Journal of Human Hypertension (2012) 26, 463–475

www.nature.com/jhh

REVIEW

The sympathetic nervous system and blood pressure in humans: implications for hypertension

JP Fisher[1] and JFR Paton[2]
[1]*School of Sport and Exercise Sciences, College of Life & Environmental Sciences, University of Birmingham, Birmingham, UK and* [2]*School of Physiology & Pharmacology, Bristol Heart Institute, Medical Sciences Building, University of Bristol, Bristol, UK*

A neurogenic component to primary hypertension (hypertension) is now well established. Along with raised vasomotor tone and increased cardiac output, the chronic activation of the sympathetic nervous system in hypertension has a diverse range of pathophysiological consequences independent of any increase in blood pressure. This review provides a perspective on the actions and interactions of angiotensin II, inflammation and vascular dysfunction/brain hypoperfusion in the pathogenesis and progression of neurogenic hypertension. The optimisation of current treatment strategies and the exciting recent developments in the therapeutic targeting of the sympathetic nervous system to control hypertension (for example, catheter-based renal denervation and carotid baroreceptor stimulation) will be outlined.
Journal of Human Hypertension (2012) **26,** 463–475; doi:10.1038/jhh.2011.66; published online 7 July 2011

Keywords: sympathetic nerve activity; neurogenic hypertension; immune-to-brain signalling

The sympathetic renaissance

Primary (or essential) hypertension (termed hypertension from here on) accounts for the vast majority of hypertensive cases (~95%).[1] Although the aetiology of this condition is incompletely understood, it appears that along with genetic factors, several environmental and behavioural 'hypertensiogenic' factors have been identified, such as obesity, insulin resistance, high-salt intake, low physical activity levels and stress.[1] Given the elevated risk of stroke, renal failure, myocardial infarction and coronary heart disease in those afflicted with high blood pressure, the elucidation of the key pathogenic features and optimisation of effective therapeutic strategies are critical.

The most common form of hypertension is neurogenic hypertension, defined as high blood pressure with sympathetic overdrive, loss of parasympathetically mediated cardiac variability and excessive angiotensin II (Ang II) activity.[2] The importance of the sympathetic nervous system in the short-term regulation of blood pressure via the modulation of peripheral vascular tone and cardiac output is well established, while the role of the sympathetic nerve activity (SNA) in long-term blood pressure control is more controversial.[3–5] Although the concept of a potential neurogenic component to hypertension is not new,[4] it has perhaps received less attention than the renin–angiotensin system (RAS), which has been a prominent therapeutic and research target in hypertension over the past few decades. Nevertheless, the activation of the sympathetic nervous system and the RAS in hypertension appears inextricably, and reciprocally, linked. Evidence from studies in both patients and animal models of hypertension strongly implicate the chronic sympathetic neural activation in the aetiology and progression of hypertension (Figure 1).[2,6–9]

The use of regional surgical sympathectomy to treat hypertension over 50 years ago before the availability of antihypertensive medications that lower sympathetic activity provides an early indication of the clinical appreciation for a significant neurogenic component to hypertension.[10] Recent clinical interventions showing impressive blood pressure lowering effects by targeting reductions in SNA[11–14] and progress in the elucidation of the central sympathetic regulatory pathways altered in hypertension[15–17] are part of a renaissance of interest in the control of the sympathetic nervous system

Correspondence: Dr JP Fisher, School of Sport and Exercise Sciences, College of Life & Environmental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.
E-mail: J.P.Fisher@bham.ac.uk or Dr JFR Paton, School of Physiology & Pharmacology, Bristol Heart Institute, Medical Sciences Building, University of Bristol, Bristol BS8 1TD, UK.
E-mail: Julian.F.R.Paton@bristol.ac.uk
Received 28 March 2011; revised 23 May 2011; accepted 31 May 2011; published online 7 July 2011

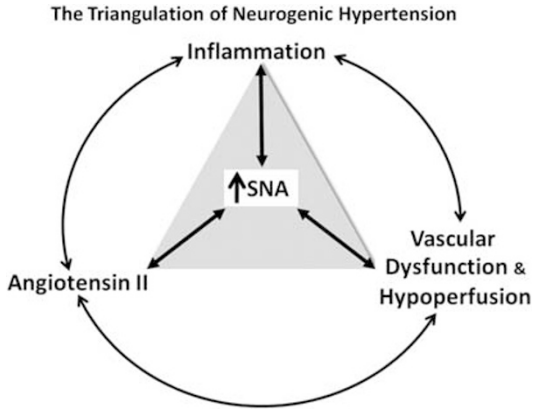

Figure 1 Triangulation of neurogenic hypertension. The establishment of positive feedback loops between Ang II, inflammation and vascular dysfunction/brain hypoperfusion may form the basis of refractory hypertension.

and its utility as a clinical target. The purpose of the present review is to provide a perspective on the evidence for a neurogenic component to hypertension. We will address the issue of a causal role of heightened SNA in the onset of hypertension, highlight some novel putative causal mechanisms and recent developments in the targeting of the sympathetic nervous system as a therapeutic strategy to control hypertension.

'Neuro-adrenergic' overdrive in hypertension

With the advent of sensitive assays for the quantification of plasma noradrenaline concentrations, direct evidence for an elevated activation of the sympathetic nervous system in hypertensive patients was provided.[18] However, this was not a universal finding, perhaps partly owing to the assessment of plasma noradrenaline providing a limited measure of sympathetic nervous activation.[18] Although being a convenient 'global' index of whole-body SNA,[18,19] it is not known whether high levels of circulating noradrenaline result from increased central sympathetic outflow, or can be explained by facilitated release of noradrenaline from peripheral adrenergic stores, or from altered synthesis and metabolism of noradrenaline (for example, altered local reuptake mechanisms).[20] Furthermore, plasma catecholamine measurements neglect the fact that the sympathetic nervous system has distinct organ-specific differential control.[21]

These limitations can be circumvented by more technically advanced, albeit more invasive methods whereby noradrenaline spillover from individual organs can be quantified (for example, brain, heart and kidneys).[19,20] Additionally, direct intraneural recordings of sympathetic vasoconstrictor traffic directed to the cutaneous and skeletal muscle blood vessels can be made using the microneurography technique.[22] Using such approaches, it has been estimated that a neurogenic component is observed in 40–65% of hypertension patients,[2] with studies typically reporting an ~100–200% greater SNA targeting the brain, heart, kidneys and skeletal muscle vasculature in human hypertension.[21,23–27] Furthermore, SNA is elevated in white coat and borderline hypertensives[6,9] and the magnitude of the elevation in SNA is related to the magnitude of hypertension.[28,29] Indeed, Grassi *et al.*[29] reported that the increase in blood pressure from control subjects ($135 \pm 4/83 \pm 3$ mm Hg), to mildly hypertensive ($140 \pm 4/97 \pm 4$ mm Hg), to more severely hypertensive patients ($150 \pm 5/107 \pm 4$ mm Hg) was accompanied by a parallel increase in muscle SNA (40 ± 3, 56 ± 4 and 68 ± 4 bursts per 100 heart beats, respectively). Although, it is acknowledged that reports of an elevation in muscle SNA in hypertension have not been universal.[30] Reductions in cardiac parasympathetic nerve activity, estimated with heart rate variability analyses, are also an established feature of hypertension and have been associated with increased mortality.[31,32]

As in hypertensive patients, studies of the adult spontaneously hypertensive rat (SHR) have also identified a reduced cardiac parasympathetic nerve activity,[33] elevated SNA and increased noradrenaline release.[34,35] Notably, neonatal sympathectomy prevents the SHR from developing hypertension,[36] while our group,[7] and others,[37] have shown that SNA is elevated in young SHR *prior to* the development of hypertension. An amplified burst pattern of SNA that is respiratory related and contributes to the elevations in vascular resistance and blood pressure has also been identified in rat models of hypertension[7,38] while our preliminary investigations suggest alterations in respiratory–sympathetic coupling in human hypertension.[39,40] The functional implications of this remain to be verified.

Clinical implications of elevated SNA

Chronic activation of the sympathetic nervous system is not only associated with raised vasomotor tone and increased cardiac output, but also with a plethora of pathophysiological consequences independent of any increase in blood pressure (Figure 2).[15] Indeed, the infusion of subpressor doses of noradrenaline increases myocardial mass and left ventricle wall thickness in animals,[41] while in patients with hypertension left ventricular hypertrophy is related to elevations in sympathetic outflow determined with microneurography.[42] Furthermore, both left ventricular hypertrophy and high cardiac SNA promote cardiac arrhythmias, and precipitate sudden cardiac death, particularly when parasympathetic tone is low, when it is in neurogenic hypertension.[43,44] Experimental infusion of noradrenaline can elicit vascular remodelling and increase aortic medial thickening[33] without marked changes in mean blood pressure,[45] while vertebral

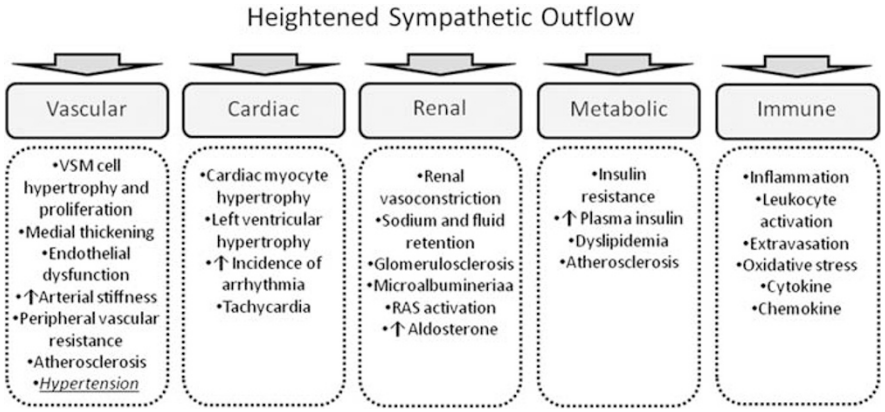

Figure 2 Deleterious consequences of heightened sympathetic neural outflow in hypertension. VSM, vascular smooth muscle cell.

and basilar artery stenosis have been reported in the pre-hypertensive SHR,[16,46] which may be reversed with angiotensin-converting enzyme (ACE) inhibition.[47,48] Such pathophysiological alterations in the vasculature may be expected to modify the functional properties of the blood vessels. Notably, increases in large artery stiffness have been reported in hypertensives and prehypertensives, and have been identified as a powerful predictor of cardiovascular risk in hypertensive humans.[49,50] Notably, increases in muscle SNA are associated with increased carotid–femoral pulse wave velocity, an index of arterial stiffness.[51] Furthermore, Grassi *et al.*[52] demonstrated that local pharmacological blockade of the high tonic sympathetic activity noted in chronic heart failure patients improved the distensibility of the radial artery. Taken together, these findings indicate that sympathetic neural activity can influence the mechanical properties of the arteries. Elevated SNA in pro-atherosclerotic[53] and flow-mediated endothelium-dependent dilatation can be reduced by acute sympathetic activation,[54] while reductions in nitric oxide bioavailability associated with elevations in oxidative stress can augment sympathetic vasoconstriction in the SHR[55] and humans with hypertension.[56] This is significant as endothelial dysfunction is associated with poor survival rates in hypertension.[57] Aside from deleterious alterations in cardiovascular health, sympathetic hyperactivity has also been shown to contribute to metabolic,[58] renal[59] and immune[60] dysfunction, and is an independent risk factor of mortality in several clinical populations.[61–63]

Therapeutic targeting to reduce SNA

Current recommendations for the treatment of hypertension are broadly governed by the severity of the elevation in blood pressure and the coexistence of cardiovascular risk factors, complications and/or target organ damage.[64,65] Standard treatment options include lifestyle modifications (for example, weight loss, physical activity, smoking cessation, alcohol and dietary alterations) and pharmacological treatment (for example, ACE inhibitor, Ang II type 1 receptor (AT1-R) blocker, β-adrenoceptor blocker, calcium channel antagonist, diuretic and α-adrenoceptor blocker). A thorough discussion of this topic is beyond the scope of the present review, but as might be expected the implementation of a specific lifestyle modification should be specific to the needs of the patient (for example, weight loss in the overweight individual), while the choice of pharmacological treatment should be determined by several factors including the presence of co-morbidities (for example, diabetes and coronary artery disease), whether the patient has high cardiac output or peripheral vascular resistance, and the extent to which the patient is responsive to treatment.[64,65]

The potential for SNA lowering in primary hypertension, with conventional pharmacological agents prescribed as a monotherapy or in combination, remains incompletely understood. The activity of both the systemic and tissue RAS in hypertension is upregulated in many patients with primary hypertension.[66] Ang II can directly modulate blood pressure via activation of AT1-R in vascular smooth muscle cells and the kidney, thus causing vasoconstriction and sodium and water retention. AT1-R has also been identified in several other tissues (for example, heart and central nervous system) and may also indirectly modulate blood pressure. Hypertension evoked by chronic infusion of Ang II in experimental normotensive animals is believed to be mediated, at least in part, by amplification of SNA.[67] Yet, in hypertensive animals raised sympathetic nervous system enhances the activity of RAS (Figure 1).[16] The temporal coupling between elevated activation of the sympathetic nervous system and RAS requires clearer elucidation in human hypertension. Irrespectively, it may be argued that successful blood pressure lowering strategies must break into the positive reciprocating feedback

relationship between the sympathetic nervous system and RAS. Inhibition of ACE with imidapril (5–10 mg per day) in hypertensive humans for 12 weeks significantly decreases muscle SNA and blood pressure.[68] ACE inhibition also prevents development of hypertension in newborn SHR.[48] However, reductions in blood pressure with shorter duration ACE inhibitor treatment are not associated with reductions in SNA[69] (2 months, lispinopril, 10 mg per day). This contrasting effect may be related to differing pharmokinetic properties of the drugs, interactions with the blood–brain barrier and methods of SNA assessment. Nevertheless, the observation that SNA remains elevated whereas Ang II and blood pressure are lowered with ACE inhibition[69] suggests that changes in SNA and RAS do not always occur in parallel and may be independently regulated in hypertension. Krum *et al.*[70] reported no alteration in muscle SNA or whole-body norepinephrine spillover following 4 weeks administration of AT1-R antagonism with eprosartan (600 mg per day) or losartan (50 mg per day) in patients with uncomplicated hypertension. β-adrenergic blockade also appears to have a negligible effect on muscle SNA in human hypertension (6–29 weeks, metoprolol, 200 mg per day).[71] However, the actions of metoprolol within the central nervous system appear to exert favourable effects on the failing rat heart, likely due to reductions in cardiac sympathetic outflow.[72] Whether these previously unrecognised pleiotropic effects of β-adrenergic blockade are manifested in human hypertension remains to be determined. Of note, despite lowering blood pressure certain diuretics (for example, chlorthalidone[73]), dihydropridine calcium channel blockers[74] and combination therapies (for example, AT1-R antagonism plus diuretic[75]) may actually raise SNA due to baroreceptor unloading. Said differently, assuming the baroreceptors are not desensitised by these drugs, a fall in arterial pressure may trigger a baroreflexly mediated increase in sympathetic activity and arterial pressure.

Ganglionic blockade (for example, hexamethonium), reserpine and guanethidine were early pharmacological approaches (replacing sympathectomy) to directly interrupt SNA in hypertensives.[76] Although blood pressure lowering could be successfully achieved, these strategies suffered from side effects, for example the vagolytic effects of ganglionic blockade can elicit constipation, mydriasis and impotence.[76] Alternatively, central pharmacological inhibition of SNA may be achieved by administration of sympatholytic agents, which act on α_2-adrenoceptors or imidazoline receptors within the brain.[27] Based on animal experiments, central activity generated by catecholamine-containing neurons (for example, C1 and A2) may contribute to high levels of sympathetic activity as has been described in the SHR.[77] Both α-methyldopa and clonidine have been recognised as antihypertensive agents for many years, although side effects such as orthostatic intolerance have limited their widespread use.[78] Newer central sympatholytics such as moxonidine and rilmenidine appear to be better tolerated, and shown to reduce SNA and blood pressure in humans.[79,80] The time course of the relationship between reductions in SNA and blood pressure during treatment with such central sympatholytic agents is presently unknown, although examining this may provide a mechanistic insight into the temporal coupling between sympathetic and vasomotor tone in hypertension, especially if the effect is reversible.

Non-pharmacological, lifestyle interventions have been associated with reductions in SNA and blood pressure in hypertension. Anecdotal reports indicating a hypotensive effect of acute aerobic exercise (for example, running) first arose in the 19th century,[81] and since then a substantial number of studies have highlighted the blood pressure lowering effects of aerobic endurance exercise training in patients with hypertension.[82] Indeed, regular (3–5 days per week), moderate intensity (50–80% of maximal oxygen consumption) exercise using a large muscle mass (for example, jogging, cycling and swimming) appears to achieve a 10 mm Hg average fall in systolic and diastolic blood pressure in hypertensive patients.[82] To the authors' knowledge, only one study in humans has examined the potential sympatho-inhibitory effects of exercise training in hypertensive patients. Laterza *et al.*[83] reported that a 4-month programme of aerobic exercise training reduced muscle SNA (by ~37%) and blood pressure (145/94 to 130/84 mm Hg) in never-treated hypertensives. Exercise training consisted of three 60 min exercise sessions per week, comprising stretching exercise (10 min), leg cycling (40 min at 70% of maximal oxygen consumption) and resistance exercise (10 min). Although the mechanism underlying the impressive reduction in sympathetic neural activity remains unclear, the ability of exercise to upregulate central antioxidant concentrations, reduce pro-oxidant levels and increase central nitric oxide synthase activity (endothelial function) have been shown.[84] Weight loss following exercise training and/or caloric intake can also reduce SNA,[85,86] which is significant given that a neurogenic component to obesity-related hypertension has been implied.[87] Chronic psychosocial stress has been associated with heighted sympathetic activation and high blood pressure,[88] thus stress reduction measures may reduce SNA and blood pressure in hypertension. In a recent meta-analysis, transcendental meditation was reported to effectively lower blood pressure in patients with hypertension, whereas psychological approaches to stress management were deemed ineffective.[89] Intriguingly, the results of several studies indicate that device-guided, home-based training with slow, deep breathing can effectively reduce blood pressure in patients with hypertension,[90–92] although this has

not been a universal finding.[93] These findings are particularly intriguing given the recent identification of an amplified bursting of SNA related to the respiratory cycle that appears to contribute to the progression and maintenance of hypertension in rats,[7] and the alterations in respiratory–sympathetic coupling recently reported in human hypertension.[39,40] Further studies are required to determine whether central sympathetic outflow is decreased by stress reduction programs, which effectively reduce blood pressure.

Drug-resistant hypertension—how to treat?

The success of a treatment paradigm in lowering blood pressure via targeting the sympathetic nervous system may depend upon the timing of an intervention. Indeed, the pathophysiological progression of the disease state may be important in terms of guiding treatment regimes (or preventative treatment). In fact, certain drugs may fail to reduce SNA because other drivers of SNA have emerged or become predominant in elevating SNA, and these are independent of the standard armoury of antihypertensive strategies and better-described 'early' mechanisms. Notably, of the one-billion individuals worldwide with hypertension,[94] it is estimated that ~20% have resistant hypertension, defined as elevated blood pressure despite treatment with three or more antihypertensive medications of different classes.[95] The scale of this problem highlights the need to better understand the underlying causal mechanisms, optimise existing treatment strategies and develop new approaches.

Surgical methods have shown recent promise in tackling refractory or drug-resistant hypertension. Such approaches include ablation of afferent and efferent renal artery nerves, carotid baroreflex stimulation and deep brain stimulation. As these have been the subject of recent detailed reviews,[96,97] they will only be mentioned briefly here. It has been known for some time that renal denervation reduces blood pressure in several experimental animal models of hypertension.[59] Subsequent to ground breaking human work by Krum *et al.*[13] in a recent multicentre, prospective, randomised trial, catheter-based renal sympathetic denervation in patients with resistant hypertension was shown to elicit marked and sustained blood pressure lowering.[12] Indeed, the Simplicity HTN-2 trial reported reductions in office-based blood pressure from 178/96 to 146/84 mm Hg 6 months after the catheter-based renal denervation procedure in treatment-resistant hypertensives ($n=52$).[12] Notably, all patients remained on hypertensive medication, although crucially no deleterious effect on renal function was observed and no serious complications relating to the device or surgical procedure were noted over this period. However, the efficacy of this approach in longer-term blood pressure lowering and the potential benefit to patients with less marked hypertension remains to be determined as do the mechanisms through which this treatment works. Physiological increases in renal SNA have multiple pro-hypertensive effects including increased renin secretion, sodium retention and renal vasoconstriction,[59] thus ablation of efferent renal SNA is likely to be a major contributor to the consequent blood pressure lowering. However, renal denervation has also been shown to elicit marked reductions in muscle SNA (by ~66%) at 1 and 12 months after the procedure, suggesting that removal of sensory afferent activity from the kidney and a consequent general suppression of sympathetic vasoconstrictor drive may also make an important contribution to the antihypertensive effects of this treatment.[98]

Following animal studies first conducted over 50 years ago[99,100] and extensive technical development work,[101,102] surgical implantation of a device eliciting chronic carotid baroreflex stimulation (Rheo, CVRx, Minneapolis, MN, USA) has recently been demonstrated to effectively lower blood pressure and muscle SNA in humans.[14,71,72,103,104] This has been based on the recently resurrected idea that arterial baroreceptors control arterial pressure in the long term.[105] In his original study, Thrasher (2002) showed that unloading of baroreceptors at one carotid sinus (with all other arterial baroreceptors denervated) caused a sustained pressor response lasting up to 3 weeks in conscious dogs.[105] Lohmeier *et al.*[106] electrically stimulated the carotid sinus directly and also showed reductions in arterial pressure for up to 3 weeks. Subsequently, carotid sinus stimulation has been performed in humans with hypertension. This requires placement of a battery-powered impulse generator at the infraclavicular space and surgical exposure of the carotid sinus for bilateral placement of electrodes around the carotid sinus adventitia. This avoids activation of the carotid sinus nerve containing the peripheral chemoreceptor afferents that are sympathoexcitatory in function. It also bypasses the baroreceptor transducer (mechanoreceptor), which is prone to adaptation when exposed to persistently high blood pressure.[107,108] Potential caveats to this approach include its relative invasive nature compared with the renal nerve ablation technique, the potential for peri-operative complications and that significant blood pressure lowering is not always evident.[14]

Intriguingly, deep brain stimulation of the ventrolateral periaqueductal grey matter area has also been shown to effectively reduce blood pressure in refractory hypertension.[109,110] Animal studies have identified the ventrolateral periaqueductal grey as a depressor area and shown that its stimulation elicits hypotension with peripheral vasodilatation, indicative of sympathetic withdrawal.[111] Owing to its analgesic effects, this region is clinically targeted with chronic electrical stimulation in patients with chronic pain, however long-term blood pressure lowering can be independent of pain.[110] Notably, in

one particular patient, the normalisation of blood pressure with deep brain stimulation meant that all prescribed antihypertensive medications could be withdrawn and when the stimulator was turned off after 3 years, blood pressure remained low, suggesting that a central resetting of blood pressure control had occurred.[110]

New horizons in central regulation of SNA in hypertension

Recent progress in the elucidation of the central pathways contributing to the genesis of neurogenic hypertension may precipitate the next generation of therapeutic strategies for hypertensive patients. In this rapidly developing field, a multitude of putative mechanisms and potentially interconnected working hypotheses are emerging, which implicate functional alterations in several autonomic nuclei, neurotransmitters, neuromodulators, circulating factors and peripheral afferent inputs in neurogenic hypertension. A perspective on the potential actions and interactions of Ang II, inflammation and vascular dysfunction follows.

The brainstem is the principal regulatory site of central sympathetic outflow (Figure 3).[112] Sympathetic pre-ganglionic neurones located in the intermediolateral cell column of the spinal cord receive strong excitatory drive from 'pre-sympathetic' motoneurones of the rostral ventrolateral medulla (RVLM)—a 'vasomotor centre' located within the medulla oblongata. This intrinsic excitatory drive from the RVLM may be modulated by neural inputs from supramedullary sites (for example, pontine and hypothalamic regions) and local chemical mediators. Oxidative stress in the brain (for example, at the RVLM and paraventricular nucleus) contributes to neurogenic hypertension in the SHR and stroke-prone SHR[17,113,114] and renovascular hypertension[115] (Figure 4). Increased reactive oxygen species (for example, superoxide) may directly activate or sensitise sympathetic neurones and also scavenge nitric oxide, which ordinarily acts to tonically restrain central sympathetic outflow.[17] A major source of central reactive oxygen species generation in the hypertensive brain is the enzyme NADPH oxidase, which can be upregulated via activation of AT1-Rs.[17,79,116] Notably, renal SNA is increased following upregulation of NADPH oxidase in the RVLM.[117] While elevated local brain RAS has been implicated in the upregulation of NADPH,[118] the observation that experimental renovascular hypertension (2-kidney 1-clip rat model) elicits increased oxidative stress at the RVLM and neurogenic hypertension suggests that elevated circulating Ang II may also be able to promote central prooxidant and hypertensive effects.[114,115] The central actions of circulating Ang II may occur by its actions at the circumventricular organs, which lack a blood–brain barrier and are rich in AT1-Rs.[119]

The interaction between the sympathetic nervous system and RAS is well established. It has been

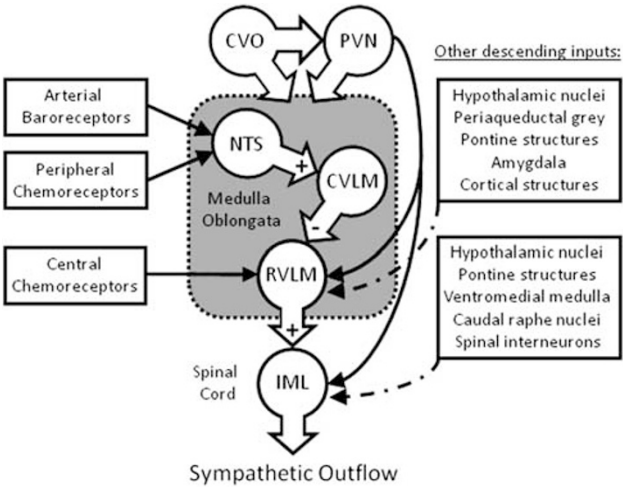

Figure 3 Central neural sites involved in the regulation of sympathetic outflow. CVLM, caudal ventrolateral medulla; CVO, circumventricular organs; IML, intermediolateral cell column; PVN, paraventricular nucleus; RVLM, rostral ventrolateral medulla.

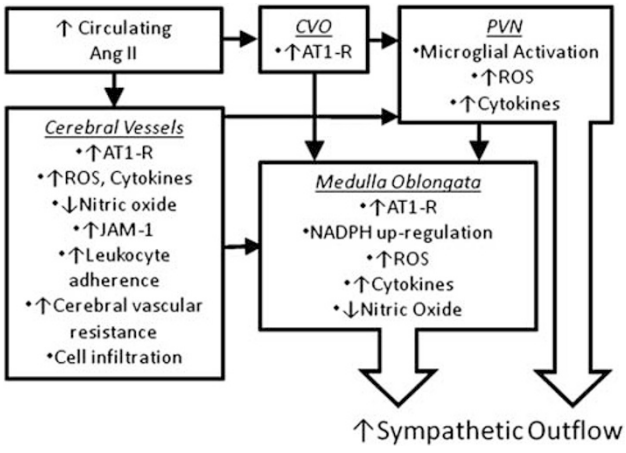

Figure 4 Putative contribution of angiotensin II (Ang II), inflammation and vascular dysfunction to elevated sympathetic neural outflow in hypertension. Elevated circulating Ang II activates AT1 receptors (AT1-R) at the circumventricular organs (CVO) and/or paraventricular nucleus (PVN) directly. The resultant signals cause microglial activation, increased reactive oxygen species (ROS) and cytokine generation in the PVN. Nicotinamide adenine dinucleotide phosphate-mediated increase in oxidative stress in autonomic nuclei within the medulla oblongata (for example, RVLM) also results as a consequence of Ang II activity. Increased oxidative stress and cytokine concentration at the PVN and RVLM augment sympathetic neuronal activity. Sympathetic neural outflow will also be facilitated by the upregulation of AT1-R on cerebral blood vessels due to elevated circulating Ang II levels. The associated local oxidative stress, inflammation and upregulation of junctional adhesion molecules (for example, junctional adhesion molecule-1) promote leukocyte adhesion within the brain microvasculature. The subsequently increased cerebral vascular tone could impair perfusion, cause local tissue hypoxia and evoke reflex sympathoexcitation (that is, Cushing response).

known since 1961 that increased circulating angiotensin stimulates the sympathetic nervous system,[120] while renal sympathetic activation facilitates renin release from the juxtaglomerular apparatus. The sympathetic nervous system and RAS share a number of common pro-hypertensive actions (for example, increased vascular resistance and endothelial dysfunction) and both have been implicated in activating the immune system.[60,121,122] Primary hypertension is associated with increased circulating concentration of several inflammatory molecules such as tumour necrosis factor alpha (TNFα), interleukin-6, C-reactive protein and adhesion molecules (for example, P-selectin and intercellular adhesion molecule-1), and vascular inflammation may contribute to the pathophysiology of hypertension.[88,123,124] T-lymphocytes appear particularly critical for Ang II and deoxycorticosterone acetate-salt-induced hypertension and the concomitant vascular and kidney dysfunction.[121,122,125] T-cell activation is increased by Ang II and leads to the production of pro-inflammatory cytokines.[121] Intriguingly, anti-TNFα therapy (etanercept) has been shown to prevent Ang II-induced hypertension and vascular oxidative stress.[121]

The importance of peripheral vascular inflammation in hypertension is clear;[123] however, the significance of inflammation within the microvasculature of the brainstem is also gaining increased recognition. Waki *et al.* (2007) demonstrated that inducing inflammation in the brainstem triggered hypertension in a normotensive rat.[126] Specifically, increased expression of junctional adhesion molecule-1 in normotensive rats led to leukocyte adhesion in the microvasculature of the nucleus of the solitary tract (NTS) and hypertension. Importantly, junctional adhesion molecule-1 expression is significantly increased in the NTS of the SHR,[126] and it is possible that the resulting leukocyte accumulation can cause platelet aggregation, cellular migration and infiltration and cytokine release. As indicated below, the latter could then directly or indirectly influence central autonomic control and raise blood pressure.[126] Intriguingly, single-nucleotide polymorphisms in the junctional adhesion molecule-1 gene have recently been associated with blood pressure on a population-wide basis.[127]

Experimental elevations in Ang II have been shown to concomitantly raise blood pressure and cause central inflammation and oxidative stress.[114] Specifically, Ang II-mediated hypertension is associated with increased brain levels of TNFα, nuclear factor κB and reactive oxygen species.[128,129] Studies by Raizada and colleagues[130] suggest that Ang II infusion increases microglial cell and pro-inflammatory cytokine activation at the paraventricular nucleus, a region which receives descending neural inputs from the circumventricular organs. Notably, intracerebroventricular administration of the anti-inflammatory antibiotic minocycline inhibits the Ang II-mediated hypertension and the activation of microglia and cytokines. The effects of administering antibiotics anti-inflammatory properties, such as minocycline, on SNA in human hypertension remain to be determined. In fact, most studies to date that have examined the relationship between the sympathetic nervous system and immune system have focused on one arm of this interaction, that is, sympathetic modulation of immune cells in various lymphoid organs.[60] However, accumulating evidence from animal investigations suggests that pro-inflammatory cytokines are powerful modulators of central neural circuits responsible for regulating sympathetic nerve discharge.[131–133] Intracerebroventricular administration of interleukin-6 increases splenic SNA,[134] while central administration of IL-1β increases adrenal, splenic and renal SNA.[135] Furthermore, microinjection of interleukin-6 into the NTS decreases baroreflex sensitivity,[131] while abnormal gene expression of specific inflammatory molecules have been identified in the NTS in the SHR (for example, chemokine CcI5), which may contribute to the hypertensive phenotype.[136] Injection of TNFα into central sympathetic nuclei, such as the paraventricular nucleus and RVLM, increases SNA, blood pressure and heart rate in rats.[137] Intravenous administration of TNFα elicits similar sympathetic and cardiovascular effects.[137] This suggests that although blood-borne cytokines do not readily cross the blood–brain barrier, they still may trigger the central neurocircuitry-mediating alterations in sympathetic function possibly by acting via the circumventricular organ or a soluble mediator (for example, prostaglandins).[137] In addition, the disruption of blood–brain barrier integrity in hypertension may permit infiltration of inflammatory cells into the brain parachyma, thus precipitating microglial cell activation and elevating pro-inflammatory cytokine levels at central sites, such as the paraventricular nucleus, consequently augmenting central sympathetic outflow.[130]

Aside from elevating central cytokine concentration, leukocyte accumulation within the brain microvasculature may precipitate neurogenic hypertension by raising cerebral vascular resistance, impairing perfusion and causing local tissue hypoxia (that is, Cushing response).[16,138] Neurons within the RVLM and spinal cord are known to be sensitive to hypoxia and can produce sympathoexcitation.[139,140] In humans, arterial compression at the ventrolateral medulla elevates muscle SNA[141] and causes hypertension, which can be reversed by surgical decompression.[142] Intriguingly, narrower lumens and thicker vessel walls are observed in the vertebral and basilar arteries of the pre-hypertensive SHR compared with normotensive rats.[16,143] Similarly, in humans with hypertension, the vertebral arteries also appear to be narrowed and thickened and their vascular resistance is highly correlated with arterial pressure levels.[138] It has

been proposed that triggering of SNA and systemic hypertension in response to inadequate cerebral blood flow is a protective mechanism to maintain perfusion.[16,46,143,144] This warrants further exploration as a potential mediator of human hypertension.

Perspective

Accumulating evidence suggests that neurogenic hypertension is associated with a triangulation of raised Ang II, inflammation and vascular dysfunction/brain hypoperfusion, where each intercommunicates positively and reciprocally setting up a cascade of interrelated cardiovascular pathology, which becomes increasingly more difficult to treat with time (Figure 1). The resultant increase in central oxidative stress drives up central sympathetic outflow to the periphery, but in a vicious cycle this itself can potentiate increases in Ang II and consequently drive inflammation and vascular dysfunction.[16,17,116,121] Breaking into this vicious cycle could be the key to successful treatment of neurogenic hypertension. However, the success of a therapeutic strategy may vary as the pathophysiology of this dynamic condition changes. As more positive feedback loops between Ang II, inflammation and vascular dysfunction/brain hypoperfusion are established over time, the hypertension may become more resistant to treatment, and ultimately refractory. Tremendous advances have been made in the development of blood pressure lowering strategies, but the staggering prevalence of the condition, particularly resistant hypertension ($\sim$20% of hypertension),[95] highlights that we do not fully understand the aetiology of the disease, particularly in the later stages. Given the costs associated with the development of completely new strategies for targeting hypertension, the optimisation of present strategies is desirable.[95] We propose that the overactivity of the sympathetic nervous system is both a major early prognostic indicator for hypertension and conspirator affecting the heart, vasculature, RAS and immune system. As sympathetic overactivity appears to be present before the hypertensive phenotype,[7,9,28] its early antagonism should be considered a potential preventative measure before end organ damage becomes irreversible and hypertension becomes drug resistant. This implies that SNA should be measured in patients first presenting hypertensive trends and targeted to arrest the inevitable pathological cascade and ultimate disease progression. It is tempting to speculate that early targeting of an overactive sympathetic nervous system would reduce the likelihood of future progression to drug-resistant hypertension.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The authors acknowledge the support of the British Heart Foundation and the National Institutes of Health (HL033610). JFR Paton is a recipient of a Royal Society Wolfson Research Merit Award.

References

1 Carretero OA, Oparil S. Essential hypertension. Part I: definition and etiology. *Circulation* 2000; **101**(3): 329–335.
2 Esler M. The 2009 Carl Ludwig Lecture: pathophysiology of the human sympathetic nervous system in cardiovascular diseases: the transition from mechanisms to medical management. *J Appl Physiol* 2010; **108**(2): 227–237.
3 Esler M, Lambert E, Schlaich M. Point: chronic activation of the sympathetic nervous system is the dominant contributor to systemic hypertension. *J Appl Physiol* 2010; **109**(6): 1996–1998; discussion 2016.
4 Folkow B. Physiological aspects of primary hypertension. *Physiol Rev* 1982; **62**(2): 347–504.
5 Navar LG. Counterpoint: activation of the intrarenal renin-angiotensin system is the dominant contributor to systemic hypertension. *J Appl Physiol* 2010; **109**(6): 1998–2000; discussion 2015.
6 Anderson EA, Sinkey CA, Lawton WJ, Mark AL. Elevated sympathetic nerve activity in borderline hypertensive humans. Evidence from direct intraneural recordings. *Hypertension* 1989; **14**(2): 177–183.
7 Simms AE, Paton JF, Pickering AE, Allen AM. Amplified respiratory-sympathetic coupling in the spontaneously hypertensive rat: does it contribute to hypertension? *J Physiol* 2009; **587**(Part 3): 597–610.
8 Smith PA, Graham LN, Mackintosh AF, Stoker JB, Mary DA. Sympathetic neural mechanisms in white-coat hypertension. *J Am Coll Cardiol* 2002; **40**(1): 126–132.
9 Smith PA, Graham LN, Mackintosh AF, Stoker JB, Mary DA. Relationship between central sympathetic activity and stages of human hypertension. *Am J Hypertens* 2004; **17**(3): 217–222.
10 Morrissey DM, Brookes VS, Cooke WT. Sympathectomy in the treatment of hypertension; review of 122 cases. *Lancet* 1953; **1**(6757): 403–408.
11 Krum H, Sobotka P, Mahfoud F, Bohm M, Esler M, Schlaich M. Device-based antihypertensive therapy: therapeutic modulation of the autonomic nervous system. *Circulation* 2011; **123**(2): 209–215.
12 Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; **376**(9756): 1903–1909.
13 Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K *et al.* Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; **373**(9671): 1275–1281.
14 Wustmann K, Kucera JP, Scheffers I, Mohaupt M, Kroon AA, de Leeuw PW *et al.* Effects of chronic baroreceptor stimulation on the autonomic cardiovascular regulation in patients with drug-resistant

arterial hypertension. *Hypertension* 2009; **54**(3): 530–536.
15 Fisher JP, Young CN, Fadel PJ. Central sympathetic overactivity: maladies and mechanisms. *Auton Neurosci* 2009; **148**(1–2): 5–15.
16 Paton JF, Waki H, Abdala AP, Dickinson J, Kasparov S. Vascular-brain signaling in hypertension: role of angiotensin II and nitric oxide. *Curr Hypertens Rep* 2007; **9**(3): 242–247.
17 Peterson JR, Sharma RV, Davisson RL. Reactive oxygen species in the neuropathogenesis of hypertension. *Curr Hypertens Rep* 2006; **8**(3): 232–241.
18 Goldstein DS. Plasma catecholamines and essential hypertension. An analytical review. *Hypertension* 1983; **5**(1): 86–99.
19 Grassi G, Esler M. How to assess sympathetic activity in humans. *J Hypertens* 1999; **17**(6): 719–734.
20 Esler M, Jennings G, Lambert G, Meredith I, Horne M, Eisenhofer G. Overflow of catecholamine neurotransmitters to the circulation: source, fate, and functions. *Physiol Rev* 1990; **70**(4): 963–985.
21 Esler M, Lambert G, Jennings G. Increased regional sympathetic nervous activity in human hypertension: causes and consequences. *J Hypertens Suppl* 1990; **8**(7): S53–S57.
22 Vallbo AB, Hagbarth KE, Torebjork HE, Wallin BG. Somatosensory, proprioceptive, and sympathetic activity in human peripheral nerves. *Physiol Rev* 1979; **59**(4): 919–957.
23 Esler M, Jennings G, Korner P, Willett I, Dudley F, Hasking G *et al.* Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. *Hypertension* 1988; **11**(1): 3–20.
24 Grassi G, Colombo M, Seravalle G, Spaziani D, Mancia G. Dissociation between muscle and skin sympathetic nerve activity in essential hypertension, obesity, and congestive heart failure. *Hypertension* 1998; **31**(1): 64–67.
25 Huggett RJ, Burns J, Mackintosh AF, Mary DA. Sympathetic neural activation in nondiabetic metabolic syndrome and its further augmentation by hypertension. *Hypertension* 2004; **44**(6): 847–852.
26 Lambert E, Straznicky N, Schlaich M, Esler M, Dawood T, Hotchkin E *et al.* Differing pattern of sympathoexcitation in normal-weight and obesity-related hypertension. *Hypertension* 2007; **50**(5): 862–868.
27 Esler M, Lambert G, Vaz M, Thompson J, Kaye D, Kalff V *et al.* Central nervous system monoamine neurotransmitter turnover in primary and obesity-related human hypertension. *Clin Exp Hypertens* 1997; **19**(5–6): 577–590.
28 Grassi G. Role of the sympathetic nervous system in human hypertension. *J Hypertens* 1998; **16**(12 Part 2): 1979–1987.
29 Grassi G, Cattaneo BM, Seravalle G, Lanfranchi A, Mancia G. Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. *Hypertension* 1998; **31**(1): 68–72.
30 Joyner MJ, Charkoudian N, Wallin BG. A sympathetic view of the sympathetic nervous system and human blood pressure regulation. *Exp Physiol* 2008; **93**(6): 715–724.
31 Singh JP, Larson MG, Tsuji H, Evans JC, O'Donnell CJ, Levy D. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. *Hypertension* 1998; **32**(2): 293–297.
32 Gerritsen J, Dekker JM, TenVoorde BJ, Kostense PJ, Heine RJ, Bouter LM *et al.* Impaired autonomic function is associated with increased mortality, especially in subjects with diabetes, hypertension, or a history of cardiovascular disease: the Hoorn Study. *Diabetes Care* 2001; **24**(10): 1793–1798.
33 Friberg P, Karlsson B, Nordlander M. Sympathetic and parasympathetic influence on blood pressure and heart rate variability in Wistar-Kyoto and spontaneously hypertensive rats. *J Hypertens Suppl* 1988; **6**(4): S58–S60.
34 Judy WV, Farrell SK. Arterial baroreceptor reflex control of sympathetic nerve activity in the spontaneously hypertensive rat. *Hypertension* 1979; **1**(6): 605–614.
35 Lundin S, Ricksten SE, Thoren P. Renal sympathetic activity in spontaneously hypertensive rats and normotensive controls, as studied by three different methods. *Acta Physiol Scand* 1984; **120**(2): 265–272.
36 Cabassi A, Vinci S, Calzolari M, Bruschi G, Borghetti A. Regional sympathetic activity in pre-hypertensive phase of spontaneously hypertensive rats. *Life Sci* 1998; **62**(12): 1111–1118.
37 Korner P, Bobik A, Oddie C, Friberg P. Sympathoadrenal system is critical for structural changes in genetic hypertension. *Hypertension* 1993; **22**(2): 243–252.
38 Zoccal DB, Paton JF, Machado BH. Do changes in the coupling between respiratory and sympathetic activities contribute to neurogenic hypertension? *Clin Exp Pharmacol Physiol* 2009; **36**(12): 1188–1196.
39 Fisher JP, McIntyre D, Farquhar WB, Pickering AE, Lip GYH, Paton JFR. Influence of respiratory phase on muscle sympathetic nerve activity in human hypertension. *FASEB J* 2011; **25**: 1076.2.
40 Fisher JP, Reynolds RF, Farquhar WB, Pickering AE, Lip GYH, Paton JFR. Respiratory modulation of muscle sympathetic nerve activity in patients with hypertension. *Proc Physiol Soc* 2010; **20**: PC28.
41 Patel MB, Loud AV, King BD, Anversa P, Sack D, Hintze TH. Global myocardial hypertrophy in conscious dogs with chronic elevation of plasma norepinephrine levels. *J Mol Cell Cardiol* 1989; **21** (Suppl 5): 49–61.
42 Burns J, Sivananthan MU, Ball SG, Mackintosh AF, Mary DA, Greenwood JP. Relationship between central sympathetic drive and magnetic resonance imaging-determined left ventricular mass in essential hypertension. *Circulation* 2007; **115**(15): 1999–2005.
43 Lown B, Verrier RL. Neural activity and ventricular fibrillation. *N Engl J Med* 1976; **294**(21): 1165–1170.
44 Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; **322**(22): 1561–1566.
45 Dao HH, Lemay J, de Champlain J, deBlois D, Moreau P. Norepinephrine-induced aortic hyperplasia and extracellular matrix deposition are endothelin-dependent. *J Hypertens* 2001; **19**(11): 1965–1973.
46 Paton JF, Dickinson CJ, Mitchell G. Harvey Cushing and the regulation of blood pressure in giraffe, rat and man: introducing 'Cushing's mechanism'. *Exp Physiol* 2009; **94**(1): 11–17.

47 Harrap SB. Angiotensin converting enzyme inhibitors, regional vascular hemodynamics, and the development and prevention of experimental genetic hypertension. *Am J Hypertens* 1991; **4**(3 Part 2): 212S–216S.
48 Harrap SB, Van der Merwe WM, Griffin SA, Macpherson F, Lever AF. Brief angiotensin converting enzyme inhibitor treatment in young spontaneously hypertensive rats reduces blood pressure long-term. *Hypertension* 1990; **16**(6): 603–614.
49 Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* 1999; **33**(5): 1111–1117.
50 Gedikli O, Kiris A, Ozturk S, Baltaci D, Karaman K, Durmus I *et al.* Effects of prehypertension on arterial stiffness and wave reflections. *Clin Exp Hypertens* 2010; **32**(2): 84–89.
51 Swierblewska E, Hering D, Kara T, Kunicka K, Kruszewski P, Bieniaszewski L *et al.* An independent relationship between muscle sympathetic nerve activity and pulse wave velocity in normal humans. *J Hypertens* 2010; **28**(5): 979–984.
52 Grassi G, Giannattasio C, Failla M, Pesenti A, Peretti G, Marinoni E *et al.* Sympathetic modulation of radial artery compliance in congestive heart failure. *Hypertension* 1995; **26**(2): 348–354.
53 Kaplan JR, Manuck SB. Using ethological principles to study psychosocial influences on coronary atherosclerosis in monkeys. *Acta Physiol Scand Suppl* 1997; **640**: 96–99.
54 Hijmering ML, Stroes ES, Olijhoek J, Hutten BA, Blankestijn PJ, Rabelink TJ. Sympathetic activation markedly reduces endothelium-dependent, flow-mediated vasodilation. *J Am Coll Cardiol* 2002; **39**(4): 683–688.
55 Miyagawa K, Ohashi M, Yamashita S, Kojima M, Sato K, Ueda R *et al.* Increased oxidative stress impairs endothelial modulation of contractions in arteries from spontaneously hypertensive rats. *J Hypertens* 2007; **25**(2): 415–421.
56 Lembo G, Vecchione C, Izzo R, Fratta L, Fontana D, Marino G *et al.* Noradrenergic vascular hyper-responsiveness in human hypertension is dependent on oxygen free radical impairment of nitric oxide activity. *Circulation* 2000; **102**(5): 552–557.
57 Perticone F, Ceravolo R, Pujia A, Ventura G, Iacopino S, Scozzafava A *et al.* Prognostic significance of endothelial dysfunction in hypertensive patients. *Circulation* 2001; **104**(2): 191–196.
58 Landsberg L. Insulin-mediated sympathetic stimulation: role in the pathogenesis of obesity-related hypertension (or, how insulin affects blood pressure, and why). *J Hypertens* 2001; **19**(3 Part 2): 523–528.
59 DiBona GF, Esler M. Translational medicine: the antihypertensive effect of renal denervation. *Am J Physiol Regul Integr Comp Physiol* 2010; **298**(2): R245–R253.
60 Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev* 2000; **52**(4): 595–638.
61 Barretto AC, Santos AC, Munhoz R, Rondon MU, Franco FG, Trombetta IC *et al.* Increased muscle sympathetic nerve activity predicts mortality in heart failure patients. *Int J Cardiol* 2008; **135**(3): 302–307.
62 Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS *et al.* Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984; **311**(13): 819–823.
63 Zoccali C, Mallamaci F, Parlongo S, Cutrupi S, Benedetto FA, Tripepi G *et al.* Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation* 2002; **105**(11): 1354–1359.
64 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL *et al.* Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003; **42**(6): 1206–1252.
65 Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF *et al.* Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004; **18**(3): 139–185.
66 Catt KJ, Cran E, Zimmet PZ, Best JB, Cain MD, Coghlan JP. Angiotensin II blood-levels in human hypertension. *Lancet* 1971; **1**(7697): 459–464.
67 Ferrario CM. Neurogenic actions of angiotensin II. *Hypertension* 1983; **5**(6 Part 3): V73–V79.
68 Miyajima E, Shigemasa T, Yamada Y, Tochikubo O, Ishii M. Angiotensin II blunts, while an angiotensin-converting enzyme inhibitor augments, reflex sympathetic inhibition in humans. *Clin Exp Pharmacol Physiol* 1999; **26**(10): 797–802.
69 Grassi G, Turri C, Dell'Oro R, Stella ML, Bolla GB, Mancia G. Effect of chronic angiotensin converting enzyme inhibition on sympathetic nerve traffic and baroreflex control of the circulation in essential hypertension. *J Hypertens* 1998; **16**(12 Part 1): 1789–1796.
70 Krum H, Lambert E, Windebank E, Campbell DJ, Esler M. Effect of angiotensin II receptor blockade on autonomic nervous system function in patients with essential hypertension. *Am J Physiol Heart Circ Physiol* 2006; **290**(4): H1706–H1712.
71 Wallin BG, Sundlof G, Stromgren E, Aberg H. Sympathetic outflow to muscles during treatment of hypertension with metoprolol. *Hypertension* 1984; **6**(4): 557–562.
72 Gourine A, Bondar SI, Spyer KM, Gourine AV. Beneficial effect of the central nervous system beta-adrenoceptor blockade on the failing heart. *Circ Res* 2008; **102**(6): 633–636.
73 Menon DV, Arbique D, Wang Z, Adams-Huet B, Auchus RJ, Vongpatanasin W. Differential effects of chlorthalidone versus spironolactone on muscle sympathetic nerve activity in hypertensive patients. *J Clin Endocrinol Metab* 2009; **94**(4): 1361–1366.
74 Grassi G, Seravalle G, Turri C, Bolla G, Mancia G. Short-versus long-term effects of different dihydropyridines on sympathetic and baroreflex function in hypertension. *Hypertension* 2003; **41**(3): 558–562.
75 Fu Q, Zhang R, Witkowski S, Arbab-Zadeh A, Prasad A, Okazaki K *et al.* Persistent sympathetic activation during chronic antihypertensive therapy: a potential mechanism for long term morbidity? *Hypertension* 2005; **45**(4): 513–521.
76 DeQuattro V, Li D. Sympatholytic therapy in primary hypertension: a user friendly role for the future. *J Hum Hypertens* 2002; **16**(Suppl 1): S118–S123.
77 Duale H, Waki H, Howorth P, Kasparov S, Teschemacher AG, Paton JF. Restraining influence of A2

neurons in chronic control of arterial pressure in spontaneously hypertensive rats. *Cardiovasc Res* 2007; **76**(1): 184–193.
78 Amery AK, Bossaert H, Fagard RH, Verstraete M. Clonidine versus methyldopa. A double blind cross-over study comparing side effects of clonidine and methyldopa administered together with chlorthalidone at a dosage producing the same blood pressure lowering effect. *Acta Cardiol* 1972; **21**(1): 82–99.
79 Wenzel RR, Spieker L, Qui S, Shaw S, Luscher TF, Noll G. I1-imidazoline agonist moxonidine decreases sympathetic nerve activity and blood pressure in hypertensives. *Hypertension* 1998; **32**(6): 1022–1027.
80 Esler M, Lux A, Jennings G, Hastings J, Socratous F, Lambert G. Rilmenidine sympatholytic activity preserves mental stress, orthostatic sympathetic responses and adrenaline secretion. *J Hypertens* 2004; **22**(8): 1529–1534.
81 Tipton CM. Concerning postexercise hypotension. *Exerc Sport Sci Rev* 2011; **39**(2): 109.
82 American College of Sports Medicine. Position stand. Physical activity, physical fitness, and hypertension. *Med Sci Sports Exerc* 1993; **25**(10): i–x.
83 Laterza MC, de Matos LD, Trombetta IC, Braga AM, Roveda F, Alves MJ *et al.* Exercise training restores baroreflex sensitivity in never-treated hypertensive patients. *Hypertension* 2007; **49**(6): 1298–1306.
84 Zucker IH, Patel KP, Schultz HD, Li YF, Wang W, Pliquett RU. Exercise training and sympathetic regulation in experimental heart failure. *Exerc Sport Sci Rev* 2004; **32**(3): 107–111.
85 Straznicky NE, Lambert EA, Nestel PJ, McGrane MT, Dawood T, Schlaich MP *et al.* Sympathetic neural adaptation to hypocaloric diet with or without exercise training in obese metabolic syndrome subjects. *Diabetes* 2010; **59**(1): 71–79.
86 Trombetta IC, Batalha LT, Rondon MU, Laterza MC, Kuniyoshi FH, Gowdak MM *et al.* Weight loss improves neurovascular and muscle metaboreflex control in obesity. *Am J Physiol Heart Circ Physiol* 2003; **285**(3): H974–H982.
87 Mancia G, Bousquet P, Elghozi JL, Esler M, Grassi G, Julius S *et al.* The sympathetic nervous system and the metabolic syndrome. *J Hypertens* 2007; **25**(5): 909–920.
88 Lucini D, Di Fede G, Parati G, Pagani M. Impact of chronic psychosocial stress on autonomic cardiovascular regulation in otherwise healthy subjects. *Hypertension* 2005; **46**(5): 1201–1206.
89 Rainforth MV, Schneider RH, Nidich SI, Gaylord-King C, Salerno JW, Anderson JW. Stress reduction programs in patients with elevated blood pressure: a systematic review and meta-analysis. *Curr Hypertens Rep* 2007; **9**(6): 520–528.
90 Oneda B, Ortega KC, Gusmao JL, Araujo TG, Mion Jr D. Sympathetic nerve activity is decreased during device-guided slow breathing. *Hypertens Res* 2010; **33**(7): 708–712.
91 Viskoper R, Shapira I, Priluck R, Mindlin R, Chornia L, Laszt A *et al.* Nonpharmacologic treatment of resistant hypertensives by device-guided slow breathing exercises. *Am J Hypertens* 2003; **16**(6): 484–487.
92 Anderson DE, McNeely JD, Windham BG. Regular slow-breathing exercise effects on blood pressure and breathing patterns at rest. *J Hum Hypertens* 2010; **24**(12): 807–813.
93 Altena MR, Kleefstra N, Logtenberg SJ, Groenier KH, Houweling ST, Bilo HJ. Effect of device-guided breathing exercises on blood pressure in patients with hypertension: a randomized controlled trial. *Blood Press* 2009; **18**(5): 273–279.
94 Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; **365**(9455): 217–223.
95 Plump A. Accelerating the pulse of cardiovascular R&D. *Nat Rev Drug Discov* 2010; **9**(11): 823–824.
96 Fisher JP, Fadel PJ. Therapeutic strategies for targeting excessive central sympathetic activation in human hypertension. *Exp Physiol* 2010; **95**(5): 572–580.
97 Schlaich MP, Krum H, Esler MD. New therapeutic approaches to resistant hypertension. *Curr Hypertens Rep* 2010; **12**(4): 296–302.
98 Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic-nerve ablation for uncontrolled hypertension. *N Engl J Med* 2009; **361**(9): 932–934.
99 Bilgutay AM, Lillehei CW. Treatment of Hypertension with an implantable electronic device. *JAMA* 1965; **191**: 649–653.
100 Epstein SE, Beiser GD, Goldstein RE, Stampfer M, Wechsler AS, Glick G *et al.* Circulatory effects of electrical stimulation of the carotid sinus nerves in man. *Circulation* 1969; **40**(3): 269–276.
101 Illig KA, Levy M, Sanchez L, Trachiotis GD, Shanley C, Irwin E *et al.* An implantable carotid sinus stimulator for drug-resistant hypertension: surgical technique and short-term outcome from the multicenter phase II Rheos feasibility trial. *J Vasc Surg* 2006; **44**(6): 1213–1218.
102 Lohmeier TE, Barrett AM, Irwin ED. Prolonged activation of the baroreflex: a viable approach for the treatment of hypertension? *Curr Hypertens Rep* 2005; **7**(3): 193–198.
103 Scheffers IJ, Kroon AA, Schmidli J, Jordan J, Tordoir JJ, Mohaupt MG *et al.* Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study. *J Am Coll Cardiol* 2010; **56**(15): 1254–1258.
104 Heusser K, Tank J, Engeli S, Diedrich A, Menne J, Eckert S *et al.* Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. *Hypertension* 2010; **55**(3): 619–626.
105 Thrasher TN. Unloading arterial baroreceptors causes neurogenic hypertension. *Am J Physiol Regul Integr Comp Physiol* 2002; **282**(4): R1044–R1053.
106 Lohmeier TE, Iliescu R, Dwyer TM, Irwin ED, Cates AW, Rossing MA. Sustained suppression of sympathetic activity and arterial pressure during chronic activation of the carotid baroreflex. *Am J Physiol Heart Circ Physiol* 2010; **299**(2): H402–H409.
107 Yao T, Thoren P. Characteristics of brachiocephalic and carotid sinus baroreceptors with non-medullated afferents in rabbit. *Acta Physiol Scand* 1983; **117**(1): 1–8.
108 Munch PA, Andresen MC, Brown AM. Rapid resetting of aortic baroreceptors *in vitro*. *Am J Physiol* 1983; **244**(5): H672–H680.
109 Pereira EA, Wang S, Paterson DJ, Stein JF, Aziz TZ, Green AL. Sustained reduction of hypertension by deep brain stimulation. *J Clin Neurosci* 2010; **17**(1): 124–127.

110 Patel NK, Javed S, Khan S, Papouchado M, Malizia AL, Pickering AE *et al.* Deep brain stimulation relieves refractory hypertension. *Neurology* 2011; **76**(4): 405–407.
111 Carrive P, Bandler R. Viscerotopic organization of neurons subserving hypotensive reactions within the midbrain periaqueductal grey: a correlative functional and anatomical study. *Brain Res* 1991; **541**(2): 206–215.
112 Dampney RA. Functional organization of central pathways regulating the cardiovascular system. *Physiol Rev* 1994; **74**(2): 323–364.
113 Tai MH, Wang LL, Wu KL, Chan JY. Increased superoxide anion in rostral ventrolateral medulla contributes to hypertension in spontaneously hypertensive rats via interactions with nitric oxide. *Free Radic Biol Med* 2005; **38**(4): 450–462.
114 Oliveira-Sales EB, Dugaich AP, Carillo BA, Abreu NP, Boim MA, Martins PJ *et al.* Oxidative stress contributes to renovascular hypertension. *Am J Hypertens* 2008; **21**(1): 98–104.
115 Oliveira-Sales EB, Colombari DS, Davisson RL, Kasparov S, Hirata AE, Campos RR *et al.* Kidney-induced hypertension depends on superoxide signaling in the rostral ventrolateral medulla. *Hypertension* 2010; **56**(2): 290–296.
116 Griendling KK, Sorescu D, Ushio-Fukai M. NAD(P)H oxidase: role in cardiovascular biology and disease. *Circ Res* 2000; **86**(5): 494–501.
117 Gao L, Wang W, Li YL, Schultz HD, Liu D, Cornish KG *et al.* Sympathoexcitation by central ANG II: roles for AT1 receptor upregulation and NAD(P)H oxidase in RVLM. *Am J Physiol Heart Circ Physiol* 2005; **288**(5): H2271–H2279.
118 Chan SH, Hsu KS, Huang CC, Wang LL, Ou CC, Chan JY. NADPH oxidase-derived superoxide anion mediates angiotensin II-induced pressor effect via activation of p38 mitogen-activated protein kinase in the rostral ventrolateral medulla. *Circ Res* 2005; **97**(8): 772–780.
119 Simpson JB. The circumventricular organs and the central actions of angiotensin. *Neuroendocrinology* 1981; **32**(4): 248–256.
120 Bickerton RK, Buckley JP. Evidence for a central mechanism in angiotensin induced hypertension. *Proc Soc Exp Biol Med* 1961; **106**: 14.
121 Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S *et al.* Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J Exp Med* 2007; **204**(10): 2449–2460.
122 Hoch NE, Guzik TJ, Chen W, Deans T, Maalouf SA, Gratze P *et al.* Regulation of T-cell function by endogenously produced angiotensin II. *Am J Physiol Regul Integr Comp Physiol* 2009; **296**(2): R208–R216.
123 Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. *JAMA* 2003; **290**(22): 2945–2951.
124 Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; **105**(9): 1135–1143.
125 Marvar PJ, Thabet SR, Guzik TJ, Lob HE, McCann LA, Weyand C *et al.* Central and peripheral mechanisms of T-lymphocyte activation and vascular inflammation produced by angiotensin II-induced hypertension. *Circ Res* 2010; **107**(2): 263–270.
126 Waki H, Liu B, Miyake M, Katahira K, Murphy D, Kasparov S *et al.* Junctional adhesion molecule-1 is upregulated in spontaneously hypertensive rats: evidence for a prohypertensive role within the brain stem. *Hypertension* 2007; **49**(6): 1321–1327.
127 Ong KL, Leung RY, Wong LY, Cherny SS, Sham PC, Lam TH *et al.* Association of F11 receptor gene polymorphisms with central obesity and blood pressure. *J Intern Med* 2008; **263**(3): 322–332.
128 Kang YM, Ma Y, Zheng JP, Elks C, Sriramula S, Yang ZM *et al.* Brain nuclear factor-kappa B activation contributes to neurohumoral excitation in angiotensin II-induced hypertension. *Cardiovasc Res* 2009; **82**(3): 503–512.
129 Sriramula S, Haque M, Majid DS, Francis J. Involvement of tumor necrosis factor-alpha in angiotensin II-mediated effects on salt appetite, hypertension, and cardiac hypertrophy. *Hypertension* 2008; **51**(5): 1345–1351.
130 Shi P, Diez-Freire C, Jun JY, Qi Y, Katovich MJ, Li Q *et al.* Brain microglial cytokines in neurogenic hypertension. *Hypertension* 2010; **56**(2): 297–303.
131 Takagishi M, Waki H, Bhuiyan ME, Gouraud SS, Kohsaka A, Cui H *et al.* IL-6 microinjected in the nucleus tractus solitarii attenuates cardiac baroreceptor reflex function in rats. *Am J Physiol Regul Integr Comp Physiol* 2010; **298**(1): R183–R190.
132 Waki H, Gouraud SS, Maeda M, Paton JF. Gene expression profiles of major cytokines in the nucleus tractus solitarii of the spontaneously hypertensive rat. *Auton Neurosci* 2008; **142**(1–2): 40–44.
133 Waki H, Gouraud SS, Maeda M, Paton JF. Specific inflammatory condition in nucleus tractus solitarii of the SHR: novel insight for neurogenic hypertension? *Auton Neurosci* 2008; **142**(1–2): 25–31.
134 Helwig BG, Craig RA, Fels RJ, Blecha F, Kenney MJ. Central nervous system administration of interleukin-6 produces splenic sympathoexcitation. *Auton Neurosci* 2008; **141**(1–2): 104–111.
135 Niijima A, Hori T, Aou S, Oomura Y. The effects of interleukin-1 beta on the activity of adrenal, splenic and renal sympathetic nerves in the rat. *J Auton Nerv Syst* 1991; **36**(3): 183–192.
136 Gouraud SS, Waki H, Bhuiyan ME, Takagishi M, Cui H, Kohsaka A *et al.* Down-regulation of chemokine Ccl5 gene expression in the NTS of SHR may be pro-hypertensive. *J Hypertens* 2011; **29**(4): 732–740.
137 Zhang ZH, Wei SG, Francis J, Felder RB. Cardiovascular and renal sympathetic activation by blood-borne TNF-alpha in rat: the role of central prostaglandins. *Am J Physiol Regul Integr Comp Physiol* 2003; **284**(4): R916–R927.
138 Dickinson CJ, Thomson AD. A post mortem study of the main cerebral arteries with special reference to their possible role in blood pressure regulation. *Clin Sci* 1960; **19**: 513–538.
139 Wang G, Zhou P, Repucci MA, Golanov EV, Reis DJ. Specific actions of cyanide on membrane potential and voltage-gated ion currents in rostral ventrolateral medulla neurons in rat brainstem slices. *Neurosci Lett* 2001; **309**(2): 125–129.
140 Braga VA, Paton JF, Machado BH. Ischaemia-induced sympathoexcitation in spinalyzed rats. *Neurosci Lett* 2007; **415**(1): 73–76.
141 Smith PA, Meaney JF, Graham LN, Stoker JB, Mackintosh AF, Mary DA *et al.* Relationship of neurovascular compression to central sympathetic discharge and essential hypertension. *J Am Coll Cardiol* 2004; **43**(8): 1453–1458.

142 Naraghi R, Gaab MR, Walter GF, Kleineberg B. Arterial hypertension and neurovascular compression at the ventrolateral medulla. A comparative microanatomical and pathological study. *J Neurosurg* 1992; **77**(1): 103–112.
143 Cates MJ, Steed PJ, Abdala APL, Langton PD, Paton JFR. Elevated vertebrobasilar artery resistance in neonatal spontaneously hypertensive rats. *J Appl Physiol* 2011 (in press).
144 Osborn JW. Hypothesis: set-points and long-term control of arterial pressure. A theoretical argument for a long-term arterial pressure control system in the brain rather than the kidney. *Clin Exp Pharmacol Physiol* 2005; **32**(5–6): 384–393.