HHS Public Access

Author manuscript

Hypertension. Author manuscript; available in PMC 2021 August 01.

Published in final edited form as:

Hypertension. 2020 August ; 76(2): 300–311. doi:10.1161/HYPERTENSIONAHA.120.14521.

Neuronal Networks in Hypertension: Recent Advances

Patrice G. Guyenet[1], **Ruth L. Stornetta**[1], **George M.P.R. Souza**[1], **Stephen B.G. Abbott**[1], **Virginia L. Brooks**[2]

[1]University of Virginia, Department of Pharmacology, Charlottesville, VA, USA

[2]Oregon Health & Sciences University, Department of Chemical Physiology and Biochemistry, Portland, OR, USA

Abstract

Neurogenic hypertension is associated with excessive sympathetic nerve activity (SNA) to the kidneys and portions of the cardiovascular system. Here we examine the brain regions that cause heightened SNA in animal models of neurogenic hypertension and we discuss the triggers responsible for the changes in neuronal activity within these regions. We highlight the limitations of the evidence and, whenever possible, we briefly address the pertinence of the findings to human hypertension.

The arterial baroreflex reduces BP variability and contributes to the BP set-point. This set-point can also be elevated by a newly described cerebral blood flow-dependent and astrocyte-mediated sympathetic reflex. Both reflexes converge on the presympathetic neurons of the rostral medulla oblongata (RVLM PSNs) and both are plausible causes of neurogenic hypertension. Sensory afferent dysfunction (reduced baroreceptor activity, increased renal or carotid body afferent) contributes to many forms of neurogenic hypertension. Neurogenic hypertension can also result from activation of brain nuclei or sensory afferents by excess circulating hormones (leptin, insulin, AngII) or sodium. Leptin raises blood vessel SNA by activating the carotid bodies and subsets of arcuate neurons. AngII works in the lamina terminalis and probably throughout the brainstem and hypothalamus. Sodium is sensed primarily in the lamina terminalis. Regardless of its cause, the excess SNA is mediated to some extent by activation of presympathetic neurons (PSNs) located in the rostral ventrolateral medulla (RVLM) or the paraventricular nucleus of the hypothalamus. Increased activity of the orexinergic neurons also contributes to hypertension in selected models.

Neurogenic hypertension refers to a chronic increase in arterial blood pressure (BP) that is associated with and presumably driven by excessive sympathetic nerve activity (SNA) to the kidneys and various parts of the cardiovascular system[1–4]. We will not discuss here how a global or regional increase in SNA causes or maintains the hypertensive state[5–7]. Instead, we focus on two specific aspects of neurogenic hypertension research: the brain regions responsible for heightened SNA in animal models and the triggers responsible for the changes in neuronal activity within these regions (e.g. sensory afferent dysfunction, brain hypoperfusion, gliotransmission, excess circulating hormones, hypernatremia, etc.). The

Correspondence to: Patrice G. Guyenet PhD, University of Virginia, Department of Pharmacology, 1340 Jefferson park Avenue, P.O.Box 800735, Charlottesville, VA 22908-0735. Tel: (434) 924-9974; Fax: (434) 982-3878. pgg@virginia.edu.

Disclosures: none.

topic is vast and the space limited. Despite their importance, oxidative stress and inflammation are not discussed.

The ventrolateral medulla and hypertension

The rostral ventrolateral medulla (RVLM) is a major node of the BP regulating neural network[8, 9]. Silencing RVLM neurons indiscriminately produces large reductions of BP and SNA in anesthetized or conscious rodents[9–11]. These effects are attributed to the inhibition of excitatory neurons with monosynaptic projections to sympathetic preganglionic neurons, a.k.a. RVLM presympathetic neurons (PSNs). Many RVLM PSNs (C1 cells) synthesize catecholamines inclusive of epinephrine, the rest do not (non-C1)[12–14]. Estimates of the ratio between non-C1 and C1 PSNs varies widely (33 to 300%)[12, 13, 15, 16]. C1 and non-C1 PSNs are glutamatergic and express varying levels of neuropeptides (PACAP, NPY, substance P, enkephalins)[9].

The degree to which the C1 and other RVLM neurons contribute to resting BP in an intact unstressed and unanesthetized mammal is unsettled. Extensive lesions of the C1 neurons (>85%) compromise BP stability during hypoxic or hypotensive stresses but cause very little hypotension at rest (<10 mmHg in rats)[17, 18] suggesting that the contribution of these neurons to BP is small under resting conditions. Consistent with this view, in freely behaving rats at rest, bilateral optogenetic C1 cell inhibition (with the proton pump archaerhodopsin) also reduced BP very little (~5mmHg)[19]. Yet, a more substantial BP drop (−27 mmHg) was observed using a pharmacogenetic approach (allatostatin receptor)[20]. The same type of vector (lentivirus with a Phox2b-enhanced promoter, PRSx8) was used in both studies. This vector does not transduce catecholaminergic neurons with total selectivity. The allatostatin receptor is a G-protein coupled receptor and, as such, presumably needs a much lower level of membrane expression than the proton pump to be an effective actuator, thus increasing the probability of off-target effects[21]. Conversely, archaerhodopsin requires a high level of expression for efficacy; its use could have led to the underestimation of the contribution of the C1 neurons to resting BP. Finally, the autonomic effects caused by a purely psychological stress may not be mediated via the RVLM[22].

SNA to various organs or tissues is differentially regulated (e.g.[23, 24]). This point is notable because hypertension may be caused by preferential activation of SNA to the heart, resistance vessels or splanchnic capacitance[25]. The differential control of regional SNA may occur via differential recruitment of subsets of RVLM premotor neurons that control sympathetic efferents to particular vascular beds (e.g. splanchnic vs. muscle or capacitance vs. resistance) and different regions of the kidneys or the myocardium(Figure 1)[9, 26–28]. However, the RVLM also contains highly collateralized PSNs, e.g. C1 cells, that can activate multiple sympathetic efferent pathways simultaneously[29, 30].

RVLM PSNs, C1 included, innervate many brain regions implicated in BP control besides the spinal cord including the solitary tract nucleus (NTS), parabrachial region, locus coeruleus, periaqueductal gray matter and raphe pallidus (Figure 2)[9, 31]. Non-bulbospinal RVLM neurons, including C1 neurons, also target hypothalamic nuclei of prime importance to cardiovascular control, notably orexin neurons and the PVN[31, 32]. In brief, the notion that

RVLM controls SNA exclusively via its spinal projections to preganglionic neurons has not been tested rigorously and seems a priori inconsistent with the available anatomical data.

Many factors (synaptic, intrinsic or paracrine) determine the discharge rate of the PSNs. Conventional excitatory and inhibitory synaptic inputs clearly play a role[18]. The neurons antecedent to RVLM PSNs reside within the lower brainstem reticular formation, with fewer neurons located in the dorsal vagal complex, dorsolateral pons, midbrain and hypothalamus[33, 34]. The inhibition of RVLM PSNs elicited by arterial baroreceptor activation is mediated by GABAergic interneurons located in the caudal VLM (CVLM; Figure 1); these interneurons are also strongly respiratory modulated and therefore must contribute to the respiratory modulation of RVLM PSNs and, ultimately, SNA[8, 13, 35–38]. The CVLM region, in turn, receives extensive input from the dorsal vagal complex and the hypothalamus[39].

The activity of C1 and other RVLM PSNs is also partly independent of conventional ionotropic synaptic transmission[40, 41]. This activity relies on intrinsic properties (auto-depolarization) and local factors such as hypoxia, oxidative stress, circulating hormones and paracrine signals released by the surrounding vasculature or glia (ATP, lactate, PGE2, NO)[42–47].

The RVLM contributes to several forms of neurogenic hypertension[48–51]. Somewhat higher c-Fos expression has been reported in the RVLM of SH rats[52]. Inhibiting RVLM neurons indiscriminately produces a greater BP drop in hypertensive than normotensive control strains (e.g. SH vs. Wistar-Kyoto) or in a given strain after it has been subjected to a treatment that produces hypertension (salt, overfeeding)[48–51]. The favored interpretation of such results is that the discharge rate of the PSNs is higher in hypertensive animals but there other possibilities exist. RVLM unit activity could be unchanged or only marginally increased but downstream efferent connections, e.g. SPGNs, could be hyper-responsive to their input; RVLM unit activity and SNA could both be virtually unchanged but vascular reactivity could be enhanced by sympathetic hyper-innervation and arteriolar hypertrophy[53, 54] or via sensitized neuroeffector coupling[25]. Finally, the RVLM could raise BP via projections elsewhere than the spinal cord (e.g. the hypothalamus). These alternative possibilities have been minimally tested[50] and never in conscious animals. What is generally underappreciated is that the discharge rate of RVLM PSNs depends to an extreme degree on the resting BP and the degree of impairment of the baroreflex, both of which are highly affected by the preparation and the type and depth of anesthesia. In halothane-anesthetized rats, no difference was found between SH and Wistar-Kyoto except a resetting of the baroreflex[55]. In neonatal brainstem spinal preparations, RVLM bulbospinal (putative PSNs) neurons discharged at higher rates (e.g.[56]) and in the arterially perfused SH rat the only difference was an increased respiratory modulation of the PSNs[57, 58] which, as discussed later, could be related to excess accumulation of metabolically produced CO_2 in preparations with higher vascular resistance. Finally, preferential C1 cell inhibition produced the same BP reduction in control rats as in rats rendered hypertensive by chronic intermittent hypoxia[20]. This result could mean that the C1 neurons are not hyperactive after CIH and that the postulated heightened SNA might have another cause[59].

In sum, the RVLM contributes somehow to the elevated BP present in most hypertensive animal models. PSN hyperactivity is a plausible explanation in need of further evidence.

Cardiorespiratory coupling and hypertension

This topic has been recently reviewed[9] and will only be briefly updated. SNA exhibits respiratory-synchronous fluctuations for two reasons. First, cardiopulmonary receptors (including baroreceptors) discharge in phase with chest movements and these periodic fluctuations are transmitted to the network that generates SNA without obligatory relay through the respiratory pattern generator. Secondly the network that generates the SNA, for example CVLM neurons and RVLM PSNs receive inputs from the respiratory pattern generator[8, 13, 57]. In this section, we discuss whether these inputs are abnormally strong in two animal models of neurogenic hypertension, the SH rat and rats subjected to CIH.

Arterially perfused preparations of SH rats have a higher central respiratory pattern activity than control Wistar rats; this is manifested by narrow, non-ramping, phrenic nerve discharges and by the presence of late expiratory activity in abdominal nerves[58]. In this model, enhanced respiratory modulation of SNA and RVLM PSNs has been observed in all three phases of the respiratory cycle (inspiration, post-inspiration and late expiration) with qualitative differences between individual RVLM PSNs, between sympathetic nerves and according to the animals' age[57, 58, 60]. Similar observations have been made in rats subjected to CIH except that SNA appears enhanced predominantly during the inspiratory or late-expiratory phases, depending on the animals' sex[13, 61]. The exaggerated respiratory phasic components of SNA have been attributed to enhanced central respiratory-sympathetic coupling[13, 57]. However, the enhanced respiratory fluctuations of SNA may be the normal consequence of an increase in central chemoreceptor activity because the abnormal pattern of the hypertensive animals is normalized by lowering perfusate PCO_2[58, 62]. This explanation has been rejected by some authors because they could not find any difference in the respiratory chemoreflex of the SH rat[60]. Yet, hypertensive strains have an elevated cerebrovascular resistance[60, 63]. If flow is limited, metabolically produced CO_2 will inevitably accumulate to a higher level and overstimulate the brain chemoreceptors, ultimately enhancing fictive breathing and the respiratory modulation of SNA[64–66].

Unlike in a perfused rodent preparation, breathing at rest is the same in intact unanesthetized SH and WKY rats[67] and neither breathing nor the respiratory fluctuations of SNA differ noticeably between normotensive humans and individuals with essential hypertension[68]. One study did report the presence of active expiration in a few awake rats subjected to CIH but these rats were equally hypertensive during sleep despite the absence of active expiration[69]. Finally, although daytime SNA is indeed elevated in patients with OSA, resting breathing and SNA respiratory fluctuations seem normal[70]. That breathing is unaffected in the awake resting state might appear counterintuitive given the well-documented hyperactivity of the carotid bodies (see next section); the powerful countervailing effect of the central chemoreceptors on breathing is one explanation[71].

Sensory afferent dysfunction and hypertension

Renal afferents, most of which are unmyelinated, contribute to hypertension and cause a widespread increase in SNA in the DOCA-salt and the 2K-1C (2-kidney-1 clip) models[72, 73]. Renal inflammation is the suspected trigger. Unmyelinated afferents typically terminate in the dorsal-most laminae of the spinal cord. This region projects in turn to the intermediolateral cell column, the NTS, the parabrachial nucleus and the rostral medulla, all of which could contribute to raise SNA[74].

The arterial baroreflex is critically important to BP. Sinoaortic denervation (SAD) causes BP lability. Baroreflex modulation elicited by CNS inputs to the NTS, the CVLM and elsewhere, is likely required for BP to rise or fall appropriately during various behaviors (Figure 1)[75]. The arterial baroreflex is down-regulated by carotid body afferents, which contributes to various forms of neurogenic hypertension[76]. Incomplete resetting of the baroreceptor afferents may also cause hypertension even though SAD produces very small BP increases (<10 mmHg)[6, 19, 77, 78]. Silencing baroreceptors in mice by deleting both Piezo channels from vagal afferents (*Phox2bCre*$^{+}$*;Piezo1*$^{fl/fl}$*Piezo2*$^{fl/fl}$) produces hypertension (~15 mmHg) and a modest but significant increase of BP lability[79]. This genetic approach has limitations (gene knock-out from early developmental stage; gene excision not limited to baroreceptor afferents, etc.) but it suggests that a chronic reduction of the activity of baroreceptor afferents and, by extension incomplete baroreceptor resetting, may indeed cause hypertension.

Why SAD does not cause hypertension remains unexplained. SNA and the activity of the C1 PSNs are greatly elevated immediately after SAD in rats but return to control within a few days[19]. Accordingly, whatever mechanism restores SNA and BP to control after SAD likely resides within or upstream from the RVLM (NTS, CVLM). This adaptation could result from some form of intrinsic neuron homeostasis[80], enhanced synaptic inhibition driven by sensory afferents other than the arterial baroreceptors or an enhancement of the cerebral blood flow-mediated regulation of RVLM neuronal activity[81]. Interestingly, chronic baroreceptor stimulation produces a reduction in SNA and BP that persists for weeks with very little adaptation[6]. This remarkable property justifies the use of arterial baroreceptor stimulation to chronically reduce BP in individuals with drug-resistant hypertension[82].

Carotid body hyperactivity is another trigger of hypertension. These sensory organs are activated by arterial hypoxia in a pH-dependent manner; they also respond to hypoglycemia, temperature, hormones (angiotensin, leptin) and low blood flow[83–86]. Carotid body sensory afferents innervate the NTS via the glossopharyngeal nerve and respond primarily to ATP and acetylcholine, transmitters released by the oxygen sensing Type-I glomus cells. Acutely, carotid body stimulation can activate RVLM PSNs via at least four mechanisms whose relative importance to neurogenic hypertension is unsettled: direct excitatory inputs from the NTS to the RVLM, enhanced cardiorespiratory coupling, arterial baroreflex down-regulation and, if the stimulus is intense enough, general arousal[87–89]. The carotid bodies contribute to the elevated BP of SH rats[76], leptin-treated mice[90], 2K-1C hypertensive rat[91], rats subjected to a hypercaloric diet[92] or rodents exposed to chronic intermittent hypoxia (CIH)[93, 94]. In rodents, the arterial baroreflex is down-regulated when the carotid bodies are activated[76].

Carotid body denervation in juvenile SH rats also delays the development of hypertension[76, 95]. In every model, the principal evidence is that bilateral carotid body excision or denervation attenuates the hypertension.

In several of these models (SH rats, CIH) carotid body afferents develop a heightened responsiveness to stimuli (cyanide, hypoxia) and "tonicity", defined as an increased discharge at rest[96–98]. In the SH rat, this hyperexcitability is attributed to the upregulation of channels expressed by carotid body afferents such as ASIC3, TASK1 (Kcnk3) or P2X3[76, 96, 99]. In CIH, it is attributed to excessive ROS production by type-I glomus cells[100]. In mice, hyperleptinemia activates the carotid bodies by activating leptin receptors that are coupled to Trpm7 channels[90]. Carotid body hyperplasia may also contribute to the outsized influence of these organs on the sympathetic outflow in hypertension[85, 101, 102]. Finally, the carotid bodies receive a dense sympathetic innervation from the superior cervical ganglion. CIH hypertension is greatly attenuated by both sympathectomy and angiotensin II (AngII) receptor blockade[85, 93] suggesting that carotid body hyperactivity could be driven by SNA in a feed-forward loop involving AngII, blood flow restriction via catecholamine-mediated vasoconstriction or a proinflammatory action[85].

Unilateral carotid body ablation produced transient BP reductions in a few individuals with essential hypertension[103]. The potentially deleterious effects of bilateral glomectomy (loss of hypoxic ventilatory reflex, hypoventilation during sleep, breathing difficulties at altitude including in commercial air planes, effects during and after general anesthesia)[85] and the possibility of surgical mishaps reduce the translational potential of this intervention but a pharmacological approach based on the use of P2X3 receptor antagonists is promising[96].

The hypothalamic paraventricular nucleus (PVN)

Besides the circulation, the parvocellular portion of the PVN controls food intake, appetitive responses to sodium deficiency, gastric, pancreatic and esophageal function, glucose counter-regulation, ventilation, the protection of the cornea and various mucosal tissues and the regulation of cerebral blood flow and possibly body temperature[39, 104, 105]. Based on their projections, PVN neurons have the potential to elicit cardiovascular stimulation (e.g. via their direct projections to the SPGNs, the caudal pressor area, the C1 neurons), or depression (via sympathoinhibition and parasympathetic bradycardia)[39, 106] or the differential regulation of regional SNA[107]. The PVN undoubtedly regulates SNA and BP but we still do not know whether a subset of PVN neurons is dedicated to regulating the cardiovascular system or whether every PVN neuron influences the cardiovascular system in a unique manner that is best suited to the particular behavior to which this subset of neurons contribute (feeding, drinking, arousal, etc.).

The PVN has been implicated in countless hypertension models and in other conditions associated with increased SNA such as heart failure[108]. The following section focuses on the SH rat. The contribution of PVN to obesity or salt-dependent hypertension is examined later.

Silencing PVN neurons produces a larger BP drop in the SH rat than in Wistar normotensive controls, anesthetized or conscious[109, 110] suggesting that PVN neurons could be

"hyperactive". This interpretation is subject to similar caveats as those evoked for the RVLM. PVN neuron discharge rate was not directly monitored, PVN is a very small nucleus that cannot be selectively manipulated except in mice lines in which Cre recombinase is restricted to this nucleus[111] or to subsets of its neurons[112]. The BP reduction evoked by inhibiting PVN in a hypertensive animal could be larger, not because these neurons are more active, but because of increased vascular reactivity to SNA, increased excitability of the downstream circuits engaged by PVN stimulation, increased or decreased expression of secondary transmitters by PVN neurons, etc. Finally, assuming that PVN activity is indeed elevated, the cause is still speculative e.g. enhanced input from orexin neurons, the VLM, the carotid bodies, direct effects of local inflammation, neuroplasticity and perhaps a difference in gut microbiota[32, 108, 113, 114].

The arcuate nucleus (ARC) and obesity-related hypertension

Obesity and a high-fat diet cause a mild hypertension typically associated with elevated muscle SNA in humans and animals[115, 116]. Hyperleptinemia, hyperinsulinemia, AngII, or even hypoxia caused by hypoventilation are suspected triggers.

The ARC is the primary CNS target of leptin and insulin, blood-borne hormones that control appetite and weight gain (Figure 3)[117]. ARC neurons elicit behaviors and sensations required for energy homeostasis (appetitive, hedonic, motor), and regulate metabolism and BP via the autonomic nervous system[117]. Global activation of the ARC can raise or lower BP via changes in SNA and activates brown adipose tissue (BAT) SNA[118, 119]. ARC lightly innervates the SPGNs and the RVLM[120–122] but it probably exerts its effects on SNA predominantly via hypothalamic relays (paraventricular, dorsomedial, and ventromedial nuclei)[121, 123, 124].

Microinjection of leptin into the ARC increases BP and SNA to the kidneys, the lumbar chain, and thermogenic BAT[117, 125]. Deletion of the leptin receptor from the ARC eliminates the effect of systemic leptin administration on BP but leptin may also act elsewhere in the hypothalamus[126]. Insulin, on the other hand, probably acts solely in the ARC to increase SNA[127, 128]. Leptin[90], contrary to insulin[129], can also increase SNA by activating the carotid bodies (Figure 3). After binding to receptors in the ARC, leptin and insulin regulate SNA via projections from both POMC and AgRP neurons to the PVN (Figure 3). The POMC neurons release α–melanocyte-stimulating hormone (α-MSH) that binds to MC4R and AgRP neurons release neuropeptide Y (NPY) that binds to Y1R. In short, leptin and insulin cause sympathoexcitation by enhancing the excitatory effect of POMC neurons and by reducing the inhibitory effect of NPY neurons in the PVN[130].

Hypothalamic sites shown to support basal SNA in diet-induced obese animals include the ARC via leptin[126] and insulin[131] stimulation, the PVN via α-MSH and glutamatergic stimulation[131] and via loss of tonic NPY inhibition[132], and the VMH, driven by leptin and α-MSH[133]. Actions of leptin in the DMH may also support increased BP in mice[134] but this point is controversial[131, 133].

Leptin has received much attention as the link between increased adiposity and sympathoexcitation and hypertension, yet obese Zucker rats, lacking a functional leptin receptor, also exhibit elevated SNA[135]. Excessive but leptin-independent activation of MC3/4R may underlie the hypertension[136] and CNS mediators other than leptin also contribute to hypertension in this obesity model. Candidates include AngII in the RVLM[51] and orexin in the PVN[137].

ARC neurons can generate complex patterns of autonomic responses, including a rise in BP, depending on which cell type is recruited. Activation of ARC POMC neurons by leptin and insulin increases BP and SNA to resistance vessels[117]. This effect is mediated by the release of α-MSH in the PVN and perhaps elsewhere (VMH). One may surmise that in lean and healthy animals, the BP changes elicited by ARC neurons are transient and adapted to periods of food seeking and consumption. Overfeeding may exacerbate and prolong the sympathetic stimulation elicited by ARC under the combined effect of hyperleptinemia, hyperinsulinemia and local tissue inflammation[138].

Orexin and hypertension

The orexin neurons reside in the perifornical and lateral hypothalamic region; they are implicated in brain functions as diverse as the control of food intake and energy expenditure, breathing and blood pressure, motivation, circadian rhythm of sleep and wake, memory, cognitive functions, and the cardiovascular, thermoregulatory and respiratory effects of various stresses (including transient hypercapnia)[139–143]. The orexin neurons are active during waking, when postural muscle tone is high, less active during quiet waking in the absence of movement, and virtually cease firing during sleep[144]. These neurons are probably further activated by any form of stress including hypercapnia or hypoxia, and they clearly activate breathing and BP[143, 145, 146].

The orexin system contributes to hypertension in the SH rat, the Schlager BPH/2J mouse and the obese Zucker rat[114, 145, 147]. The principal evidence is that systemic administration of a broad-spectrum orexin receptor antagonist, almorexant, reduces BP and plasma catecholamines[147–149]. This evidence is predicated on two assumptions: the selectivity of almorexant and the belief that orexin does not have pertinent peripheral effects. Also, the brain of the SH rat contains greater numbers of detectably orexin-immunoreactive neurons, increased orexin-A mRNA and denser brainstem orexinergic projections than normotensive controls[149–151]. In addition, the RVLM seems hyper-responsive to orexin in this strain[150]. Finally, the orexin system may also contribute to hypertension in the Dahl salt-sensitive (Dahl-S) rat by enhancing vasopressin synthesis in the PVN[114, 152].

The SH rat and the BPH/2J mice are also models of behavioral hyperactivity and orexin neuron firing is highly correlated with locomotor activity[144]. Orexin neurons regulate spontaneous physical activity, non-exercise thermogenesis, the effects of psychological stress and their autonomic correlates (hyperpnea and elevated BP)[153]. The BP of the SH rat and the BPH/2J mice is partially normalized by amygdala lesions[148, 154, 155] implying that a limbic forebrain dysfunction could be driving the orexin system in these rodents. The autonomic effects of increased orexinergic neuron activity are probably relayed through

several hypothalamic and brainstem nuclei[142, 156]. Almorexant reduces CSF noradrenaline dramatically in rats[157], possibly because this drug nullifies the excitatory effect of orexin on the locus coeruleus, a major waking-promoting structure[158, 159]. Orexin also excites the dorsal raphe[160]. By reducing noradrenaline and serotonin release, orexin receptor antagonists such as almorexant reduce the ability of rodents to wake up from sleep and likely produce sedation[161, 162]. Accordingly, the sympathoinhibition and hypotension elicited in animal models by orexin receptor antagonists could largely result from a reduction in locomotor activity and, during rest, from interference with wake-promoting systems and circuits (noradrenaline, serotonin)[148].

There is no clear indication that the orexin system contributes to hypertension in humans[163]. Orexin-receptor antagonists could conceivably be effective antihypertensive agents in humans but their current therapeutic use is as sedative-hypnotic drugs[164]. From past experience, sympatholytic drugs with notable sedative effects (e.g. alpha-2 adrenergic receptor agonists) have fared poorly as anti-hypertensive agents.

The OVLT-PVN connection and hypertension

The lamina terminalis (anterior wall of the 3rd ventricle) includes the median preoptic nucleus (MnPO) and two circumventricular organs, the subfornical organ (SFO) and the organum vasculosum lamina terminalis (OVLT)[24, 165, 166]. SFO and OVLT detect circulating and brain AngII, [Na^+], osmolality and cytokines via receptors expressed by principal neurons, astrocytes and ependymal cells (Figure 4)[167–169]. The SFO and OVLT have significant reciprocal connections with the MnPO which serves as an integrative hub for signaling from multiple subcortical structures that regulate neuroendocrine and autonomic function and behavior[165]. The interoceptive function of the SFO and OVLT, like that of the arcuate nucleus[170], is regulated by synaptic inputs from regions implicated in drinking and food consumption, thermoregulation, circadian and diurnal patterns, and cardiovascular reflexes[166, 171]. Sodium sensing by the OVLT and SFO is attributed to several mechanisms. Na(x), a sodium channel encoded by the *Scn7a* gene and expressed by astrocytes and ependymal cells may be the primary sensing mechanism (Figure 4)[167]. Other candidates include an N-terminal variant of the transient receptor potential cation channel subfamily V member 1 (TRPV1) and the epithelial sodium channel (ENaC)[7].

Components of the lamina terminalis (SFO or OVLT or MnPO) contribute to BP elevation in several hypertension models: DOCA-salt[172], AngII infusion[168], chronic intermittent hypoxia[59] and high-salt diet[7, 167]. The sympathetic component of the hypertension probably occurs via an MnPO-PVN connection and PVN projections to SPGNs (direct and indirect via the RVLM; Figure 4)[7, 39, 59, 167, 173].

Other brain regions potentially involved in hypertension

SNA is regulated at some level by the entire brain[174]. Important regions that are little explored from a hypertension perspective include the periaqueductal gray matter, the dorsal colliculi and the cerebellum, dorsomedial hypothalamic nucleus (DMH) and the midline medulla[175–178]. The DMH relays the cardiovascular response to stress[179] and could

therefore play a role in stress-induced hypertension. Stimulation of the ventral periaqueductal gray matter may relieve hypertension associated with chronic pain in humans[180]. The midline medulla oblongata contains the majority of the PSNs identified using the retrograde transport of pseudorabies virus[30, 181] and regulates cutaneous flow, the cardiac output and the sympathetic innervation of the brown adipose fat in the context of thermoregulation and body weight homeostasis[182, 183].

Hypertension: role of brainstem hypoperfusion and hypoxia

Recent work has reinvigorated the theory that hypertension could be an adaptive mechanism to maintain cerebral blood flow when cerebrovascular resistance increases[81, 184–186]. A relatively moderate (7–20 mmHg) rise in cerebral pressure increases BP and SNA in unanesthetized sheep and humans[186, 187]. In anesthetized rats, the BP rise requires the exocytotic release of ATP by RVLM astrocytes[81] and ATP may directly activate the PSNs (Figure 5)[188]. This enticing theory is predicated on the assumption that there is no off-target expression of dnSNARE (in neurons, vessels, etc.) when adeno-associated vectors engineered with an artificial GFAP promoter are used to transduce astrocytes[81]. Also, whether this glial mechanism can cause hypertension or merely mediates the transient effects of severe brainstem hypoxia or brain hypoperfusion on BP merits additional scrutiny. Finally, BP also rises when blood flow is reduced through the NTS only[189], therefore astrocytes may contribute to SNA regulation there too.

The physiological variable detected by astrocytes when cerebral blood flow is limited could be hypoxia, acidification, mechanical stretch of astrocytic end-feet or chemical signals from the vasculature[43, 81]. In the absence of baroreceptors, this CBF-dependent pathway could conceivably mediate BP homeostasis[190].

This astrocyte-mediated homeostatic mechanism evidently does not prevent the substantial hypotension elicited by chronic baroreceptor activation (>25 mmHg; 3 weeks)[6]. Maybe, baroreceptor activation elicits a countervailing cerebrovascular response that maintains brainstem blood flow despite the hypotension. Alternately, the capacity of astrocytes to depolarize the RVLM PSNs may be limited and may be overridden by the powerful GABA-mediated hyperpolarization elicited by baroreceptor activation (Figure 5). Also unknown is whether excessive flow through the medulla produces the opposite effect, namely sympathoinhibition, and whether this could explain the return to normotension following baroreceptor denervation[19].

Conclusions

Myriad brain regions and sensory afferents have now been implicated in various forms of neurogenic hypertension. Progress is constrained by the difficulty to record SNA or brain neurons in conscious animals for long periods and to compare the data between animals. Progress is also limited by our imperfect knowledge of the network that controls SNA and BP. Powerful methods to interrogate the CNS connectome have been recently developed[191]. They should be more intensively applied to the neural control of BP.

Neurogenic hypertension is typically, and plausibly, attributed to an increase in the activity of RVLM PSNs. However, the supportive evidence has largely consisted of showing that silencing the RVLM (with drugs or vector-delivered actuators), modifying the RVLM redox state or manipulating the RVLM glia produces a larger BP drop in hypertensive rodents. What is actually being measured by these manipulations is the "neurogenic pressor potential" of this brain region, which depends not only on the discharge rate of RVLM neurons but also on a long series of integrative processes that occur between these neurons and vascular smooth muscle and cardiac contraction[192]. The primacy of the RVLM in BP control is a notion that derives primarily from experiments conducted under anesthesia when the PSNs are disinhibited and sympathetic tone is extremely elevated. SPGNs receive direct input from many sources besides the RVLM e.g. spinal cord, hypothalamus and several brainstem regions[193]. Most likely, every type of PSN contributes to the differential regulation of regional SNA, albeit in distinct physiological contexts. Brainstem regions such as the NTS and CVLM are clearly as important as the RVLM to BP control and deserve far more attention in the context of hypertension.

Lesions that attenuate hypertension typically enhance the baroreflex (carotid bodies or PVN in SH rats, renal nerves in the 2K-1C model)[76, 109, 194] suggesting that baroreflex down-regulation could be a major contributing factor to hypertension. This calls for further investigations of the role of the CVLM and the NTS in hypertension.

The SH rats have been the subjects of most studies. Countless factors are described as playing a "critical" role in the elevated BP of the SH rat (orexin: −33mmHg[157], carotid bodies: −17 mmHg[95], PVN: −26 mmHg[109] or −61 mmHg[110]; intestinal dysbiosis, −38 mmHg[113], amygdala −15 mmHg[155], RVLM: −40 mmHg[11]). This is paradoxical. The homeostasis principle would predict that large and, especially, persistent hypotension should require interfering with multiple pathways simultaneously. Perhaps, at rest, the orexin system, PVN, carotid bodies, amygdala etc. contribute to a roughly comparable extent to the excitatory drive of SPGNs and most of the input summation occurs below action potential threshold in these neurons. If so, the removal of any one of the various inputs could dramatically reduce their firing rate, giving the impression that each is "essential".

Carotid body hyperactivity contributes to several forms of hypertension but is generally not the predominant factor except when the hypertension results from chronic intermittent hypoxia[94]. This type of hypertension is also eliminated by adrenal demedullation, sympathetic blockade, AT1 receptor blockade and lesions of the AV3V region[59, 93]. It is difficult to conceptualize why each of these manipulations would eliminate rather than merely attenuate the effect of carotid body hyperactivity.

SNA elevation and neurogenic hypertension can be caused by excessive levels of circulating hormones (leptin, insulin, AngII). Leptin raises blood vessel SNA by activating the carotid bodies and subsets of ARC neurons but other sites of action may exist[195]. AngII works in the lamina terminalis and probably throughout the brainstem and hypothalamus via its proinflammatory activity and by reducing the blood brain barrier. Its neurogenic action probably also includes the facilitation of noradrenaline release by sympathetic

postganglionic neurons. Sodium works in part via astrocytes and ependymal cells located in the circumventricular organs (OVLT, SFO).

One would also like to know which of the many detected abnormalities have a common origin. Perhaps, all organs with a high metabolic demand (brain, kidneys and the carotid bodies), regulate their blood flow at the expense of systemic BP by eliciting sympathoexcitatory reflexes and the root cause of these neural reflexes is a cerebral or peripheral vascular abnormality. Is hypoxia, oxidative stress or inflammation the trigger in both carotid bodies and brainstem? Are the astrocytes located in the RVLM fundamentally different from those located elsewhere in the brainstem or from type II glomus cells? Finally, the SH rat also highlights the importance of environmental factors (gut microbiome) in hypertension even in this most genetic of models.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of Funding:

This work was supported by the National Institutes of Health - R01HL028785 (P.G. Guyenet), RO1HL148004 (S.B.G. Abbott) and RO1HL128181 (V.L. Brooks) and the American Heart Association (#19POST34430205 [G.M.P.R.Souza]).

Abbreviations:

A1, A2, A5	pontomedullary noradrenergic nuclei
AgRP	agouti-related peptide
AngII	angiotensin II
ARC	arcuate nucleus
AV3V region	see lamina terminalis
BP	arterial blood pressure
C1	RVLM adrenergic/glutamatergic neuron
CBF	cerebral blood flow
CIH	chronic intermittent hypoxia
CSF	cerebrospinal fluid
CVLM	caudal ventrolateral medulla
DMH	dorsomedial hypothalamic nucleus
DOCA	di-hydroxy corticosterone acetate
ECF	extracellular fluid

2K-1C	two-kidney one clip
LC	locus coeruleus
MCR	melanocortin receptor
MnPO	median preoptic nucleus
αMSH	melanocyte-stimulating hormone
Na(x)	sodium channel encoded by *Scn7a*
NPY	neuropeptide Y
NTS	solitary tract nucleus
Orx	orexin
OSA	obstructive sleep apnea
OVLT	organum vasculosum lamina terminalis
PAG	periaqueductal gray matter
PBL	lateral parabrachial nucleus
POMC	proopiomelanocortin
PSN	presympathetic neuron
PVN	paraventricular nucleus of hypothalamus
ROS	radical oxygen species
RPa	raphe pallidus
RVLM	rostral ventrolateral medulla
SAD	sinoaortic denervation
SFO	subfornical organ
SGN	sympathetic (post) ganglionic neuron
SH rat	spontaneously hypertensive rat
SNA	sympathetic nerve activity
SNS	sympathetic nervous system
SPGN	sympathetic pre-ganglionic neuron
VMH	ventromedial hypothalamic nucleus

REFERENCES

1. Mann SJ. Neurogenic hypertension: pathophysiology, diagnosis and management. Clin Auton Res 2018;28:363–374. doi:10.1007/s10286-018-0541-z [PubMed: 29974290]
2. DiBona GF. Sympathetic nervous system and hypertension. Hypertension. 2013;61:556–560. doi:10.1161/HYPERTENSIONAHA.111.00633 [PubMed: 23357181]
3. Grassi G, Mark A, Esler M. The sympathetic nervous system alterations in human hypertension. Circ Res 2015;116:976–990. doi:10.1161/CIRCRESAHA.116.303604 [PubMed: 25767284]
4. Stocker SD, Kinsman BJ, Sved AF. Recent Advances in Neurogenic Hypertension: Dietary Salt, Obesity, and Inflammation. Hypertension. 2017;70:474–478. doi:10.1161/HYPERTENSIONAHA.117.08936
5. Malpas SC. Sympathetic nervous system overactivity and its role in the development of cardiovascular disease. Physiol Rev 2010;90:513–557. doi:10.1152/physrev.00007.2009 [PubMed: 20393193]
6. Lohmeier TE, Iliescu R. The baroreflex as a long-term controller of arterial pressure. Physiology (Bethesda). 2015;30:148–158. doi:10.1152/physiol.00035.2014 [PubMed: 25729060]
7. DeLalio LJ, Sved AF, Stocker SD. Sympathetic Nervous System Contributions to Hypertension: Updates and Therapeutic Relevance. Can J Cardiol 2020;36:712–720. doi:10.1016/j.cjca.2020.03.003 [PubMed: 32389344]
8. Schreihofer AM, Sved AF. The ventrolateral medulla and sympathetic regulation of arterial pressure In: Llewellyn-Smith IJ, Verberne AJ, eds. Central regulation of autonomic functions. New-York: Oxford University Press; 2011:78–97.
9. Guyenet PG, Stornetta RL, Holloway BB, Souza G, Abbott SBG. Rostral Ventrolateral Medulla and Hypertension. Hypertension. 2018;72:559–566. doi:10.1161/HYPERTENSIONAHA.118.10921 [PubMed: 30354763]
10. Menezes RC, Fontes MA. Cardiovascular effects produced by activation of GABA receptors in the rostral ventrolateral medulla of conscious rats. Neuroscience. 2007;144:336–343. doi:10.1016/j.neuroscience.2006.08.062 [PubMed: 17049168]
11. Geraldes V, Goncalves-Rosa N, Liu B, Paton JF, Rocha I. Essential role of RVL medullary neuronal activity in the long term maintenance of hypertension in conscious SHR. Auton Neurosci 2014;186:22–31. doi:10.1016/j.autneu.2014.09.002 [PubMed: 25283065]
12. Schreihofer AM, Guyenet PG. Identification of C1 presympathetic neurons in rat rostral ventrolateral medulla by juxtacellular labeling in vivo. J Comp Neurol 1997;387:524–536. doi:10.1002/(sici)1096-9861(19971103)387:4<524::aid-cne4>3.0.co;2-4 [PubMed: 9373011]
13. Moraes DJ, da Silva MP, Bonagamba LG, Mecawi AS, Zoccal DB, Antunes-Rodrigues J, Varanda WA, Machado BH. Electrophysiological properties of rostral ventrolateral medulla presympathetic neurons modulated by the respiratory network in rats. J Neurosci 2013;33:19223–19237. doi:10.1523/JNEUROSCI.3041-13.2013 [PubMed: 24305818]
14. Reis DJ, Granata AR, Joh TH, Ross CA, Ruggiero DA, Park DH. Brain stem catecholamine mechanisms in tonic and reflex control of blood pressure. Hypertension. 1984;6:II7–I15. doi:10.1161/01.hyp.6.5_pt_2.ii7 [PubMed: 6150001]
15. Lipski J, Kanjhan R, Kruszewska B, Smith M. Barosensitive neurons in the rostral ventrolateral medulla of the rat *in vivo*: Morphological properties and relationship to C1 adrenergic neurons. Neuroscience. 1995;69:601–618. doi:10.1016/0306-4522(95)92652-z [PubMed: 8552253]
16. Ross CA, Armstrong DM, Ruggiero DA, Pickel VM, Joh TH, Reis DJ. Adrenaline neurons in the rostral ventrolateral medulla innervate thoracic spinal cord: a combined immunocytochemical and retrograde transport demonstration. Neurosci Lett 1981;25:257–262. doi:10.1016/0304-3940(81)90401-8 [PubMed: 6270602]
17. Madden CJ, Stocker SD, Sved AF. Attenuation of homeostatic responses to hypotension and glucoprivation after destruction of catecholaminergic rostral ventrolateral medulla (RVLM) neurons. Am J Physiol Regul Integr Comp Physiol 2006;291:R751–R759. doi:10.1152/ajpregu.00800.2005 [PubMed: 16627690]

18. Sved AF, Ito S, Sved JC. Brainstem mechanisms of hypertension: role of the rostral ventrolateral medulla. Curr Hypertens Rep 2003;5:262–268. doi:10.1007/s11906-003-0030-0 [PubMed: 12724060]
19. Wenker IC, Abe C, Viar KE, Stornetta DS, Stornetta RL, Guyenet PG. Blood Pressure Regulation by the Rostral Ventrolateral Medulla in Conscious Rats: Effects of Hypoxia, Hypercapnia, Baroreceptor Denervation, and Anesthesia. J Neurosci 2017;37:4565–4583. doi:10.1523/JNEUROSCI.3922-16.2017 [PubMed: 28363984]
20. Moraes DJA, Bonagamba LGH, da Silva MP, Paton JFR, Machado BH. Role of ventral medullary catecholaminergic neurons for respiratory modulation of sympathetic outflow in rats. Sci Rep 2017;7:16883. doi:10.1038/s41598-017-17113-7 [PubMed: 29203815]
21. Fischer KB, Collins HK, Callaway EM. Sources of off-target expression from recombinase-dependent AAV vectors and mitigation with cross-over insensitive ATG-out vectors. Proc Natl Acad Sci U S A 2019 doi:10.1073/pnas.1915974116
22. Carrive P, Gorissen M. Premotor sympathetic neurons of conditioned fear in the rat. EurJ Neurosci 2008;28:428–446. doi:10.1111/j.1460-9568.2008.06351.x [PubMed: 18702716]
23. Ramchandra R, Barrett CJ, Guild SJ, Malpas SC. Evidence of differential control of renal and lumbar sympathetic nerve activity in conscious rabbits. Am J Physiol Regul Integr Comp Physiol 2005 doi:10.1152/ajpregu.00504.2005
24. Kinsman BJ, Simmonds SS, Browning KN, Stocker SD. Organum Vasculosum of the Lamina Terminalis Detects NaCl to Elevate Sympathetic Nerve Activity and Blood Pressure. Hypertension. 2017;69:163–170. doi:10.1161/HYPERTENSIONAHA.116.08372 [PubMed: 27895193]
25. Fink GD. Exaggerated Sympathetic Neurovascular Transduction as a Mechanism of Neurogenic Hypertension: It Is Not All About Activity. Hypertension. 2018;71:64–65. doi:10.1161/HYPERTENSIONAHA.117.10300 [PubMed: 29203626]
26. Campos RR, McAllen RM. Cardiac sympathetic premotor neurons. Am J Physiol Regul Integr Comp Physiol 1997;272:R615–R620. doi:10.1152/ajpregu.1997.272.2.R615
27. McAllen RM, May CN, Campos RR. The supply of vasomotor drive to individual classes of sympathetic neuron. Clin Exp Hypertens 1997;19:607–618. doi:10.3109/10641969709083173 [PubMed: 9247742]
28. Guyenet PG, Stornetta RL, Bochorishvili G, Depuy SD, Burke PG, Abbott SB. C1 neurons: the body's EMTs. Am J Physiol Regul Integr Comp Physiol 2013;305:R187–204. doi:10.1152/ajpregu.00054.2013 [PubMed: 23697799]
29. Farmer DGS, Pracejus N, Dempsey B, Turner A, Bokiniec P, Paton JFR, Pickering AE, Burguet J, Andrey P, Goodchild AK, McAllen RM, McMullan S. On the presence and functional significance of sympathetic premotor neurons with collateralized spinal axons in the rat. J Physiol 2019;597:3407–3423. doi:10.1113/JP277661 [PubMed: 31077360]
30. Jansen ASP, Nguyen XV, Karpitskiy V, Mettenleiter TC, Loewy AD. Central command neurons of the sympathetic nervous system:basis of the fight-or flight response. Science. 1995;270:644–646. doi:10.1126/science.270.5236.644 [PubMed: 7570024]
31. Card JP, Sved JC, Craig B, Raizada M, Vazquez J, Sved AF. Efferent projections of rat rostroventrolateral medulla C1 catecholamine neurons: Implications for the central control of cardiovascular regulation. J Comp Neurol 2006;499:840–859. doi:10.1002/cne.21140 [PubMed: 17048222]
32. Abbott SB, DePuy SD, Nguyen T, Coates MB, Stornetta RL, Guyenet PG. Selective optogenetic activation of rostral ventrolateral medullary catecholaminergic neurons produces cardiorespiratory stimulation in conscious mice. J Neurosci 2013;33:3164–3177. doi:10.1523/JNEUROSCI.1046-12.2013 [PubMed: 23407970]
33. Dempsey B, Le S, Turner A, Bokiniec P, Ramadas R, Bjaalie JG, Menuet C, Neve R, Allen AM, Goodchild AK, McMullan S. Mapping and Analysis of the Connectome of Sympathetic Premotor Neurons in the Rostral Ventrolateral Medulla of the Rat Using a Volumetric Brain Atlas. Front Neural Circuits. 2017;11:9. doi:10.3389/fncir.2017.00009 [PubMed: 28298886]

34. Stornetta RL, Inglis MA, Viar KE, Guyenet PG. Afferent and efferent connections of C1 cells with spinal cord or hypothalamic projections in mice. Brain Struct Funct 2016;221:4027–4044. doi:10.1007/s00429-015-1143-3 [PubMed: 26560463]
35. Mandel DA, Schreihofer AM. Central respiratory modulation of barosensitive neurones in rat caudal ventrolateral medulla. J Physiol 2006;572:881–896. doi:10.1113/jphysiol.2005.103622 [PubMed: 16527859]
36. Schreihofer AM, Guyenet PG. Baro-activated neurons with pulse-modulated activity in the rat caudal ventrolateral medulla express GAD67 mRNA. J Neurophysiol 2003;89:1265–1277. doi:10.1152/jn.00737.2002 [PubMed: 12612005]
37. Guyenet PG. Cardiorespiratory integration In: Llewellyn-Smith IJ, Verberne AJ, eds. Central regulation of autonomic functions. New-York: Oxford University Press; 2011:180–201.
38. Guyenet PG. Regulation of breathing and autonomic outflows by chemoreceptors. Compr Physiol 2014;4:1511–1562. doi:10.1002/cphy.c140004 [PubMed: 25428853]
39. Geerling JC, Shin JW, Chimenti PC, Loewy AD. Paraventricular hypothalamic nucleus: axonal projections to the brainstem. J Comp Neurol 2010;518:1460–1499. doi:10.1002/cne.22283 [PubMed: 20187136]
40. Accorsi-Mendonca D, da Silva MP, Souza GM, Lima-Silveira L, Karlen-Amarante M, Amorim MR, Almado CE, Moraes DJ, Machado BH. Pacemaking Property of RVLM Presympathetic Neurons. Front Physiol 2016;7:424. doi:10.3389/fphys.2016.00424 [PubMed: 27713705]
41. Li YW, Bayliss DA, Guyenet PG. C1 neurons of neonatal rats: intrinsic beating properties and alpha 2-adrenergic receptors. Am J Physiol 1995;269:R1356–1369. doi:10.1152/ajpregu.1995.269.6.R1356 [PubMed: 8594938]
42. Tang F, Lane S, Korsak A, Paton JF, Gourine AV, Kasparov S, Teschemacher AG. Lactate-mediated glia-neuronal signalling in the mammalian brain. Nat Commun 2014;5:3284. doi:10.1038/ncomms4284 [PubMed: 24518663]
43. Angelova PR, Kasymov V, Christie I, Sheikhbahaei S, Turovsky E, Marina N, Korsak A, Zwicker J, Teschemacher AG, Ackland GL, Funk GD, Kasparov S, Abramov AY, Gourine AV. Functional Oxygen Sensitivity of Astrocytes. J Neurosci 2015;35:10460–10473. doi:10.1523/JNEUROSCI.0045-15.2015 [PubMed: 26203141]
44. Serrats J, Schiltz JC, Garcia-Bueno B, van RN, Reyes TM, Sawchenko PE. Dual roles for perivascular macrophages in immune-to-brain signaling. Neuron 2010;65:94–106. doi:10.1016/j.neuron.2009.11.032 [PubMed: 20152116]
45. Van Kempen TA, Dodos M, Woods C, Marques-Lopes J, Justice NJ, Iadecola C, Pickel VM, Glass MJ, Milner TA. Sex differences in NMDA GluN1 plasticity in rostral ventrolateral medulla neurons containing corticotropin-releasing factor type 1 receptor following slow-pressor angiotensin II hypertension. Neuroscience. 2015;307:83–97. doi:10.1016/j.neuroscience.2015.08.029 [PubMed: 26306872]
46. Reis DJ, Golanov EV, Ruggiero DA, Sun M-K. Sympatho-excitatory neurons of the rostral ventrolateral medulla are oxygen sensors and essential elements in the tonic and reflex control of the systemic and cerebral circulations. J Hypertens. 1994;12 Suppl. 10:S159–S180.
47. Chen D, Jancovski N, Bassi JK, Nguyen-Huu TP, Choong YT, Palma-Rigo K, Davern PJ, Gurley SB, Thomas WG, Head GA, Allen AM. Angiotensin type 1A receptors in C1 neurons of the rostral ventrolateral medulla modulate the pressor response to aversive stress. J Neurosci 2012;32:2051–2061. doi:10.1523/JNEUROSCI.5360-11.2012 [PubMed: 22323719]
48. Stocker SD, Meador R, Adams JM. Neurons of the rostral ventrolateral medulla contribute to obesity-induced hypertension in rats. Hypertension. 2007;49:640–646. doi:10.1161/01.HYP.0000254828.71253.dc [PubMed: 17190873]
49. Ito S, Komatsu K, Tsukamoto K, Sved AF. Tonic excitatory input to the rostral ventrolateral medulla in dahl salt-sensitive rats. Hypertension. 2001;37:687–691.
50. Ito S, Komatsu K, Tsukamoto K, Sved AF. Excitatory amino acids in the rostral ventrolateral medulla support blood pressure in spontaneously hypertensive rats. Hypertension. 2000;35:413–417. doi:10.1161/01.hyp.35.1.413 [PubMed: 10642334]

51. Huber DA, Schreihofer AM. Altered regulation of the rostral ventrolateral medulla in hypertensive obese Zucker rats. Am J Physiol Heart Circ Physiol 2011;301:H230–240. doi:10.1152/ajpheart.00075.2011 [PubMed: 21536848]
52. Minson J, Arnolda L, Llewellyn-Smith I, Pilowsky P, Chalmers J. Altered c-fos in rostral medulla and spinal cord of spontaneously hypertensive rats. Hypertension. 1996;27:433–441. doi:10.1161/01.hyp.27.3.433 [PubMed: 8698450]
53. Peruzzi D, Hendley ED, Forehand CJ. Hypertrophy of stellate ganglion cells in hypertensive, but not hyperactive, rats. Am J Physiol 1991;261:R979–984. doi:10.1152/ajpregu.1991.261.4.R979 [PubMed: 1928445]
54. Wilson C, Zhang X, Buckley C, Heathcote HR, Lee MD, McCarron JG. Increased Vascular Contractility in Hypertension Results From Impaired Endothelial Calcium Signaling. Hypertension. 2019;74:1200–1214. doi:10.1161/HYPERTENSIONAHA.119.13791 [PubMed: 31542964]
55. Sun MK, Guyenet PG. Medullospinal sympathoexcitatory neurons in normotensive and spontaneously hypertensive rats. Am J Physiol 1986;250:R910–R917. doi: 10.1152/ajpregu.1986.250.5.R910 [PubMed: 3706576]
56. Matsuura T, Kumagai H, Kawai A, Onimaru H, Imai M, Oshima N, Sakata K, Saruta T. Rostral ventrolateral medulla neurons of neonatal Wistar-Kyoto and spontaneously hypertensive rats. Hypertension. 2002;40:560–565. doi:10.1161/01.hyp.0000032043.64223.87 [PubMed: 12364363]
57. Menuet C, Le S, Dempsey B, Connelly AA, Kamar JL, Jancovski N, Bassi JK, Walters K, Simms AE, Hammond A, Fong AY, Goodchild AK, McMullan S, Allen AM. Excessive Respiratory Modulation of Blood Pressure Triggers Hypertension. Cell Metab 2017;25:739–748. doi:10.1016/j.cmet.2017.01.019 [PubMed: 28215844]
58. Moraes DJ, Machado BH, Paton JF. Specific respiratory neuron types have increased excitability that drive presympathetic neurones in neurogenic hypertension. Hypertension. 2014;63:1309–1318. doi:10.1161/HYPERTENSIONAHA.113.02283 [PubMed: 24688126]
59. Marciante AB, Wang LA, Little JT, Cunningham JT. Caspase lesions of PVN-projecting MnPO neurons block the sustained component of CIH-induced hypertension in adult male rats. Am J Physiol Heart Circ Physiol 2020;318:H34–H48. doi:10.1152/ajpheart.00350.2019 [PubMed: 31675258]
60. 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;587:597–610. doi:10.1113/jphysiol.2008.165902 [PubMed: 19064613]
61. Souza GM, Bonagamba LG, Amorim MR, Moraes DJ, Machado BH. Inspiratory modulation of sympathetic activity is increased in female rats exposed to chronic intermittent hypoxia. Exp Physiol 2016;101:1345–1358. doi:10.1113/EP085850 [PubMed: 27615665]
62. Molkov YI, Zoccal DB, Baekey DM, Abdala AP, Machado BH, Dick TE, Paton JF, Rybak IA. Physiological and pathophysiological interactions between the respiratory central pattern generator and the sympathetic nervous system. Prog Brain Res 2014;212:1–23. doi:10.1016/B978-0-444-63488-7.00001-X [PubMed: 25194190]
63. Walas D, Nowicki-Osuch K, Alibhai D, von Linstow Roloff E, Coghill J, Waterfall C, Paton JF. Inflammatory pathways are central to posterior cerebrovascular artery remodelling prior to the onset of congenital hypertension. J Cereb Blood Flow Metab 2018:271678X18769180. doi:10.1177/0271678X18769180
64. Guyenet PG, Stornetta RL, Souza G, Abbott SBG, Shi Y, Bayliss DA. The Retrotrapezoid Nucleus: Central Chemoreceptor and Regulator of Breathing Automaticity. Trends Neurosci 2019;42:807–824. doi:10.1016/j.tins.2019.09.002 [PubMed: 31635852]
65. Molkov YI, Shevtsova NA, Park C, Ben-Tal A, Smith JC, Rubin JE, Rybak IA. A closed-loop model of the respiratory system: focus on hypercapnia and active expiration. PLoS One. 2014;9:e109894. doi:10.1371/journal.pone.0109894 [PubMed: 25302708]
66. Molkov YI, Zoccal DB, Moraes DJ, Paton JF, Machado BH, Rybak IA. Intermittent hypoxia-induced sensitization of central chemoreceptors contributes to sympathetic nerve activity during late expiration in rats. J Neurophysiol 2011;105:3080–3091. doi:10.1152/jn.00070.2011 [PubMed: 21471394]

67. Li A, Roy SH, Nattie EE. An augmented CO2 chemoreflex and overactive orexin system are linked with hypertension in young and adult spontaneously hypertensive rats. J Physiol 2016;594:4967–4980. doi:10.1113/JP272199 [PubMed: 27061304]
68. Fatouleh R, Macefield VG. Respiratory modulation of muscle sympathetic nerve activity is not increased in essential hypertension or chronic obstructive pulmonary disease. J Physiol 2011;589:4997–5006. doi:10.1113/expphysiol.2013.077511 [PubMed: 21844003]
69. Bazilio DS, Bonagamba LGH, Moraes DJA, Machado BH. Cardiovascular and respiratory profiles during the sleep-wake cycle of rats previously submitted to chronic intermittent hypoxia. Exp Physiol 2019;104:1408–1419. doi:10.1113/EP087784 [PubMed: 31099915]
70. Fatouleh R, McKenzie DK, Macefield VG. Respiratory modulation of muscle sympathetic nerve activity in obstructive sleep apnoea. Exp Physiol 2014;99:1288–1298. doi:10.1113/expphysiol.2013.077511 [PubMed: 24887112]
71. Guyenet PG, Bayliss DA, Stornetta RL, Kanbar R, Shi Y, Holloway BB, Souza G, Basting TM, Abbott SBG, Wenker IC. Interdependent feedback regulation of breathing by the carotid bodies and the retrotrapezoid nucleus. J Physiol 2018;596:3029–3042. doi:10.1113/JP274357 [PubMed: 29168167]
72. Banek CT, Knuepfer MM, Foss JD, Fiege JK, Asirvatham-Jeyaraj N, Van Helden D, Shimizu Y, Osborn JW. Resting Afferent Renal Nerve Discharge and Renal Inflammation: Elucidating the Role of Afferent and Efferent Renal Nerves in Deoxycorticosterone Acetate Salt Hypertension. Hypertension. 2016;68:1415–1423. doi:10.1161/HYPERTENSIONAHA.116.07850 [PubMed: 27698066]
73. Ong J, Kinsman BJ, Sved AF, Rush BM, Tan RJ, Carattino MD, Stocker SD. Renal sensory nerves increase sympathetic nerve activity and blood pressure in 2-kidney 1-clip hypertensive mice. J Neurophysiol 2019;122:358–367. doi:10.1152/jn.00173.2019 [PubMed: 31091159]
74. Craig AD. Distribution of brainstem projections from spinal lamina I neurons in the cat and the monkey. J Comp Neurol 1995;361:225–248. doi:10.1002/cne.903610204 [PubMed: 8543660]
75. Dampney RAL. Resetting of the Baroreflex Control of Sympathetic Vasomotor Activity during Natural Behaviors: Description and Conceptual Model of Central Mechanisms. Front Neurosci 2017;11:461. doi:10.3389/fnins.2017.00461 [PubMed: 28860965]
76. McBryde FD, Abdala AP, Hendy EB, Pijacka W, Marvar P, Moraes DJ, Sobotka PA, Paton JF. The carotid body as a putative therapeutic target for the treatment of neurogenic hypertension. Nat Commun 2013;4:2395. doi:10.1038/ncomms3395 [PubMed: 24002774]
77. Cowley AW Jr. Long-term control of arterial blood pressure. Physiol Rev 1992;72:231–300. doi:10.1152/physrev.1992.72.1.231 [PubMed: 1731371]
78. Dampney RA. Central neural control of the cardiovascular system: current perspectives. Adv Physiol Educ 2016;40:283–296. doi:10.1152/advan.00027.2016 [PubMed: 27445275]
79. Zeng WZ, Marshall KL, Min S, Daou I, Chapleau MW, Abboud FM, Liberles SD, Patapoutian A. PIEZOs mediate neuronal sensing of blood pressure and the baroreceptor reflex. Science. 2018;362:464–467. doi:10.1126/science.aau6324 [PubMed: 30361375]
80. Marder E, Goaillard JM. Variability, compensation and homeostasis in neuron and network function. Nat Rev Neurosci 2006;7:563–574. doi:10.1038/nrn1949 [PubMed: 16791145]
81. Marina N, Christie IN, Korsak A, Doronin M, Brazhe A, Hosford PS, Wells JA, Sheikhbahaei S, Humoud I, Paton JFR, Lythgoe MF, Semyanov A, Kasparov S, Gourine AV. Astrocytes monitor cerebral perfusion and control systemic circulation to maintain brain blood flow. Nat Commun 2020;11:131. doi:10.1038/s41467-019-13956-y [PubMed: 31919423]
82. Lohmeier TE, Hall JE. Device-Based Neuromodulation for Resistant Hypertension Therapy. Circ Res 2019;124:1071–1093. doi:10.1161/CIRCRESAHA.118.313221 [PubMed: 30920919]
83. Nurse CA. Synaptic and paracrine mechanisms at carotid body arterial chemoreceptors. J Physiol 2014;592:3419–3426. doi:10.1113/jphysiol.2013.269829 [PubMed: 24665097]
84. Prabhakar NR. Sensing hypoxia: physiology, genetics and epigenetics. J Physiol 2013;591:2245–2257. doi:10.1113/jphysiol.2012.247759 [PubMed: 23459758]
85. Ortega-Saenz P, Lopez-Barneo J. Physiology of the Carotid Body: From Molecules to Disease. Annu Rev Physiol 2019 doi:10.1146/annurev-physiol-020518-114427

86. Zera T, Moraes DJA, da Silva MP, Fisher JP, Paton JFR. The Logic of Carotid Body Connectivity to the Brain. Physiology (Bethesda). 2019;34:264–282. doi:10.1152/physiol.00057.2018 [PubMed: 31165684]
87. Koshiya N, Guyenet PG. NTS neurons with carotid chemoreceptor inputs arborize in the rostral ventrolateral medulla. Am J Physiol 1996;270:R1273–R1278. doi:10.1152/ajpregu.1996.270.6.R1273 [PubMed: 8764294]
88. Koshiya N, Huangfu D, Guyenet PG. Ventrolateral medulla and sympathetic chemoreflex in the rat. Brain Res 1993;609:174–184. doi:10.1016/0006-8993(93)90871-j [PubMed: 8508301]
89. Marshall JM, Metcalfe JD. Analysis of the cardiovascular changes induced in the rat by graded levels of systemic hypoxia. J Physiol 1988;407:385–404. doi:10.1113/jphysiol.1988.sp017422 [PubMed: 3256622]
90. Shin MK, Eraso CC, Mu YP, Gu C, Yeung BHY, Kim LJ, Liu XR, Wu ZJ, Paudel O, Pichard LE, Shirahata M, Tang WY, Sham JSK, Polotsky VY. Leptin Induces Hypertension Acting on Transient Receptor Potential Melastatin 7 Channel in the Carotid Body. Circ Res 2019;125:989–1002. doi:10.1161/CIRCRESAHA.119.315338 [PubMed: 31545149]
91. Pijacka W, McBryde FD, Marvar PJ, Lincevicius GS, Abdala AP, Woodward L, Li D, Paterson DJ, Paton JF. Carotid sinus denervation ameliorates renovascular hypertension in adult Wistar rats. J Physiol 2016;594:6255–6266. doi:10.1113/JP272708 [PubMed: 27510951]
92. Ribeiro MJ, Sacramento JF, Gonzalez C, Guarino MP, Monteiro EC, Conde SV. Carotid body denervation prevents the development of insulin resistance and hypertension induced by hypercaloric diets. Diabetes. 2013;62:2905–2916. doi:10.2337/db12-1463 [PubMed: 23530003]
93. Fletcher EC. Invited review: Physiological consequences of intermittent hypoxia: systemic blood pressure. J Appl Physiol 2001;90:1600–1605. doi:10.1152/jappl.2001.90.4.1600 [PubMed: 11247966]
94. Del Rio R, Andrade DC, Lucero C, Arias P, Iturriaga R. Carotid Body Ablation Abrogates Hypertension and Autonomic Alterations Induced by Intermittent Hypoxia in Rats. Hypertension. 2016;68:436–445. doi:10.1161/HYPERTENSIONAHA.116.07255 [PubMed: 27381902]
95. Abdala AP, McBryde FD, Marina N, Hendy EB, Engelman ZJ, Fudim M, Sobotka PA, Gourine AV, Paton JF. Hypertension is critically dependent on the carotid body input in the spontaneously hypertensive rat. J Physiol 2012;590:4269–4277. doi:10.1113/jphysiol.2012.237800 [PubMed: 22687617]
96. Pijacka W, Moraes DJ, Ratcliffe LE, Nightingale AK, Hart EC, da Silva MP, Machado BH, McBryde FD, Abdala AP, Ford AP, Paton JF. Purinergic receptors in the carotid body as a new drug target for controlling hypertension. Nat Med 2016;22:1151–1159. doi:10.1038/nm.4173 [PubMed: 27595323]
97. Prabhakar NR, Peng YJ, Kumar GK, Pawar A. Altered carotid body function by intermittent hypoxia in neonates and adults: Relevance to recurrent apneas. Respir Physiol Neurobiol 2007;157:148–153. doi:10.1016/j.resp.2006.12.009 [PubMed: 17317339]
98. Kumar P, Prabhakar NR. Peripheral chemoreceptors: function and plasticity of the carotid body. Compr Physiol 2012;2:141–219. doi:10.1002/cphy.c100069 [PubMed: 23728973]
99. Tan ZY, Lu Y, Whiteis CA, Simms AE, Paton JF, Chapleau MW, Abboud FM. Chemoreceptor hypersensitivity, sympathetic excitation, and overexpression of ASIC and TASK channels before the onset of hypertension in SHR. Circ Res 2010;106:536–545. doi:10.1161/CIRCRESAHA.109.206946 [PubMed: 20019330]
100. Nanduri J, Peng YJ, Wang N, Prabhakar NR. Neural Activation of Molecular Circuitry in Intermittent Hypoxia. Curr Opin Physiol 2019;7:9–14. doi:10.1016/j.cophys.2018.11.003 [PubMed: 31544168]
101. Sobrino V, Gonzalez-Rodriguez P, Annese V, Lopez-Barneo J, Pardal R. Fast neurogenesis from carotid body quiescent neuroblasts accelerates adaptation to hypoxia. EMBO Rep 2018;19 doi:10.15252/embr.201744598
102. Cramer JA, Wiggins RH, Fudim M, Engelman ZJ, Sobotka PA, Shah LM. Carotid body size on CTA: correlation with comorbidities. Clin Radiol 2014;69:e33–36. doi:10.1016/j.crad.2013.08.016 [PubMed: 24156799]

103. Narkiewicz K, Ratcliffe LE, Hart EC, Briant LJ, Chrostowska M, Wolf J, Szyndler A, Hering D, Abdala AP, Manghat N, Burchell AE, Durant C, Lobo MD, Sobotka PA, Patel NK, Leiter JC, Engelman ZJ, Nightingale AK, Paton JF. Unilateral Carotid Body Resection in Resistant Hypertension: A Safety and Feasibility Trial. JACC Basic Transl Sci 2016;1:313–324. doi:10.1016/j.jacbts.2016.06.004 [PubMed: 27766316]

104. Morrison SF, Nakamura K. Central neural pathways for thermoregulation. Front Biosci 2011;16:74–104. doi:10.2741/3677

105. Atasoy D, Betley JN, Su HH, Sternson SM. Deconstruction of a neural circuit for hunger. Nature. 2012;488:172–177. [PubMed: 22801496]

106. Dergacheva O, Yamanaka A, Schwartz AR, Polotsky VY, Mendelowitz D. Direct projections from hypothalamic orexin neurons to brainstem cardiac vagal neurons. Neuroscience. 2016;339:47–53. doi:10.1016/j.neuroscience.2016.09.038 [PubMed: 27693474]

107. Stocker SD, Lang SM, Simmonds SS, Wenner MM, Farquhar WB. Cerebrospinal Fluid Hypernatremia Elevates Sympathetic Nerve Activity and Blood Pressure via the Rostral Ventrolateral Medulla. Hypertension. 2015;66:1184–1190. doi:10.1161/HYPERTENSIONAHA.115.05936 [PubMed: 26416846]

108. Dampney RA, Michelini LC, Li DP, Pan HL. Regulation of sympathetic vasomotor activity by the hypothalamic paraventricular nucleus in normotensive and hypertensive states. Am J Physiol Heart Circ Physiol 2018;315:H1200–H1214. doi:10.1152/ajpheart.00216.2018 [PubMed: 30095973]

109. Geraldes V, Goncalves-Rosa N, Liu B, Paton JF, Rocha I. Chronic depression of hypothalamic paraventricular neuronal activity produces sustained hypotension in hypertensive rats. Exp Physiol 2014;99:89–100. doi:10.1113/expphysiol.2013.074823 [PubMed: 24142454]

110. Allen AM. Inhibition of the hypothalamic paraventricular nucleus in spontaneously hypertensive rats dramatically reduces sympathetic vasomotor tone. Hypertension. 2002;39:275–280. [PubMed: 11847197]

111. Mukerjee S, Gao H, Xu J, Sato R, Zsombok A, Lazartigues E. ACE2 and ADAM17 Interaction Regulates the Activity of Presympathetic Neurons. Hypertension. 2019;74:1181–1191. doi:10.1161/HYPERTENSIONAHA.119.13133 [PubMed: 31564162]

112. Krashes MJ, Shah BP, Madara JC, Olson DP, Strochlic DE, Garfield AS, Vong L, Pei H, Watabe-Uchida M, Uchida N, Liberles SD, Lowell BB. An excitatory paraventricular nucleus to AgRP neuron circuit that drives hunger. Nature. 2014;507:238–242. doi:10.1038/nature12956 [PubMed: 24487620]

113. Toral M, Robles-Vera I, de la Visitacion N, Romero M, Yang T, Sanchez M, Gomez-Guzman M, Jimenez R, Raizada MK, Duarte J. Critical Role of the Interaction Gut Microbiota - Sympathetic Nervous System in the Regulation of Blood Pressure. Front Physiol 2019;10:231. doi:10.3389/fphys.2019.00231 [PubMed: 30930793]

114. Huber MJ, Chen QH, Shan Z. The Orexin System and Hypertension. Cell Mol Neurobiol 2018;38:385–391. doi:10.1007/s10571-017-0487-z [PubMed: 28349223]

115. Brooks VL, Shi Z, Holwerda SW, Fadel PJ. Obesity-induced increases in sympathetic nerve activity: sex matters. Auton Neurosci 2015;187:18–26. doi:10.1016/j.autneu.2014.11.006 [PubMed: 25435000]

116. Lambert GW, Schlaich MP, Eikelis N, Lambert EA. Sympathetic activity in obesity: a brief review of methods and supportive data. Ann N Y Acad Sci 2019;1454:56–67. doi:10.1111/nyas.14140 [PubMed: 31268175]

117. Rahmouni K Cardiovascular Regulation by the Arcuate Nucleus of the Hypothalamus: Neurocircuitry and Signaling Systems. Hypertension. 2016;67:1064–1071. doi:10.1161/HYPERTENSIONAHA.115.06425 [PubMed: 27045026]

118. Nakamura T, Bhatt S, Sapru HN. Cardiovascular responses to hypothalamic arcuate nucleus stimulation in the rat: role of sympathetic and vagal efferents. Hypertension. 2009;54:1369–1375. doi:10.1161/HYPERTENSIONAHA.109.140715 [PubMed: 19884562]

119. Chitravanshi VC, Kawabe K, Sapru HN. Stimulation of the hypothalamic arcuate nucleus increases brown adipose tissue nerve activity via hypothalamic paraventricular and dorsomedial

nuclei. Am J Physiol Heart Circ Physiol 2016;311:H433–444. doi:10.1152/ajpheart.00176.2016 [PubMed: 27402666]

120. Sim LJ, Joseph SA. Arcuate nucleus projections to brainstem regions which modulate nociception. J Chem Neuroanat 1991;4:97–109. doi:10.1016/0891-0618(91)90034-a [PubMed: 1711859]
121. Wang D, He X, Zhao Z, Feng Q, Lin R, Sun Y, Ding T, Xu F, Luo M, Zhan C. Whole-brain mapping of the direct inputs and axonal projections of POMC and AgRP neurons. Front Neuroanat 2015;9:40. doi:10.3389/fnana.2015.00040 [PubMed: 25870542]
122. Elias CF, Lee C, Kelly J, Aschkenasi C, Ahima RS, Couceyro PR, Kuhar MJ, Saper CB, Elmquist JK. Leptin activates hypothalamic CART neurons projecting to the spinal cord. Neuron 1998;21:1375–1385. doi:10.1016/s0896-6273(00)80656-x [PubMed: 9883730]
123. Kawabe T, Kawabe K, Sapru HN. Cardiovascular responses to chemical stimulation of the hypothalamic arcuate nucleus in the rat: role of the hypothalamic paraventricular nucleus. PLoS One. 2012;7:e45180. doi:10.1371/journal.pone.0045180 [PubMed: 23028831]
124. Shi Z, Madden CJ, Brooks VL. Arcuate neuropeptide Y inhibits sympathetic nerve activity via multiple neuropathways. J Clin Invest 2017;127:2868–2880. doi:10.1172/JCI92008 [PubMed: 28628036]
125. Rahmouni K, Morgan DA. Hypothalamic arcuate nucleus mediates the sympathetic and arterial pressure responses to leptin. Hypertension. 2007;49:647–652. doi:10.1161/01.HYP.0000254827.59792.b2 [PubMed: 17190874]
126. Harlan SM, Morgan DA, Agassandian K, Guo DF, Cassell MD, Sigmund CD, Mark AL, Rahmouni K. Ablation of the leptin receptor in the hypothalamic arcuate nucleus abrogates leptin-induced sympathetic activation. Circ Res 2011;108:808–812. doi:10.1161/CIRCRESAHA.111.240226 [PubMed: 21311043]
127. Cassaglia PA, Hermes SM, Aicher SA, Brooks VL. Insulin acts in the arcuate nucleus to increase lumbar sympathetic nerve activity and baroreflex function in rats. J Physiol 2011;589:1643–1662. doi:10.1113/jphysiol.2011.205575 [PubMed: 21300750]
128. Luckett BS, Frielle JL, Wolfgang L, Stocker SD. Arcuate nucleus injection of an anti-insulin affibody prevents the sympathetic response to insulin. Am J Physiol Heart Circ Physiol 2013;304:H1538–1546. doi:10.1152/ajpheart.00081.2013 [PubMed: 23542919]
129. Limberg JK, Johnson BD, Mozer MT, Holbein WW, Curry TB, Prabhakar NR, Joyner MJ. Role of the carotid chemoreceptors in insulin-mediated sympathoexcitation in humans. Am J Physiol Regul Integr Comp Physiol 2020;318:R173–R181. doi:10.1152/ajpregu.00257.2019 [PubMed: 31746629]
130. Shi Z, Wong J, Brooks VL. Obesity: sex and sympathetics. Biol Sex Differ 2020;11:10. doi:10.1186/s13293-020-00286-8 [PubMed: 32160920]
131. Shi Z, Zhao D, Cassaglia PA, Brooks VL. Sites and sources of sympathoexcitation in obese male rats: role of brain insulin. Am J Physiol Regul Integr Comp Physiol 2020 doi:10.1152/ajpregu.00317.2019
132. Shi Z, Cassaglia PA, Pelletier NE, Brooks VL. Sex differences in the sympathoexcitatory response to insulin in obese rats: role of neuropeptide Y. J Physiol 2019;597:1757–1775. doi:10.1113/JP277517 [PubMed: 30628058]
133. Lim K, Barzel B, Burke SL, Armitage JA, Head GA. Origin of Aberrant Blood Pressure and Sympathetic Regulation in Diet-Induced Obesity. Hypertension. 2016;68:491–500. doi:10.1161/HYPERTENSIONAHA.116.07461 [PubMed: 27296999]
134. Simonds SE, Pryor JT, Ravussin E, Greenway FL, Dileone R, Allen AM, Bassi J, Elmquist JK, Keogh JM, Henning E, Myers MG Jr., Licinio J, Brown RD, Enriori PJ, O'Rahilly S, Sternson SM, Grove KL, Spanswick DC, Farooqi IS, Cowley MA. Leptin mediates the increase in blood pressure associated with obesity. Cell. 2014;159:1404–1416. doi:10.1016/j.cell.2014.10.058 [PubMed: 25480301]
135. Morgan DA, Anderson EA, Mark AL. Renal sympathetic nerve activity is increased in obese Zucker rats. Hypertension. 1995;25:834–838. doi:10.1161/01.hyp.25.4.834 [PubMed: 7721440]

136. do Carmo JM, da Silva AA, Rushing JS, Hall JE. Activation of the central melanocortin system contributes to the increased arterial pressure in obese Zucker rats. Am J Physiol Regul Integr Comp Physiol 2012;302:R561–567. doi:10.1152/ajpregu.00392.2011 [PubMed: 22204957]

137. Zhou JJ, Ma HJ, Shao J, Wei Y, Zhang X, Zhang Y, Li DP. Downregulation of Orexin Receptor in Hypothalamic Paraventricular Nucleus Decreases Blood Pressure in Obese Zucker Rats. J Am Heart Assoc 2019;8:e011434. doi:10.1161/JAHA.118.011434 [PubMed: 31213116]

138. Jais A, Bruning JC. Hypothalamic inflammation in obesity and metabolic disease. J Clin Invest 2017;127:24–32. doi:10.1172/JCI88878 [PubMed: 28045396]

139. Sieminski M, Szypenbejl J, Partinen E. Orexins, Sleep, and Blood Pressure. Curr Hypertens Rep 2018;20:79. doi:10.1007/s11906-018-0879-6 [PubMed: 29992504]

140. Harris GC, Aston-Jones G. Arousal and reward: a dichotomy in orexin function. Trends Neurosci 2006;29:571–577. doi:10.1016/j.tins.2006.08.002 [PubMed: 16904760]

141. Carrive P, Kuwaki T. Orexin and Central Modulation of Cardiovascular and Respiratory Function. Curr Top Behav Neurosci 2017;33:157–196. doi:10.1007/7854_2016_46 [PubMed: 27909989]

142. Kuwaki T Thermoregulation under pressure: a role for orexin neurons. Temperature (Austin) 2015;2:379–391. doi:10.1080/23328940.2015.1066921 [PubMed: 27227052]

143. Kuwaki T Orexin links emotional stress to autonomic functions. Auton Neurosci 2010;161:20–27. doi:10.1016/j.autneu.2010.08.004 [PubMed: 20813590]

144. Lee MG, Hassani OK, Jones BE. Discharge of identified orexin/hypocretin neurons across the sleep-waking cycle. J Neurosci 2005;25:6716–6720. doi:10.1523/JNEUROSCI.1887-05.2005 [PubMed: 16014733]

145. Li A, Nattie E. Orexin, cardio-respiratory function, and hypertension. Front Neurosci 2014;8:22. doi:10.3389/fnins.2014.00022 [PubMed: 24574958]

146. Kuwaki T, Zhang W, Nakamura A, Deng BS. Emotional and state-dependent modification of cardiorespiratory function: role of orexinergic neurons. Auton Neurosci 2008;142:11–16. doi:10.1016/j.autneu.2008.03.004 [PubMed: 18440283]

147. Jackson KL, Head GA, Gueguen C, Stevenson ER, Lim K, Marques FZ. Mechanisms Responsible for Genetic Hypertension in Schlager BPH/2 Mice. Front Physiol 2019;10:1311. doi:10.3389/fphys.2019.01311 [PubMed: 31681017]

148. Jackson KL, Dampney BW, Moretti JL, Stevenson ER, Davern PJ, Carrive P, Head GA. Contribution of Orexin to the Neurogenic Hypertension in BPH/2J Mice. Hypertension. 2016;67:959–969. doi:10.1161/HYPERTENSIONAHA.115.07053 [PubMed: 26975709]

149. Li AH, Hindmarch CCT, Nattie EE, Paton JFR. Antagonism of orexin receptors significantly lowers blood pressure in spontaneously hypertensive rats. J Physiol 2013;591:4237–4248. doi:DOI 10.1113/jphysiol.2013.256271 [PubMed: 23671161]

150. Lee YH, Tsai MC, Li TL, Dai YW, Huang SC, Hwang LL. Spontaneously hypertensive rats have more orexin neurons in the hypothalamus and enhanced orexinergic input and orexin 2 receptor-associated nitric oxide signalling in the rostral ventrolateral medulla. Exp Physiol 2015;100:993–1007. doi:10.1113/EP085016 [PubMed: 26096870]

151. Clifford L, Dampney BW, Carrive P. Spontaneously hypertensive rats have more orexin neurons in their medial hypothalamus than normotensive rats. Exp Physiol 2015;100:388–398. doi:10.1113/expphysiol.2014.084137 [PubMed: 25640802]

152. Huber MJ, Fan Y, Jiang E, Zhu F, Larson RA, Yan J, Li N, Chen QH, Shan Z. Increased activity of the orexin system in the paraventricular nucleus contributes to salt-sensitive hypertension. Am J Physiol Heart Circ Physiol 2017;313:H1075–H1086. doi:10.1152/ajpheart.00822.2016 [PubMed: 28667055]

153. Kuwaki T, Zhang W. Orexin neurons as arousal-associated modulators of central cardiorespiratory regulation. Respir Physiol Neurobiol 2010;174:43–54. [PubMed: 20416404]

154. Jackson KL, Palma-Rigo K, Nguyen-Huu TP, Davern PJ, Head GA. Major contribution of the medial amygdala to hypertension in BPH/2J genetically hypertensive mice. Hypertension. 2014;63:811–818. doi:10.1161/HYPERTENSIONAHA.113.02020 [PubMed: 24446057]

155. Folkow B, Hallback-Nordlander M, Martner J, Nordborg C. Influence of amygdala lesions on cardiovascular responses to alerting stimuli, on behaviour and on blood pressure development in

spontaneously hypertensive rats. Acta Physiol Scand 1982;116:133–139. doi:10.1111/j.1748-1716.1982.tb07121.x [PubMed: 7168349]

156. Llewellyn-Smith IJ, Martin CL, Marcus JN, Yanagisawa M, Minson JB, Scammell TE. Orexin-immunoreactive inputs to rat sympathetic preganglionic neurons. Neurosci Lett 2003;351:115–119. doi:10.1016/s0304-3940(03)00770-5 [PubMed: 14583395]
157. Li A, Hindmarch CC, Nattie EE, Paton JF. Antagonism of orexin receptors significantly lowers blood pressure in spontaneously hypertensive rats. J Physiol 2013;591:4237–4248. doi:10.1113/jphysiol.2013.256271 [PubMed: 23671161]
158. Berridge CW, Schmeichel BE, Espana RA. Noradrenergic modulation of wakefulness/arousal. Sleep Med Rev 2012;16:187–197. doi:10.1016/j.smrv.2011.12.003 [PubMed: 22296742]
159. Ivanov A, Aston-Jones G. Hypocretin/orexin depolarizes and decreases potassium conductance in locus coeruleus neurons. Neuroreport 2000;11:1755–1758. doi:10.1097/00001756-200006050-00031 [PubMed: 10852238]
160. Brown RE, Sergeeva OA, Eriksson KS, Haas HL. Convergent excitation of dorsal raphe serotonin neurons by multiple arousal systems (orexin/hypocretin, histamine and noradrenaline). J Neurosci 2002;22:8850–8859. doi:10.1523/JNEUROSCI.22-20-08850.2002 [PubMed: 12388591]
161. Iwakawa S, Kanmura Y, Kuwaki T. Orexin Receptor Blockade-Induced Sleep Preserves the Ability to Wake in the Presence of Threat in Mice. Front Behav Neurosci 2018;12:327. doi:10.3389/fnbeh.2018.00327 [PubMed: 30687033]
162. Hasegawa E, Yanagisawa M, Sakurai T, Mieda M. Orexin neurons suppress narcolepsy via 2 distinct efferent pathways. J Clin Invest 2014;124:604–616. doi:10.1172/JCI71017 [PubMed: 24382351]
163. Mansukhani MP, Covassin N, Somers VK. Neurological Sleep Disorders and Blood Pressure: Current Evidence. Hypertension. 2019;74:726–732. doi:10.1161/HYPERTENSIONAHA.119.13456 [PubMed: 31476906]
164. Herring WJ, Roth T, Krystal AD, Michelson D. Orexin receptor antagonists for the treatment of insomnia and potential treatment of other neuropsychiatric indications. J Sleep Res 2019;28:e12782. doi:10.1111/jsr.12782 [PubMed: 30338596]
165. McKinley MJ, Yao ST, Uschakov A, McAllen RM, Rundgren M, Martelli D. The median preoptic nucleus: front and centre for the regulation of body fluid, sodium, temperature, sleep and cardiovascular homeostasis. Acta Physiol (Oxf) 2015;214:8–32. doi:10.1111/apha.12487 [PubMed: 25753944]
166. Zimmerman CA, Leib DE, Knight ZA. Neural circuits underlying thirst and fluid homeostasis. Nat Rev Neurosci 2017;18:459–469. doi:10.1038/nrn.2017.71 [PubMed: 28638120]
167. Nomura K, Hiyama TY, Sakuta H, Matsuda T, Lin CH, Kobayashi K, Kobayashi K, Kuwaki T, Takahashi K, Matsui S, Noda M. [Na(+)] Increases in Body Fluids Sensed by Central Nax Induce Sympathetically Mediated Blood Pressure Elevations via H(+)-Dependent Activation of ASIC1a. Neuron 2019;101:60–75 e66. doi:10.1016/j.neuron.2018.11.017 [PubMed: 30503172]
168. Young CN, Davisson RL. Angiotensin-II, the Brain, and Hypertension: An Update. Hypertension. 2015;66:920–926. doi:10.1161/HYPERTENSIONAHA.115.03624 [PubMed: 26324508]
169. Kinsman BJ, Nation HN, Stocker SD. Hypothalamic Signaling in Body Fluid Homeostasis and Hypertension. Curr Hypertens Rep 2017;19:50. doi:10.1007/s11906-017-0749-7 [PubMed: 28528375]
170. Chen Y, Lin YC, Kuo TW, Knight ZA. Sensory detection of food rapidly modulates arcuate feeding circuits. Cell. 2015;160:829–841. doi:10.1016/j.cell.2015.01.033 [PubMed: 25703096]
171. Zimmerman CA, Lin YC, Leib DE, Guo L, Huey EL, Daly GE, Chen Y, Knight ZA. Thirst neurons anticipate the homeostatic consequences of eating and drinking. Nature. 2016 doi:10.1038/nature18950
172. Collister JP, Nahey DB, Hartson R, Wiedmeyer CE, Banek CT, Osborn JW. Lesion of the OVLT markedly attenuates chronic DOCA-salt hypertension in rats. Am J Physiol Regul Integr Comp Physiol 2018;315:R568–R575. doi:10.1152/ajpregu.00433.2017 [PubMed: 29897819]

173. Kinsman BJ, Browning KN, Stocker SD. NaCl and osmolarity produce different responses in organum vasculosum of the lamina terminalis neurons, sympathetic nerve activity and blood pressure. J Physiol 2017;595:6187–6201. doi:10.1113/JP274537 [PubMed: 28678348]
174. Blessing WW. Arterial pressure and blood flow to the tissues The lower brainstem and bodily homeostasis. New York: Oxford University Press; 1997:165–268.
175. Muller-Ribeiro FC, Dampney RA, McMullan S, Fontes MA, Goodchild AK. Disinhibition of the midbrain colliculi unmasks coordinated autonomic, respiratory, and somatomotor responses to auditory and visual stimuli. Am J Physiol Regul Integr Comp Physiol 2014;307:R1025–1035. doi:10.1152/ajpregu.00165.2014 [PubMed: 25100075]
176. Dampney RA, Furlong TM, Horiuchi J, Iigaya K. Role of dorsolateral periaqueductal grey in the coordinated regulation of cardiovascular and respiratory function. Auton Neurosci 2013 doi:10.1016/j.autneu.2012.12.008
177. Horiuchi J, McDowall LM, Dampney RA. Vasomotor and respiratory responses evoked from the dorsolateral periaqueductal grey are mediated by the dorsomedial hypothalamus. J Physiol 2009;587:5149–5162. [PubMed: 19752114]
178. Horiuchi J, McAllen RM, Allen AM, Killinger S, Fontes MA, Dampney RA. Descending vasomotor pathways from the dorsomedial hypothalamic nucleus: role of medullary raphe and RVLM. Am J Physiol Regul Integr Comp Physiol 2004;287:R824–R832. doi:10.1152/ajpregu.00221.2004 [PubMed: 15205184]
179. Fontes MA, Xavier CH, de Menezes RC, Dimicco JA. The dorsomedial hypothalamus and the central pathways involved in the cardiovascular response to emotional stress. Neuroscience. 2011;184:64–74. doi:10.1016/j.neuroscience.2011.03.018 [PubMed: 21435377]
180. O'Callaghan EL, McBryde FD, Burchell AE, Ratcliffe LE, Nicolae L, Gillbe I, Carr D, Hart EC, Nightingale AK, Patel NK, Paton JF. Deep brain stimulation for the treatment of resistant hypertension. Curr Hypertens Rep 2014;16:493. doi:10.1007/s11906-014-0493-1 [PubMed: 25236853]
181. Sams JM, Jansen ASP, Mettenleiter TC, Loewy AD. Pseudorabies virus mutants as transneuronal markers. Brain Res 1995;687:182–190. doi:10.1016/0006-8993(95)00484-8 [PubMed: 7583303]
182. Morrison SF, Nakamura K. Central Mechanisms for Thermoregulation. Annu Rev Physiol 2019;81:285–308. doi:10.1146/annurev-physiol-020518-114546 [PubMed: 30256726]
183. Morrison SF, Madden CJ. Central nervous system regulation of brown adipose tissue. Compr Physiol 2014;4:1677–1713. doi:10.1002/cphy.c140013 [PubMed: 25428857]
184. McBryde FD, Malpas SC, Paton JF. Intracranial mechanisms for preserving brain blood flow in health and disease. Acta Physiol (Oxf) 2017;219:274–287. doi:10.1111/apha.12706 [PubMed: 27172364]
185. Cushing H Concerning a definitive regulatory mechanism of the vaso-motor centre which controls blood pressure during cerebral compression. B Johns Hopkins Hosp 1901;12:290–292.
186. Schmidt EA, Despas F, Pavy-Le Traon A, Czosnyka Z, Pickard JD, Rahmouni K, Pathak A, Senard JM. Intracranial Pressure Is a Determinant of Sympathetic Activity. Front Physiol 2018;9:11. doi:10.3389/fphys.2018.00011 [PubMed: 29472865]
187. Guild SJ, Saxena UA, McBryde FD, Malpas SC, Ramchandra R. Intracranial pressure influences the level of sympathetic tone. Am J Physiol Regul Integr Comp Physiol 2018;315:R1049–R1053. doi:10.1152/ajpregu.00183.2018 [PubMed: 30207755]
188. Sun MK, Wahlestedt C, Reis DJ. Action of externally applied ATP on rat reticulospinal vasomotor neurons. Eur J Pharmacol 1992;224:93–96. doi:10.1016/0014-2999(92)94824-f [PubMed: 1451746]
189. Waki H, Bhuiyan ME, Gouraud SS, Takagishi M, Hatada A, Kohsaka A, Paton JF, Maeda M. Acute reductions in blood flow restricted to the dorsomedial medulla induce a pressor response in rats. J Hypertens 2011;29:1536–1545. doi:10.1097/HJH.0b013e3283484106 [PubMed: 21666494]
190. Osborn JW, 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 2005;288:R846–R855. doi:10.1152/ajpregu.00474.2004 [PubMed: 15793038]

191. Saleeba C, Dempsey B, Le S, Goodchild A, McMullan S. A Student's Guide to Neural Circuit Tracing. Front Neurosci 2019;13:897. doi:10.3389/fnins.2019.00897 [PubMed: 31507369]

192. Shoemaker JK, Badrov MB, Al-Khazraji BK, Jackson DN. Neural Control of Vascular Function in Skeletal Muscle. Compr Physiol 2015;6:303–329. doi:10.1002/cphy.c150004 [PubMed: 26756634]

193. Strack AM, Sawyer WB, Platt KB, Loewy AD. CNS cell groups regulating the sympathetic outflow to adrenal gland as revealed by transneuronal cell body labeling with pseudorabies virus. Brain Res 1989;491:274–296. doi:10.1016/0006-8993(89)90063-2 [PubMed: 2548665]

194. Lincevicius GS, Shimoura CG, Nishi EE, Oliveira T, Cespedes JG, Bergamaschi CT, Campos RR. Differential effects of renal denervation on arterial baroreceptor function in Goldblatt hypertension model. Auton Neurosci 2017;208:43–50. doi:10.1016/j.autneu.2017.06.002 [PubMed: 28688830]

195. Scott MM, Lachey JL, Sternson SM, Lee CE, Elias CF, Friedman JM, Elmquist JK. Leptin targets in the mouse brain. J Comp Neurol 2009;514:518–532. doi:10.1002/cne.22025 [PubMed: 19350671]

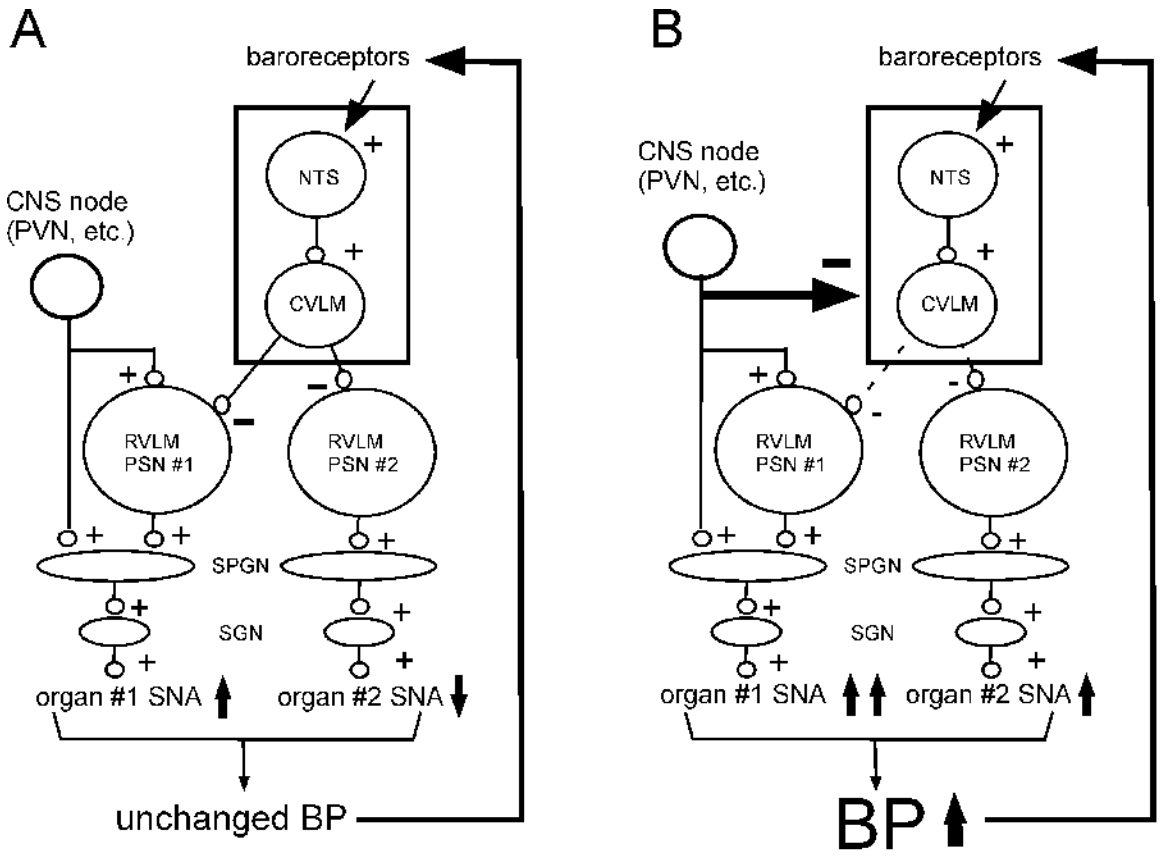

Figure 1:

Differential control of regional SNA with or without neurogenic hypertension, a hypothesis. Organ-specific SNA regulation operates via selective recruitment of RVLM presympathetic neurons and/or preganglionic neurons by inputs from a variety of CNS nodes (PVN, midline medulla, DMH, ARC, etc.; only one is represented). A) differential recruitment of regional SNA produces very little BP change if the baroreflex (NTS + CVLM; box) is unaffected. B) differential recruitment of regional SNA is associated with a rise in BP (potentially causing hypertension) if the baroreflex (NTS + CVLM; box) is simultaneously down-regulated.

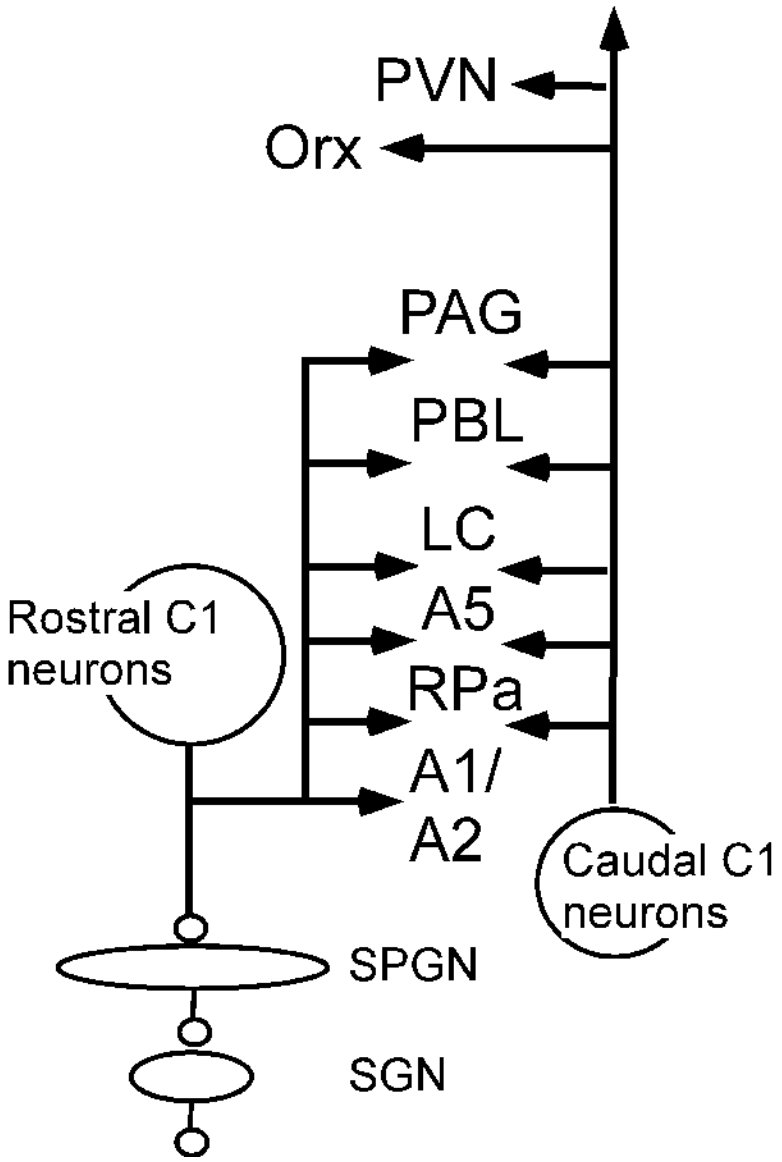

Figure 2:

The C1 neurons innervate many nuclei implicated in circulatory control besides the sympathetic preganglionic neurons (see list of abbreviations). The projections of the rostral C1 cells are shown on the left; the projections of the caudal C1 neurons are shown on the right. Note that that both populations target many of the same nuclei.

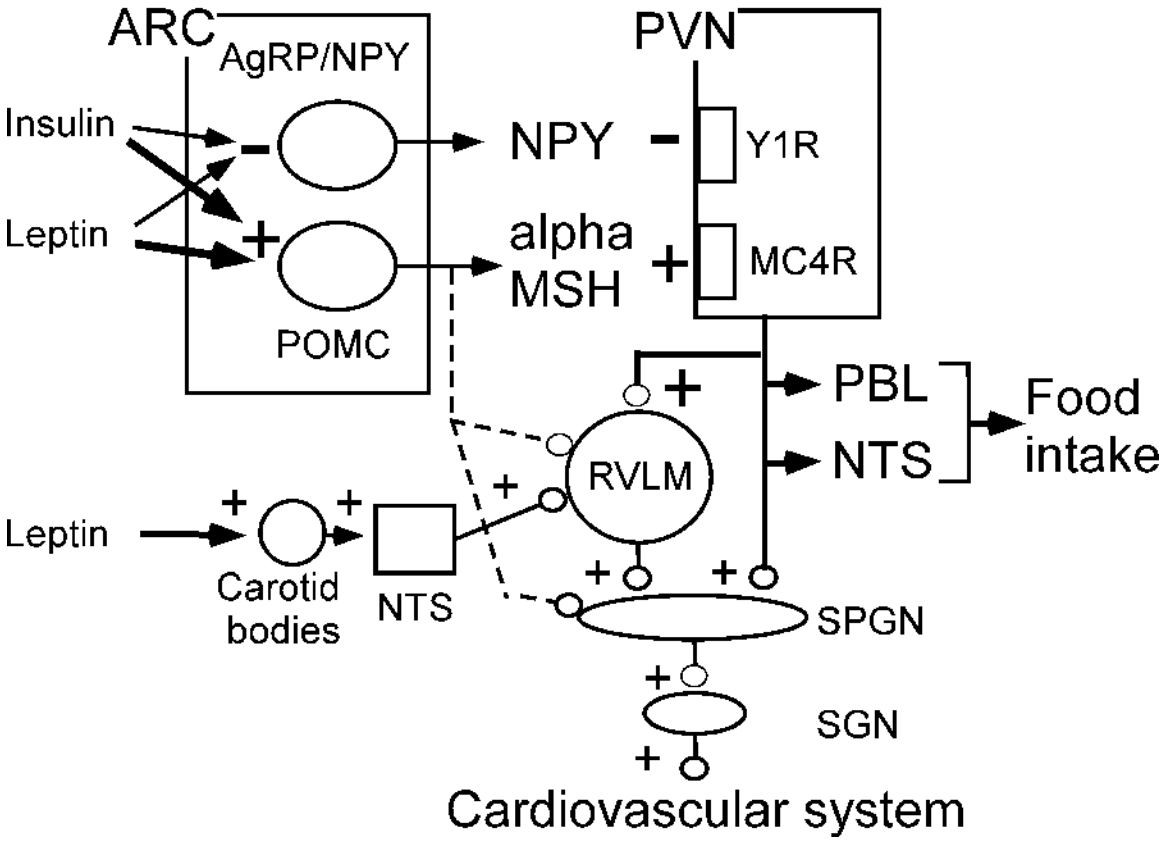

Figure 3:

leptin and insulin raise BP by activating POMC neurons and inhibiting AgRP neurons in the arcuate nucleus. POMC neurons activate PVN neurons by releasing α-MSH. AgRP neurons inhibit PVN by releasing NPY. Leptin also raises BP by stimulating the carotid bodies. Dashed lines, minor projections of POMC neurons plausibly involved in SNS control.

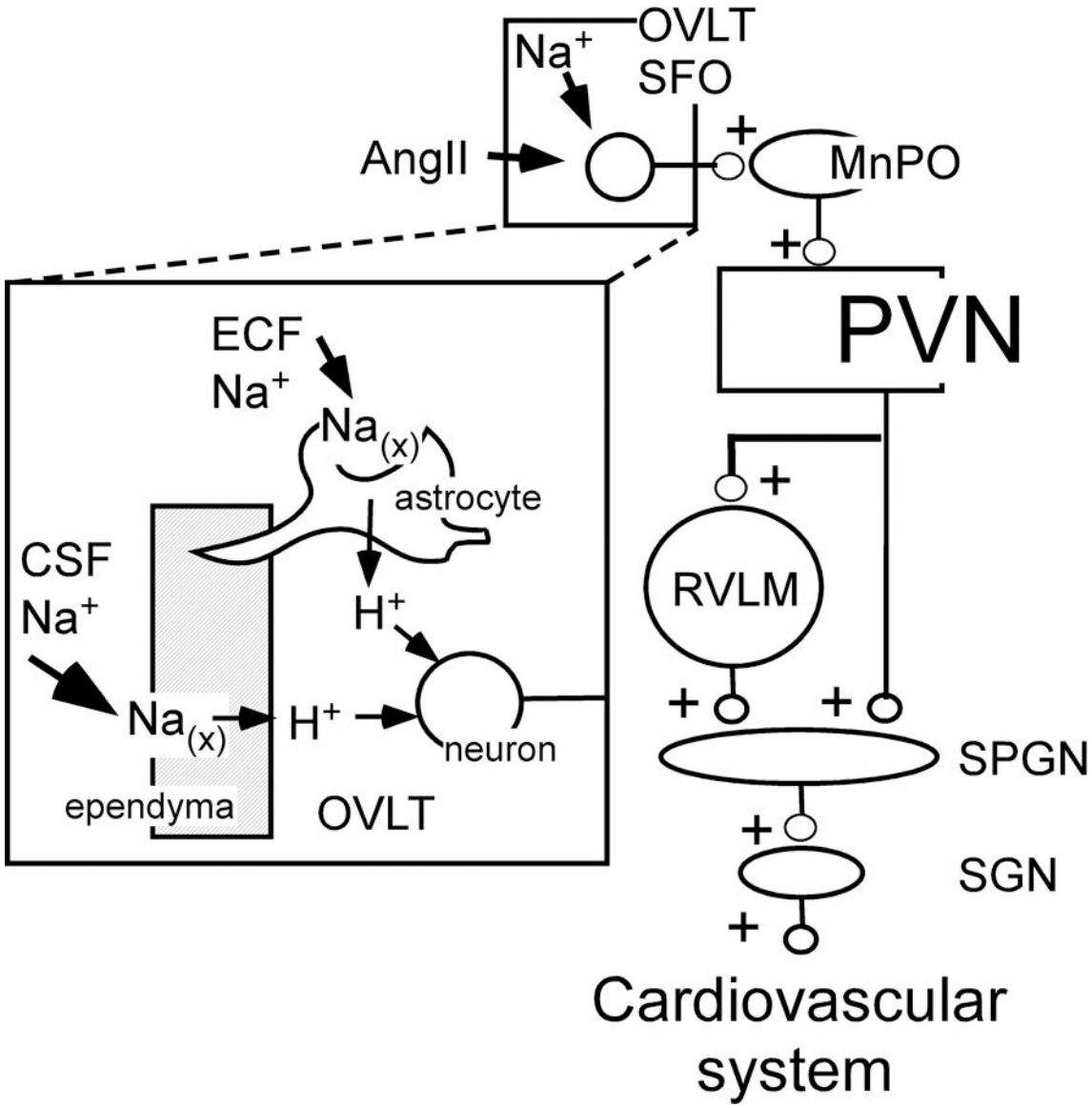

Figure 4:

Selected nuclei and pathways that contribute to salt or angiotensin-induced hypertension. Inset: mechanism of action of Na in the OVLT (after[167]). Sodium present in the CSF and ECF binds to and opens Na(x) channels, elicits the release of protons from astrocytes and ependymal cells. [H^+] activates OVLT neurons via acid-sensing ion channel-1a (ASIC). Other types of sodium sensing mechanisms have also been proposed[7] . Other abbrs: see list.

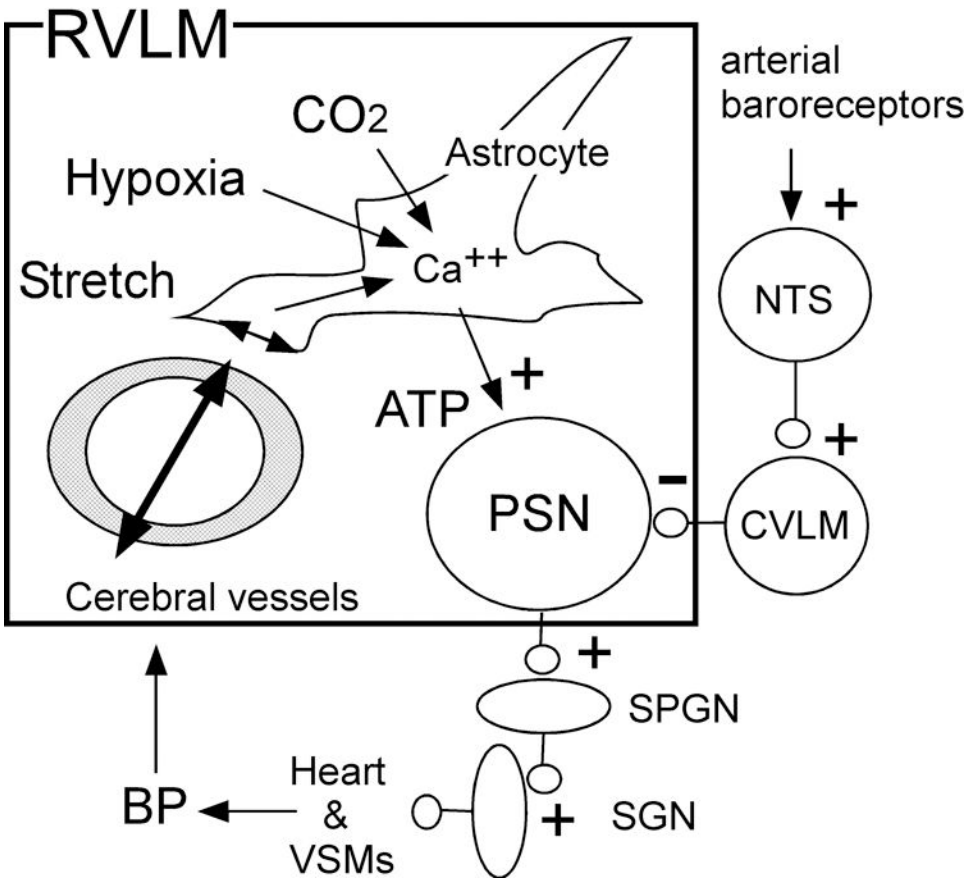

Figure 5:

BP regulation via arterial baroreceptors and brainstem perfusion: a hypothesis. A reduction in cerebral blood flow within the RVLM (box) is detected by astrocytes via hypoxia, acidification or end-feet mechanosensitivity elicited by changes in vascular diameter, the latter symbolized by double arrows. The flow-mediated reflex (slow pathway) and the conventional baroreflex (fast pathway, at right of diagram) converge on RVLM PSNs.