The sympathetic control of blood pressure

Patrice G.Guyenet

Abstract | Hypertension — the chronic elevation of blood pressure — is a major human health problem. In most cases, the root cause of the disease remains unknown, but there is mounting evidence that many forms of hypertension are initiated and maintained by an elevated sympathetic tone. This review examines how the sympathetic tone to cardiovascular organs is generated, and discusses how elevated sympathetic tone can contribute to hypertension.

Preganglionic
Autonomic neurons that have their cell bodies in the brainstem or spinal cord and synapse onto visceral motor neurons (sympathetic or parasympathetic) in peripheral ganglia.

Department of Pharmacology, Health Sciences Center, University of Virginia, 1300 Jefferson Park Avenue, Charlottesville, Virginia 22908-0735, USA.
e-mail: pgg@virginia.edu
doi:10.1038/nrn1902

The autonomic nervous system is a collection of afferent and efferent neurons that link the CNS with visceral effectors[1,2]. The two efferent arms of the autonomic nervous system — the sympathetic and parasympathetic arms — consist of parallel and differentially regulated pathways made up of cholinergic neurons (preganglionic neurons) located within the CNS that innervate ganglia (for example, para- or pre-vertebral sympathetic ganglia), glands (adrenal glands) or neural networks of varying complexity (enteric or cardiac ganglionic networks) located outside the CNS[1,2]. These peripheral ganglia and networks contain the motor neurons (ganglionic neurons) that control smooth muscles and other visceral targets. The sympathetic ganglionic neurons that control cardiovascular targets are primarily noradrenergic[2].

Blood pressure (BP) fluctuates substantially with behaviour, but the 24-h average BP is tightly regulated. Hypertension is, by definition, a chronic elevation of the 24-h average BP, and the disease is known as neurogenic if the probable cause is an abnormality of the autonomic nervous system rather than a primary vascular or renal defect. This abnormality can originate in the afferent arm of the system (for example, baroreceptors, chemoreceptors and renal afferents) or in the central circuitry.

The neural control of the circulation operates via parasympathetic neurons that innervate the heart and via three main classes of sympathetic efferent — barosensitive, thermosensitive and glucosensitive cardiovascular — that innervate blood vessels, the heart, the kidneys and the adrenal medulla. The barosensitive sympathetic efferents are under the control of arterial baroreceptors. This large group of efferents has a dominant role in both short-term and long-term BP regulation. Their level of activity at rest is presumed to be the most crucial parameter for long-term BP control. This background activity is set by a core network of neurons that reside in the rostral ventrolateral medulla (RVLM), the spinal cord, the hypothalamus and the nucleus of the solitary tract (NTS). These structures are the primary focus of this review (FIG. 1). Limbic, cortical and midbrain structures (not discussed in this review) are responsible for the rapid changes in sympathetic tone that relate to behaviour. It is generally assumed that these changes are not pertinent to the long-term regulation of BP, except perhaps in the context of stress-related hypertension.

I begin by discussing the determinants of BP and the cardiovascular sympathetic efferents that control it. The three central control regions — the RVLM, NTS and hypothalamus — that regulate the barosensitive sympathetic efferents, and consequently BP, are described, together with their potential contribution to various forms of neurogenic hypertension.

Determinants and neural control of BP

BP is a function of vascular resistance and cardiac output, two variables that are controlled by the autonomic nervous system. In turn, cardiac output is dependent on three regulated variables: end-diastolic volume; myocardial contractility; and heart rate. End-diastolic volume is the volume reached by the ventricular chamber before contraction and is determined by venous pressure, which is related to blood volume and venous smooth muscle tone, both of which are under sympathetic control. Myocardial contractility and heart rate are regulated by both the sympathetic and parasympathetic divisions of the autonomic nervous system.

On a short timescale (seconds to hours), the autonomic nervous system adjusts the circulation in keeping with behaviour (for example, feeding and exercise), the environment (for example, thermoregulation) and emotions (for example, fright)[1]. These circulatory changes are components of more global autonomic response patterns that are elaborated in large portions of the

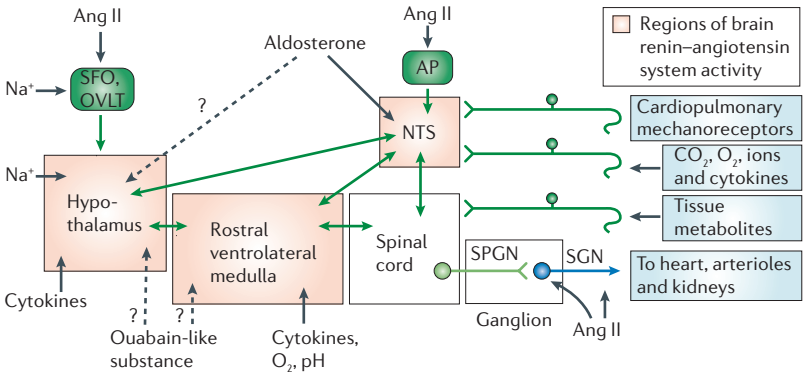

Figure 1 | **CNS network that regulates the basal sympathetic tone.** The background level of sympathetic tone present at rest is presumably crucial for long-term blood pressure (BP) control. The network that sets this background level is located in the rostral ventrolateral medulla (RVLM), the spinal cord, the hypothalamus and the nucleus of the solitary tract (NTS). Limbic, cortical and midbrain structures (not represented here) are responsible for rapid behaviour-related adjustments of sympathetic tone but are probably not involved in the long-term regulation of BP, except perhaps in the context of stress-related hypertension. The core sympathetic network is regulated by many classes of sensory afferent that project either to the NTS (for example, baroreceptors and other mechanoreceptors from the cardiopulmonary region) or to the spinal cord (somatic and sympathetic afferents that detect a range of chemical or physical parameters from muscle stretch to tissue hypoxia and metabolites). The central portion of the network is also regulated at multiple levels by circulating hormones and blood-borne factors. Peptide hormones (for example, angiotensin II (ang II)) and cytokines (for example, interleukin-1) influence this network via circumventricular organs (subfornical organ (SFO), organum vasculosum lamina terminalis (OVLT) and area postrema (AP)) or through endothelial receptors that trigger the release of mediators that subsequently cross the blood–brain barrier (for example, nitric oxide and prostaglandins[41,75]). These transendothelial mechanisms operate in the hypothalamus, the RVLM and the NTS. Freely diffusible hormones (for example, ouabain-like substance[115] and aldosterone) also act on this network, but their sites of action in the brain are not conclusively known[104,113]. The central network also responds to changes in sodium and osmolality that are detected at multiple hypothalamic sites, to carbon dioxide (CO_2) via brainstem chemoreceptors, and could detect hypoxia directly in the brainstem. Moreover, virtually every component of the central network is influenced by the brain renin–angiotensin system through increased production of radical oxygen species and, possibly, other mechanisms[8,119]. Finally, the sympathetic ganglia are also influenced by hormones, such as angiotensin II, and transmitter release by sympathetic ganglionic neurons (SGNs) is regulated presynaptically by angiotensin II and catecholamines. SPGN, sympathetic preganglionic neuron. Black arrows indicate external effect; green arrows show interactions within the network.

midbrain, limbic forebrain and cortex[3–5]. They occur via rapid changes in cardiac output and regional arteriolar resistance, and can be associated with substantial BP increases that are, in most instances, physiologically adaptive, thereby facilitating gas and nutrient exchange in metabolically active tissues (for example, muscles during exercise). Behaviour-dependent rises in BP are both enabled and moderated by the baroreflex.

Numerous brain manipulations (including lesions, overexpression of nitric oxide synthase and brain-specific expression of various components of the renin–angiotensin system) produce long-term changes in mean BP[6–8], thereby demonstrating that the CNS normally contributes to the long-term regulation of BP. The fact that renal denervation or specific brain lesions attenuate or delay the development of hypertension[9,10] also indicates that the CNS contributes to the hypertensive process. However, the exact role of the CNS in long-term BP control is not well understood. From a neurophysiological perspective, the most fundamental and still unanswered question is whether the brain is a controller of BP in the strict engineering sense (that is, has the capacity to detect changes in BP and to initiate appropriate responses)[11,12]. How a set-point for BP might be encoded by the CNS and the nature of the error signals have yet to be established. The only well identified neural sensors that encode BP are the baroreceptors, but their contribution to the long-term regulation of BP has been repeatedly questioned (discussed later)[11,12]. Numerous humoral factors (for example, sodium, angiotensin II and mineralocorticoids) alter the activity of the central autonomic network via neural mechanisms that are being described in ever greater detail. However, evidence that these substances provide error signals for a CNS BP controller is tenuous[12]. Indeed, it could be argued that the neural control of the circulation is primarily designed to regulate blood volume and blood flow (cardiac output and its apportionment) at the expense of BP.

Any discussion of neurogenic hypertension must consider the role of the kidneys. The influential model developed by Guyton postulates that the relationship between renal sodium excretion and BP (the pressure–natriuresis relationship) defines the BP homeostatic set-point[13]. According to this model, any increase in sodium retention produces an initial blood volume expansion, causing BP to increase via a rise in cardiac output. Eventually, tissue over-perfusion leads to an increase in peripheral resistance (whole-body autoregulation) that returns resting cardiac output towards normal[13]. According to this widely held theory, a resetting of the pressure–natriuresis relationship inevitably leads to hypertension, regardless of the cause of the resetting, whether it be humoral, neural, degenerative or genetic.

Although evidence that the brain regulates the 24-h average BP and contributes to the hypertensive process is very persuasive, the mechanisms are not well understood. Elevated sympathetic nerve activity (SNA) is present in most forms of human hypertension[14] (FIG. 2) and a causal relationship is suggested by the well-documented antihypertensive efficacy of sympatholytic drugs (for example, α_1- or β-adrenergic receptor antagonists)[15]. However, elevated SNA might not be the sole mechanism involved in neurogenic hypertension, and how an increase in SNA raises the 24-h mean BP has not been established. The most commonly invoked mechanism is resetting of the renal BP–natriuresis relationship to higher levels of BP by either a rise in sympathetic tone to the kidney or by hormones whose production is partly controlled by the autonomic nervous system (for example, angiotensin II). However, abnormalities in the neural control of the heart and blood vessels are not ruled out[9,13,16,17].

Sympathetic efferents that regulate BP

Cardiovascular sympathetic efferents can be broadly classified into three groups according to their dominant characteristic: thermosensitivity; glucosensitivity; or barosensitivity[18–20]. This section describes the general characteristics of each group, with a focus on the physiological properties of the barosensitive efferents.

Baroreflex
Reflex decrease in sympathetic nerve activity that is initiated by the activation of stretch-sensitive afferents located in the arterial wall.

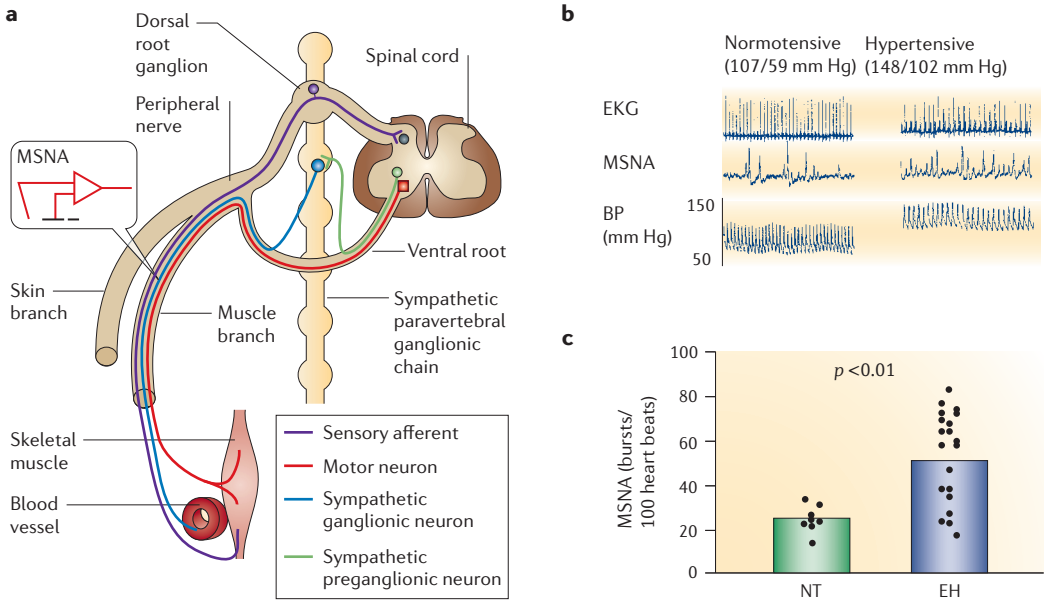

Figure 2 | **Sympathetic tone and hypertension. a** | Sympathetic nerve activity (SNA) can be measured directly in awake humans by the insertion of a metal electrode into a somatic nerve under conditions in which sensory and skeletomotor nerve activity are negligible[21]. MSNA, muscle SNA. **b**,**c** | Show examples of multifibre recordings from the peroneal nerve of normotensive (NT) and hypertensive participants, representing the resting level of activity of sympathetic postganglionic neurons that innervate muscle resistance arterioles[14]. MSNA represents the activity of a fairly homogeneous functional class of sympathetic efferent that is subject to a powerful feedback from arterial baroreceptors and has a central role in blood pressure (BP) homeostasis. Barosensitive sympathetic efferents innervate the kidneys, the heart, resistance arterioles and capacitance veins throughout the body (except in the skin). Their discharge occurs in bursts, because the pulsatile nature of arterial baroreceptor activity is transmitted polysynaptically through the entire brainstem baroreflex circuitry[1]. MSNA also fluctuates with respiration owing to feedback from other cardiopulmonary afferents and the fact that the autonomic circuits in the brainstem receive inputs from the central respiratory network[19,23]. The intensity and frequency of MSNA bursts is elevated in human essential hypertension (EH), several other forms of hypertension[14] (such as those in obesity or obstructive sleep apnoea) and in many other pathological conditions (for example, heart failure, haemorrhage and dehydration). The increased burst frequency is clearly of CNS origin. The increased intensity of the bursts is probably also of central origin but could conceivably be due, in part, to hormone-induced changes in ganglionic transmission (FIG. 1). Panels **b** and **c** adapted, with permission, from REF. 14 © (2004) American Heart Association. EKG, electrocardiogram.

Renin–angiotensin system
This is a regulated biochemical pathway with paracrine function that leads to the production of angiotensin II and related bioactive peptides in the brain. This system is active in most brain regions that regulate the sympathetic outflow and is activated in various forms of hypertension and heart failure, although the causes of its activation are still not clear.

Natriuresis
Sodium excretion by the kidney.

Sympatholytic
A drug that reduces SNA by a CNS or peripheral action or reduces transmission between sympathetic ganglionic neurons and their peripheral targets.

Classes of cardiovascular efferents. The thermosensitive group of cardiovascular efferents consists primarily of cutaneous vasoconstrictors that are activated by hypothermia, emotional stimuli and hyperventilation[19,21]. The glucosensitive group controls adrenaline release from the adrenal medulla and is activated by hypoglycaemia and physical exercise[22]. These two types of cardiovascular efferent are only weakly, if at all, regulated by arterial baroreceptors, and presumably have a secondary role in short- and long-term BP stability.

The third class, which is by far the largest group of cardiovascular sympathetic efferents, is the barosensitive group. Regardless of the organ or tissue that they innervate, these neurons show ongoing activity at rest (sympathetic tone) and they discharge in bursts that are highly synchronized with the arterial pulse and respiration[19,21,23] (FIG. 2b). Barosensitive sympathetic efferents control the heart and the kidneys, the release of noradrenaline from a subset of adrenal chromaffin cells, and constrict resistance arterioles, with the exception of those in the skin[19]. Barosensitive efferents are responsible for short-term BP fluctuations[1,19]. They are also likely to be a key determinant of the long-term neural control of BP, in part because renin secretion, renal tubular sodium reabsorption and renal blood flow are apparently all under the control of this type of sympathetic efferent[9].

Properties of barosensitive efferents. The physiological properties of barosensitive sympathetic efferents are fairly uniform and have been thoroughly characterized from recordings in anaesthetized or awake animals and from numerous recordings of ganglionic neurons in awake humans[19,21,23] (FIG. 2). Barosensitive efferents are subject to numerous reflex regulations that operate as either feedback or feedforward mechanisms[19,24]. For example, the activation of stretch-sensitive afferents by ventilation (lung afferents) and arterial pressure (carotid and aortic receptors) inhibits SNA. By contrast, muscle receptors (group III and IV) that are activated by stretch and metabolites (for example, ATP, lactate and pH) raise the discharge of barosensitive sympathetic fibres during exercise[25]. The activation of visceral nociceptors (for example, by angina) or cutaneous nociceptors elevates the activity of

barosensitive sympathetic efferents, as does the activation of peripheral (by hypoxia or hypercapnia) and central (by hypercapnia) chemoreceptors[19,26]. Barosensitive sympathetic fibres are activated by mental stress and in many disease states[1,19,21]. On the basis of recordings made when animals were anaesthetized and awake, the response of barosensitive efferents to the above-mentioned list of stimuli or physiological conditions is typically in the same direction but variable in intensity depending on the organ targeted by these neurons. An important exception is the selective inhibition of renal SNA by atrial stretch or volume expansion, a reflex that is crucial for the regulation of blood volume[27,28]. Contrary to previous assumptions, a decrease in barosensitive muscle SNA does not contribute to muscle vasodilation during exercise. Reflexly, and through central command, muscle sympathetic tone actually increases monotonically with the level of exercise, possibly to curb the hypotension that might otherwise result from excessive vasodilation due to local metabolites[21,25].

In summary, barosensitive sympathetic efferents are regulated in parallel under most circumstances, but target-specific differences in their level of activity show that these efferents are, to some extent, differentially regulated. The selective control of renal SNA by volume receptors could be the most important of these differential regulations.

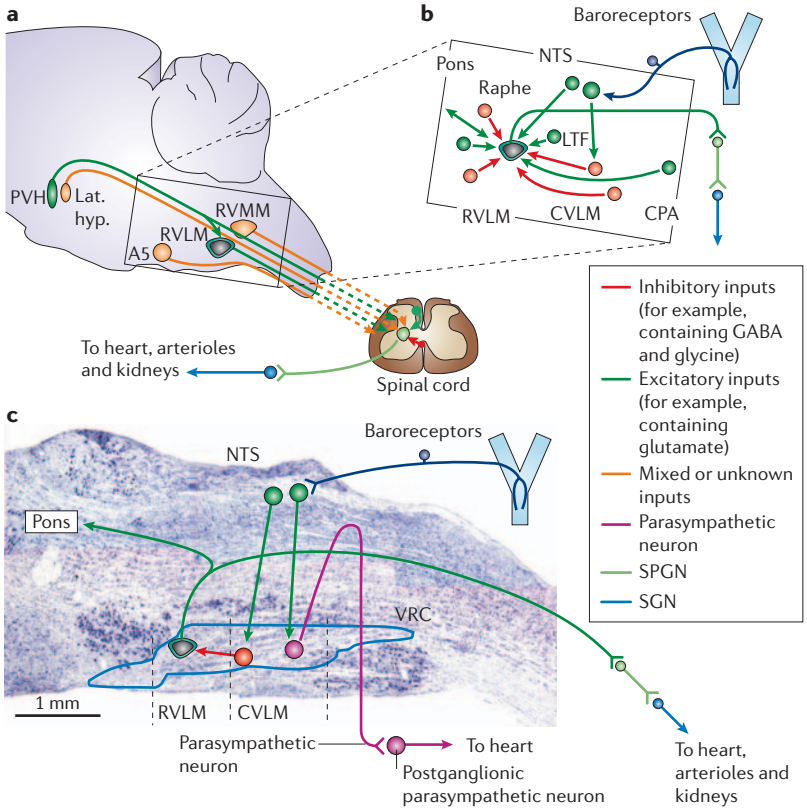

Figure 3 | **The rostral ventrolateral medulla and barosensitive sympathetic efferents. a** | All sympathetic preganglionic neurons (SPGNs), regardless of their function, receive monosynaptic inputs from overlapping subsets of neurons located in each of the regions indicated[30,36]. The extent to which each of these regions contributes to the activity of the barosensitive system of sympathetic efferents probably depends on the physiological state and the type of sympathetic efferents. The rostral ventrolateral medulla (RVLM) is the dominant source of excitatory drive to the barosensitive class of sympathetic efferent under anaesthesia. Its role is assumed, but not proved, to be equally dominant in the awake state. The RVLM input originates from a neurochemically heterogeneous collection of glutamatergic neurons, a large subset (70%) of which also synthesize adrenaline. These are called C1 neurons[30,33,36]. Spinal interneurons are considered unimportant in regulating barosensitive efferents in intact mammals, but become dominant after spinal cord damage. **b** | RVLM barosensitive neurons receive inputs from multiple areas of the brain and spinal cord. Only a few of the inputs from the medulla oblongata are represented. These inputs presumably mediate some of the many cardiovascular reflexes that are integrated by the RVLM neurons. **c** | Anatomically correct location of the RVLM and caudal ventrolateral medulla (CVLM): the parasagittal section of the rat medulla oblongata 1.8 mm lateral to the midline. RVLM barosensitive neurons innervate numerous pontomedullary regions in addition to SPGNs. This fact is symbolized by a collateral to the dorsal pons. The RVLM and CVLM are both coextensive with the ventral respiratory column (VRC; outlined in blue). The cholinergic parasympathetic neurons that control the heart are also located in the same region. Parasympathetic neurons and the barosensitive RVLM neurons receive inputs from unidentified VRC neurons that coordinate respiration and circulation. A5, noradrenergic cluster located at the pontomedullary junction; CPA, caudal pressor area; Lat. hyp., lateral hypothalamus; LTF, lateral tegmental field; NTS, nucleus of the solitary tract; PVH, paraventricular nucleus of the hypothalamus; RVMM, rostral ventromedial medulla; GABA, γ-aminobutyric acid.

The rostral ventrolateral medulla

Although anatomical experiments suggest that every sympathetic preganglionic neuron (SPGN) receives some synaptic input from the same general areas of the spinal cord, medulla oblongata and hypothalamus[29–31] (FIG. 3a), physiological evidence indicates that these CNS regions contribute unequally to the various sympathetic outflows. Barosensitive sympathetic efferents appear to be regulated primarily through the RVLM[24], whereas the cutaneous circulation is regulated predominantly through the rostral ventromedial medulla (RVMM) and medullary raphe[19,20,24]. The central control of adrenaline secretion is less well understood. Although not under baroreceptor control, it is regulated, at least in part, by the RVLM[22,32]. The next sections focus on the anatomy of the RVLM, its role in regulating the activity of the barosensitive sympathetic efferents and its potential role in neurogenic hypertension.

C1 and other RVLM BP-regulating neurons. The C1 neurons (FIG. 3) are, by definition, one of only three clusters of adrenaline-synthesizing cells in the CNS[33]. In the early 1980s, the RVLM — the portion of the ventrolateral medulla that is coextensive with C1 neurons (FIG. 3b,c) — was definitively identified as a key BP regulatory centre[1,24,34]. The RVLM neurons that are most directly linked to BP control are cells that innervate SPGNs monosynaptically (FIG. 3). These neurons have a discharge pattern that is similar to that of barosensitive sympathetic efferents and they are a nodal point for most, if not all, sympathetic reflexes that involve cardiovascular targets, with the exception of cutaneous arterioles[1,20,35–37]. All these RVLM neurons probably release glutamate, but they also synthesize various additional combinations of transmitters, including adrenaline. Those that synthesize adrenaline (~70%) belong, by definition, to the C1 group[34,38,39]. However, not all C1 cells are under baroreceptor control; the best-documented example of non-barosensitive C1 cells is those that control

adrenaline-releasing chromaffin cells[22,32]. Furthermore, neither RVLM barosensitive neurons nor the C1 cells should be viewed strictly as 'central sympathetic neurons' because these cells, as well as innervating SPGNs, also innervate many regions of the medulla, pons and midbrain[36].

The RVLM also contains C1 cells that innervate the hypothalamus. These neurons are different from those that innervate the spinal cord, but they have a range of neurochemical and electrophysiological properties that are similar to those of their bulbospinal counterparts[40]. Some of these cells presumably contribute a baroreceptor-modulated excitatory drive to the hypothalamic centres (paraventricular and median preoptic nuclei) that regulate aspects of circulation, including sodium and water balance. Other C1 cells are probably not under baroreceptor control[40] and mediate, or at least enable, the activation of the hypothalamic–pituitary axis during a range of physical stresses that is clearly not limited to cardiovascular challenges[32,41].

RVLM and sympathetic vasomotor tone. A background level of SNA that can be either withdrawn or enhanced is required for the short- and long-term stabilization of BP. As this background level is largely determined by the level of activity of RVLM barosensitive neurons, the intrinsic properties and inputs of these cells are central to understanding sympathetic tone and its pathological abnormalities. Under most anaesthetic conditions, ionotropic glutamate transmission is a minor source of drive for barosensitive neurons[36,42]. However, glutamate transmission makes a much greater contribution to the activity of these neurons in animals that are dehydrated or have abnormal blood gases (that is, high CO_2 and low O_2), or when any of a large number of sympathoexcitatory reflexes are elicited[36,37,43,44]. In short, the activity of RVLM neurons appears to depend on ionotropic drives and metabotropic transmission (for example, neuropeptides; discussed below) in proportions that vary according to the physiological circumstances.

In brain slices, C1 neurons have beating properties that rely to some extent on a persistent sodium current[45]. Dissociated C1 neurons are not spontaneously active, which suggests that their autoactivity in slices relies in part on dendritic properties or requires unidentified extracellular signals[46]. So, whether autoactivity contributes to the discharge of the barosensitive neurons, and therefore to basal vasomotor tone *in vivo*, has yet to be determined[42]. Besides GABA (γ-aminobutyric acid) and glutamate, the list of transmitters that regulate the barosensitive neurons is extensive. Acetylcholine, serotonin, corticotropin-releasing factor (CRF), oxytocin, substance P, vasopressin and orexin have all been identified in nerve terminals that synapse onto identified or presumed BP-regulating neurons (usually C1 cells)[36]. Some of these inputs (for example, acetylcholine, serotonin and orexin) probably originate from vigilance-regulating networks and could contribute to the circadian rhythm of SNA and BP[16]. Other inputs originate from the hypothalamus (for example, vasopressin, oxytocin, CRF and angiotensin II) and have a role in the cardiovascular response to internal (for example, infection, dehydration, haemorrhage and heart failure) and external (for example, social) stresses[36,43,47–50].

RVLM neurons also receive inputs from numerous sources in the medulla oblongata and pons. Few of these inputs are thoroughly characterized, with the exception of a GABA-mediated input from the caudal ventrolateral medulla (CVLM) that is crucial to the baroreflex[1,51] (FIG. 3b,c). The remaining sources of input have been identified primarily as sites at which electrical or chemical stimulation elicits changes in BP: that is, the caudal pressor area; midline depressor area; various subnuclei of the NTS; and the gigantocellular depressor area[1] (FIG. 3b). These brainstem regions are probable relays for the various somatic and visceral sympathetic reflexes (exercise pressor reflex, nociceptive reflexes and cardiopulmonary reflexes) that are mediated, at least in part, through the RVLM[52–54]. Other pontomedullary areas probably serve as an interface between the central respiratory network and the sympathetic outflow, and are responsible for the stimulatory effect of central and peripheral chemoreceptor activation on barosensitive SNA[44] (FIG. 3c). The RVLM could also contain interneurons that regulate the barosensitive neurons, given the differential sensitivity of various sympathetic reflexes to the microinjection of pharmacological agents into the RVLM (for an example, see REF. 55).

The organotopy hypothesis. The 'organotopy' theory states that separate groups of RVLM barosensitive neurons preferentially control, for example, skeletal muscle arteries, splanchnic arteries, the heart and the kidneys[56–58]. Anatomical studies have yet to provide convincing evidence in support of this hypothesis[29,31,59,60], but there is physiological evidence for some input–output diversity among RVLM barosensitive neurons. The best evidence for output diversity comes from RVLM microstimulation, which produces different activation of various sympathetic nerves, depending on the site of stimulation[56–58]. Input diversity is supported by unit recordings that show cell-specific responses to the intravenous injection of cholecystokinin and the activation of central and peripheral chemoreceptors[61,62], but these cells have a uniform response to many other stimuli. In any event, the target specific responses of barosensitive sympathetic efferents are unlikely to be entirely due to differential recruitment of RVLM barosensitive neurons. For example, direct projections from the paraventricular nucleus of the hypothalamus (PVH) to SPGNs probably contribute to the selective control of renal SNA by volume receptors[27]. The scheme proposed in FIG. 4 is an attempt to reconcile the contradictory evidence regarding the RVLM.

RVLM and long-term BP control. Adenovirus-mediated overexpression of endothelial nitric oxide synthase (eNOS) in the RVLM leads to reductions in BP 5–10 days after injection of the viral vector, presumably by enhancing GABA-mediated inhibition of barosensitive neurons[63,64]. The effect of eNOS overexpression is much greater in the spontaneously hypertensive-stroke-prone rat than in normotensive controls[63], which is consistent

Bulbospinal
Neurons located in the brainstem and innervating neurons in the spinal cord, such as sympathetic preganglionic neurons.

Sympathoexcitatory reflex
Any reflex that causes an increase in SNA (the opposite is a sympathoinhibitory reflex).

Vigilance-regulating network
Network of neurons that regulate the sleep–wake cycle. This network includes the suprachiasmatic and other hypothalamic nuclei and various brainstem aminergic cell groups.

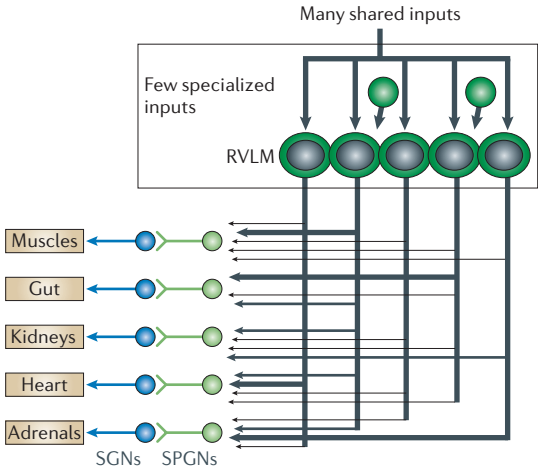

Figure 4 | **Organization of the barosensitive rostral ventrolateral medulla projection.** The degree of convergence and divergence between rostral ventrolateral medulla (RVLM) barosensitive neurons and their preganglionic targets is uncertain. The proposed scheme has a high degree of divergence to account for the anatomical data. Organs — such as muscles, gut, kidney, heart and adrenal medulla — are innervated by sympathetic ganglionic neurons (SGNs) under the control of target-specified sympathetic preganglionic neurons (SPGNs), which, in turn, are assumed to receive inputs from a large fraction of RVLM neurons. To account for the differential activation of the various outputs, the inputs must be of different proportions or strengths (thickness of arrow lines). RVLM barosensitive neurons are also represented as sharing a large number of inputs to account for their parallel activation under many experimental conditions.

with the higher resting level of SNA present in this rat strain. Destruction of the C1 cells, many of which regulate the kidneys[65,66], also causes a sustained BP reduction in awake rats[6]. The hypotension is relatively modest (10 mm Hg) presumably because the non-catecholaminergic population of RVLM barosensitive neurons are spared[39]. If it is assumed that only renal nerves can alter the BP set-point, these studies suggest that hypertension could result from the chronic hyperactivity of the RVLM barosensitive neurons that control renal SNA[17]. However, the increased activity of RVLM barosensitive neurons in hypertensive rats is unlikely to be restricted to just a few specialized neurons that control kidney natriuresis. The large and rapid drop in BP caused by inhibiting hypothalamic or RVLM neurons in animal models of neurogenic hypertension, such as the spontaneously hypertensive and the Dahl salt-sensitive rat strains, denotes a generalized increase in sympathetic tone that involves the skeletal muscles, the splanchnic beds and probably the heart[50,67,68]. The hypothesis of a global increase in the activity of RVLM barosensitive neurons in neurogenic hypertension is consistent with the upregulation of catecholaminergic gene expression observed in the RVLM of spontaneously hypertensive rats[69,70]. It is also consistent with the fact that barosensitive SNA is elevated throughout the body in most forms of human hypertension[14].

Chemoreflex
Reflex elicited by the activation of the carotid bodies (by hypoxia and hypercapnia) or central chemoreceptors (by hypercapnia).

In the following sections, I review two types of mechanism that are suspected to elevate SNA chronically, at least in part, by raising the activity of RVLM neurons. The first is a dysfunction of certain visceral reflexes (that is, baroreflex and chemoreflex) that are processed by the NTS. The second involves two key hypothalamic nuclei — the paraventricular and the dorsomedial nuclei.

The nucleus of the solitary tract and hypertension

The NTS is a principal integrative centre for circulatory control[1,71]. It receives direct input from cardiopulmonary afferents (for example, arterial baroreceptors, volume receptors and peripheral chemoreceptors) and polysynaptic inputs from many sympathetic and somatic afferents[1,71]. Arterial baroreceptors are the afferent arm of the baroreflex, which has a crucial role in short-term BP control. The activation of peripheral chemoreceptors by hypoxia and hypercapnia causes a generalized increase in the activity of barosensitive sympathetic efferents — the chemoreflex. Abnormalities of baro- or chemoreceptor afferent input, or of their processing in the NTS, could contribute to several forms of neurogenic hypertension.

Baroreceptors, the arterial baroreflex and neurogenic hypertension. The sympathetic baroreflex is a feedback loop, the afferent limb of which involves mechanoreceptors that are activated by distention of the arterial wall[1]. An increase in BP activates baroreceptors, thereby causing inhibition of cardiac, renal and vasomotor sympathetic efferents, which, in turn, leads to restoration of BP: the core circuitry of the reflex is probably as depicted in FIG. 3c. The best-known function of this reflex, together with its cardiovagal counterpart, is to dampen short-term BP fluctuations[1,72,73]. However, this reflex is also actively reset to allow BP to rise appropriately during certain behaviours such that the operating range is increased to higher BP levels without reduction in reflex sensitivity. Baroreflex resetting involves both neural and humoral mechanisms (FIG. 5). For example, GABA-mediated inputs can bias the response of NTS second-order neurons to baroreceptor afferent stimulation via both pre- and postsynaptic mechanisms, leading to a resetting of the reflex to a higher BP level[74]. Baroreflex resetting can be triggered reflexly (for example, by muscle contraction or nociceptive stimulation) or by central inputs generated by higher brain regions[23,71]. Baroreflex resetting in the NTS, together with an upregulation of the activity of RVLM neurons, is probably crucial to allow BP to rise during appropriate behaviours (FIG. 5). Transmission between baroreceptor afferents and NTS efferent neurons (presumed to be second-order neurons) is also subject to neurohumoral regulation. Circulating angiotensin II, for example, reduces this transmission by activating endothelial angiotensin II receptors type 1 (AT_1), which causes the release of nitric oxide by these cells. Nitric oxide, which is freely diffusible, migrates across the capillaries into the neuropil and potentiates GABA release[75,76] (FIG. 5). Angiotensin II derived from the brain's renin–angiotensin system could also reset the reflex by the same mechanism.

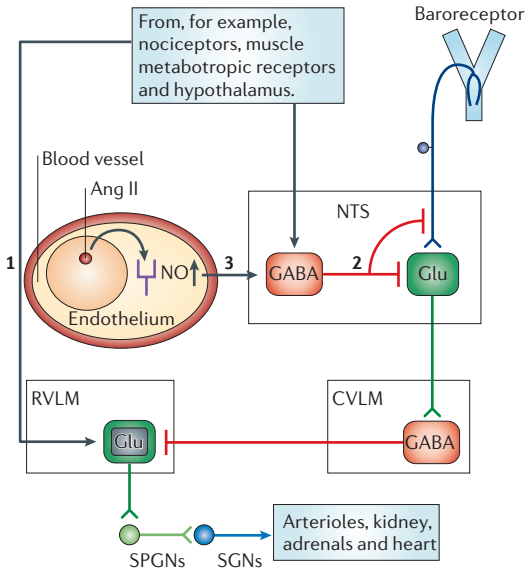

Figure 5 | **Neuronal and humoral control of the baroreflex.** Numerous factors cause rises in blood pressure (BP), for example, pain and physical exercise. Increases in BP are brought about predominantly through three mechanisms. One involves the stimulation of glutamatergic rostral ventrolateral medulla (RVLM) barosensitive neurons via spinoreticular afferents (pain and muscle receptors) or inputs from more rostral structures (central command) (**1**). A second mechanism is a reduction of the baroreceptor feedback due to a biasing of the transmission between baroreceptor afferents and second-order neurons in the nucleus of the solitary tract (NTS) (**2**). The mechanism relies on pre- and postsynaptic inhibition mediated by GABA (γ-aminobutyric acid) and other substances such as vasopressin (not represented). Last, the baroreflex is also under humoral control (**3**). Circulating angiotensin II (Ang II), for example, also reduces transmission between baroreceptor afferents and second-order neurons. The mechanism of angiotensin II control of the baroreflex involves the production of nitric oxide (NO) by the capillary endothelium, and this mechanism could have a role in neurogenic hypertension[75]. CVLM, caudal ventrolateral medulla; Glu, glutamate; SGN, sympathetic ganglionic neuron; SPGN, sympathetic preganglionic neuron.

The GABA-containing interneurons of the CVLM (FIGS 3,5) exert a continuous and powerful restraining influence on RVLM barosensitive neurons, and are more than a simple relay in the arterial baroreflex[72]. Many of these interneurons have baseline activity even without vagal afferent input, and must therefore have other sources of drive besides baroreceptors[72]. These baroreceptor-independent inputs are still largely unexplored, despite their potential importance to the long-term regulation of BP.

The literature suggests that arterial baroreceptors have little influence on the long-term average BP under unstressed conditions[77]. This point was originally made in the 1970s by Cowley[11], who showed that complete surgical elimination of arterial baroreceptors (sinoaortic denervation) produces only transient elevations of the 24-h average BP in awake dogs. The issue has been recently revisited in awake dogs and rabbits using a physiological protocol that produces an abnormally low arterial baroreceptor discharge but preserves the physical integrity of the afferents. This procedure increased mean BP for a few days, but the effect was not permanent[78] (reviewed in REF. 77), which is in agreement with Cowley's observations. However, there is increasing evidence that the slow return of BP towards control after sinoaortic denervation is associated with a gradual return of SNA towards normal[77,79]. This normalization is partly the result of the restoration of an excitatory drive to CVLM neurons that compensates for the loss of the baroreceptor input to these cells[79]. The signals responsible for normalizing the activity of the CVLM, and ultimately that of the RVLM–SNA–BP cascade, probably do not originate from cardiopulmonary receptors[77,79], but these signals have yet to be identified.

When dietary salt consumption is increased, sinoaortic denervation causes hypertension (up to 20 mm Hg), which indicates that baroreceptors do regulate the 24-h average BP under this condition[77]. This rise in BP could be due to an impaired ability to buffer the 12-h oscillatory osmotic and volume stimuli that are caused by the daily cycle of salt consumption[77]. Another possibility is that baroreceptors attenuate the stimulatory effect of sodium on SNA that is mediated by hypothalamic receptors[80] (discussed below). Arterial baroreceptor dysfunction could also contribute to the development of hypertension in the Dahl salt-sensitive rat[77]. The role of baroreceptors in salt-dependent hypertension could rely on mechanisms that are much more complex than a simple brainstem reflex dysfunction, because baroreceptors also exert powerful influences on the hypothalamus and beyond. For example, ascending C1 neurons innervate the PVH, the median preoptic nucleus and even the subfornical organ and other circumventricular organs[81–83]. Through these projections, baroreceptor afferents could influence sodium and volume regulatory mechanisms, including angiotensin II-mediated control of these mechanisms.

Chronic intermittent hypoxia and hypertension. The activation of carotid body chemoreceptor afferents by hypoxia or hypercapnia stimulates breathing, causes arousal and increases SNA to the heart and blood vessels (sympathetic chemoreflex)[44]. In obstructive sleep apnoea (OSA), repeated nocturnal episodes of airway blockade cause periodic asphyxia, leading to severe episodes of increased BP[84]. The acute increases in BP and heart rate are associated with massive rises in SNA that result from the activation of peripheral chemoreceptors with some possible contribution from central chemoreceptors[84]. The sympathetic chemoreflex originates from the caudal aspect of the NTS and requires the activation of RVLM barosensitive neurons[44,85,86]. This reflex probably involves a direct connection from the NTS to RVLM barosensitive neurons, and indirect connections to these cells via the respiratory pattern generator[44].

OSA also causes persistent day-time increases in SNA, which probably contribute to the associated hypertension[84]. Intermittent asphyxia could contribute to the chronically elevated SNA: intermittent asphyxia

Sinoaortic denervation
Surgical procedure consisting of sectioning the nerves that contain arterial baroreceptor afferents (principally the carotid sinus nerve and the aortic nerve).

Hepatoportal osmoreceptors
Sensory afferents located close to the liver that detect changes in osmolality in the blood exiting the digestive system.

sensitizes the carotid body chemoreceptors to hypoxia and causes the chemoreceptor afferents to be tonically active even when the blood oxygen concentration is normal[84,87]. However, the C1 neurons of rats exposed to hypoxia express higher levels of hypoxia-inducible factor 1-α and tyrosine hydroxylase, even when the carotid bodies have been denervated[88,89]. Therefore, C1 neurons could be directly sensitive to CNS hypoxia, as previously suggested based on the observation that these neurons are strongly activated during cerebral ischaemia[90]. Whether the oxygen-sensitivity of the C1 cells is a physiological regulator of BP designed to maintain cerebral blood flow homeostasis under more physiological circumstances has yet to be determined[77]. However, the hypoxic sensitivity of RVLM neurons could account for the hypertension that is associated with vascular compression of the ventrolateral medulla[91].

The hypothalamus and BP control

The PVH and the dorsomedial nucleus are currently seen as key hypothalamic integrative centres for circulatory control[17]. The dorsomedial hypothalamus contributes mostly to the cardiovascular responses produced by environmental stresses or threats[17,92]. The PVH is a convergence point for numerous hypothalamic regions involved in bodily homeostasis (for example, fluid regulation, metabolism, immune responses and thermoregulation)[93]. The cardiovascular portion of the sympathetic outflow is regulated through PVH neurons that reside in the parvocellular subdivision of the nucleus and innervate the lower brainstem (for example, the NTS and RVLM) and spinal cord[27,80,93]. The PVH autonomic neurons use a combination of glutamate and peptides as transmitters (for example, vasopressin, oxytocin and CRF)[93,94]. Physiological evidence suggests that subsets of PVH autonomic neurons preferentially control renal sympathetic efferents[27,28], but the overall neuroanatomical organization of PVH autonomic neurons is unclear and their peptide profile has not been matched to any specific physiological function.

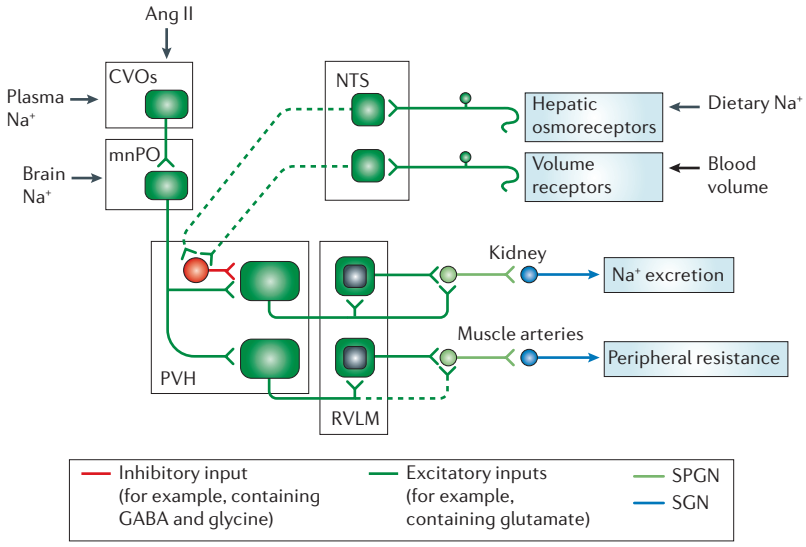

Figure 6 | **Sodium, renal sympathetic tone and blood pressure control.** A feedback loop involving atrial (volume) receptors, the nucleus of the solitary tract (NTS), the paraventricular nucleus of the hypothalamus (PVH) and the renal sympathetic nerves regulates sodium reabsorption by the kidney, and so contributes to blood volume homeostasis. The regulation of renal sympathetic nerve activity (SNA) by arterial baroreceptors operates mostly through the rostral ventrolateral medulla (RVLM) — C1 and non-adrenergic cells. Renal SNA is also regulated by blood and brain osmolality through peripheral and central osmoreceptors and by sodium acting at the level of hypothalamic receptors, including those in the median preoptic nucleus (mnPO). Integration between these competing influences seems to occur at the level of the PVH autonomic neurons and to be influenced by the level of circulating angiotensin II (Ang II) and mineralocorticoids. The PVH contains several classes of autonomic neuron that exert preferential influence over the kidneys versus resistance arteries elsewhere in the body. Dotted lines represent pathways that are not yet fully documented. CVO, circumventricular organ; SGN, sympathetic ganglionic neuron; SPGN, sympathetic preganglionic neuron.

PVH, osmolality and blood volume regulation. The activity of many PVH autonomic neurons is regulated by the competing influences of blood volume, BP and osmolality (FIG. 6). Volume expansion decreases renal SNA selectively[28]. This effect is initiated by activation of vagal mechanoreceptors located at the venous–atrial junctions of the heart[27]. Activation of these receptors excites NTS neurons[27,95] and the renal sympathetic reflex requires the integrity of the PVH region[27,96]. The pathway between the NTS and PVH does not involve the CVLM, but is otherwise poorly understood[95]. The bulk of the evidence suggests that renal nerve inhibition is produced by withdrawal of the sympathoexcitatory effect of PVH autonomic neurons that project to SPGNs and/or to the RVLM[27]. On the basis of the sensitivity of the response to the injection of receptor antagonists in the PVH region, the inhibition of PVH autonomic neurons by volume expansion probably requires the activation of still unidentified local GABA-containing interneurons (FIG. 6).

Short-term intravenous administration of hyperosmotic saline decreases renal SNA and increases lumbar SNA[97,98]. The renal nerve response is mediated by a combination of hepatoportal osmoreceptor stimulation and arterial and volume receptor activation and, therefore, appears to have little to do with central osmoreceptors[98]. The arterial-baroreceptor-independent portion of this acute response to saline infusion is attenuated by injection of a glutamate receptor antagonist in the region of the PVH or by inhibiting this region with muscimol[99], and is therefore probably due to inhibition of autonomic PVH neurons through a mechanism similar to that described above for volume expansion. Long-term increases in osmolality caused by water deprivation produce a more generalized increase in SNA, although the increase is greater and occurs earlier in the lumbar nerves than in the renal nerves[100]. Under anaesthesia, intravenous administration of hypertonic saline produces a delayed increase in lumbar SNA, whereas an immediate rise in renal SNA can be elicited by intracarotid bolus injections of hyperosmotic saline that do not change peripheral osmolality[101]. The increase in SNA caused by water deprivation correlates with a massive activation of the PVH autonomic neurons that project to the RVLM and the spinal cord[80,100]. The activation of the PVH autonomic neurons is thought to be secondary to the activation of central osmoreceptors or sodium

receptors that are located in circumventricular organs (subfornical organ and organum vasculosum lamina terminalis) or in the median preoptic nucleus[80,102]. The increase in SNA is ultimately mediated by activation of RVLM BP-regulating neurons, and glutamate is one of the transmitters involved[80,94] (FIG. 6).

The sympathoexcitatory effects caused by increased brain sodium concentration could be relevant to salt-induced hypertension[80]. Because the sympathoexcitatory effect of salt is amplified by angiotensin II and aldosterone, an inappropriate suppression of these hormones by high salt intake could synergize with the slight increase in osmolality caused by elevated salt consumption and lead to hypertension[80]. Evidence supporting this concept was recently provided by results from the deoxycorticosterone acetate (DOCA)-salt model of hypertension[103]. The neurophysiological mechanisms responsible for this synergy are still being investigated (for a discussion, see REF. 80). Aldosterone could evoke a response through a discrete group of NTS neurons that selectively respond to this hormone by virtue of the fact that they express high concentrations of mineralocorticoid receptors and of the glucocorticoid-inactivating enzyme 11-β-hydroxysteroid dehydrogenase type 2 (11βHSD2) (REF. 104). The activity of these neurons correlates with sodium appetite[104] but, given their location, these cells could also regulate autonomic efferents.

In the case of angiotensin II, increased production of intracellular oxygen radical species specifically in the subfornical organ seems to be crucial to the development of the neurogenic hypertension produced by inappropriately high levels of circulating angiotensin II (REF. 105). The subfornical organ is sensitive to both angiotensin II and sodium/osmolality, and so a synergy at this level is conceivable. The role of the brain's renin–angiotensin system in hypertension is less well understood. Angiotensin II has effects at multiple locations in the network that controls sympathetic tone (that is, the median preoptic nucleus, PVH, NTS, RVLM, SPGNs and probably all noradrenergic neurons). Transgenic mice expressing both the human renin gene, *REN*, and the human angiotensinogen gene *AGT* — the expression of the latter is controlled by a glial-specific promoter in these mice — have a 15 mm Hg increase in BP and an increased preference for salt[8]. These defects are normalized by intracerebroventricular administration of an AT_1 receptor antagonist and are therefore presumably caused by chronic overproduction of angiotensin II (REF. 8). This study reinforces the idea that an unregulated increase in brain angiotensin II can elevate the 24-h mean BP. However, the key, and still unanswered, question is what regulates the activity of the central renin–angiotensin system.

PVH and neurogenic hypertension. The hyperactivity of RVLM barosensitive neurons in several models of hypertension (for example, spontaneously hypertensive, Dahl salt-sensitive and renal hypertensive rats) relies partly on an increased excitatory drive from the parvocellular autonomic neurons[50,68]. Injection of antagonists of either angiotensin receptors or glutamate receptors into the RVLM reduces BP to a greater extent in specific hypertensive strains of rat[64,68]. These effects are tentatively attributed to increased release of glutamate and of angiotensin II by PVH neurons with RVLM projections, although other explanations are possible, including an increased local production of angiotensin II by cells resident in the RVLM, increased angiotensin II receptor numbers, or more efficient receptor–effector coupling mechanisms in the RVLM. The effect of angiotensin II on RVLM barosensitive neurons relies on several mechanisms that could be interrelated and need to be further investigated: potential mechanisms include the closure of a resting potassium conductance located on the barosensitive neurons, an increase in reactive oxygen species and a decrease in the concentration of nitric oxide of uncertain cellular origin[47,106].

Dorsomedial hypothalamus and hypertension. The dorsomedial nucleus[92] and the immediately adjacent perifornical area[107] have long been implicated in the genesis of autonomic responses to environmental stresses or threats[17]. Chemical stimulation of this region produces tachycardia that is mediated primarily by the midline medulla, as well as changes in blood flow and BP that are mediated by the RVLM[17,92]. The dorsomedial hypothalamus and RVLM are connected by both a direct projection and an indirect pathway that relays through the PVH and/or the periaqueductal grey matter, where similar types of response can be elicited[108,109]. In rats, environmental challenges, such as repeated air-jet stress, produce a chronic increase in renal SNA, which, in genetically prone strains (borderline hypertensive or Dahl salt-sensitive rats), can cause chronic hypertension by facilitating sodium retention[9]. A similar interaction between salt-sensitivity and stress also occurs in humans, and this could contribute to some forms of hypertension[9].

The PVH–RVLM axis and heart failure. Heart failure is another condition associated with a chronic activation of barosensitive sympathetic efferents. In heart failure, because the myocardium fails, increased SNA does not cause hypertension. However, the mechanisms involved in raising SNA — a mixture of reflex and hormonal dysfunction — could be highly relevant to neurogenic hypertension. Catecholamine overflow is also increased to a greater extent in the myocardium than in other locations during heart failure[110]. This peculiarity is implicitly attributed to greater sympathetic preganglionic efferent activity to the heart than other organs, but direct evidence is lacking and cardiac ganglion dysfunction could also conceivably contribute to the regional disparity in catecholamine overflow. Interestingly, heart failure is also associated with a massive upregulation of CNS catecholaminergic neurons that includes, but is not limited to, the adrenergic neurons[111]. The PVH–RVLM axis is also activated in animal models of ischaemic heart failure, and this activation undoubtedly contributes to the general state of sympathoactivation[112]. Activation of the PVH–RVLM axis is due, in part, to heightened excitatory inputs from peripheral sensory afferents that are sensitive to tissue hypoxia (cardiac receptors and, possibly, skeletal

muscle receptors) and a reduced feedback from arterial baroreceptors[112]. The brain renin–angiotensin system is also upregulated, perhaps under the influence of a heightened level of circulating adrenal mineralocorticoids or a circulating ouabain-like compound[113–115]. PVH neurons are activated by reductions in GABA- and/or nitric oxide-mediated inhibition[116]. However, upregulation of the brain renin–angiotensin system is not limited to the PVH but includes other hypothalamic regions involved in circulatory control — that is, the circumventricular organs, the RVLM and the NTS[112,117]. Many of the CNS effects of angiotensin, especially in heart failure, are attributed to a heightened production of radical oxygen species[118].

Conclusion

The basal activity of the barosensitive sympathetic efferents is generated by a complex but increasingly well understood network of neurons located in the hypothalamus and medulla oblongata. The RVLM is probably the most important nodal point of the network, but this idea derives mostly from experiments carried out under anaesthesia, and additional evidence is required to ascertain that this structure is equally important in the awake state. A specific marker common to all forms of RVLM BP-regulating neuron has not been found, which precludes the use of mouse genetics to determine how crucial these neurons really are for long-term BP control. Despite its probable importance to BP control, the RVLM is only a nodal point in a CNS network of extraordinary complexity. The activity of barosensitive SPGNs is also undoubtedly influenced by inputs from many other regions besides the RVLM (FIG. 2a). These inputs fine-tune the effects of the dominant RVLM excitatory input in ways that are poorly understood and contribute to the subtle target-dependent differential control of barosensitive sympathetic efferents. One of the most glaring holes in our understanding of BP control by the sympathetic system concerns the role of spinal interneurons and of the descending inhibitory pathways that originate from the midline medulla oblongata. Both hypothalamic nuclei — paraventricular and the dorsomedial nuclei — highlighted in this review are also mere gateways between the forebrain and the pontomedullary circuits that regulate the autonomic outflows. The CNS network that controls the circulation is also regulated by numerous blood-borne chemicals such as sodium, O_2, CO_2, hormones (for example, mineralocorticoids, ouabain-like compound and angiotensin II) and cytokines that access the CNS directly or via circumventricular organs, or influence the brain by eliciting the release of diffusible mediators (angiotensin II and interleukin-1) by the vascular endothelium. Although the complicated humoral regulation of the central autonomic network adds another layer of complexity, it could also provide therapeutic opportunities for the treatment of hypertension. Enhanced sympathetic activity and hypertension often correlate with an activation of the brain endogenous renin–angiotensin system and increased oxidative stress in subcortical structures. Given that virtually every component of the subcortical sympathetic network that has been tested responds to angiotensin II, understanding the mechanisms responsible for the activation of the brain renin–angiotensin system remains a priority.

The sympathetic efferents that innervate the kidneys are commonly presented as the only ones that are capable of influencing the 24-h average BP. If this theory is correct, a more complete knowledge of the neural pathways that selectively regulate renal SNA could be key to understanding the contribution of the CNS to hypertension. However, this theory has yet to be proved, and current evidence suggests that, in hypertensive humans and animals, the rise in the activity of barosensitive sympathetic efferents is not restricted to the renal nerves but is generalized[110]. Accordingly, it is also plausible that neurogenic hypertension could originate from CNS circuits that exert a broad influence over all barosensitive sympathetic efferents or, conceivably, over an even larger array of sympathetic efferents. The upregulation of RVLM barosensitive neurons offers a plausible explanation for the generalized increase in sympathetic tone in hypertension because many C1 cells appear to be central command neurons that regulate SNA to multiple organs[31,69]. However, the root cause of this upregulation is still to be explained, and is likely to be secondary to an increased synaptic drive from other brain structures such as the PVH.

In conclusion, dysfunctional reflexes and/or increased activity of the PVH–RVLM axis are factors that are currently suspected of contributing to the chronic elevation of barosensitive sympathetic efferents in many forms of hypertension. The key to neurogenic hypertension awaits further understanding of the CNS networks that regulate sympathetic efferents, and the humoral control of these circuits could offer new possibilities for pharmacological intervention in hypertension.

1. Blessing, W. W. in *The Lower Brainstem and Bodily Homeostasis* 165–268 (Oxford Univ. Press, New York, 1997).
Provides a rare comprehensive and insightful overview of the neural control of circulation with emphasis on the brainstem.
2. Loewy, A. D. & Spyer, K. M. *Central Regulation of Autonomic Functions* (Oxford Univ. Press, New York, 1990).
3. Saper, C. B. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *Annu. Rev. Neurosci.* **25**, 433–469 (2002).
Examines the control of BP in the more general context of the generation of autonomic patterns.
4. Morrison, S. F. Central pathways controlling brown adipose tissue thermogenesis. *News Physiol. Sci.* **19**, 67–74 (2004).
5. Westerhaus, M. J. & Loewy, A. D. Central representation of the sympathetic nervous system in the cerebral cortex. *Brain Res.* **903**, 117–127 (2001).
6. Madden, C. J. & Sved, A. F. Cardiovascular regulation after destruction of the C1 cell group of the rostral ventrolateral medulla in rats. *Am. J. Physiol. Heart Circ. Physiol.* **285**, H2734–H2748 (2003).
7. Kishi, T. *et al*. Overexpression of eNOS in the RVLM causes hypotension and bradycardia via GABA release. *Hypertension* **38**, 896–901 (2001).
This important paper demonstrates that sustained changes in BP can be produced by altering the activity of relatively few neurons in the RVLM, which is strong evidence that the brain controls the 24-h average BP, presumably through the sympathetic nerves.
8. Morimoto, S. *et al*. Elevated blood pressure in transgenic mice with brain-specific expression of human angiotensinogen driven by the glial fibrillary acidic protein promoter. *Circ. Res.* **89**, 365–372 (2001).
Suggests that hypertension can be produced by upregulation of the renin–angiotensin system. This shows that the kidneys and vasculature cannot compensate for a brain defect and, therefore, that these organs cannot be the sole regulators of long-term BP, as is often stated.

9. DiBona, G. F. & Kopp, U. C. Neural control of renal function. *Physiol. Rev.* **77**, 75–197 (1997).
Comprehensive, analytical review of the neural control of the kidney in health and disease, notably hypertension. The review argues strongly in favour of the role of renal sympathetic nerves in regulating the BP set-point.
10. Jacob, F., Clark, L. A., Guzman, P. A. & Osborn, J. W. Role of renal nerves in development of hypertension in DOCA-salt model in rats: a telemetric approach. *Am. J. Physiol. Heart Circ. Physiol.* **289**, H1519–H1529 (2005).
11. Cowley, A. W. Jr Long-term control of arterial blood pressure. *Physiol. Rev.* **72**, 231–300 (1992).
12. Osborn, J. W. 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.* **32**, 384–393 (2005).
13. Guyton, A. C. Blood pressure control — special role of the kidneys and body fluids. *Science* **252**, 1813–1816 (1991).
Essential reading to understand how the kidneys contribute to the long-term regulation of BP by adjusting sodium excretion.
14. Schlaich, M. P. *et al*. Sympathetic augmentation in hypertension: role of nerve firing, norepinephrine reuptake, and angiotensin neuromodulation. *Hypertension* **43**, 169–175 (2004).
15. Hoffman, B. B. in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (eds Brunton, L. L., Lazo, J. S. & Parker, K. L.) 845–868 (McGraw-Hill, New York, 2006).
16. Barrett, C. J., Navakatikyan, M. A. & Malpas, S. C. Long-term control of renal blood flow: what is the role of the renal nerves? *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **280**, R1534–R1545 (2001).
17. Dampney, R. A. *et al*. Long-term regulation of arterial blood pressure by hypothalamic nuclei: some critical questions. *Clin. Exp. Pharmacol. Physiol.* **32**, 419–425 (2005).
18. Lohmeier, T. E. The sympathetic nervous system and long-term blood pressure regulation. *Am. J. Hypertens.* **14**, S147–S154 (2001).
19. Janig, W. & Habler, H. J. Neurophysiological analysis of target-related sympathetic pathways — from animal to human: similarities and differences. *Acta Physiol. Scand.* **177**, 255–274 (2003).
20. Blessing, W. W. & Nalivaiko, E. Regional blood flow and nociceptive stimuli in rabbits: patterning by medullary raphe, not ventrolateral medulla. *J. Physiol. (Lond.)* **524**, 279–292 (2000).
Indicates that the RVLM is involved to only a slight extent in regulating blood flow to the skin, shaping the current belief that the RVLM selectively regulates the sympathetic efferents that are under arterial baroreceptor control and that the RVLM is important for cardiorespiratory integration and BP control.
21. Vallbo, A. B., Hagbarth, K. E. & Wallin, B. G. Microneurography: how the technique developed and its role in the investigation of the sympathetic nervous system. *J. Appl. Physiol.* **96**, 1262–1269 (2004).
22. Cao, W. H. & Morrison, S. F. Differential chemoreceptor reflex responses of adrenal preganglionic neurons. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **281**, R1825–R1832 (2001).
23. Dempsey, J. A., Sheel, A. W., St Croix, C. M. & Morgan, B. J. Respiratory influences on sympathetic vasomotor outflow in humans. *Respir. Physiol. Neurobiol.* **130**, 3–20 (2002).
24. Dampney, R. A. L. *et al*. Central mechanisms underlying short- and long-term regulation of the cardiovascular system. *Clin. Exp. Pharmacol. Physiol.* **29**, 261–268 (2002).
25. Sinoway, L. I. & Li, J. A perspective on the muscle reflex: implications for congestive heart failure. *J. Appl. Physiol.* **99**, 5–22 (2005).
26. Guo, Z. L., Lai, H. C. & Longhurst, J. C. Medullary pathways involved in cardiac sympathoexcitatory reflexes in the cat. *Brain Res.* **925**, 55–66 (2002).
27. Coote, J. H. A role for the paraventricular nucleus of the hypothalamus in the autonomic control of heart and kidney. *Exp. Physiol.* **90**, 169–173 (2005).
28. Ramchandra, R., Barrett, C. J., Guild, S. J. & Malpas, S. C. Evidence of differential control of renal and lumbar sympathetic nerve activity in conscious rabbits. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **290**, R701–R708 (2006).
29. Sved, A. F., Cano, G. & Card, J. P. Neuroanatomical specificity of the circuits controlling sympathetic outflow to different targets. *Clin. Exp. Pharmacol. Physiol.* **28**, 115–119 (2001).
30. Guyenet, P. G., Stornetta, R. L., Weston, M. C., McQuiston, T. & Simmons, J. R. Detection of amino acid and peptide transmitters in physiologically identified brainstem cardiorespiratory neurons. *Auton. Neurosci.* **114**, 1–10 (2004).
31. Jansen, A. S. P., Nguyen, X. V., Karpitskiy, V., Mettenleiter, T. C. & Loewy, A. D. Central command neurons of the sympathetic nervous system: basis of the fight or flight response. *Science* **270**, 644–646 (1995).
Illustrates the use of the pseudorabies virus in tracking the CNS networks that regulate the sympathetic nervous system. This particular paper argues that the RVLM contains neurons that innervate many types of sympathetic efferent, which is a conclusion that goes against a strict organotopic arrangement of RVLM barosensitive neurons.
32. Ritter, S., Bugarith, K. & Dinh, T. T. Immunotoxic destruction of distinct catecholamine subgroups produces selective impairment of glucoregulatory responses and neuronal activation. *J. Comp. Neurol.* **432**, 197–216 (2001).
33. Hokfelt, T., Fuxe, K., Goldstein, M. & Johansson, O. Immunohistochemical evidence for the existence of adrenaline neurons in the rat brain. *Brain Res.* **66**, 235–251 (1974).
34. Ross, C. A. *et al*. Tonic vasomotor control by the rostral ventrolateral medulla: effect of electrical or chemical stimulation of the area containing C1 adrenaline neurons on arterial pressure, heart rate, and plasma catecholamines and vasopressin. *J. Neurosci.* **4**, 474–494 (1984).
An influential paper that definitively established the pivotal role of the RVLM in controlling BP and gave strong support to the idea that the C1 cells are a crucial component of the network that regulates BP.
35. Brown, D. L. & Guyenet, P. G. Electrophysiological study of cardiovascular neurons in the rostral ventrolateral medulla in rats. *Circ. Res.* **56**, 359–369 (1985).
36. Guyenet, P. G. & Stornetta, R. L. in *Neural Mechanisms of Cardiovascular Regulation* (eds Dun, N. J., Machado, B. H. & Pilowsky, P. M.) 187–218 (Kluwer, Boston, Massachusetts, 2004).
37. Sun, M. K. Pharmacology of reticulospinal vasomotor neurons in cardiovascular regulation. *Pharmacol. Rev.* **48**, 465–494 (1996).
38. Schreihofer, A. M. & Guyenet, P. G. Identification of C1 presympathetic neurons in rat rostral ventrolateral medulla by juxtacellular labeling *in vivo*. *J. Comp. Neurol.* **387**, 524–536 (1997).
39. Schreihofer, A. M., Stornetta, R. L. & Guyenet, P. G. Regulation of sympathetic tone and arterial pressure by rostral ventrolateral medulla after depletion of C1 cells in rat. *J. Physiol. (Lond.)* **529**, 221–236 (2000).
40. Verberne, A. J. M., Stornetta, R. L. & Guyenet, P. G. Properties of C1 and other ventrolateral medullary neurones with hypothalamic projections in the rat. *J. Physiol. (Lond.)* **517**, 477–494 (1999).
41. Ericsson, A., Arias, C. & Sawchenko, P. E. Evidence for an intramedullary prostaglandin-dependent mechanism in the activation of stress-related neuroendocrine circuitry by intravenous interleukin-1. *J. Neurosci.* **17**, 7166–7179 (1997).
42. Dampney, R. A. *et al*. Medullary and supramedullary mechanisms regulating sympathetic vasomotor tone. *Acta Physiol. Scand.* **177**, 209–218 (2003).
43. Brooks, V. L., Freeman, K. L. & Clow, K. A. Excitatory amino acids in rostral ventrolateral medulla support blood pressure during water deprivation in rats. *Am. J. Physiol. Heart Circ. Physiol.* **286**, H1642–H1648 (2004).
44. Guyenet, P. G. Neural structures that mediate sympathoexcitation during hypoxia. *Respir. Physiol.* **121**, 147–162 (2000).
45. Kangrga, I. M. & Loewy, A. D. Whole-cell recordings from visualized C1 adrenergic bulbospinal neurons: ionic mechanisms underlying vasomotor tone. *Brain Res.* **670**, 215–232 (1995).
Suggests that the C1 neurons have intrinsic beating properties that are driven, in part, by a persistent sodium current in brain slices. The observation is consistent with the possibility that a portion of the vasomotor tone derives from these intrinsic properties.
46. Lipski, J., Kawai, Y., Qi, J., Comer, A. & Win, J. Whole cell patch-clamp study of putative vasomotor neurons isolated from the rostral ventrolateral medulla. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **274**, R1099–R1110 (1998).
47. Li, Y. W. & Guyenet, P. G. Neuronal excitation by angiotensin II in the rostral ventrolateral medulla of the rat *in vitro*. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **268**, R272–R277 (1995).
48. Gomez, R. E. *et al*. Vasopressinergic mechanisms in the nucleus reticularis lateralis in blood pressure control. *Brain Res.* **604**, 90–105 (1993).
49. Milner, T. A., Reis, D. J., Pickel, V. M., Aicher, S. A. & Giuliano, R. Ultrastructural localization and afferent sources of corticotropin-releasing factor in the rat rostral ventrolateral medulla: implications for central cardiovascular regulation. *J. Comp. Neurol.* **333**, 151–167 (1993).
50. Allen, A. M. Inhibition of the hypothalamic paraventricular nucleus in spontaneously hypertensive rats dramatically reduces sympathetic vasomotor tone. *Hypertension* **39**, 275–280 (2002).
51. Schreihofer, A. M. & Guyenet, P. G. Baroactivated neurons with pulse-modulated activity in the rat caudal ventrolateral medulla express GAD67 mRNA. *J. Neurophysiol.* **89**, 1265–1277 (2003).
52. Horiuchi, J. & Dampney, R. A. Evidence for tonic disinhibition of RVLM sympathoexcitatory neurons from the caudal pressor area. *Auton. Neurosci.* **99**, 102–110 (2002).
53. Verberne, A. J. M., Sartor, D. M. & Berke, A. Midline medullary depressor responses are mediated by inhibition of RVLM sympathoexcitatory neurons in rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **276**, R1054–R1062 (1999).
54. Barman, S. M., Gebber, G. L. & Orer, H. S. Medullary lateral tegmental field: an important source of basal sympathetic nerve discharge in the cat. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **278**, R995–R1004 (2000).
55. Makeham, J. M., Goodchild, A. K. & Pilowsky, P. M. NK1 receptor activation in rat rostral ventrolateral medulla selectively attenuates somato-sympathetic reflex while antagonism attenuates sympathetic chemoreflex. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **288**, R1707–R1715 (2005).
56. Campos, R. R. & McAllen, R. M. Cardiac sympathetic premotor neurons. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **272**, R615–R620 (1997).
57. McAllen, R. M., May, C. N. & Shafton, A. D. Functional anatomy of sympathetic premotor cell groups in the medulla. *Clin. Exp. Hypertens.* **17**, 209–221 (1995).
58. McAllen, R. M. & Dampney, R. A. Vasomotor neurons in the rostral ventrolateral medulla are organized topographically with respect to type of vascular bed but not body region. *Neurosci. Lett.* **110**, 91–96 (1990).
59. Stornetta, R. L., McQuiston, T. J. & Guyenet, P. G. GABAergic and glycinergic presympathetic neurons of rat medulla oblongata identified by retrograde transport of pseudorabies virus and *in situ* hybridization. *J. Comp. Neurol.* **479**, 257–270 (2004).
60. Kerman, I. A., Enquist, L. W., Watson, S. J. & Yates, B. J. Brainstem substrates of sympatho-motor circuitry identified using trans-synaptic tracing with pseudorabies virus recombinants. *J. Neurosci.* **23**, 4657–4666 (2003).
61. Sartor, D. M. & Verberne, A. J. Cholecystokinin selectively affects presympathetic vasomotor neurons and sympathetic vasomotor outflow. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **282**, R1174–R1184 (2002).
62. Haselton, J. R. & Guyenet, P. G. Central respiratory modulation of medullary sympathoexcitatory neurons in rat. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **256**, R739–R750 (1989).
63. Kishi, T. *et al*. Cardiovascular effects of overexpression of endothelial nitric oxide synthase in the rostral ventrolateral medulla in stroke-prone spontaneously hypertensive rats. *Hypertension* **39**, 264–268 (2002).
64. Sved, A. F., Ito, S. & Sved, J. C. Brainstem mechanisms of hypertension: role of the rostral ventrolateral medulla. *Curr. Hypertens. Rep.* **5**, 262–268 (2003).
65. Ding, Z. Q., Li, Y. W., Wesselingh, S. L. & Blessing, W. W. Transneuronal labelling of neurons in rabbit brain after injection of Herpes simplex virus type-1 into the renal nerve. *J. Auton. Nerv. Syst.* **42**, 23–32 (1993).
66. Dean, C., Seagard, J. L., Hopp, F. A. & Kampine, J. P. Differential control of sympathetic activity to kidney and skeletal muscle by ventral medullary neurons. *J. Auton. Nerv. Syst.* **37**, 1–10 (1992).

67. Akine, A., Montanaro, M. & Allen, A. M. Hypothalamic paraventricular nucleus inhibition decreases renal sympathetic nerve activity in hypertensive and normotensive rats. *Auton. Neurosci.* **108**, 17–21 (2003).
68. Ito, S. *et al*. Ventrolateral medulla AT_1 receptors support arterial pressure in Dahl salt-sensitive rats. *Hypertension* **41**, 744–750 (2003).
69. Reja, V., Goodchild, A. K. & Pilowsky, P. M. Catecholamine-related gene expression correlates with blood pressures in SHR. *Hypertension* **40**, 342–347 (2002).
70. Reja, V., Goodchild, A. K., Phillips, J. K. & Pilowsky, P. M. Tyrosine hydroxylase gene expression in ventrolateral medulla oblongata of WKY and SHR: a quantitative real-time polymerase chain reaction study. *Auton. Neurosci.* **98**, 79–84 (2002).
71. Potts, J. T. *et al*. Contraction-sensitive skeletal muscle afferents inhibit arterial baroreceptor signalling in the nucleus of the solitary tract: role of intrinsic GABA interneurons. *Neuroscience* **119**, 201–214 (2003).
72. Schreihofer, A. M. & Guyenet, P. G. The baroreflex and beyond: control of sympathetic vasomotor tone by GABAergic neurons in the ventrolateral medulla. *Clin. Exp. Pharmacol. Physiol.* **29**, 514–521 (2002).
73. Pilowsky, P. M. & Goodchild, A. K. Baroreceptor reflex pathways and neurotransmitters: 10 years on. *J. Hypertens.* **20**, 1675–1688 (2002).
74. Andresen, M. C., Doyle, M. W., Jin, Y. H. & Bailey, T. W. Cellular mechanisms of baroreceptor integration at the nucleus tractus solitarius. *Ann. NY Acad. Sci.* **940**, 132–141 (2001).
75. Paton, J. F. *et al*. Adenoviral vector demonstrates that angiotensin II-induced depression of the cardiac baroreflex is mediated by endothelial nitric oxide synthase in the nucleus tractus solitarii of the rat. *J. Physiol. (Lond.)* **531**, 2–58 (2001).
76. Paton, J. F., Boscan, P., Murphy, D. & Kasparov, S. Unravelling mechanisms of action of angiotensin II on cardiorespiratory function using *in vivo* gene transfer. *Acta Physiol. Scand.* **173**, 127–137 (2001).
77. Osborn, J. W., Jacob, F. & Guzman, P. A neural set point for the long-term control of arterial pressure: beyond the arterial baroreceptor reflex. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **288**, R846–R855 (2005).
78. Thrasher, T. N. Baroreceptors, baroreceptor unloading, and the long-term control of blood pressure. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **288**, R819–R827 (2005).
79. Schreihofer, A. M., Ito, S. & Sved, A. F. Brain stem control of arterial pressure in chronic arterial baroreceptor denervated rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **289**, R1746–R1755 (2005).
80. Brooks, V. L., Haywood, J. R. & Johnson, A. K. Translation of salt retention to central activation of the sympathetic nervous system in hypertension. *Clin. Exp. Pharmacol. Physiol.* **32**, 426–432 (2005).
Interesting paper that describes potential CNS mechanisms of salt-dependent hypertension.
81. Kawano, H. & Masuko, S. Synaptic contacts between nerve terminals originating from the ventrolateral medullary catecholaminergic area and median preoptic neurons projecting to the paraventricular hypothalamic nucleus. *Brain Res.* **817**, 110–116 (1999).
82. McKinley, M. J. *et al*. Neural pathways from the lamina terminalis influencing cardiovascular and body fluid homeostasis. *Clin. Exp. Pharmacol. Physiol.* **28**, 990–992 (2001).
83. Babic, T., Roder, S. & Ciriello, J. Direct projections from caudal ventrolateral medullary depressor sites to the subfornical organ. *Brain Res.* **1003**, 113–121 (2004).
84. Wolk, R., Shamsuzzaman, A. S. M. & Somers, V. K. Obesity, sleep apnea, and hypertension. *Hypertension* **42**, 1067–1074 (2003).
85. Blessing, W. W., Yu, Y. H. & Nalivaiko, E. Medullary projections of rabbit carotid sinus nerve. *Brain Res.* **816**, 405–410 (1999).
86. Paton, J. F. R., Deuchars, J., Li, Y. W. & Kasparov, S. Properties of solitary tract neurones responding to peripheral arterial chemoreceptors. *Neuroscience* **105**, 231–248 (2001).
87. Prabhakar, N. R., Peng, Y. J., Jacono, F. J., Kumar, G. K. & Dick, T. E. Cardiovascular alterations by chronic intermittent hypoxia: importance of carotid body chemoreflexes. *Clin. Exp. Pharmacol. Physiol.* **32**, 447–449 (2005).
The authors suggest that changes in the discharge characteristics of peripheral chemoreceptors at rest and in response to hypoxia could contribute to the development of hypertension associated with increased sympathetic tone caused by obstructive sleep apnoea.
88. Roux, J. C. *et al*. O_2-sensing after carotid chemodenervation: hypoxic ventilatory responsiveness and upregulation of tyrosine hydroxylase mRNA in brainstem catecholaminergic cells. *Eur. J. Neurosci.* **12**, 3181–3190 (2000).
89. Pascual, O. *et al*. Selective cardiorespiratory and catecholaminergic areas express the hypoxia-inducible factor-1α (HIF-1α) under *in vivo* hypoxia in rat brainstem. *Eur. J. Neurosci.* **14**, 1981–1991 (2001).
90. Reis, D. J., Golanov, E. V., Galea, E. & Feinstein, D. L. Central neurogenic neuroprotection: central neural systems that protect the brain from hypoxia and ischemia. *Ann. NY Acad. Sci.* **835**, 168–186 (1997).
The authors postulate that the brain could protect itself from hypoxia by elevating BP via increases in SNA. They also propose that the C1 neurons potentially have a central role in this process.
91. Levy, E. I., Scarrow, A. M. & Jannetta, P. J. Microvascular decompression in the treatment of hypertension: review and update. *Surg. Neurol.* **55**, 2–10 (2001).
92. Dimicco, J. A., Samuels, B. C., Zaretskaia, M. V. & Zaretsky, D. V. The dorsomedial hypothalamus and the response to stress: part renaissance, part revolution. *Pharmacol. Biochem. Behav.* **71**, 469–480 (2002).
93. Benarroch, E. E. Paraventricular nucleus, stress response, and cardiovascular disease. *Clin. Auton. Res.* **15**, 254–263 (2005).
94. Stocker, S. D., Simmons, J. R., Stornetta, R. L., Toney, G. M. & Guyenet, P. G. Water deprivation activates a glutamatergic projection from the hypothalamic paraventricular nucleus to the rostral ventrolateral medulla. *J. Comp. Neurol.* **494**, 673–685 (2006).
95. Shafton, A. D., Ryan, A., McGrath, B. & Badoer, E. Volume expansion does not activate neuronal projections from the NTS or depressor VLM to the RVLM. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **277**, R39–R46 (1999).
96. Haselton, J. R., Goering, J. & Patel, K. P. Parvocellular neurons of the paraventricular nucleus are involved in the reduction in renal nerve discharge during isotonic volume expansion. *J. Auton. Nerv. Syst.* **50**, 1–12 (1994).
97. Weiss, M. L., Claassen, D. E., Hirai, T. & Kenney, M. J. Nonuniform sympathetic nerve responses to intravenous hypertonic saline infusion. *J. Auton. Nerv. Syst.* **57**, 109–115 (1996).
98. Morita, H., Nishida, Y. & Hosomi, H. Neural control of urinary sodium excretion during hypertonic NaCl load in conscious rabbits: role of renal and hepatic nerves and baroreceptors. *J. Auton. Nerv. Syst.* **34**, 157–169 (1991).
99. Badoer, E., Ng, C. W. & De, M. R. Glutamatergic input in the PVN is important in renal nerve response to elevations in osmolality. *Am. J. Physiol. Renal Physiol.* **285**, F640–F650 (2003).
100. Stocker, S. D., Hunwick, K. J. & Toney, G. M. Hypothalamic paraventricular nucleus differentially supports lumbar and renal sympathetic outflow in water-deprived rats. *J. Physiol. (Lond.)* **563**, 249–263 (2005).
101. Brooks, V. L., Freeman, K. L. & O'Donaughy, T. L. Acute and chronic increases in osmolality increase excitatory amino acid drive of the rostral ventrolateral medulla in rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **287**, R1359–R1368 (2004).
102. Grob, M., Drolet, G. & Mouginot, D. Specific Na^+ sensors are functionally expressed in a neuronal population of the median preoptic nucleus of the rat. *J. Neurosci.* **24**, 3974–3984 (2004).
103. O'Donaughy, T. L. & Brooks, V. L. Deoxycorticosterone acetate-salt rats. Hypertension and sympathoexcitation driven by increased NaCl levels. *Hypertension* **47**, 680–685 (2006).
104. Geerling, J. C., Engeland, W. C., Kawata, M. & Loewy, A. D. Aldosterone target neurons in the nucleus tractus solitarius drive sodium appetite. *J. Neurosci.* **26**, 411–417 (2006).
Provides the first definitive identification of brain neurons that are capable of detecting the circulating level of mineralocorticoid selectively. The study shows that the activity of these neurons correlates with sodium appetite.
105. Zimmerman, M. C., Lazartigues, E., Sharma, R. V. & Davisson, R. L. Hypertension caused by angiotensin II infusion involves increased superoxide production in the central nervous system. *Circ. Res.* **95**, 210–216 (2004).
106. Kishi, T. *et al*. Increased reactive oxygen species in rostral ventrolateral medulla contribute to neural mechanisms of hypertension in stroke-prone spontaneously hypertensive rats. *Circulation* **109**, 2357–2362 (2004).
107. Smith, O. A., DeVito, J. L. & Astley, C. A. Neurons controlling cardiovascular responses to emotion are located in lateral hypothalamus-perifornical region. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **259**, R943–R954 (1990).
108. Lovick, T. A. The periaqueductal gray–rostral medulla connection in the defense reaction: efferent pathways and descending control mechanisms. *Behav. Brain Res.* **58**, 19–25 (1993).
109. Bandler, R., Carrive, P. & Zhang, S. P. Integration of somatic and autonomic reactions within the midbrain periaqueductal grey: viscerotopic, somatotopic and functional organization. *Prog. Brain Res.* **87**, 269–305 (1991).
110. Esler, M. & Kaye, D. Sympathetic nervous system activation in essential hypertension, cardiac failure and psychosomatic heart disease. *J. Cardiovasc. Pharmacol.* **35**, S1–S7 (2000).
This important paper documents a generalized increase in sympathetic tone in various forms of hypertension.
111. Lambert, G. W. *et al*. Increased central nervous system monoamine neurotransmitter turnover and its association with sympathetic nervous activity in treated heart failure patients. *Circulation* **92**, 1813–1818 (1995).
112. Felder, R. B. *et al*. Heart failure and the brain: new perspectives. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **284**, R259–R276 (2003).
113. Huang, B. S. & Leenen, F. H. Blockade of brain mineralocorticoid receptors or Na^+ channels prevents sympathetic hyperactivity and improves cardiac function in rats post-MI. *Am. J. Physiol. Heart Circ. Physiol.* **288**, H2491–H2497 (2005).
114. Zhang, W. G., Huang, B. S. & Leenen, F. H. H. Brain renin–angiotensin system and sympathetic hyperactivity in rats after myocardial infarction. *Am. J. Physiol. Heart Circ. Physiol.* **276**, H1608–H1615 (1999).
115. Hamlyn, J. M., Hamilton, B. P. & Manunta, P. Endogenous ouabain, sodium balance and blood pressure: a review and a hypothesis. *J. Hypertens.* **14**, 151–167 (1996).
116. Weiss, M. L., Kenney, M. J., Musch, T. I. & Patel, K. P. Modifications to central neural circuitry during heart failure. *Acta Physiol. Scand.* **177**, 57–67 (2003).
117. Francis, J., Wei, S. G., Weiss, R. M. & Felder, R. B. Brain angiotensin-converting enzyme activity and autonomic regulation in heart failure. *Am. J. Physiol. Heart Circ. Physiol.* **287**, H2138–H2146 (2004).
118. Lindley, T. E., Doobay, M. F., Sharma, R. V. & Davisson, R. L. Superoxide is involved in the central nervous system activation and sympathoexcitation of myocardial infarction-induced heart failure. *Circ. Res.* **94**, 402–409 (2004).
119. Zimmerman, M. C. & Davisson, R. L. Redox signaling in central neural regulation of cardiovascular function. *Prog. Biophys. Mol. Biol.* **84**, 125–149 (2004).

Acknowledgement
This work was supported by grants from the National Institutes of Health, Heart, Lung and Blood Institute (P.G.G.).

Competing interests statement
The author declares no competing financial interests.

DATABASES
The following terms in this article are linked online to:
Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
11βHSD2 | AT_1 | *AGT* | *REN*
Access to this links box is available online.