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Sympathetic Nervous System Contributions to Hypertension: Updates and Therapeutic Relevance

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Abstract

The sympathetic nervous system plays a pivotal role in the long-term regulation of arterial blood pressure through the ability of the central nervous system to integrate neurohumoral signals and differentially regulate sympathetic neural input to specific end organs. Part 1 of this review will discuss neural mechanisms of salt-sensitive hypertension, obesity-induced hypertension, and the ability of prior experiences to sensitize autonomic networks. Part 2 of this review focuses on new therapeutic advances to treat resistant hypertension including renal denervation and carotid baroactivation. Both advances lower arterial blood pressure by reducing sympathetic outflow. We discuss potential mechanisms and areas of future investigation to target the sympathetic nervous system.

RÉSUMÉ

Le système nerveux sympathique joue un rôle essentiel dans la régulation à long terme de la pression artérielle grâce à la capacité du système nerveux central à intégrer les signaux neurohumoraux et à réguler de manière différentielle la contribution neurale sympathique à des organes terminaux précis. La première partie de cette revue de littérature portera sur les mécanismes neuronaux de l'hypertension sensible à l'apport en sel, de l'hypertension induite par l'obésité et sur la capacité des expériences passées à sensibiliser les réseaux autonomes. La deuxième partie de cette revue de littérature se concentre sur les nouvelles avancées thérapeutiques pour traiter l'hypertension résistante, y compris la dénervation rénale et la stimulation des barorécepteurs de la carotide. Ces deux avancées permettent de réduire la pression artérielle en diminuant la réponse sympathique. Nous discutons des mécanismes potentiels et des domaines de recherche future ciblant le système nerveux sympathique.

The sympathetic nervous system regulates arterial blood pressure (ABP) by functionally influencing the vasculature, kidney, and heart. Indeed, altered sympathetic function is firmly established in the development, maintenance, and pathophysiology of numerous cardiovascular diseases including hypertension.[1,2] Sympathetic hyperactivity in human

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hypertension has been revealed through elevated norepinephrine spillover, increased muscle sympathetic nerve activity via microneurography, surgical sympathectomy, and greater depressor responses to acute ganglionic blockade (see the paper by Grassi et al.[2] for review). Notably, some antihypertensive pharmacotherapies lower ABP by targeting the sympathetic nervous system.[2,3] Recent advances regarding the role of the sympathetic nervous system in hypertension have focused on brain pathways or associated signalling mechanisms that increase or decrease ABP. Parallel investigations have attempted to identify which sympathetic nerve(s) become hyperactive or whose modulation lowers ABP. This article discusses recent insights regarding the role of the brain and sympathetic nervous system in hypertension that specifically pertains to high salt intake and salt-sensitive hypertension, obesity-induced hypertension, and neuroplasticity driven by prior experiences. The second half of the article will discuss renal denervation and carotid baroactivation—two therapeutic advances to treat drug-resistant hypertension by targeting the sympathetic nervous system.

Salt-Sensitive Hypertension

Salt-sensitive hypertension is simply defined as an increase (or decrease) in ABP during chronic salt-loading (or salt-restriction). To date, clinical criteria or tests to identify salt-sensitive subjects have not been established, and the magnitude of the ABP changes (and change in dietary salt content) to define salt-sensitive hypertension varies from study to study. However, a neurogenic component of salt-sensitive hypertension is strongly supported by several lines of evidence that include the following: (1) salt-sensitive hypertension is associated with activation of the sympathetic nervous system,[4–7] (2) blockade of sympathetic outflow or sympathetic nerve transection lowers ABP,[8,9] (3) interruption of neurotransmission in several sympathetic-regulatory nuclei lowers and even normalizes sympathetic nerve activity (SNA) and/or ABP,[10–12] and (4) lesion of the anteroventral third ventricular region of the hypothalamus prevents/attenuates the development or severity of multiple experimental models of salt-sensitive hypertension.[13–15]

One signal postulated to initiate and support sympathoexcitation in salt-sensitive hypertension is elevated plasma or cerebrospinal fluid NaCl concentration.[16] A high-salt diet elevates plasma or cerebrospinal fluid [NaCl] by 2–6 mM in multiple experimental models including Dahl salt-sensitive, spontaneously hypertensive rat, Grollman renal wrap, and deoxycorticosterone-salt.[7,17–25] Similar observations have been reported in human subjects.[7,18,26,27] However, plasma electrolyte measurements from many human studies should be interpreted with caution as the majority of samples are collected in fasted subjects that may not reflect daytime electrolyte values. Acutely, an infusion of hypertonic NaCl in experimental animals produces a complex sympathetic response characterized by increased lumbar (or muscle) and adrenal SNA,[28,29] no change in cardiac or splanchnic SNA,[28–30] and decreased renal SNA.[28–30] In humans, acute elevation in plasma NaCl increases muscle SNA.[31] Both acute and chronic intracerebroventricular infusion of hypertonic NaCl to produce physiological changes in cerebrospinal fluid [NaCl] increase ABP.[29,32–34] The relative importance of changes in plasma vs cerebrospinal fluid [NaCl] is not yet defined. Furthermore, the specific sympathetic nerve(s) or end organ(s) that contribute to salt-sensitive hypertension are not yet defined. However, celiac ganglionectomy reduces ABP in angiotensin II (AngII)-salt and Dahl-salt–sensitive hypertension,[9,35] whereas renal

denervation reduces ABP in deoxycorticosterone-salt and late-stage Dahl-salt–sensitive models.[35,36]

Changes in extracellular NaCl concentration are detected by specialized neurons located in circumventricular nuclei of the rostral hypothalamus—the subfornical organ and organum vasculosum of the lamina terminalis (OVLT)[37,38] (Fig. 1). These structures are juxtaposed to the third ventricle and lack a complete blood-brain barrier, thereby sensing and responding to changes in electrolyte concentrations and neurohumoral factors in the circulation and cerebrospinal fluid.[22,37,39] These structures project mono- or polysynaptically to hypothalamic, thalamic, and cortical structures to impact autonomic function.[37–40] OVLT neurons are intrinsically sensitive to extracellular [NaCl] within physiological ranges (2–10 mM).[28] Local injection of hypertonic NaCl into the OVLT increased lumbar SNA, adrenal SNA, and ABP. Inhibition of these neurons attenuated sympathoexcitatory responses to central infusion of hypertonic NaCl.[28] Finally, the lesion of the OVLT region attenuates both AngII-salt and deoxycorticosterone-salt hypertension.[41,42] The mechanism by which circumventricular organ neurons sense changes in [NaCl] remains unknown, but candidates include an N-terminal variant of the transient receptor potential vanilloid-1, Na_x, ouabain, and the epithelial sodium channel (see the papers by Stocker et al.,[16] Kinsman et al.,[38] and Blaustein et al.[43] for reviews) (Fig. 1).

The downstream pathways by which NaCl-sensitive pathways regulate SNA likely involve the hypothalamic paraventricular nucleus and rostral ventrolateral medulla (Fig. 1). Blockade of excitatory amino acid, AngII type 1, or vasopressin receptors in the hypothalamic paraventricular nucleus blunt acute pressor responses to hypertonic NaCl.[44,45] Neurons of the hypothalamic paraventricular nucleus project to sympathetic preganglionic neurons of the spinal cord or bulbospinal neurons of the rostral ventrolateral medulla. The sympathoexcitatory and pressor responses to acute, central infusion of hypertonic NaCl are mediated by the latter.[29] This circuitry is clinically significant as blockade of excitatory amino receptors or angiotensin type I receptors in the rostral ventrolateral medulla reduced ABP in Dahl-salt–sensitive rats fed a high-salt diet.[10,11] Whether signalling mechanisms within these critical nuclei or circumventricular organs located outside the blood-brain barrier can be exploited for future therapeutic targets remains an area of future investigation.

Dietary salt intake may also sensitize autonomic circuits and predispose animals or humans to the development of hypertension. The majority of laboratory animals are “salt-resistant,” but excess dietary salt intake exaggerates or amplifies sympathetic and ABP responses of these animals to activation of sciatic afferents,[46,47] exercise,[48] stimulation of the aortic depressor nerve or vagal afferents,[47,49] volume expansion,[47] air-jet stress,[33] insulin,[50] and central NaCl.[33,47] These effects occur independent of changes in baseline mean ABP or basal level of SNA.[33,47] These amplified responses are attributed to a direct change in the excitability of neurons in the rostral ventrolateral medulla[17,46,49,51,52] (Fig. 1). Exaggerated sympathetic reflexes due to chronic high salt intake were also associated with increased blood pressure variability.[47] This observation has significant clinical ramifications as increased blood pressure variability predisposes individuals to end-organ damage and development of cardiovascular disease.[53,54] In fact, increased blood pressure variability is a well-established predictor of future adverse cardiovascular events and disease.[55–57] The

mechanism(s) by which a high-salt diet “sensitizes” central autonomic networks without changes in baseline SNA or ABP has not been identified.

Obesity-Induced Hypertension

Obesity is a major risk factor for hypertension and may account for approximately two-thirds of essential hypertension.[58,59] Sympathoexcitation in obesity-induced hypertension is supported by: (1) increased renal, but not cardiac, norepinephrine spillover in obese vs lean subjects;[60,61] (2) muscle SNA is elevated in obese vs lean humans;[62,63] (3) chronic sympathetic nerve recordings in rats or rabbits fed high-fat diets indicate that obesity has elevated lumbar or renal SNA;[64–66] (4) pharmacologic blockade of adrenergic receptors[67] or ganglionic blockade[68] reduces ABP more in obesity vs lean subjects; and (5) bilateral renal denervation prevents the development of hypertension in dogs fed high-fat diet.[69]

The sympathoexcitation in obesity may be driven by several factors, most notably the peptide hormone insulin and the adipokine leptin (Fig. 2).[58,59] Acute administration of leptin or insulin increases SNA in rodents and/or humans. Importantly, intracerebroventricular infusion of leptin or insulin receptor antagonists lowers ABP in high-fat–fed rabbits; however, receptor blockade for leptin but not insulin reduces renal SNA.[70]

The sympathoexcitatory actions of leptin and insulin are mediated by two distinct neuronal populations in the hypothalamic arcuate nucleus (Fig. 2). First, injection of leptin or insulin into the arcuate nucleus (location of proopiomelanocortin and agouti related peptide / neuropeptide Y neurons) increases SNA and/or ABP.[71,72] Second, deletion of leptin receptors[73] or neutralization of insulin via anti-insulin affibody[71] within the arcuate nucleus attenuates the sympathoexcitatory responses. Third, deletion of leptin receptors in the arcuate nucleus lowers ABP in diet-induced obese mice.[73] Downstream pathways likely involve the melanocortin system as pharmacologic blockade of central melanocortin receptors or deletion of melanocortin-4 receptors attenuates acute and chronic sympathoexcitatory effects.[66,74–76] Selective deletion of leptin receptors on proopiomelanocortin neurons lowers ABP and prevents leptin-induced hypertension.[77] The latter effects are replicated by interruption of leptin-associated signalling in arcuate and/or proopiomelanocortin neurons such as Src homology-2 tyrosine phosphatase, signal transducer and activator of transcription 3, insulin receptor substrate-2, and mammalian target of rapamycin (see the papers by Lim et al.[58] and do Carmo et al.[59] for review). Leptin and insulin may also act in multiple hypothalamic nuclei including the ventromedial or dorsomedial nuclei, the subfornical organ, hypothalamic paraventricular nucleus, and rostral ventrolateral medulla to increase SNA (see the papers by Lim et al.[58] and do Carmo et al.[59] for review). A parallel neuropeptide Y pathway may also contribute to leptin and insulin-induced sympathoexcitation.[78,79]

Sensitization of Autonomic Pathways to Produce Hypertension

Hypertension likely results from the combination of predisposing prior experiences, environmental factors, and genetic backgrounds. Recent evidence suggests that autonomic circuits can be sensitized by prior exposures to stimuli that subsequently alter future

cardiovascular responses.[80] For example, a 1-week subpressor AngII infusion followed by a 1-week washout produced exaggerated hypertensive responses to a second infusion of AngII.[81] Central administration of AngII produced a similar sensitization effect that was prevented by brain AngII-receptor blockade.[81] In addition, aldosterone,[82] high-fat diet,[83] leptin,[84] and tumour necrosis-factor-alpha[83] can also sensitize the hypertensive effect of a subsequent AngII infusion. Importantly, these effects are not specific to AngII-induced hypertension as prior exposures can exaggerate hypertensive effects of 2% NaCl loading.[85] Within the brain, the mechanisms for autonomic circuit sensitization may be mediated by the brain renin-angiotensin-aldosterone system, N-methyl-D-aspartate receptor function, changes in cellular excitability via growth factors (ie, brain-derived neurotropic growth factor), and transcription factors.[80] Notably, the prior discussion suggested that dietary salt intake "sensitizes" autonomic networks to a variety of inputs. A key difference between the two paradigms is the timing of the manipulations. As described above, various sympathetic reflexes were assessed during chronic salt loading. Here, the two stimuli are separated by time. Either situation produces exaggerated neurogenic cardiovascular responses to the second stimulus. Although the molecular mechanism(s) still need to be defined, the relevance of this paradigm is evident in considering life experiences that may impact the development of hypertension.

Therapeutic Advances to Treat Hypertension That Target the Sympathetic Nervous System

Hypertension increases the risk for adverse cardiovascular events.[86] Although traditional lifestyle modifications and pharmacotherapies effectively reduce ABP, a significant proportion of hypertensive individuals remain uncontrolled due to treatment nonadherence or resistant hypertension.[87,88] This population is associated with elevated or inappropriate levels of SNA.[2,87,88] For this reason, novel adjunctive therapies have been developed. Here, we briefly discuss two advancements to reduce ABP through modulation of the sympathetic nervous system.

Renal nerves and renal denervation

Several, but not all, models of experimental hypertension are associated with elevated renal SNA, and renal denervation has been repeatedly reported to lower ABP in these particular models (see the papers by Lohmeier and Hall,[89] Kiuchi et al.,[90] and Osborn and Foss[91] for review). Previous and ongoing clinical trials use various technology-based platforms (radio-frequency ablation, ultrasound energy deliver, vascular brachytherapy, and chemical ablation) to denervate renal nerves and lower ABP in human subject populations (reviewed elsewhere[89,90]). The majority of clinical trials report a reduction in systolic of approximately 6–9 mm Hg for 24-hour ABP and approximately 11–16 mm Hg for office ABP measurements after sham group and baseline adjustments.[89,90]

Renal nerves are composed of efferent (sympathetic) and afferent (sensory) fibres that coordinate renal function, central haemodynamics, and ABP (Fig. 3). Renal efferent nerves increase renin secretion, promote tubular sodium reabsorption, and regulate renal blood flow.[92] These three functions are proposed to underlie the antihypertensive effects of renal

nerve denervation.[91,93,94] Alternatively, stimulation of renal afferent fibres in animals increases ABP,[95–97] and renal afferent nerve activity is elevated in deoxycorticosterone-salt rats[36] and renovascular hypertensive mice.[97] In these models, dorsal rhizotomy[98,99] or selective chemical ablation of renal afferent fibres reduces ABP to the same extent as total renal denervation.[97] Importantly, renal afferent denervation does not always lower ABP in a model where total renal denervation is effective.[89,100] In human studies, renal denervation has been reported to lower muscle SNA[101–103] and plasma glucose,[104,105] and reduce cardiac arrhythmias,[106] thereby supporting a potential role for a neurohumoral signal originating from the kidney. Renal afferent fibres densely innervate the pelvic wall, renal vasculature, and tubules,[107,108] and respond to both mechano- and chemosensitive stimuli (Fig. 3). These neurons contain calcitonin gene-related peptide and substance P,[109] but the neurochemical profiles have not been linked to sensory modalities and haemodynamic responses. Whether neurochemically distinct populations of renal efferent or afferent neurons, brain pathways, or signalling mechanisms are useful to manipulate systemic haemodynamics in hypertension warrants future investigation.

Major obstacles regarding the clinical applicability of renal denervation are assessment of the degree of denervation and identification of patient cohorts who effectively respond to denervation therapy. First, there is currently no intraoperative validation measurement to test the degree of denervation after adjunctive ablation. Outcome measurements largely rely on follow-up ABP measurements. Transvascular pacing of the aorticorenal ganglion,[110] renal norepinephrine spillover measurements,[111] and guided intraoperative renal nerve stimulation[112,113] have emerged as potential solutions to: (1) test the degree of renal denervation after ablation and (2) improve denervation efficacy by anatomically mapping renal arteries for neurally innervated regions. Second, a subset of experimental hypertension models have elevated or inappropriate levels of renal SNA. Currently, there is no routine or reliable technique to assess renal SNA in clinical practice. Thus, the failure of renal denervation to lower ABP in experimental or human hypertension should not be interpreted as a lack of sympathetic hyperactivity, but rather a function of hypertension etiology. In fact, celiac ganglionectomy has recently been shown to reduce ABP in experimental models associated with normal or reduced renal SNA.[9,35,114,115]

Baroreceptors and chronic baroactivation

Arterial baroreceptors provide a continuous ABP signal to the brain through mechanosensitive sensory endings embedded mainly in the aortic arch or carotid sinus[116–118] (Fig. 4). These afferent fibres (composed of A and C types with distinct properties) travel through the carotid sinus and aortic depressor nerve, project to the brainstem via IXth and Xth cranial nerves, and synapse on second-order sensory neurons in the nuclei of the solitary tracts. Increased afferent activity due to an elevated ABP causes a reflexive decrease in ABP that reduces SNA directed to the vasculature and heart (thereby decreasing total peripheral resistance and cardiac output) and increases parasympathetic drive to the heart (thereby decreasing cardiac output). There is still uncertainty regarding the mechanosensitive transduction mechanisms[116] and how such mechanisms respond to chronic disease states. Although baroreceptors likely adapt to chronic changes, referred to as

baroreceptor resetting, how much baroreflex resetting occurs or can be attributed to peripheral vs central processing remains unclear.[116–118]

Multiple clinical trials have reported that chronic electrical stimulation of carotid baroreceptor afferent nerves lowers ABP (see the paper by Lohmeier and Hall[89] for review) and is supported by experimental work that showed sustained reductions in SNA to reduce ABP.[89] Moreover, chronic bilateral stimulation of baroreceptor afferent nerves in normotensive dogs decreased ABP by 20 mm Hg over 3 weeks and reduced plasma norepinephrine levels and norepinephrine spillover.[119,120] Sustained reductions in ABP were similarly obtained in a high-fat model of obesity-induced hypertension, but not AngII-induced hypertension.[121,122] Why is there a differential effect of carotid baroactivation between models, and could this identify patient populations that respond to such treatments? Lohmeier et al. suggest that the lack of a sustained response in AngII hypertension is consistent with a lower level of renal SNA.[89,121] Although this may explain reduced baroactivation responses, it does not fully explain why ABP reductions are not sustained during AngII-hypertension compared with obesity-induced hypertension and chronic baroactivation, and may reflect how SNA is differentially regulated. Nonetheless, these observations are important as the therapeutic efficacy may be variable and dependent on the etiology of the hypertension.

An interesting observation from both clinical and experimental studies is the rapid increase in ABP when stimulators are turned off. Clearly, chronic activation of carotid afferents suppresses ABP. This raises interesting questions regarding the synaptic integration and processing of baroreceptor inputs. For example, how are inputs from the aortic depressor nerve and the electrically stimulated carotid sinus afferents integrated within the brainstem? How are the synaptic dynamics of A- vs C-fibres impacted? Although questions remain, the clinical and experimental work of carotid stimulation to reduce ABP again highlights the sympathetic nervous system as a potential therapeutic target for the treatment of hypertension.

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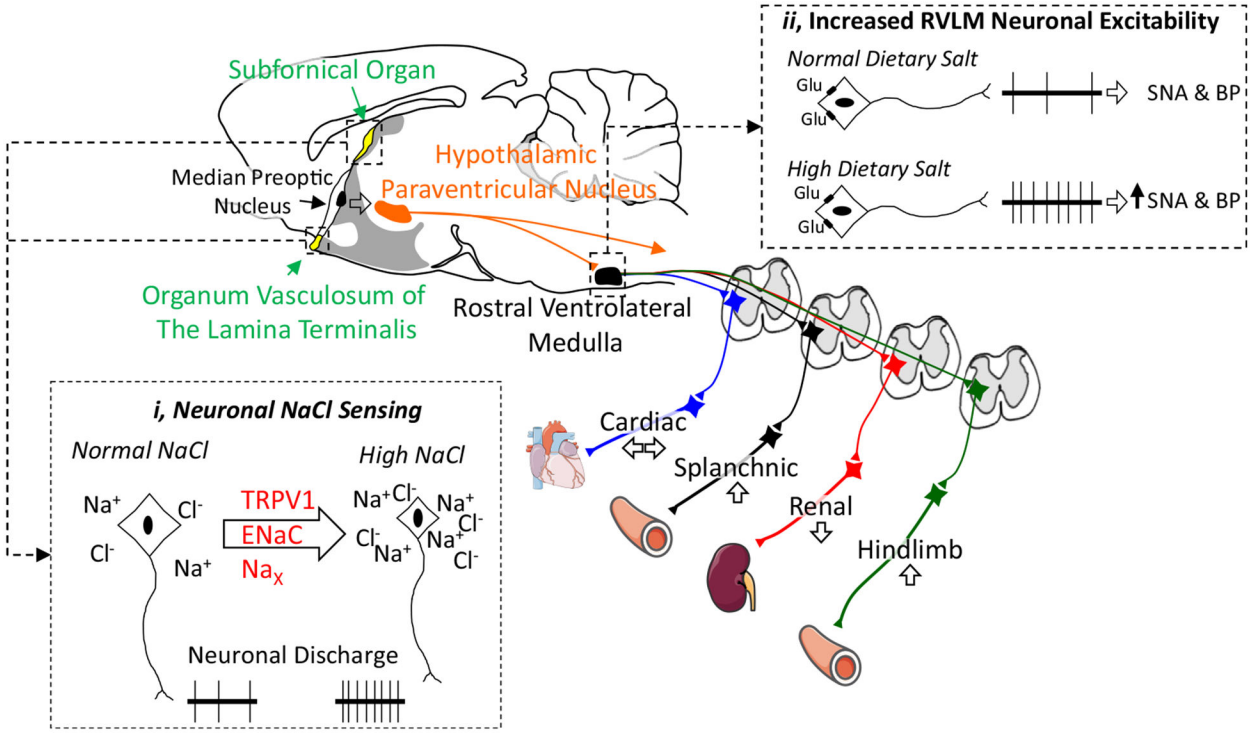

Figure 1.

Dietary salt alters autonomic function by excitation of NaCl-sensing neurons in the lamina terminalis or increasing gain/excitability of bulbospinal neurons in the rostral ventrolateral medulla. Salt-sensitive hypertension is associated with increased sympathetic outflow to the splanchnic or hindlimb vasculature. A midsagittal section of the rodent brain illustrates key autonomic centres involved in salt-sensitive hypertension. (**i**) Neurons in the organum vasculosum of the lamina terminalis and subfornical organ sense changes in extracellular NaCl to increase sympathetic nerve activity. Potential NaCl-sensing mechanisms include an N-terminal variant of the transient receptor potential cation channel subfamily V member 1 (TRPV1), the epithelial sodium channel (ENaC), and the Na_x channel. (**ii**) Dietary salt also increases the excitability or gain of bulbospinal sympathetic neurons of the rostral ventrolateral medulla. Thus, glutamatergic (or GABAergic) input onto RVLM neurons results in an exaggerated discharge and change in sympathetic nerve activity. BP, blood pressure; RVLM, rostral ventrolateral medulla; SNA, sympathetic nerve activity. Adapted from Servier Medical Art by Servier licensed under a Creative Commons Attribution 3.0 Unported License (https://smart.servier.com).

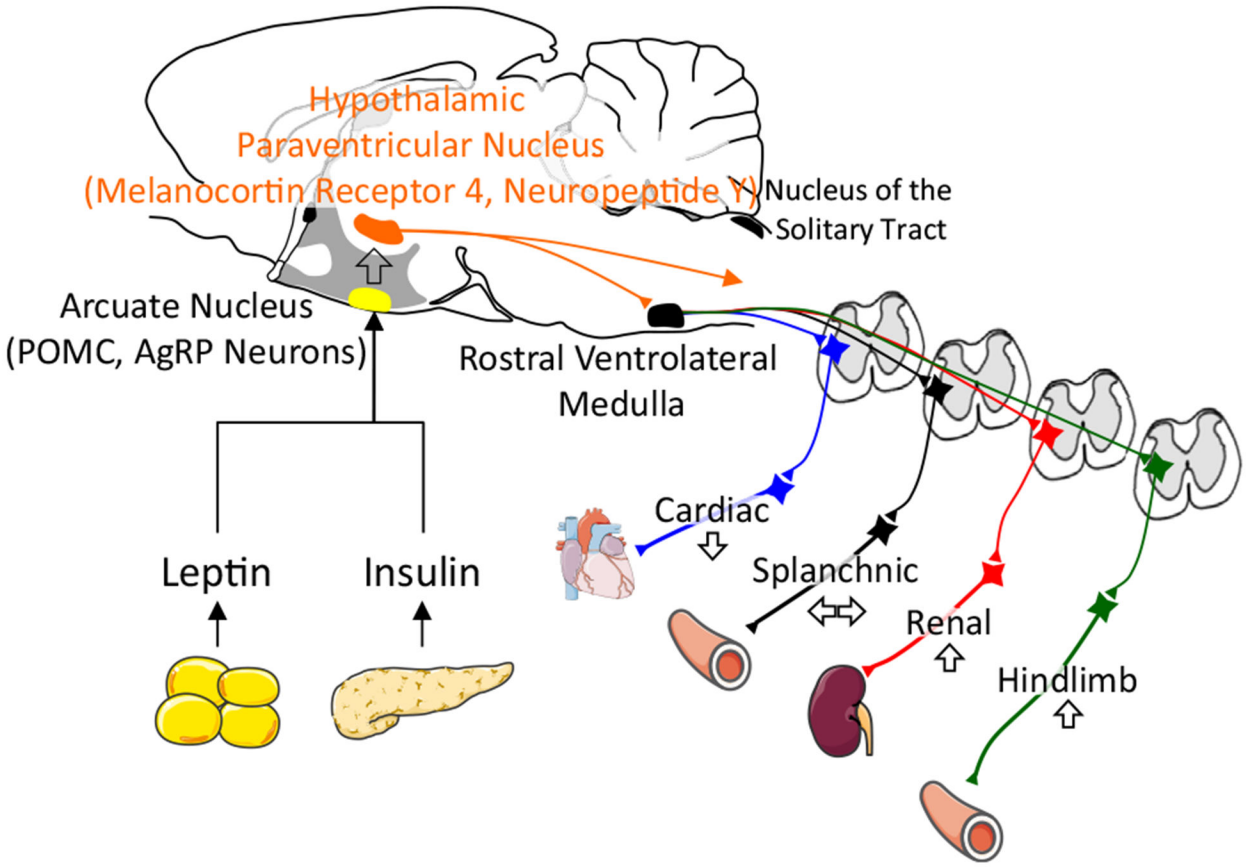

Figure 2.

Model of sympathoexcitation in obesity-induced hypertension. Adipokines such as leptin and insulin act through proopiomelanocortin (POMC) or agouti related peptide/neuropeptide Y (AgRP) neurons in the arcuate nucleus to activate downstream pathways through the hypothalamic paraventricular nucleus and rostral ventrolateral medulla to increase sympathetic nerve activity to the kidney and hindlimb vasculature. Adapted from Servier Medical Art by Servier licensed under a Creative Commons Attribution 3.0 Unported License (https://smart.servier.com).

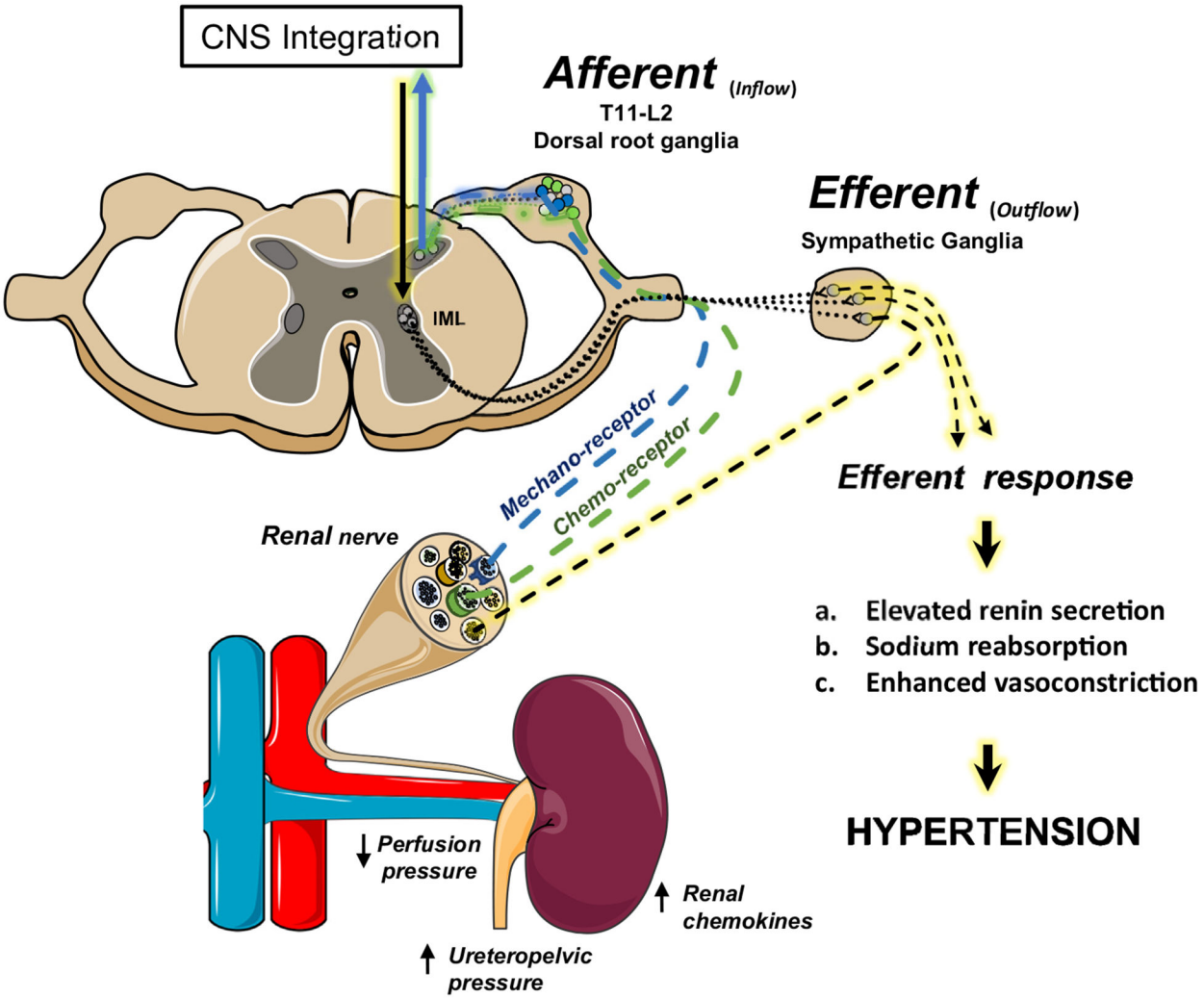

Figure 3.

Renal efferent and/or afferent fibres contribute to hypertension. Sympathetic efferent nerves increase renin secretion, promote tubular sodium reabsorption, and regulate renal blood flow. Renal sensory nerves are activated by altered renal perfusion pressure or accumulation of parenchymal chemokines and project through the dorsal root ganglion to the central nervous system (CNS). Adjunctive renal nerve ablation interrupts both afferent sensory responses and efferent signals crucial for regulating the renin-angiotensin-aldosterone system, fluid-electrolyte balance, and peripheral haemodynamics. IML, intermediolateral cell column. Adapted from Servier Medical Art by Servier licensed under a Creative Commons Attribution 3.0 Unported License (https://smart.servier.com).

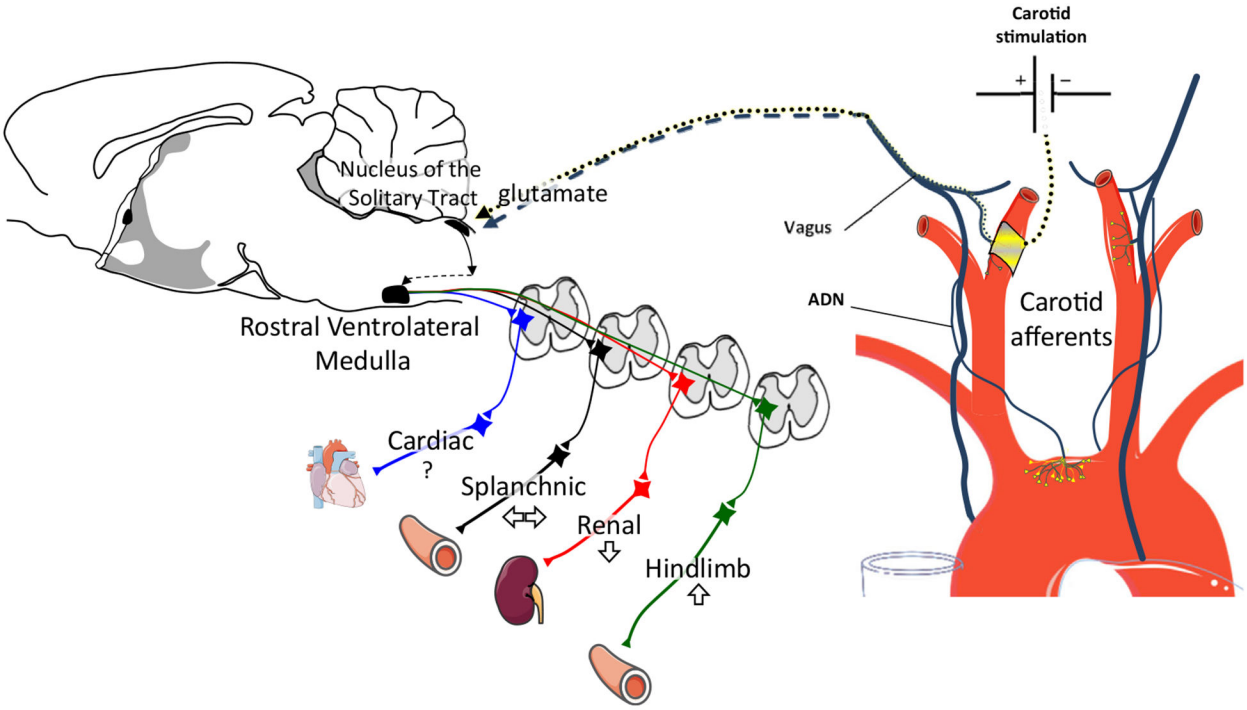

Figure 4.

Carotid baroactivation lowers ABP. Chronic electrical stimulation of carotid afferent fibres produces a renal sympathoinhibition and reduces hypertension in some but not all experimental models of hypertension. The chronic activation of carotid afferent fibres likely activates a multisynaptic pathway in the hindbrain to increase GABAergic-mediated inhibition of bulbospinal neurons in the rostral ventrolateral medulla. How the elevated activity of carotid afferents due to the electrical stimulation is integrated with aortic baroreceptor afferents (which are not electrically stimulated) to produce a sustained decrease in sympathetic nerve activity and ABP remains unknown. ABP, arterial blood pressure; ADN, aortic depressor nerve. Adapted from Servier Medical Art by Servier licensed under a Creative Commons Attribution 3.0 Unported License (https://smart.servier.com).