

Circulating Angiotensin II and Dietary Salt: Converging Signals for Neurogenic Hypertension

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Circulating angiotensin II (Ang II) combined with high salt intake increases sympathetic nerve activity (SNA) in some forms of hypertension. Ang II-induced increases in SNA are modest, delayed, and specific to certain vascular beds. The brain targets for circulating Ang II are neurons in the area postrema (AP), subfornical organ (SFO), and possibly other circumventricular organs. Ang II signaling is integrated with sodium-sensitive neurons in the SFO and/or organum vasculosum of the lamina terminalis (OVLT) and drives sympathetic premotor neurons in the rostral ventrolateral medulla (RVLM) via the paraventricular nucleus (PVN). It is likely that, over time, new patterns of gene expression emerge within neurons of the SFO-PVN-RVLM pathway that transform their signaling properties. This transformation is critical in maintaining increased SNA. Identification of a novel gene supporting this process may provide new targets for treatment of neurogenic hypertension.

Introduction

In this paper, we present the hypothesis that a powerful link exists between circulating angiotensin II (Ang II) and the sympathetic nervous system in some forms of hypertension. Figure 1 summarizes our hypothesis, which is explained in detail in subsequent sections. We propose that moderate elevations in Ang II concentrations in blood increase mean arterial pressure (MAP) predominantly through indirect mechanisms. The primary and most important of the indirect mechanisms involve an increase in sympathetic nerve activity (SNA). This increase in SNA is modest in magni-

tude, delayed in time, specific to certain cardiovascular regions, and potentiated by a high-salt diet. Sympathetic activation by circulating Ang II occurs as a result of its actions on the brain. Specific brain targets are neurons in the area postrema (AP), subfornical organ (SFO), and possibly other circumventricular organs (CVOs). These neurons link to the major descending bulbospinal pathways in the rostral ventrolateral medulla (RVLM) by way of hypothalamic (eg, paraventricular nucleus [PVN]) and brainstem circuits whose anatomical and neurochemical organization remain to be fully defined. Activation of RVLM neurons leads in the short term to regionally specific increases in SNA that are strongly modulated by arterial and cardiopulmonary baroreceptor and osmoreceptor (sodium sensor) activity. Sustained increases in SNA depend, in part, on time-dependent alterations in the pathways mediating both RVLM activation and peripheral afferent modulation. In addition, over time, new patterns of gene expression emerge within this neural circuitry that produce a fundamental transformation in its electrophysiological and/or signaling properties (neural plasticity) and this transformation is critical in maintaining increased SNA.

SNA in Human and Experimental Hypertension: Role of Circulating Ang II and Dietary Salt

Elevated SNA as an etiologic factor in human essential hypertension was once controversial, but is now widely accepted [1]. Difficulty with the idea derived in part from the following facts. Increased SNA is most clearly expressed in the early stages of hypertension development and less consistently as time passes. Furthermore, increased SNA does not occur equally in all tissues, and has a larger effect on MAP when it occurs in key organs [1]. Finally, a large number of physiological and environmental factors (eg, age, sex, race, diet, physical activity, and body weight) can influence SNA [1]. To understand hypertension, it is therefore critical to elucidate the details of time-dependent, region-specific regulation of SNA by

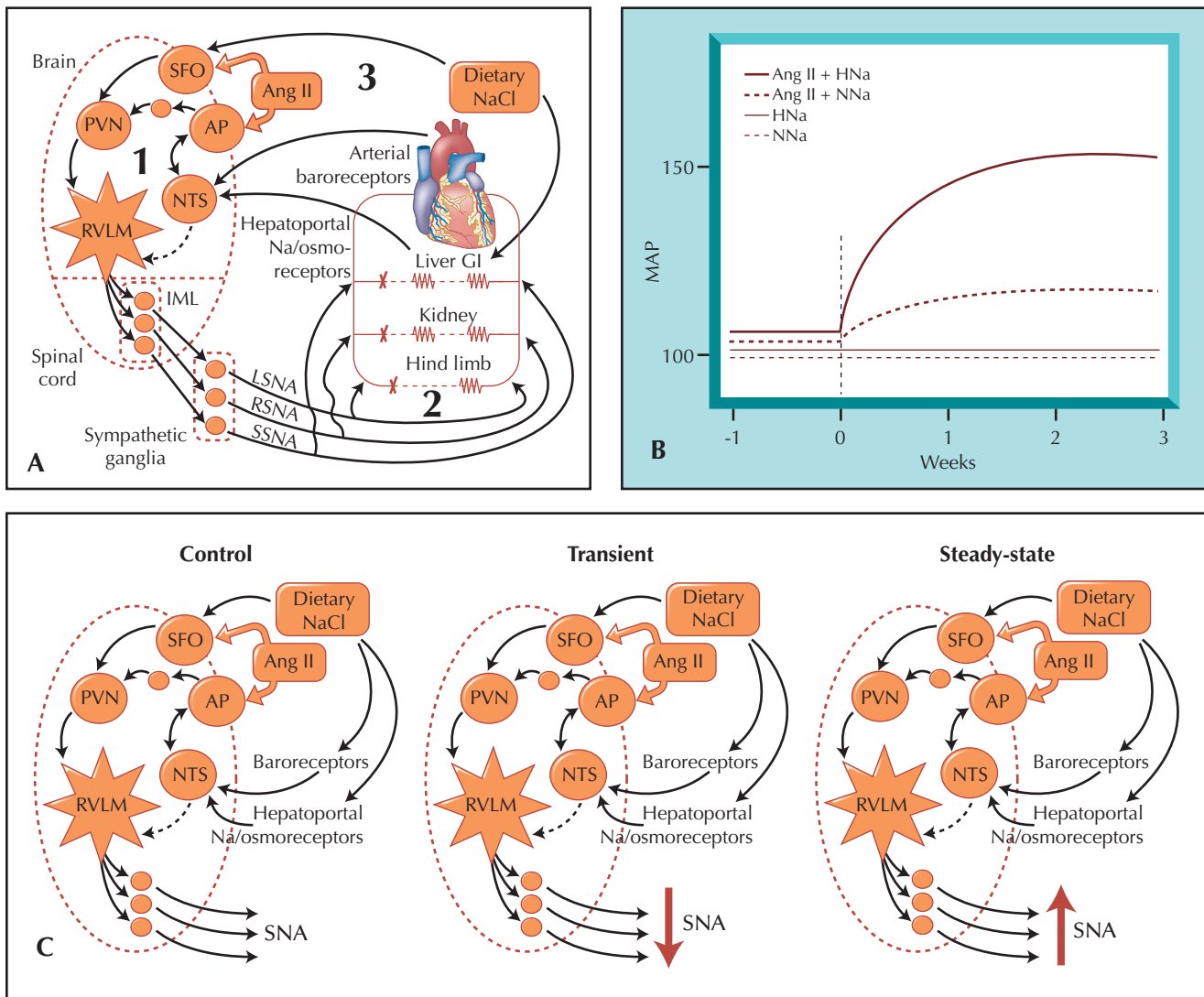


Figure 1. Stylized representation of the proposed central hypothesis. **A**, 1) Hypothesized central nervous system pathways involved in angiotensin II (Ang II)–salt-dependent hypertension. The inhibitory projection from the nucleus tractus solitarius via the caudal ventrolateral medulla is not shown for simplicity. 2) Interface between neural pathways and cardiovascular target organs. 3) Putative input pathways by which Ang II and dietary sodium chloride (salt; NaCl) influence neural control of the cardiovascular system. **B**, Hypothesized time-dependent interactions of circulating Ang II and dietary salt on sympathetic nerve activity (SNA) and mean arterial pressure (MAP) in animal models of Ang II–salt hypertension. *Dotted line* at Time 0 indicates administration of exogenous Ang II in Ang II + HNa and Ang II + NNa groups. **C**, Stylized pathways represent hypothesized changes in activity of central pathways over time in Ang II + HNa group. During the transient phase, MAP is increased by non-neural mechanisms and SNA actually may be decreased to some vascular beds by the arterial baroreceptor reflex. However, by steady-state phase, sustained elevation of Ang II activates hypothetical pathways that drive the RVLM and SNA. AP—area postrema; GI—gastrointestinal; HNa—high salt; IML—intermediolateral cell column; LSNA—lumbar SNA; NNa—normal salt; NTS—nucleus tractus solitarius; PVN—paraventricular nucleus; RSNA—renal SNA; RVLM—rostral ventrolateral medulla; SFO—subfornical organ; SSNA—splanchnic SNA.

well-known controllers (eg, baroreceptors and other afferents) and also by other less well-characterized factors (eg, circulating hormones). Although a wide range of peripheral and central inputs could be responsible for increased SNA in hypertension, this review focuses on just one, circulating Ang II.

The idea that Ang II increases SNA in humans is controversial [2]. The best evidence is probably in obesity-related hypertension [3•]. Nevertheless, acute intravenous infusion of Ang II increases muscle SNA as long as barore-

flex-mediated sympathoinhibition is prevented [4]. Studies in patients with chronic angiotensin-dependent renovascular hypertension generally have demonstrated sympathetic activation whose magnitude is correlated with circulating Ang II concentrations [5]. Furthermore, angiotensin-converting enzyme inhibitors [6] and angiotensin receptor blockers [7] tend to suppress SNA when used to lower MAP in hypertensive humans. The mechanisms linking circulating Ang II and SNA are not fully known. Because detailed mechanistic insights are often possible only from

laboratory studies, we direct most attention to work in experimental animals.

The literature supports the concept that Ang II mediates sympathoexcitation in many animal models of hypertension [4]. Sympathoexcitation by circulating Ang II was first demonstrated more than three decades ago, and details of the central pathways involved were subsequently elucidated by Ferrario [8]. Increased muscle SNA can be readily demonstrated during acute infusions of Ang II as long as baroreflex sympathoinhibition is prevented [9]. However, two traditional methods of determining the importance of increased SNA in hypertension caused by increased circulating Ang II yielded conflicting results. Chemical sympathectomy was reported both to have no effect [10] and to totally block [11] hypertension during Ang II infusion in rats. Plasma norepinephrine concentration was unchanged by chronic Ang II infusion in one study [12] and increased in another [13]. There is strong evidence, however, that baroreflexes modulate plasma norepinephrine (thus SNA) during chronic Ang II infusion [14]. Other methods of assessing sympathetic control of MAP consistently indicate increased net neurogenic pressor activity during Ang II infusion. Ganglion blockade, adrenergic receptor blockade, and centrally acting sympatholytic drugs all cause a much larger fall in MAP in Ang II-infused animals than in normotensive controls [4].

One likely explanation for the disparate results obtained in studies attempting to relate Ang II and SNA is that the magnitude of the sympathoexcitatory actions of Ang II are affected by other physiological conditions. One of these clearly seems to be the prevailing sodium chloride (salt) intake. We hypothesize that the magnitude of the sympathoexcitatory response to circulating Ang II is directly related to the level of dietary salt intake. For example, in one study chronic infusion of Ang II in rats did not increase plasma norepinephrine in rats with normal salt intake, but did so in rats with high salt intake [13]. The mechanisms whereby increased salt intake may exacerbate the sympathoexcitatory actions of circulating Ang II are described in a later section.

Increased SNA and Hypertension: Peripheral Mechanisms

One of the challenges in this field is the translation of data from acute neurophysiological studies in animals and humans to understanding the hemodynamic responses to SNA that lead to hypertension. Several questions remain unanswered. First, how are increases in SNA expressed hemodynamically during the initiation and maintenance phases of hypertension? Second, to what extent is SNA increased differentially to various vascular beds and what is the independent contribution of each vascular bed to the development of hypertension? Finally, if primary neurogenic vasoconstriction does lead to hypertension, what

are the relative contributions of changes in arteriolar (resistance) versus venous (capacitance) constriction?

Sympathetic nervous system activity and the temporal hemodynamic profile of hypertension

At any point in time, MAP is a function of the product of cardiac output (CO) and total peripheral resistance (TPR). The contribution of these two variables to the development and maintenance of hypertension has been studied, but their temporal relationship has not been resolved. Although it is generally accepted that the established phase of hypertension is associated with increased TPR and normal CO, the relationship of these variables during the early stages of hypertension is uncertain and several hemodynamic profiles have been reported [15,16]. One explanation for the variable hemodynamic patterns might be differential activation of SNA to various cardiovascular targets under different conditions. Although the hemodynamic mechanisms leading to hypertension and the relative contributions of SNA and blood volume regulation are still unresolved, most studies are consistent with at least three hemodynamic profiles.

Profile 1 is characterized by a primary increase in TPR that is sustained over time with no change in CO. Theoretically, this could result from an increase in arteriolar SNA, and hypertension under these conditions would not require blood volume expansion. In contrast, Profile 2 is initiated by a transient increase in CO and a delayed but sustained increase in TPR. This could be mediated by two distinct patterns of sympathetic activity. One is an increase in renal SNA resulting in blood volume expansion, increased CO, and (according to the whole-body autoregulation hypothesis) a steady-state increase in TPR with a return of CO and blood volume towards normal [17]. However, Profile 2 could also result from an increase in venous SNA increasing mean circulatory filling pressure and CO followed by an autoregulatory mediated increase in resistance. This would result in the same hemodynamic profile caused by increased renal SNA in the absence of an increase in "actual" blood volume but with an increase in "effective" blood volume. Although the transient cause-and-effect relationships are entirely different for Profiles 1 and 2, the steady-state hemodynamic "snapshot" is identical: increased TPR with near-normal blood volume and CO. Finally, Profile 3 is characterized by a primary and sustained increase in CO with no change in resistance. As in Profile 2, this could be mediated by increased renal or venous SNA but without subsequent autoregulatory mediated arteriolar constriction.

Relatively few studies have characterized the hemodynamic responses to the combination of Ang II and high salt intake in animals. In rats in which plasma Ang II was clamped at high levels, salt-induced hypertension was mediated entirely by an increase in CO, which is consistent with Profile 3. However, in this study MAP was normalized when salt intake was returned to control, and

this was mediated by a fall in TPR, whereas CO remained elevated [18]. It was concluded this vasodilatory response was mediated by a decrease of vasomotor SNA [18]. Another study of salt-dependent hypertension in dogs infused with a subpressor dose of Ang II was consistent with the theory of autoregulation (Profile 2) [19]. However, a subsequent study in dogs from the same laboratory showed that CO was also elevated by increased salt intake in controls and MAP remained constant as a result of systemic vasodilation [20]. These studies together suggest that salt loading increases CO similarly in control and Ang II-infused dogs, but that Ang II causes hypertension by attenuating the vasodilatory response to salt loading. Although the mechanism of impaired vasodilation in Ang II-infused dogs was not investigated, this response is consistent with an inappropriately high level of vasomotor SNA. Taken together, these animal studies [18–20] are consistent with the hypothesis that the hemodynamic profile of Ang II–salt hypertension is mediated in part by SNA regulation of vascular function.

Differential SNA regulation in hypertension: increased SNA is not uniformly distributed

A few investigations examined regional changes in SNA during chronic Ang II infusion. Kline et al. [21] found no change in norepinephrine turnover in heart, kidney, skeletal muscle, or intestine of the rat in response to Ang II, suggesting that Ang II did not alter SNA in these tissues. On the other hand, direct recording of splanchnic SNA in conscious rats [22] revealed a significant increase in SNA to that region during chronic Ang II infusion. There is, however, general agreement that renal SNA is decreased, at least during the early stages of Ang II infusion [23].

Studies using tissue norepinephrine spillover reveal substantial regional SNA heterogeneity in different subgroups of human hypertensives, with renal and muscle SNA consistently increased but SNA to the heart, skin, and other regions more variable [1]. Such heterogeneity in regional norepinephrine spillover has also been measured in animal models of hypertension [24]. This pattern of regional activation probably plays a critical part in determining the ultimate cardiovascular consequences of increased SNA.

Vascular capacitance versus arteriolar resistance in hypertension: modulation by SNA and Ang II

Although it has received relatively little research attention, vascular capacitance is strongly influenced by SNA, and is likely to be an important factor in the pathogenesis of hypertension. Vascular capacitance refers to the volume of blood contained in a vascular segment at a given distending pressure. The compliance of veins is many times higher than arteries, thus total vascular capacitance is largely synonymous with venous capacitance. The veins of the splanchnic organs hold the largest amount of blood (about 40% of total blood volume) and total vascular capacitance largely depends on vessels in this region [25]. Veins are

innervated by sympathetic vasoconstrictor fibers, with innervation especially dense in the splanchnic vascular bed. Thus, splanchnic veins and venules account for most of the active vascular capacitance responses in the circulation [26]. Consequently, increased splanchnic SNA causes a significant shift of blood towards the heart, increases diastolic filling, and thus increases CO [26]. Reduced vascular capacitance has been found consistently in humans with essential hypertension in both early and late phases [25]. This would be expected to redistribute blood stored in the splanchnic organs into the cardiothoracic circulation, and just such a “central” shift in blood volume is found early in the development of hypertension [27].

Acute infusion of Ang II increases mean circulatory filling pressure (MCFP; an index of venoconstriction and inversely related to vascular capacitance) in rats, in part via a neurogenic mechanism [28]. A recent study reported that chronic infusion of Ang II increases MCFP, but only in rats on a high-salt diet [29••]. This occurred without a measurable change in total blood volume, so the increased MCFP was due to reduced vascular capacitance (venoconstriction). Both the hypertension and the venoconstriction were fully reversed by ganglion blockade; thus, both were likely caused by sympathoexcitatory effects of Ang II [29••].

Central Neural Pathways Mediating Increased Peripheral SNA in Hypertension: Role of Ang II and Salt

The RVLM: key integrative site for regulating SNA and critical player in neurogenic hypertension

Many studies have documented the importance of the RVLM in cardiovascular regulation and the maintenance of MAP [30•,31]. Briefly, acute inhibition of RVLM neurons reduces MAP and SNA (at least in some nerves) to the same extent as cervical spinal transection or ganglionic blockade, suggesting that the RVLM is the sole area supporting basal SNA. More recent studies have shown that chronic alteration of the neurochemical milieu of the RVLM can produce sustained changes in MAP in normotensive and hypertensive rats [31]. A large body of evidence supports the presence of RVLM neurons providing an excitatory innervation of sympathetic preganglionic neurons. This RVLM-spinal projection is an essential link in the baroreceptor reflex, as well as other cardiovascular reflexes. The emerging picture is that many stimuli that elicit increases in MAP and SNA do so by increasing the activity of RVLM-spinal neurons that excite preganglionic sympathetic vasomotor neurons.

Data from several laboratories and in several models of hypertension support a role of the RVLM in maintaining the elevated MAP and SNA in hypertension [31]. For example, in spontaneously hypertensive rats (SHR) and Dahl salt-sensitive rats microinjection into the RVLM of antagonists of glutamate or angiotensin II type 1 (AT1) receptors decreases MAP to normotensive levels. Although

the role of the RVLM in Ang II–salt hypertension has not been investigated previously, work in other models suggests that the RVLM likely will play a critical role [4,31].

The RVLM also appears to be involved in the effects of increased dietary salt on cardiovascular regulation. In particular, it has been shown that the magnitude of cardiovascular responses elicited from the RVLM is directly related to the dietary salt intake [32], though cellular mechanisms of this response are not known.

Central neural circuits driving increased RVLM activity in hypertensive rats likely involve PVN

The neural inputs that support the tonic activity of RVLM vasomotor neurons in normotensive and hypertensive rats are largely unknown [30,31]. Recent studies in several models of hypertension support the hypothesis that stimulation of AT1 receptors in RVLM, driven by input from the PVN, supports the elevated MAP and SNA [31,33]. For example, in SHR (but not in normotensive rats) injection of an AT1 antagonist into the RVLM or injection of muscimol into PVN both decrease MAP, and one response occludes the other [31]. However, this is not the only RVLM input altered in this and other models of hypertension [31]. In addition to changes in the activity of RVLM inputs, changes in the responsiveness of the RVLM neurons themselves must also be considered. However, to date few studies have focused on the electrophysiological properties of RVLM neurons in hypertensive rats, and these studies have been contradictory [34,35].

Role of CVO in mediating Ang II–induced hypertension

Numerous studies suggest that Ang II enhances sympathetic pressor activity by its actions on the central nervous system, sympathetic ganglia, sympathetic nerve terminals, and the end organ [4]. However, growing evidence supports the idea that blood-borne Ang II increases SNA primarily by binding to AT1 receptors in two prominent CVOs, the AP in the hindbrain, and the SFO in the forebrain. This concept was initially supported by lesion of the anteroventral third ventricle (AV3V), which eliminates efferents from the SFO and ablates the median preoptic nucleus (MnPO) and organum vasculosum of the lamina terminalis (OVLT). AV3V lesion prevented and/or reversed renovascular hypertension in rats [36]. Similarly, it was shown that AP lesion attenuates the steady-state level of chronic Ang II hypertension in the rat, but does not affect MAP in the early phase [37]. This supports our hypothesis that the initial pressor response to Ang II–induced hypertension is not neurogenically mediated, while the later stages are.

Comparisons of the effects of lesions of the SFO (SFOX) on the response to exogenous Ang II are not as consistent as AP lesion (APX) studies, but this may be related to the time scale of these studies. An earlier report showed that SFOX did not alter the pressor response to Ang II during a 5-day infusion in conscious rats [38].

However, a more recent study has shown that the SFOX attenuated the steady-state hypertensive response to Ang II during longer periods of administration [39].

Ang II and Salt Synergism in the Central Nervous System: Cellular Mechanisms

According to our hypothesis and evidence cited above, elevated levels of circulating Ang II and dietary salt likely converge on similar populations of sympathetic regulatory neurons. Activation of these control neurons depends on sensory neurons residing mainly in CVOs of the forebrain (ie, SFO and OVLT) and brainstem (ie, AP). Time-dependent interactions between Ang II and salt promote elevated SNA and hypertension even when Ang II is administered at subpressor doses. Because central actions of Ang II and sodium/osmolality each have been reviewed recently [40,41], we focus on key evidence for cellular and network interactions between Ang II and salt.

At the most fundamental level, Ang II and salt (via increasing tissue osmolality) could have convergent excitatory actions on a common subset of sensory neurons, thereby increasing activity at distal synaptic targets. One mechanism whereby this could occur was introduced by Chakfe and Bourque [42]. They reported that excitatory neuropeptides, like Ang II, activate an inward current in magnocellular hypothalamic neurons. They further showed that this involved activation of stretch-inactivated cation (SIC) channels, which have been reported to mediate excitatory neuronal responses to hyperosmotic stimulation [43]. Accordingly, SIC channels have been proposed to represent a point of “molecular convergence” for excitatory actions of Ang II and hyperosmolality. More recent evidence indicates that elevated osmolality can increase magnocellular cell activity in the hypothalamic supraoptic nucleus through a mechanism that depends on expression and gating of an N-terminal variant of transient receptor potential vanilloid type 1 (TRPV1) channels [44]. At the whole-animal level, TRPV1-deficient mice exhibit pronounced plasma hyperosmolality and diminished vasopressin release in response to acute hyperosmolality [44]. Importantly, osmosensitive signal transduction was absent from OVLT neurons in TRPV1-null mice, which correlates with having blunted drinking responses to systemic hypertonicity as well [45].

Hyperosmolality and Ang II are thought to each act at the SFO and OVLT. When considered with the recent demonstration that TRPV1 channels are expressed in the same regions [46], it is reasonable to propose that mechanisms involving TRPV1 contribute significantly to activation of downstream sympathetic regulatory neurons. However, TRPV1 channels may not be the sole mediator of cellular interactions between Ang II

and hyperosmolality. For example, *in vitro* electrophysiological studies of SFO neurons indicate that these cells are intrinsically osmosensitive, and yet the underlying mechanism appears unlikely to depend on SIC/TRPV1 channels [47].

How might downstream synaptic interactions contribute to sympathetic activation and hypertension induced by Ang II and salt? *In vivo* recordings from SFO neurons demonstrate that their firing rate can be increased by elevated Ang II or hyperosmolality, with a subpopulation responding to both stimuli [48]. Consistent with individual SFO neurons integrating Ang II and sodium/osmotic information, *in vitro* patch clamp recordings of SFO neurons retrogradely labeled from the hypothalamic PVN indicate that Ang II and hyperosmolality each evoke an inward current with similar characteristics [47]. These findings may indicate that an SFO-PVN pathway is dominated by individual neurons responsive to both Ang II and hyperosmolality. If this is the case, then Ang II and hyperosmotic information from the SFO would be transmitted as an integrated signal to the PVN. Consequently, additive or facilitative interactions between Ang II and sodium/osmolality could be required to ensure that excitatory SFO inputs depolarize the membrane potential of PVN neurons beyond action potential threshold.

In vivo recordings from SFO neurons with unidentified efferent projections have revealed that neurons most often respond either to Ang II or hyperosmolality, but rarely to both [49–51]. This suggests that Ang II and osmotic information may also be transmitted, in part, through separate SFO pathways. Consistent with this concept, neurons of the MnPO, which are a major recipient of SFO efferents [52], exhibit heterogeneous responses to Ang II and hyperosmolality *in vivo* [53•,54] and *in vitro* [55]. Indeed, MnPO neurons with axonal projections to the PVN exhibit mostly excitatory responses to Ang II alone, hyperosmotic stimulation alone, or to both stimuli. However, these excitatory responses are often opposed by visceral afferent inputs arising from arterial and putative cardiopulmonary baroreceptors [53•,54]. When various response patterns observed among SFO-PVN and MnPO-PVN neurons are considered together, it seems that Ang II and osmotic information is transmitted from the forebrain to the hypothalamus both through separate pathways and as an integrated signal. The challenge is to uncover how this information is distributed as it descends through the hypothalamus to the brainstem and eventually to the spinal cord to modulate sympathetic outflow to specific end organs. Clearly this will require *in vivo* and *in vitro* recording methodologies and strategies to cross-correlate the resulting information.

Neural Plasticity and Ang II–salt Hypertension: Genetic Mechanisms

The neural circuits described above rapidly and continuously communicate via synaptic transmission, providing a

substrate for dynamic control of the cardiovascular system. It is likely that during the development of hypertension, either contributing to its evolution or in response to it, changes occur within this circuitry over time. Whether these changes relate to long-term alteration in synaptic efficacy, alterations in neural connections, or other types of neural plasticity, changes in gene expression would occur to support these changes. Thus, we expect that critical changes in gene expression in RVLM, PVN, and other neural structures will contribute to the development and maintenance of Ang II–salt hypertension (and other forms of hypertension) in rats. This notion would suggest that examining the changes in gene expression accompanying the development of Ang II–salt hypertension will allow a further understanding of the pathogenesis of neurogenic hypertension and, importantly, potentially point to target molecules critical to the hypertensive process. Many studies have examined potential changes in individual molecules in the brain associated with hypertension, and recent studies have begun to apply gene expression and proteomic approaches to study genetic models of hypertension; however, we believe that the Ang II–salt model may be the ideal model to study these changes because the hypertension develops with a tractable time course that can be compared to an animal with an identical genetic makeup. Although it is too early to point to individual changes in gene expression that may contribute to the development of Ang II–salt hypertension, it is important to note that application of gene expression approaches to the study of hypertension in SHR has begun to point to a variety of novel molecules (eg, translin, adducin, epoxide hydrolase, PI3-kinase) being involved in the neural changes underlying hypertension [56•,57,58]. Once genes are identified that change in specific brain loci in association with the development of hypertension, it is possible with current approaches (eg, viral vectors) to increase or decrease the local expression of the specific gene (or genes) to examine the functional impact of altered expression of that gene. This general approach has the potential to identify novel genes involved in the pathogenesis of neurogenic hypertension and thereby target new avenues of therapeutic intervention.

Conclusions

Elevated SNA as an etiologic factor in human essential hypertension was once controversial but now is widely accepted. Although the underlying mechanisms of neurogenic hypertension remain to be elucidated, accumulating evidence strongly suggests that a synergistic relationship exists between circulating Ang II and dietary salt intake in many forms of human and experimental hypertension. A detailed understanding of the genetic and cellular mechanisms mediating Ang II–salt neurogenic hypertension will provide a framework for future development of novel therapeutic strategies for the prevention and treatment of this and other forms of neurally mediated cardiovascular diseases.

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