

Recent Advances in Neurogenic Hypertension Dietary Salt, Obesity, and Inflammation

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Neurogenic hypertension has been a fixture in the hypertension literature for well over half a century. Early reports documented an increase in arterial blood pressure (ABP) after manipulation of baroreceptor afferent nerve signaling, so the hypertension was clearly of neural origin. Today, neurogenic hypertension often refers to a sympathetically driven increase in ABP.¹ However, it could also refer to increased ABP caused by hormonal outputs of the brain or even any form of hypertension that involves neural signaling. Neurogenic hypertension applies whether the true origin of the hypertension is neural (ie, the primary underlying issue is in the brain or in afferent or efferent nerves) or the origin is non-neural but results in neurally mediated increase in ABP. This is a distinction worth making, as the causative factors are quite distinct. Indeed, the term neurogenic hypertension may encompass too much and relate forms of hypertension that share little in terms of pathogenic mechanism or common mechanistic output.

Even if one considers a limited definition of neurogenic hypertension as hypertension resulting from increased sympathetic drive to the cardiovascular system, this could result from an increased activity (or increased relative normal for the given physiological conditions) of different sympathetic nerves with different targets (ie, the sympathetic signature).² Yet, what factor(s) increase sympathetic nerve activity (SNA) or enhance neurotransmitter release from sympathetic terminals? If, for example, a circulating substance derived from a certain tissue acted on the brain (or afferent or efferent neurons) to produce a pattern of sympathetic outflow resulting in hypertension, would the hypertension be neurogenic (ie, of neural origin) or neurally mediated hypertension?

Nonetheless, primary alterations in neural function can result in hypertension, that is, true neurogenic hypertension. Indeed, several recent advances in understanding central neural control of cardiovascular function have focused on hypertension resulting from specific manipulations in the central nervous system of experimental animals. More typically, however, the recent advances have been in understanding neural changes that may underlie different experimental models of hypertension and how interfering with those neural signals can lower ABP. As noted below, many recent reports apply this approach and shed light on how targeting the brain can be used to treat hypertension. Below, we highlight some recent

advances related to neurogenic hypertension, fitting these into this framework. In particular, we focus on recent reports providing new insight into the neural mediation of hypertension associated with high dietary salt intake, obesity, and inflammatory states. We acknowledge several other factors, such as the brain renin–angiotensin system,³ renal denervation,⁴ and altered respiratory–sympathetic coupling,⁵ that play important roles but were recently reviewed and lie outside the scope of this brief update.

Dietary Salt

Excess dietary salt intake is a major contributing factor to the pathogenesis of hypertension and may exert multiple actions to affect the regulation of SNA and ABP. For example, high dietary salt elevates plasma and cerebrospinal fluid NaCl concentrations ≈ 3 to 6 mmol/L in both experimental models of salt-sensitive hypertension and salt-sensitive humans to elevate SNA and ABP.⁶ Historically, a high salt diet does not affect plasma electrolytes, but the majority, if not all of these measurements, are performed in fasted subjects which likely does not accurately reflect daily electrolyte values. Consistent with this notion, acute and chronic intracerebroventricular infusion of hypertonic NaCl produces physiological changes in NaCl concentrations and concomitant rise in ABP.^{7–10} Interestingly, acute infusion of hypertonic NaCl across many species elicits a differential sympathetic response characterized by an increase in lumbar (or muscle SNA in humans) and adrenal SNA,^{7,11} no change in cardiac or splanchnic SNA,^{7,11,12} and decrease in renal SNA.^{7,11,12}

Changes in extracellular NaCl levels or osmolality are detected by specialized neurons located in 2 circumventricular organs—the organum vasculosum of the lamina terminalis or subfornical organ (SFO).^{13,14} These structures are juxtaposed to the third ventricle and lack a complete blood–brain barrier thereby serving as a sensory interface between the circulation, cerebrospinal fluid, and central nervous system. Organum vasculosum of the lamina terminalis neurons intrinsically sense changes in extracellular NaCl concentrations within physiological ranges (2.5–10 mmol/L).¹¹ Direct stimulation of organum vasculosum of the lamina terminalis neurons with injection of hypertonic NaCl increases lumbar SNA, adrenal SNA, and ABP in a concentration-dependent

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manner.¹¹ Importantly, inhibition of organum vasculosum of the lamina terminalis neurons largely attenuates sympathoexcitatory responses to central infusion of hypertonic NaCl.¹¹ Central hypernatremia increases glutamatergic activation of bulbospinal neurons in the rostral ventrolateral medulla (RVLM) to increase SNA.⁷ Interestingly, central NaCl stimulation produced 3 divergent responses in RVLM neurons, including an increase in discharge, no change, or a decrease in cell discharge.⁷ The complexity of the RVLM responses likely reflects the sympathetic signature associated with changes in plasma or cerebrospinal fluid NaCl concentrations. A major caveat of the above studies is that the manipulations in NaCl concentrations were acute. Yet, blockade of excitatory amino receptors or angiotensin type I receptors in the RVLM reduces ABP in Dahl salt-sensitive rats fed a high salt diet.^{15,16} Future investigations need to define the impact of chronic elevation in NaCl concentrations on the level of SNA across different end organs, the activity of NaCl-sensing neurons, and how such neurons sense NaCl.¹⁷

Dietary salt intake also alters the excitability of hypothalamic vasopressin (VP) neurons to exaggerate VP secretion or regulate SNA. Neurons maintain low intracellular chloride concentrations through Cl⁻ influx via NKCC1 (sodium-potassium-2-chloride transporter 1) and efflux via KCC2 (potassium-chloride-cotransporter 2).¹⁸ Excess salt intake shifts the E_{Cl⁻} to a more positive or depolarized value—the net effect is a loss of GABAergic-mediated inhibition. For example, VP neurons of deoxycorticosterone-salt hypertensive rats display a depolarized E_{Cl⁻}, a GABAergic excitation of VP neurons and pressor response, and a reversal of baroreceptor-mediated inhibition to excitation of VP neuronal activity.^{19,20} Blockade of brain NKCC1 with bumetanide attenuates the altered E_{Cl⁻} and lowers ABP in deoxycorticosterone-salt hypertension.^{19,20} Chronic salt loading via access to 2% NaCl also shifts E_{Cl⁻} of VP neurons to a depolarized value through a reduction in KCC2 expression via brain-derived neurotrophic factor.²¹ The net effect is a loss of baroreceptor-mediated inhibition of VP neurons and hypertension, at least partly, mediated by circulating VP levels. Finally, VP may also regulate SNA through local release within the hypothalamic paraventricular nucleus (PVH).²² Blockade of V1a receptors in the PVH decreases lumbar SNA and ABP after chronic salt loading.²³

Although a high salt diet does not raise ABP in laboratory animals (classically known as salt resistance), excess salt intake exaggerates sympathoexcitatory and sympathoinhibitory responses evoked from the RVLM.^{24–27} These responses are functionally significant as salt-resistant rats fed a high salt diet display exaggerated SNA and ABP responses to the activation of sciatic afferents,²⁸ exercise,²⁹ stimulation of the aortic depressor nerve or vagal afferents,²⁸ volume expansion,²⁸ and intracerebroventricular infusion of NaCl.²⁸ These effects occur independently of changes in baseline SNA or mean ABP.²⁸ Interestingly, a high salt diet increases ABP variability in salt-resistant animals.²⁸ This observation has significant clinical ramifications as increased ABP variability is a risk factor for end-organ damage, development of CV disease, and predictor for future adverse CV events.^{30,31} Collectively, these data suggest that dietary salt may adversely affect the gain of sympathetic regulatory networks. Future experiments need to

identify the mechanism(s) by which this occurs and establish whether dietary salt similarly impacts sympathetic regulation in humans.

Obesity

The sympathetic nervous system contributes to obesity-related hypertension.³² Two recent studies in animals provide concrete evidence for elevated SNA using telemetry to perform chronic sympathetic nerve recordings. Female rats fed a high-caloric, cafeteria-style diet for 15 days display an increase in lumbar SNA as reflected by a greater burst amplitude but not frequency.³³ In addition, high-fat feeding in rabbits increases renal SNA³⁴ through a greater burst amplitude.³⁵ These direct and chronic recordings of SNA corroborate the earlier findings using indirect indices of SNA. However, the sympathetic signature of obesity-related hypertension, as suggested by studies on a variety of species, includes elevated renal and lumbar (or muscle) SNA but decrease in cardiac SNA frequency^{33–35} (reviewed elsewhere³²). The sympathoexcitation in obesity results from multiple factors, including leptin and insulin. Intracerebroventricular infusion of leptin or insulin receptor antagonists lowers ABP in high-fat-fed rabbits.³⁶ Leptin, but not insulin, receptor blockade reduces renal SNA.³⁶ Moreover, deletion of leptin receptors on specific hypothalamic neuronal populations using transgenic mice also prevents leptin-induced hypertension.^{37,38} Parallel experiments with knockdown or deletion of insulin receptors and the impact on obesity-induced hypertension have not yet been performed.

The sympathoexcitatory actions of leptin and insulin are mediated by activation of melanocortin but inhibition of neuropeptide Y pathways. The central actions of leptin and insulin largely originate in the arcuate nucleus: (1) injection of leptin or insulin into the arcuate nucleus (location of proopiomelanocortin and neuropeptide Y neurons) increases SNA and ABP,^{39,40} (2) deletion of leptin receptors via Cre-lox³⁷ or neutralization of insulin via anti-insulin affibody³⁹ within the arcuate nucleus attenuates the sympathoexcitatory responses, and (3) deletion of leptin receptors in the arcuate nucleus lowers ABP in diet-induced obese mice.³⁷ Furthermore, leptin and insulin act through the melanocortin pathway as pharmacological blockade of central melanocortin receptors or deletion of melanocortin-4 receptors attenuates these acute and chronic sympathoexcitatory effects.^{35,41–43} Selective deletion of leptin receptors on proopiomelanocortin neurons lowers ABP and prevents leptin-induced hypertension.³⁸ The latter effects are also produced by the interruption of leptin-associated signaling mechanisms in arcuate and proopiomelanocortin neurons such as Src homology-2 tyrosine phosphatase,⁴⁴ signal transducer and activator of transcription 3,⁴⁵ insulin receptor substrate-2,⁴⁶ and mammalian target of rapamycin.⁴⁷ Leptin may also act in multiple other hypothalamic nuclei, including the ventromedial³⁵ or dorsomedial⁴⁸ nuclei and the SFO⁴⁹ to increase SNA.

A parallel neuropeptide Y pathway also contributes to leptin- and insulin-induced sympathoexcitation. Blockade of neuropeptide Y receptors in the PVH raises SNA and ABP,⁵⁰ and PVH injection of neuropeptide Y suppresses the sympathoexcitatory response to insulin.⁵¹ Future studies are needed

to address the contribution of neuropeptide Y to obesity-related hypertension.

Neural–Immune Interactions in Hypertension

Peripheral immune events and inflammation elevate SNA and contribute to neurally mediated hypertension. For example, intravenous or intracranial carotid artery injection of proinflammatory cytokines TNF- α (tumor necrosis factor- α) or IL-1 β (interleukin-1 β) increases renal SNA, heart rate, and ABP,⁵² and lesion of the SFO attenuates these responses.⁵² Microinjection of either TNF- α or IL-1 β into the SFO increases renal SNA and ABP. SFO pretreatment with either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker attenuates these responses.⁵³ Furthermore, injection of TNF- α or IL-1 β into the SFO increases expression of inflammatory signaling pathways in PVH,⁵³ and these signaling pathways in the PVH can increase ABP.^{54,55} Collectively, these observations suggest that proinflammatory cytokines act in the SFO via renin–angiotensin system to activate a downstream pathway to the PVH and elevate SNA and ABP.

Hypertension also activates microglia cells to further exacerbate the level of ABP. Angiotensin II–induced hypertension increases microglial activation in the PVH,⁵⁶ and inhibition of microglia with minocycline markedly attenuates this hypertension.⁵⁶ Pretreatment with activated microglia enhances the pressor response to central injection of angiotensin II,⁵⁷ whereas targeted deletion of brain microglia reduces ABP in both angiotensin II–induced and L-NAME (*N*-nitroarginine methyl ester)–induced hypertension.⁵⁷ Furthermore, ablation of bone marrow populations in the spontaneous hypertensive rat (SHR) and reconstitution using Wistar-Kyoto bone marrow transplants attenuates SHR hypertension and microglial activation in the PVH.⁵⁸ However, plasma norepinephrine levels are similar between SHR/Wistar-Kyoto versus SHR rats with SHR bone marrow. This investigation raises the question: does central or peripheral immune activation initiate a neurogenic contribution to hypertension?

Sensitization and Neuroplasticity in Hypertension

Essential hypertension is a complex disease that likely originates from a constellation of contributing factors summated over time. Rather than a single stimulus or challenge, hypertension may result from the integration of previous challenges or experiences with current environmental factors but temporally separated. These previous experiences or exposures impact how the brain responds to subsequent stimuli. For example, in 1 study, rats received saline or a subpressor dose of angiotensin II (week 1), no infusion or rest period (week 2), and then a slow pressor infusion of angiotensin II (weeks 3–4).⁵⁹ The angiotensin II–induced hypertension was much greater in rats initially treated with a subpressor dose of angiotensin II versus saline. This is a neurally mediated effect as pretreatment with central administration of angiotensin II also enhances angiotensin II–induced hypertension. Intracerebroventricular administration of angiotensin receptor blocker attenuates these effects. Subsequent studies show that angiotensin II–induced hypertension is also exacerbated by pre-exposure with aldosterone,⁶⁰ high-fat diet,⁶¹ leptin,⁶² and

TNF- α .⁶¹ Furthermore, pretreatment with a subpressor angiotensin II or aldosterone exaggerates hypertension induced by chronic 2% NaCl loading.⁶³ Several potential candidates have been implicated in the central sensitization, including the brain renin–angiotensin–aldosterone system, N-methyl-D-aspartate receptor function, changes in cellular excitability via growth factors (ie, brain-derived neurotrophic growth factor), and transcription factors.⁶⁴ Although the molecular mechanism(s) still need to be defined, the innovative aspect of this paradigm is the previous life experiences or exposures may impact the development of hypertension.

Summary

Neurally mediated hypertension results from a dysregulation of sympathetic and neuroendocrine mechanisms to increase ABP. Multiple factors may exert multiple central effects to alter neural circuits and produce unique sympathetic signatures and elevate ABP. In this brief review, we have discussed novel observations about 3 contributing factors: dietary salt intake, obesity, and inflammation. However, the interaction among these and other factors is likely much more complex; recent studies suggest a previous exposure to 1 stimulus may sensitize the response to a subsequent hypertensive stimulus. Insight into the central mechanisms by which these factors selectively alter SNA or cooperatively interact to impact hypertension may represent a platform for novel therapeutic treatment strategies.

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Disclosures

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