaline after its release is more dependent on neuronal reuptake in the heart than in all

other organs (Esler *et al.* 1991), incomplete grades of impairment of noradrenaline transporter function would be most likely to be phenotypically evident there. We found that the fractional extraction of plasma tritiated noradrenaline in passage through the heart, determined primarily by neuronal noradrenaline uptake (Esler *et al.* 1991), was reduced in patients with essential hypertension (Rumantir *et al.* 2000a). Cardiac release of the tritiated noradrenaline metabolite, 3H DHPG, produced intraneuronally by monoamine oxidase after uptake of 3H noradrenaline by the transporter, was also reduced. These findings indicate that neuronal reuptake of noradrenaline is impaired in the heart in essential hypertension. By amplifying the neural signal such a defect, especially if present in the sympathetic nerves of the kidneys also, could constitute a neurogenic variant of essential hypertension.

Clinical relevance of the neural pathophysiology of essential hypertension? There is some evidence that increased sympathetic nervous activity present contributes to adverse cardiovascular events. Sympathetically mediated vasoconstriction in skeletal muscle vascular beds, in reducing delivery of glucose to muscle, is a basis for insulin resistance and hyperinsulinaemia (Julius *et al.* 1992). Cardiac sympathetic stimulation contributes to the development of left ventricular hypertrophy and, most likely, to the genesis of ventricular arrhythmias and sudden death.

Given that sympathetic activation in essential hypertension seems to contribute both to blood pressure elevation and adverse metabolic and other cardiovascular effects, it would seem logical to specifically recommend antihypertensive therapies inhibiting the sympathetic nervous system. The current attention being given by many pharmaceutical companies to research on pharmacogenomic guidance of antihypertensive therapy illustrates the attractiveness of this concept of 'tailored' antihypertensive therapy.

Tailoring of antihypertensive therapy to pathophysiology, however well based logically, given our present state of knowledge to this point cannot be the primary therapeutic principle in hypertension care. Overriding clinical considerations commonly apply in the choice of initial therapy, including the presence of coexisting illnesses carrying particular pharmaceutical recommendations (such as the avoidance of β -adrenergic blockers in asthmatics, or their use with coexisting angina), the potential surgical cure of a secondary hypertension, safety for the foetus in pregnancy-induced hypertension, and the intolerance of elderly patients for postural hypotension in the face of inhibition of neurocirculatory reflexes. This point being made, the important and actively researched but to this stage incompletely answered question remains: of all antihypertensive

drugs, do those inhibiting the sympathetic nervous system best reduce cardiovascular risk?

Stress reduction measures are part of a general therapeutic prescription in hypertension, along with exercise training, restriction of dietary sodium intake and avoidance of excess alcohol consumption. Given recent evidence (Rumantir *et al.* 2000b) and a decision by a government advisory body (Specialist Medical Review Council 2002) for the probable importance of mental stress as a basis for chronic sympathetic activation underlying the development of hypertension, further formal evaluation of the efficacy of stress reduction programmes is needed.

Cardiac failure

The concentration of the sympathetic nervous neurotransmitter, noradrenaline, is reduced in the failing human heart, with left ventricular myocardial noradrenaline concentration typically being 50% or less of that present in health (Chidsey *et al.* 1963). This finding by Chidsey and colleagues was long taken to signify the existence of both functional and anatomical cardiac sympathetic denervation in the failing heart, and provided the underpinnings of an historically serious misadventure in heart failure therapy; β -adrenergic antagonists were held in most quarters, although not all (Waagstein *et al.* 1993), to be specifically contraindicated, while adrenergic cardiac inotropes were widely used but eventually proven to increase mortality.

The application of organ-specific tracer kinetic techniques using radiolabelled noradrenaline has allowed demonstration that the sympathetic nervous outflow to the heart is, in fact, preferentially stimulated in severe congestive cardiac failure (Hasking *et al.* 1986). Rates of noradrenaline spillover from the failing human heart to plasma are up to 50 times normal in untreated patients (Hasking *et al.* 1986), approximately equivalent to the rate of noradrenaline release observed in the healthy heart during near maximal exercise. This increased spillover of the neurotransmitter from the heart is largely attributable to increased rates of sympathetic nerve firing, as it is accompanied by increased overflow from the heart of the noradrenaline precursor, DOPA (3,4-dihydroxyphenylalanine; indicating that noradrenaline synthesis is increased), and of the sympathetic cotransmitter, neuropeptide Y (Kaye *et al.* 1994), which unlike noradrenaline is not subject to neuronal reuptake.

The afferent circulatory stimulus responsible for sympathoexcitation in congestive heart failure remains to be fully elucidated. A strong relationship has been demonstrated between cardiac sympathetic activity and pulmonary artery and pulmonary wedge pressures in heart failure patients (Kaye *et al.* 1994), raising the

possibility of reflex linkage of cardiopulmonary baroreceptors with efferent cardiac sympathetic activity. The central nervous system neuronal circuitry involved remains uncertain. In the rat coronary ligation heart failure model, Patel & Zhang (1996) describe increased neuronal activity in the locus coeruleus, the major group of noradrenergic neurones in the brain, and the paraventricular nucleus of the hypothalamus, to which it projects. Cardiopulmonary volume receptor afferents do project to the noradrenergic nuclei of the locus coeruleus, and the firing rate of locus coeruleus neurones is changed by alterations in cardiopulmonary pressures (Elam *et al.* 1984). An association between activation of suprabulbar projections of noradrenergic brainstem neurones and sympathetic nervous tone has been demonstrated in human heart failure (Aggarwal *et al.* 2002).

Relevance of the neural pathophysiology of cardiac failure to clinical management. The preferential activation of the cardiac sympathetic outflow in heart failure contributes to arrhythmia development and sudden death, and to the progressive damage of cardiac myocytes underlying progressive heart failure. Actuarial cardiac mortality is strongly related to both cardiac noradrenaline spillover measurements (Kaye *et al.* 1995) and to measures of myocardial noradrenaline depletion (Fig. 2), the latter being linked in particular to progressive myocardial failure (Brunner-La Rocca *et al.* 2002).

These findings provided the theoretical underpinning for the highly successful introduction of β -adrenergic blockade as a heart failure therapy. Mortality in heart failure is reduced by 30–60% by β -adrenergic blockade (CIBIS II Investigators and Committee 1991, Packer *et al.* 1996). Following on this demonstrable benefit of β -adrenergic blockade in heart failure, additional antiadrenergic measures are under investi-

gation, including central suppression of sympathetic outflow with imidazoline-binding agents such as clonidine, blocking of noradrenaline synthesis by dopamine- β -hydroxylase inhibition, and antagonism of neuro peptide Y.

Syndromes of sympathetic nervous failure

Syndromes with disabling postural hypotension exist which are attributable to chronic sympathetic nervous system failure. The pathophysiological spectrum of sympathetic failure encompasses pure autonomic failure, characterized by peripheral sympathetic nerve degeneration, Shy-Drager syndrome and Parkinsonism, in which there is degeneration of the CNS centres involved in integrated sympathetic circulatory control, and dopamine- β -hydroxylase deficiency, in which there is a genetic synthetic defect in noradrenaline and adrenaline synthesis.

Pure autonomic failure

This disorder is characterized by widespread degeneration of post-ganglionic sympathetic fibres. Near total sympathetic denervation of the heart is the norm, leading to markedly reduced cardiac spillover of DOPA, noradrenaline and its metabolites (Meredith *et al.* 1991b, Goldstein *et al.* 1997). The cause remains uncertain, although the absence of the neurotrophin, NGF, in the venous drainage of the heart and in arterial plasma (Fig. 3) suggests that defective neurotrophic support of sympathetic nerves might be the pathogenic mechanism.

Dopamine- β -hydroxylase deficiency

In this rare syndrome of sympathetic failure, sufferers present with postural hypotension and a variety of allied

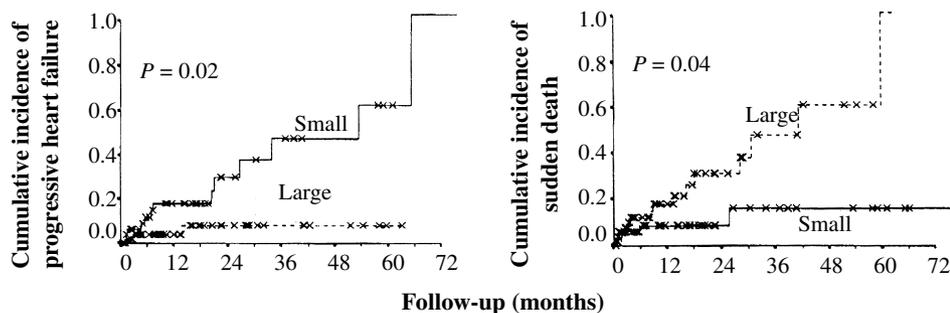


Figure 2 The noradrenaline stores of the heart can be measured by quantifying the conversion of tritiated noradrenaline to its intraneuronal metabolite, tritiated dihydroxyphenylglycol (DHPG) inside sympathetic nerves during the course of an infusion of the tracer, coupled with measurement of the specific activity of DHPG in coronary sinus plasma (Eisenhofer *et al.* 1996, Brunner-La Rocca *et al.* 2002). Reduced cardiac noradrenaline content in heart failure patients, largely attributable to sympathetic neuronal rarefaction, is predictive of progressive myocardial deterioration and death from intractable heart failure (left panel), but seems to protect against death from arrhythmia (right panel).

symptoms attributable to the underlying defect, total lack of capacity to synthesize adrenaline and noradrenaline (Robertson *et al.* 1986, Man In't Veld *et al.* 1987). Sympathetic nerve firing rates are high at rest, to increase further with upright posture, but there is electrochemical dissociation in the sympathetic varicosities as the vesicles contain no noradrenaline (Thompson *et al.* 1995). The key to diagnosis is the high concentration of dopamine and its metabolites in plasma and urine, resulting from a synthesis block at the point of hydroxylation of dopamine to noradrenaline (Robertson *et al.* 1986, Man *et al.* 1987).

Relevance of the neural pathophysiology of syndromes of sympathetic failure to their clinical management

Differentiating between causes of sympathetic failure underlying postural hypotension is important in terms of both prognostication and treatment. Long-term survival without deteriorating brain function is the norm in pure autonomic failure, in contrast to Shy-Drager syndrome, in which a progressively downward course is common. Recently described differences in pathophysiology uncovered by noradrenaline isotope dilution methodology and myocardial sympathetic nerve scanning provide the key to successful diagnosis (Meredith *et al.* 1991b, Goldstein *et al.*

1997). Patients with pure autonomic failure have very low rates of whole body noradrenaline spillover at rest and near total sympathetic denervation in the heart demonstrable with cardiac noradrenaline spillover measurements and myocardial scanning (Meredith *et al.* 1991a, Goldstein *et al.* 1997). In contrast, in Shy-Drager syndrome resting noradrenaline release rates are normal and there is no sympathetic denervation of the heart (Goldstein *et al.* 1997). Unequivocal differentiation of Parkinson's disease with autonomic failure from Shy-Drager syndrome is now possible: unexpectedly, in Parkinson's disease with autonomic failure the heart has been found to be extensively sympathetically denervated (Goldstein *et al.* 1997).

Preferred drug therapy for each condition flows logically from the neural pathophysiology. For dopamine- β -hydroxylase syndrome, very effective treatment is available in the form of oral administration of the noradrenaline precursor L-dihydroxyphenylserine (L-DOPS), which is decarboxylated to noradrenaline directly, in a process bypassing the dopamine β -hydroxylation step (Robertson *et al.* 1986, Man *et al.* 1987).

All of the degenerative syndromes of sympathetic failure are helped by the sodium-retaining mineralocorticoid, fludrocortisone, but beyond this treatment responses differ. The indirect-acting sympathomimetic, ephedrine, which acts by releasing noradrenaline from sympathetic nerves, is beneficial in Shy-Drager syndrome but, as expected, not in pure autonomic failure, where sympathetic innervation is absent. The partial adrenergic agonist, dihydroergotamine, which is a relatively selective vasoconstrictor, works best in the presence of adrenoceptor denervation hypersensitivity, in patients with pure autonomic failure.

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References

- Aggarwal, A., Esler, M.D., Lambert, G.W., Hastings, J., Johnston, L. & Kaye, D.M. 2002. Norepinephrine turnover is increased in suprabulbar subcortical brain regions and is related to whole-body sympathetic activity in human heart failure. *Circulation* 105, 1031–1033.
- Allman, K.C., Wieland, D.M., Muzik, O., Degrado, T.R., Wolfe, E.R. & Schwaiger, M. 1993. Carbon-11-hydroxyephedrine with positron emission tomography for serial assessment of cardiac adrenergic neuronal function after acute myocardial infarction in humans. *J Am Coll Cardiol* 22, 368–375.
- Brunner-La Rocca, H.P., Esler, M.D., Jennings, G.L. & Kaye, D.M. 2002. Effect of cardiac sympathetic nervous activity on mode of death in congestive heart failure. *Eur Heart J* 22, 1136–1143.

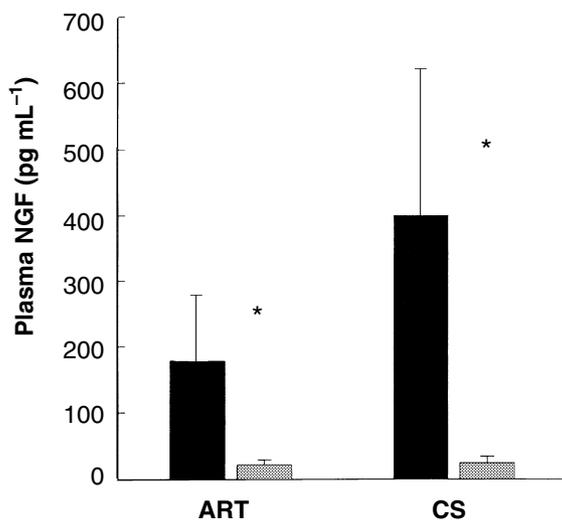


Figure 3 Healthy subjects (black bars) had measurable amounts of the neurotrophin, nerve growth factor (NGF) in arterial plasma and demonstrable release of NGF from the heart into the coronary sinus (CS). In patients with pure autonomic failure and sympathetic degeneration (grey bars), NGF was barely detectable in arterial plasma and not released by the heart, suggesting that in them the loss of sympathetic innervation is due to lack of neurotrophic support by NGF. * $P < 0.05$.

- Cassis, L.A., Stitzel, R.E. & Head, R.J. 1985. Hypernoradrenergic innervation of the caudal artery of the spontaneously hypertensive rat: an influence upon neuroeffector mechanisms. *J Pharmacol Exp Ther* **234**, 792–803.
- Chidsey, C.A., Braunwald, E., Morrow, A.G. & Mason, D.T. 1963. Myocardial norepinephrine concentration in man: effects of reserpine and of congestive heart failure. *N Engl J Med* **269**, 653–658.
- Eisenhofer, G., Friberg, P., Rundqvist, B. et al. 1996. Cardiac sympathetic nerve function in congestive heart failure. *Circulation* **93**, 1667–1676.
- Elam, M., Yao, T., Svensson, H. & Thoren, P. 1984. Regulation of locus coeruleus neurons and splanchnic sympathetic nerves by cardiovascular afferents. *Brain Res* **290**, 281–287.
- Esler, M., Julius, S., Zweifler, A. et al. 1977. Mild high-renin essential hypertension: a neurogenic human hypertension? *N Engl J Med* **296**, 405–411.
- Esler, M., Jennings, G., Korner, P., Blombery, P., Sacharias, N. & Leonard, P. 1984a. Measurement of total and organ-specific norepinephrine kinetics in humans. *Am J Physiol* **247**, E21–E28.
- Esler, M., Jennings, G., Leonard, P. et al. 1984b. Contribution of individual organs to total noradrenaline release in humans. *Acta Physiol Scand Suppl* **527**, 11–16.
- Esler, M., Jennings, G., Korner, P. et al. 1988. The assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. *Hypertension* **11**, 3–20.
- Esler, M., Wallin, G., Dorward, P. et al. 1991. Effects of desipramine on sympathetic nerve firing and norepinephrine spillover to plasma in man. *Am J Physiol* **260**, R817–R823.
- Esler, M. 2002. Differentiation of the effects of the angiotensin II receptor blocker class on autonomic function. *J Hypertens* **20** (suppl. 5):S13–19.
- Ferrier, C., Jennings, G., Eisenhofer, G. et al. 1993. Evidence for increased noradrenaline release from subcortical brain regions in essential hypertension. *J Hypertens* **11**, 1217–1227.
- Goldstein, D.S., Chang, P.C., Eisenhofer, G., Miletich, R., Finn, R. & Bacher, J. 1990. Positron emission tomographic imaging of cardiac sympathetic innervation and function. *Circulation* **81**, 1606–1621.
- Goldstein, D.S., Holmes, C., Cannon, R.O.III., Eisenhofer, G. & Kopin, I.J. 1997. Sympathetic cardioneuropathy in dysautonomias. *N Engl J Med* **336**, 696–702.
- Grassi, G., Colombo, M., Seravalle, G., Spaziani, D. & Mancia, G. 1998. Dissociation between muscle and skin sympathetic nerve activity in essential hypertension, obesity, and congestive heart failure. *Hypertension* **31**, 64–67.
- Hagbarth, K.-E. & Vallbo, A.B. 1968. Pulse and respiratory grouping of sympathetic impulses in human muscle nerves. *Acta Physiol Scand* **74**, 98–108.
- Hasking, G., Esler, M., Jennings, G., Burton, D., Johns, J. & Korner, P. 1986. Norepinephrine spillover to plasma in congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. *Circulation* **73**, 615–621.
- CIBIS II Investigators and Committee. 1991. The cardiac insufficiency bisoprolol study II (CIBIS II). *Lancet* **353**, 9–13.
- Julius, S., Gundrandsson, T., Jamerson, K. & Andersson, O. 1992. The interconnection between sympathetics, microcirculation and insulin resistance in hypertension. *Blood Press* **1**, 9–19.
- Kaye, D.M., Lambert, G.W., Lefkovits, J., Morris, M., Jennings, G.L. & Esler, M.D. 1994. Neurochemical evidence of cardiac sympathetic activation and increased central nervous system norepinephrine turnover in severe congestive heart failure. *J Am Coll Cardiol*, **23**, 570–578.
- Kaye, D.M., Lefkovits, J., Jennings, G.L., Bergin, P., Broughton, A. & Esler, M.D. 1995. Adverse consequences of high sympathetic nervous activity in the failing human heart. *J Am Coll Cardiol* **26**, 1257–1263.
- Lambert, G.W., Ferrier, C., Kaye, D., Cox, H.S., Turner, A.G., Jennings, G.L. & Esler, M.D. 1994. Monoaminergic neuronal activity in subcortical brain regions in essential hypertension. *Blood Press* **3**, 55–66.
- Macefield, V., Wallin, B.G. & Vallbo, A.B. 1994. The discharge behaviour of single vasoconstrictor motoneurons in human muscle nerves. *J Physiol (Lond)* **481**, 799–809.
- Majewski, H., Rand, M.J. & Tung, I.H. 1981. Activation of prejunctional β -adrenoceptors in rat atria by adrenaline applied exogenously or released as a co-transmitter. *Br J Pharmacol* **73**, 669–679.
- Man In't Veld, A.J., Boomsma, F., Moleman, P. & Schalekamp, M.A.D.H. 1987. Congenital dopamine beta-hydroxylase deficiency: a novel orthostatic syndrome. *Lancet* **1**, 183–187.
- Meredith, I.T., Friberg, P., Jennings, G.L. et al. 1991a. Regular exercise lowers renal but not cardiac sympathetic activity in man. *Hypertension* **18**, 575–582.
- Meredith, I.T., Esler, M.D., Cox, H.S., Lambert, G.W., Jennings, G.L. & Eisenhofer, G. 1991b. Biochemical evidence of sympathetic denervation of the heart in pure autonomic failure. *Clin Auton Res* **1**, 187–194.
- Messerli, F.H., Sundgaard-Riise, K., Reisin, E., Dreslinski, G., Dunn, F.G. & Frohlich, E. 1983. Disparate cardiovascular effects of obesity and arterial hypertension. *Am J Med* **74**, 808–812.
- Packer, M., Bristow, M.R., Colucci, W.S., Fowler, M.B., Gilbert, E.M. & Shusterman, N.H. 1996. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* **334**, 1349–1355.
- Patel, K.P. & Zhang, K. 1996. Neurohumoral activation in heart failure. *Clin Exp Pharmacol Physiol* **23**, 722–726.
- Poulter, N.R., Khaw, K.T., Hopwood, B.E.C. et al. 1990. The Kenyan Luo migration study: observations on the initiation of the rise in blood pressure. *Br Med J* **300**, 967–972.
- Robertson, D.M., Goldberg, R., Onrot, J. et al. 1986. Isolated failure of autonomic noradrenergic neurotransmission. Evidence for impaired β -hydroxylation of dopamine. *N Engl J Med* **314**, 1494–1497.
- Rumantir, M.S., Vaz, M., Jennings, G.L. et al. 1999. Neural mechanisms in human obesity-related hypertension. *J Hypertens* **17**, 1125–1133.

- Rumantir, M.S., Kaye, D.M., Jennings, G.L., Vaz, M., Hastings, J.A. & Esler, M.D. 2000a. Phenotypic evidence of faulty neuronal noradrenaline reuptake in essential hypertension. *Hypertension* 36, 824–829.
- Rumantir, M.S., Jennings, G.L., Lambert, G.W., Kaye, D.M., Seals, D.R. & Esler, M.D. 2000b. The 'adrenaline hypothesis' of hypertension revisited: evidence for adrenaline release from the heart of patients with essential hypertension. *J Hypertens* 18, 717–723.
- Specialist Medical Review Council. 2002. *Statements of Principles Nos. 31 and 32 of 2001 Concerning Hypertension*. Commonwealth of Australia Government Gazette. Australian Government Printer, Canberra, March 27.
- Sundlof, G. & Wallin, B.G. 1977. The variability of muscle sympathetic nerve activity in resting recumbent man. *J Physiol (Lond)* 272, 383–397.
- Thompson, J.M., O'Callaghan, C.J., Kingwell, B.A., Lambert, G.W., Jennings, G.L. & Esler, M.D. 1995. Total nor-epinephrine spillover, muscle sympathetic nerve activity and heart rate spectral analysis in a patient with dopamine-beta-hydroxylase deficiency. *J Auton Nerv Syst* 55, 198–206.
- Timio, M., Verdechioia, P., Rononi, M., Gentili, S., Francucci, B. & Bichisao, E. 1988. Age and blood pressure changes: a 20 year follow-up study of nuns of a secluded order. *Hypertension* 12, 457–461.
- Waagstein, F., Bristow, M.R., Swedberg, K. *et al.* 1993. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 342, 1441–1446.
- Wilkinson, D.J.C., Thompson, J.M., Lambert, G.W. *et al.* 1998. Sympathetic activation in patients with panic disorder at rest, under laboratory mental stress, and during panic attacks. *Arch Gen Psychiatry* 55, 511–520.