Brainstem Mechanisms of Hypertension: Role of the Rostral Ventrolateral Medulla

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The central nervous system plays a key role in the regulation of cardiovascular function, and alterations in the central neural mechanisms that control blood pressure may underlie the vast majority of cases of primary hypertension. The well-studied baroreceptor reflex powerfully regulates arterial pressure, though its involvement in the pathogenesis of chronic hypertension is likely to be only of minor importance. Supraspinal maintenance of sympathetic vasomotor outflow appears to emanate from neurons in the rostral ventrolateral medulla, and the tonic drive exerted on sympathetic vasomotor activity by the rostral ventrolateral medulla appears to be increased in several animal models of hypertension. In particular, the excitation of the rostral ventrolateral medulla by excitatory amino acid neurotransmitters and by stimulation of AT_1 angiotensin receptors appears to be increased in experimental hypertension. The current data support the view that neurogenic hypertension is mediated by increased excitatory drive of rostral ventrolateral medulla sympathoexcitatory neurons.

Introduction

It has long been appreciated that the brain plays an essential role in control of cardiovascular function. Blockade of sympathetic outflow from the spinal cord to the vasculature and heart decreases arterial blood pressure, and this sympathetic outflow is maintained by supraspinal influences. Transection of the spinal cord decreases blood pressure, and the minimal necessary input to the spinal cord to maintain blood pressure arises from the rostral ventrolateral region of the medulla oblongata. For more than a century it has been known that the brainstem is critical in mediating baroreceptor reflex responses and other reflex adjustments of the cardiovascular system. This short review addresses the brainstem circuits involved in cardiovascular regulation, and extends this framework to consider the role of the brain in the long-term, baroreceptor-independent control of blood pressure, especially as it relates to hypertension. Indeed, an argument can be made that many, if not most, cases of primary hypertension have a neurogenic component [1].

The Baroreceptor Reflex

Much of the early work on the role of the brain in cardiovascular regulation focused on the baroreceptor reflex. This powerful negative feedback reflex involves brainstem circuitry that has now been established in experimental animals, both in terms of the neural projections and the neurotransmitters used by these projections [2]. The basic circuitry involves baroreceptor sensory nerves that project from the carotid sinus and aortic arch, via the IXth and Xth cranial nerves, respectively, to the nucleus tractus solitarius (NTS) in the dorsal medial brainstem. This input is excitatory to second order sensory neurons in the NTS, evoking increased activity of these NTS neurons in response to increases in blood pressure. Considerable processing of this signal appears to occur in the NTS, both as a result of intrinsic synaptic mechanisms (*eg*, frequency dependent modulation) and inter-neuronal connections (*eg*, local feedback involving γ-aminobutyric acid [GABA] interneurons) [3,4]. The baroreceptor output of the NTS, at least as it relates to baroreceptor regulation of sympathetic vasomotor activity, is an excitatory, glutamatergic projection to the caudal ventrolateral medulla (CVLM). Though pharmacologic evidence of this pathway has existed for more than 15 years [5], convincing functional anatomical data have only recently been presented [6]. The CVLM provides inhibitory GABAergic input to rostral ventrolateral medulla (RVLM) presympathetic neurons [7]. RVLM neurons in turn synapse on sympathetic preganglionic neurons in the spinal cord, providing an excitatory input. Although presympathetic neurons in the RVLM have been categorized into two populations based on the presence or absence of catecholamine biosynthetic enzymes, the C1 and non-C1 neuronal populations, respectively, recent data suggest that both populations use glutamate as their primary neurotransmitter [8].

Though the baroreceptor reflex circuitry is often viewed as a simple reflex circuit, it is certainly true that each of the areas involved is considerably more complex than a simple relay. Each of the brain regions noted above, NTS, CVLM, and RVLM functions more than to just simply pass along the information they receive, and each region contributes to cardiovascular regulation independent of its role in the baroreceptor reflex [9]. Nonbaroreceptor reflex mechanisms of

cardiovascular regulation involving these regions, and their integration with acute reflex responses such as baroreceptor reflexes and chemoreceptor reflexes, represent an important topic in central neural control of the circulation that remains inadequately explored. The functional heterogeneity of these brainstem regions involved in the baroreceptor reflex further complicates their study. In particular, the CVLM and RVLM are not clearly defined structures, but rather represent overlapping populations of neurons extending in a column through the ventrolateral medullary reticular formation.

It is within the context of the baroreceptor reflex and its brainstem circuitry that much of the central neural control of cardiovascular function has been viewed. Clearly, alteration of any aspect of this circuit leads to predictable acute changes in blood pressure and heart rate. For example, stimulation of the NTS or CVLM produces a baroreceptor reflex-like decrease in blood pressure and heart rate, whereas inhibiting these areas increases blood pressure, consistent with the powerful tonic nature of this reflex. Conversely, stimulation of the RVLM elicits marked increases in blood pressure, whereas inhibition of the RVLM decreases blood pressure to the same extent as total blockade of sympathetic vasomotor tone, a response mimicking baroreceptor-evoked silencing of sympathetic vasomotor nerve activity [10]. However, as noted above, it would be a massive oversimplification of the system to consider all of these changes exclusively in the context of the baroreceptor reflex. Furthermore, many cardiovascular changes have been described as a shifting of the baroreceptor reflex, though it is often not clear precisely what is meant by this. The semantic difference between shifting the baroreceptor reflex and having that shift be what drives changes in blood pressure, does not seem different from changing the level at which the brain is setting blood pressure around which cardiovascular reflexes, including the baroreceptor reflex, are superimposed.

A Move Toward Long-term Control of Blood Pressure

Though much of the research on the central neural control of blood pressure has focused on the baroreceptor reflex, there is reason to believe that the baroreceptor reflex is more involved with the short-term stabilization of pressure than the long-term setting of blood pressure. Baroreceptor denervation, either by cutting the carotid sinus and aortic arch baroreceptor afferent nerves or by destroying their site of termination in the NTS, initially results in an acute increase in blood pressure. Chronically, however, what develops is normal average blood pressure with decreased stability (*ie*, increased lability) [11]. The restoration of normal average blood pressure in the absence of baroreceptor input following baroreceptor denervation occurs in association with a return of sympathetic outflow toward normal. In chronic baroreceptor denervated rats, sympathetic vasomotor outflow still appears to be dependent upon RVLM neuronal activity, as inhibition of this region still results in a fall in blood pressure equivalent to that produced in baroreceptor intact rats and by total autonomic blockade [12] (Schreihofer *et al.*, Unpublished observations]. The fact that the RVLM appears to maintain sympathetic vasomotor tone at normal levels despite an absence of the normally powerful inhibitory input from baroreceptors suggests that mechanisms exist, independent of baroreceptors, to set the activity of RVLM vasomotor neurons and therefore sympathetic vasomotor outflow. This highlights the important issue of what normally determines the activity of these neurons. The baroreceptor reflex provides a powerful negative modulatory influence on these neurons, but that modulation must work in conjunction with a level of excitatory drive to these cells.

Can Changes in the Activity of Rostral Ventrolateral Medulla Neurons Chronically Change Blood Pressure?

It is noteworthy that despite the accepted critical role of the RVLM in cardiovascular regulation, few studies have examined the impact of changes in this region on cardiovascular regulation in conscious animals, and fewer still have examined chronic treatments. This is due, at least in large part, to the involvement of adjacent regions in controlling respiration. The few studies that have attempted to microinject drugs directly into the RVLM of conscious rats have generally reported responses similar to those observed in anesthetized rats [13,14]. Recent studies using a selective immunotoxin to selectively destroy the C1 cell population of RVLM presympathetic neurons [15], have revealed blood pressure to be slightly lower (approximately 10 mm Hg) in conscious tethered rats studied 14 days postlesion (Madden and A. Sved, Unpublished observations). This observation provides evidence that these neurons might be involved in the chronic setting of baseline blood pressure. The most convincing evidence that the RVLM is a critical component in the chronic regulation of blood pressure comes from a recent series of experiments by Kishi *et al*. [16••]. Using an adenovirus vector to increase expression of nitric oxide synthase (NOS) restricted to the RVLM in rats, they found that during overexpression of NOS (days 5–10 post-transfection) there was a decrease in blood pressure and heart rate of approximately 20 mm Hg and 80 beats per minute, respectively. Furthermore, the decrease in blood pressure and heart rate they observed occurred in association with an increase in GABA levels in the RVLM, as assessed by in vivo microdialysis, and increased inhibition of RVLM vasomotor neurons produced by GABA, as assessed by the acute increase in blood pressure caused by injection of the GABA antagonist bicuculline into RVLM. This is an important study because it demonstrates that chronic changes in the neurochemical milieu of the RVLM can have a chronic and sustained impact on blood pressure in conscious animals.

Research on what tonically drives RVLM activity is still in its early stages. Reports that these neurons might have pacemaker potential [10,17] failed to be substantiated by in vivo intracellular recording studies, which show that these neurons are controlled seemingly exclusively by exci-

tatory and inhibitory synaptic currents [18,19]. The tonic inhibitory inputs, both baroreceptor related and baroreceptor independent, to RVLM vasomotor neurons appear to arise largely from the CVLM [7,9]. In contrast, the nature of the tonic excitatory inputs to RVLM vasomotor neurons is currently unclear. Initial reports showing that injection of the excitatory amino acid (EAA) receptor antagonist kynurenic acid (KYN) into the RVLM had little effect on blood pressure in anesthetized rats, were interpreted as an indication that RVLM vasomotor neurons are not tonically driven by inputs utilizing EAA [20,21]. However, more recent experiments have suggested that tonically active EAA-mediated inputs to RVLM do provide a tonic excitatory input to the RVLM, but this input is balanced by EAA-mediated inputs to the RVLM that also drive an inhibitory input to the RVLM vasomotor neurons [22,23].

Other neurotransmitter antagonists have been reported to decrease blood pressure when injected into the RVLM, suggesting that tonic excitation of the RVLM may be maintained by a variety of neurotransmitter systems. Among these, the most dramatic response is produced by a series of 1-sarcosine-containing peptide antagonists of angiotensin receptors such as sarthran and sarile [24]. Curiously, injections of these drugs into the RVLM decrease blood pressure to the same extent as total inhibition of the RVLM, though they produce this effect totally independent of their action on AT_1 angiotensin receptors [25,26]. The mechanism by which they produce this dramatic effect is presently unknown. Selective antagonists of the AT_1 angiotensin receptor, the primary angiotensin receptor subtype located in the RVLM [27], have no effect on blood pressure or sympathetic nerve activity when injected into the RVLM of normotensive rats, though they do totally block the pressor response evoked by injection of angiotensin II into the RVLM [28••].

Antagonists of muscarinic cholinergic receptors injected into the RVLM have also been reported to decrease blood pressure in anesthetized normotensive rats [29,30], suggesting that cholinergic inputs to the RVLM might act to help maintain baseline sympathetic vasomotor tone. Clearly, acetylcholine in the RVLM increases the activity of RVLM vasomotor neurons [31]. However, the notion that cholinergic inputs to the RVLM contribute to the maintenance of baseline blood pressure relies on observations obtained with what might be excessively large doses of muscarinic antagonists. For example, whereas atropine, a well-known muscarinic receptor antagonist, can decrease blood pressure when injected directly into the RVLM [30], the doses required for this response exceed the doses required to antagonize the pressor effects of acetylcholine (Ito and A. Sved, Unpublished observations). A similar dissociation of doses of atropine needed to block acetylcholine responses and those needed to elicit changes in baseline blood pressure has also been reported for injections into NTS, where it has been shown that the large doses of atropine needed to change baseline blood pressure are not specific for blocking muscarinic receptors [32]. Doses of methylatropine necessary to completely block the actions of acetylcholine do not alter baseline blood pressure when injected into either the NTS [32] or RVLM [Ito and A. Sved, Unpublished observation]. Thus, when interpreting results of experiments relying on the local administration of drugs, it is important to keep in mind the specificity of the drugs and the doses used. Therefore, based on these conflicting data, the potential role of cholinergic inputs to the RVLM in controlling blood pressure requires further study.

Several other neurotransmitters have been shown to increase blood pressure when injected into the RVLM [33], but there is little, if any, evidence for their involvement in the control of baseline blood pressure. For example, vasopressin injected into the RVLM increased blood pressure, though similar injections of a vasopressin receptor antagonist, in a dose required to block the actions of vasopressin, had no effect on baseline blood pressure [34].

Role of Rostral Ventrolateral Medulla in Maintaining Elevated Blood Pressure in Hypertensive Rats

Clinical hypertension is often associated with increased sympathetic outflow [1], as is the case with many experimental models of hypertension. Several studies have addressed whether in hypertensive rats the elevated sympathetic vasomotor outflow is driven by the RVLM. Inhibition of the RVLM in hypertensive rats, for example by local injection of the neuroinhibitory drug muscimol, reduces mean arterial pressure to the same extent as autonomic blockade [35••,36]. These findings imply that increased activity of RVLM neurons is responsible for the increased sympathetic vasomotor tone. Although there are a few reports that the electrophysiological activity of RVLM neurons in spontaneously hypertensive rats (SHR) is increased compared with Wistar-Kyoto (WKY) rats [37,38], the literature is inconsistent [39]. Increased immunocytochemical detection of the protein product of the early response gene *c-fos* in the RVLM of SHR compared with WKY rats has been interpreted as reflecting chronically increased activity of these neurons [40].

Chronic Setting of Blood Pressure: The Balance Between Excitation and Inhibition of Rostral Ventrolateral Medulla Vasomotor Neurons

Following the assumption that increased activity of RVLM vasomotor neurons causes increased sympathetic outflow in hypertension, then the hypothesis that shifting the balance of tonically active inputs to the RVLM toward excitation lies at the core of hypertension. Indeed, in several models of hypertension there is evidence for such an imbalance of excitatory and inhibitory drive leading to increased activity of the RVLM.

Though the EAA receptor antagonist KYN had no effect on blood pressure in anesthetized normotensive rats, KYN injected into the RVLM decreased blood pressure in SHR [35••], Dahl salt-sensitive rats on a high-salt diet [41], and a

model of renal hypertension [36]. This observation is worth highlighting, as it provides a qualitative difference between hypertensive and normotensive animals, strongly suggesting that the RVLM influence on blood pressure is altered in hypertensive rats, in a manner that may help explain the elevated blood pressure.

In the context of increased excitation of RVLM vasomotor neurons, the ability of KYN to decrease blood pressure when injected into the RVLM of hypertensive rats could be viewed as either increased EAA-mediated excitation of RVLM vasomotor neurons or decreased inhibition of RVLM vasomotor neurons driven by an EAA-mediated input to RVLM [23]. Reports by Smith and Barron [42,43], which show that excitation of the CVLM produces an exaggerated decrease in blood pressure in SHR whereas inhibition of the CVLM produces an attenuated increase in blood pressure in SHR, have been interpreted as reduced inhibition of the RVLM by CVLM in SHR rats leading to increased sympathetic vasomotor tone in these animals. However, other laboratories have failed to confirm that the RVLM is under less tonic inhibitory drive in SHR [9,35••,44]. Furthermore, EAA stimulation of the RVLM elicits similarly large increases in blood pressure in SHR and WKY rats [42–44], indicating that the inhibitory drive of the RVLM is not grossly abnormal in SHR [22]. Similar studies addressing the level of tonic inhibition of the RLVM produced by the CVLM have not been reported for other models of hypertension.

Kynurenic acid is not the only neurotransmitter antagonist reported to decrease blood pressure when injected into the RVLM of hypertensive rats but not normotensive rats. Of particular interest are the observations that AT_1 angiotensin receptor antagonists injected into the RVLM substantially decrease blood pressure in SHR [28••,45], Dahl salt-sensitive hypertensive rats [46], and transgenic rats with over-expression of a mouse renin gene [47], though they have no effect on blood pressure in normotensive rats. This antihypertensive effect of AT_1 angiotensin receptor antagonists injected into the RVLM appears to be independent of the antihypertensive action of KYN, since the responses to these two drugs are additive in SHR [28••], the only model in which this has been tested.

The observation that AT_1 angiotensin receptor antagonists have an antihypertensive action when microinjected directly into the RVLM in rats with either high plasma renin activity (the transgenic model over-expressing renin) or low plasma renin activity (the Dahl model) is consistent with the clinical observation that AT_1 receptor antagonists are useful in the treatment of hypertension whether or not it is accompanied by elevated circulating levels of angiotensin. Indeed, despite the widespread belief that AT_1 receptor blockers act by blocking the actions of angiotensin on blood vessels, the evidence supports an action of AT_1 receptor blockers to decrease sympathetic vasomotor tone [48], possibility by acting at the level of the brain. Though the site at which systemically administered AT_1 receptor blockers act to decrease sympathetic vasomotor tone in hypertensive subjects is unclear [48], the results reviewed above indicate that the RVLM is one site to consider.

Given that AT_1 receptor antagonists injected into the RVLM decrease blood pressure in hypertensive rats but not normotensive rats, the question arises as to what drives the tonic excitation of RVLM AT_1 receptors in hypertension. The report by Tagawa and Dampney [49], indicating that activating the hypothalamic paraventricular nucleus (PVN) can increase blood pressure via stimulation of RVLM AT_1 receptors, prompted investigation of the role of the PVN in the stimulation of RVLM AT_1 receptors in hypertensive rats. Inhibition of the PVN decreases blood pressure in SHR [28••,50] and Dahl salt-sensitive rats on a high-salt diet [46], similar to the action of AT_1 antagonists injected into the RVLM; inhibition of PVN has also been reported to decrease blood pressure in a model of renal hypertension [51]. Furthermore, at least in SHR, the decreases in blood pressure caused by inhibition of the PVN and blockade of RVLM AT_1 receptors occlude each other [28••], suggesting that they represent the same mechanism. Though it is presently unclear why a PVN-driven input to RVLM AT_1 receptors may be enhanced in models of hypertension, this seems to be an important question to be addressed in future research.

The cellular actions of angiotensin II on RVLM neurons help clarify the effects of angiotensin II in the RVLM on blood pressure. Studies by Li and Guyenet [52,53] on RVLM slices from neonatal rats indicate that angiotensin II acts on AT_1 receptors in the RVLM to increase the activity of these neurons by closing a K^+ channel, thereby depolarizing these neurons and increasing their input resistance. The actions of angiotensin II were largely, if not exclusively, confined to the C1 cell population in the RVLM [53], consistent with studies localizing AT_1 receptors to these neurons in rats [54] and humans [55]. Importantly, the cellular actions of angiotensin II to cause depolarization and an increase in membrane resistance in the RVLM would enhance the responsiveness of these RVLM presympathetic neurons to other excitatory inputs. Interestingly, a recent study by Matsuura *et al.* [38] suggests that angiotensin II may have a greater action on RVLM spinal neurons in SHR compared with WKY rats, consistent with the possibility of more AT_1 angiotensin receptors in the RVLM of SHR [56–58].

The cellular actions of angiotensin II on neurons requires the activities of certain intracellular signal transduction pathways [59], and Seyedabadi *et al.* [60] recently provided evidence that different signal transduction pathways in RVLM neurons may be involved in the maintenance of blood pressure in SHR and WKY rats. Injection into the RVLM of an inhibitor of mitogen activated protein (MAP)-kinase decreased blood pressure to the same extent in both SHR and WKY, whereas wortmannin, an inhibitor of phosphatidylinositol 3 (PI3)-kinase decreased blood pressure only in SHR. Interestingly, while the MAP-kinase inhibitor alone blocked the pressor response evoked by injection of angiotensin II into the RVLM in WKY rats, inhibition of both MAP-kinase and PI3-kinase was necessary to block the action of angio-

tensin II in SHR. These results highlight yet another difference in the RVLM between SHR and WKY rats, and can be related back to differences in the role of angiotensin II in the RVLM supporting the elevated blood pressure in SHR.

These studies showing decreases in blood pressure in response to neurotransmitter antagonists injected directly into RLVM in hypertensive but not control rats are very important because they demonstrate qualitative differences in the central neural control of blood pressure in association with hypertension. Furthermore, these changes in the central neural mechanisms controlling blood pressure are such that they can help explain why the blood pressure is elevated in these different models of hypertension. However, they all rely on acute evoked changes in blood pressure to infer something about chronic regulation. Important insight into the role of the RVLM in chronic hypertension comes from studies by Kishi *et al.* [61] showing that overexpression of NOS in RVLM of stroke-prone SHR (SP-SHR) can chronically reduce blood pressure. The general approach of using viral vectors to produce a change in the neurochemical milieu of the RVLM coupled to chronic cardiovascular recording provides a powerful experimental tool. However, in the case of the report by Kishi *et al.* [61], the observation that increased NOS expression lowered blood pressure in both normotensive and hypertensive rat strains makes it difficult to evaluate whether the responses observed reflect some unique change associated with hypertension. Nonetheless, the study provides important new evidence that changes in the RVLM can chronically impact cardiovascular regulation in a manner that might be relevant to neurogenic hypertension.

A hypothesis has also been presented that clinical hypertension results from vascular compression of the rostral ventrolateral brainstem due to an artery that loops along the surface of this area [62]. This hypothesis has received support from studies in rats showing that pulsatile compression of the rostral ventral lateral medullary surface increases blood pressure and activates RVLM neurons [63,64]. Furthermore, the increase in blood pressure produced by pulsatile compression of the rat RVLM can be blocked by local inhibition of EAA receptors [63]. The potential that chronic pulsatile compression of the ventrolateral brainstem might alter the neurochemical milieu of the RVLM to cause chronically increased blood pressure appears to warrant further study.

Conclusions

Taken together, this body of evidence suggests that the RVLM is a critical site from which increased sympathetic vasomotor tone emanates in hypertension. Tonic excitation of RVLM vasomotor neurons by EAA-mediated inputs and AT_1 angiotensin receptors contribute to the elevated sympathetic vasomotor tone found in at least some models of experimental hypertension. These data fit more generally into a framework of considering neurogenic hypertension in the context of tonic excitatory drive of RVLM vasomotor neurons, and the balance between excitatory and inhibitory inputs to these neurons.

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