Role of the Medulla Oblongata in Hypertension

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Abstract—Brain pathways controlling arterial pressure are distributed throughout the neuraxis and are organized in topographically selective networks. In this brief review, we will focus on the medulla oblongata. The nucleus tractus solitarius (NTS) is the primary site of cardiorespiratory reflex integration. It is well accepted that lesions or other perturbations in the NTS can result in elevations of arterial pressure (AP), with many of the associated features so commonly found in humans. However, recent studies have shown 2 distinct subpopulations of neurons within the NTS that can influence AP in opposite ways. Commissural NTS neurons located on the midline may contribute to maintenance of hypertension in spontaneously hypertensive rats (SHR), because small lesions in this area result in a very significant reduction in AP. Also involved in this blood pressure regulation network are 2 distinct regions of the ventrolateral medulla: caudal (CVLM) and rostral (RVLM). Neurons in CVLM are thought to receive baroreceptor input and to relay rostrally to control the activity of the RVLM. Projections from CVLM to RVLM are inhibitory, and a lack of their activity may contribute to development of hypertension. The RVLM is critical to the tonic and reflexive regulation of AP. In different experimental models of hypertension, RVLM neurons receive significantly more excitatory inputs. This results in enhanced sympathetic neuronal activity, which is essential for the development and maintenance of the hypertension. (Hypertension. 2001;38[part 2]:549-554.)

Key Words: brain ■ chemoreceptors ■ homeostasis ■ hypertension, experimental ■ sympathetic nervous system ■ nitric oxide ■ angiotensin ■ sympathectomy

Essential hypertension is one of the most common disorders affecting human health. That the sympathetic nervous system participates in control of arterial pressure is indisputable; the controversy regards its role in the pathogenesis of human hypertension. Over the past decade, there has been an increasing awareness that the central nervous system (CNS) has a critical role in the development and maintenance of elevated arterial pressure. Presently, it seems clear that in both clinical and experimental hypertension, an increased vascular resistance to flow is an essential ingredient of the disorder. We could say, narrowing down the problem, that the disagreement rests on the answer to a simple question: which comes first, the neural or the humoral factor? Certainly this controversy is not going to finish here, but our purpose is to show how recent experimental data have put a re-emphasis on the neural factor and, by consequence, on the sympathetic nervous system, in particular the medulla oblongata.

Re-emphasis is indeed the correct word, because in the 1930s the treatment for serious hypertension was mainly surgical, not clinical, and the approach was interruption of the splanchnic nerves. By the beginning of the 1940s, 2 approaches had been developed to remove the sympathetic chain, one by Keith Grimson1 and another, less radical, by Reginald Smithwick.2 These surgical procedures naturally led to the idea that drugs that could produce chemical sympathectomy might be useful, which was followed by quick progress in pharmacology. As a result, the surgical treatment of hypertension became obsolete, but certainly not the idea of the involvement of the sympathetic nervous system in the disease.

What are the main arguments used by those who refute the participation of the sympathetic nervous system in the long- and short-term regulation of arterial pressure and, consequence, in the development of hypertension? First, baroreceptor denervation greatly increases the short-term lability of arterial pressure but does not induce arterial hypertension chronically. Second, an increase in sympathetic tone alone is not sufficient to elevate arterial pressure because pathologic conditions such as heart failure and cirrhosis, although they are associated with profound sympathetic activation, are not characterized by elevated arterial pressure. Finally, it has been postulated that an increase in sympathetic tone cannot cause persistent hypertension in the absence of alterations of the kidneys.3

The development of new techniques made possible the demonstration of sympathetic activation in hypertension. Measurement of regional sympathetic activity by electrophysiological and neurochemical techniques (recording of

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sympathetic nerve activity and measurement of norepinephrine spillover) brought clear evidence of activation of sympathetic outflow to heart, kidney, and skeletal muscle vasculature in both essential and secondary hypertension. The crucial question of baroreceptor denervation and neurogenic hypertension was simplified when dietary salt intake was increased and hypertension developed.\textsuperscript{4,5}

Arterial pressure is a highly regulated cardiovascular variable. Although easily measured, it represents the product of 2 other variables: peripheral resistance and cardiac output. The nervous system directly influences arterial pressure, largely through actions of the sympathetic nervous system and the cardiac vagal nerves. Postganglionic sympathetic neurons regulate peripheral resistance by regulating contraction of arterioles; they control cardiac output by increasing rate and force of myocardial contraction, and they also modulate blood volume by constriction of veins.

Within the CNS, the networks controlling arterial pressure are contained within topographically selective networks represented at all levels of the neuraxis. The development of these networks from early life, when reflex control is often refractory, to adulthood is intriguing. Adaptations in this control network may lead to labile changes in autonomic functions. The development of neurogenic hypertension, for instance, may involve inappropriate modifications of synaptic function within these networks. In this brief review, we shall focus on the medulla oblongata, which contains networks that project to the 2 major visceral motor outputs controlling circulation: (1) preganglionic sympathetic neurons in the intermediolateral columns of the thoracic and lumbar cord and (2) the vagal motor neurons.

**Nucleus of the Solitary Tract**

Many years ago, Reis and colleagues\textsuperscript{6} proposed that hypertension may result from an imbalance between the central neural networks that serve to excite sympathetic vasomotor neurons and those that inhibit them with the imbalance favoring sympathetic discharge. This concept has been termed the central neural imbalance hypothesis of hypertension. According to this hypothesis, local imbalances in the brain can produce chronic hypertension in animals. Reis and colleagues\textsuperscript{6} focused their studies on one region of the medulla, the intermediate third of the nucleus of the solitary tract (NTS). This portion of the NTS (intermediate) and the commissural subnucleus, can be termed the “cardiovascular NTS” for several reasons: (1) it is the principal site of termination of baroreceptor afferent fibers;\textsuperscript{7,8} and as such, it mediates the inhibitory actions of baroreceptors on sympathetic discharge; (2) electrical stimulation of the cardiovascular NTS elicits baroreceptor-like responses, such as hypotension, apnea, and bradycardia;\textsuperscript{9} (3) in anesthetized animals, lesions at this site abolish baroreceptor reflex responses;\textsuperscript{9} (4) this area contains many neurotransmitters and/or neuromodulators that are thought to be important in cardiovascular control; and (5) the intermediate portion of the NTS is richly innervated by fibers arising from different brain nuclei that are known to have an important role in cardiovascular control, including the parabrachial nucleus, the medial hypothalamus, and the amygdala.\textsuperscript{11}

The consequences of impaired function of neurotransmission in the NTS on blood pressure control were first demonstrated by Doba and Reis,\textsuperscript{12,13} when they performed bilateral electrolytic lesions of the NTS in rats. These lesions caused a dramatic increase in blood pressure within minutes after the rats had recovered from anesthesia. The elevation of systolic pressure was entirely due to a profound peripheral vasoconstriction consequent to discharge of preganglionic sympathetic neurons. The vasoconstriction is regionally differentiated, being more intense in skin, muscle, and portions of the gastrointestinal tract.\textsuperscript{13} The increase in total peripheral resistance leads to ventricular overload, reduction in cardiac output, progressive heart failure, and pulmonary edema, and ends in death within 3 to 4 hours.\textsuperscript{12} The same response can be elicited by destroying NTS neurons with a high dose of kainic acid,\textsuperscript{14} an analogue of L-glutamate. In larger animals, bilateral electrolytic lesions of the NTS do not elicit a fulminant hypertension ending with a malignant heart failure as they do in rats. In cats and dogs, such lesions produce lability of arterial pressure, chronic sustained hypertension, exaggerated responsiveness of arterial pressure during spontaneous or evoked behaviors or in response to environmental stimulation, sustained tachycardia, absence or marked attenuation of baroreceptor reflexes, and facilitated conditioning of arterial pressure.\textsuperscript{15,16} As a result of these findings, it became generally accepted that the NTS is crucial in cardiovascular regulation, and that damage in this area can result in elevations of arterial pressure leading to fulminant or chronic sustained hypertension.

More recently, several laboratories have identified subpopulations of neurons within the NTS that can influence arterial pressure in opposite ways.\textsuperscript{17,18} That is, different areas within the NTS respond differently to microinjection of L-glutamate. Injections from the calamus scriptorium to ~1 mm rostral to it cause depressor and bradycardic responses. In contrast, midline injections in the commissural NTS (0.1 to 0.5 mm caudal to the calamus scriptorium) cause pressor and bradycardic responses.

Very recent work suggests that function of the commissural NTS may be altered in spontaneously hypertensive rats (SHR). In SHR, electrolytic lesions of the commissural NTS in the midline region elicit a dramatic fall in arterial pressure, which remains at almost normotensive levels for several days after lesion.\textsuperscript{19} In addition, microinjections of GABA in the midline commissural NTS reduce arterial pressure and decrease splanchnic sympathetic nerve activity in anesthetized SHR but not in normotensive Wistar-Kyoto and Sprague-Dawley rats.\textsuperscript{20} These data suggest that neurons in the commissural NTS are tonically active in SHR and are less active in normotensive strains.\textsuperscript{20}

The reason for such a change in activity of the commissural NTS in SHR is not clear, but it may be related to a change in the processing of information from chemoreceptors. The commissural NTS is the site of termination of chemoreceptor afferents,\textsuperscript{21} and neurons of the commissural NTS are necessary for the sympathoexcitation and pressor responses evoked by peripheral hypoxia.\textsuperscript{22} However, chemoreflexes in SHR differ in several respects from those in normotensive controls. First, SHR hyperventilate and this characteristic seems to
pressure produced by such denervation.28 These findings of the subnucleus of the NTS is important for the increase in blood pressure that is elicited by acute denervation of RVLM vasomotor neurons in SHR.

Recent studies have shown that bilateral microinjections of kynurenic acid into the rostral ventrolateral medulla (RVLM) reduce arterial pressure in SHR but have little effect on arterial pressure in normotensive Wistar-Kyoto rats.26 This suggests that in SHR, vasomotor neurons in the RVLM receive an enhanced glutamatergic drive. Although the source of excitation of these RVLM neurons is not clear at present, the commissural NTS may contribute, because electrophysiological studies suggest that there is a direct projection from the commissural NTS to the RVLM.27 Therefore, we suggest that neurons in the commissural NTS, possibly those activated by peripheral chemoreceptor afferents, may contribute through a glutamate-mediated input to an enhanced excitation of RVLM vasomotor neurons in SHR.

Other studies have shown that lesions of the commissural NTS prevent the hypertension elicited by acute denervation of the aortic baroreceptor, suggesting that the integrity of this subnucleus of the NTS is important for the increase in blood pressure produced by such denervation.28 These findings reinforce the evidence that the commissural NTS is not only the chemoreceptor projection site, but also a possible source of excitation of vasomotor neurons in the RVLM. In summary, the NTS has 2 major regions that influence the arterial pressure. The commissural NTS seems to be important to sustain the hypertension and may contribute to hypertension in SHR. The intermediate third of the NTS has the opposite role, because its destruction or inhibition results in fulminant or chronic sustained hypertension.

**Caudal Ventrolateral Medulla**

The caudal ventrolateral medulla (CVLM) is a major vasodepressor area in the brain stem. Initial observations on the CVLM were made by Feldberg and Guertzenstein in 1976,29 soon after their classic description of the rostral medulla as the vasomotor center, but our knowledge about the CVLM has advanced only slowly, for several reasons. While the location of sympathoexcitatory neurons in the RVLM is restricted and well defined, CVLM vasodepressor neurons are scattered along a large area in the rostrocaudal axis of the medulla from the edge of the RVLM to the junction of medulla and spinal cord. Several observations suggest that this area is functionally heterogeneous: it contains at least 2, and probably more, distinct cell populations involved with diverse components of cardiovascular regulation.

Chemical stimulation of the CVLM produces hypotension and bradycardia due to a reduction in sympathetic nerve activity (SNA).30–32 Accordingly, CVLM stimulation produces vasodilation in the renal, mesenteric, and the hindlimb vascular beds.33 CVLM neurons produce a tonic sympathoinhibition: inactivation or lesions of CVLM neurons produce hypertension due to increased SNA, and this acute hypertension can lead to ventricular failure and pulmonary edema.32,34

 Cardiovascular responses to lesion or stimulation of the CVLM are mediated through RVLM neurons.35 Both anatomical and functional data suggest that CVLM neurons inhibit sympathoexcitatory neurons in the RVLM.

Retrograde tracing studies indicate that the CVLM contains cells that project to the RVLM.36 These neurons form symmetric (inhibitory) synapses with adrenergic and nonadrenergic neurons in the RVLM.37 Initially it was thought that the cells that project to the RVLM were near the ventral medullary surface and were part of the A1 noradrenergic cell group, but later it became clear that these cells are scattered around the periamigdual area in the medullary tegmentum and are not part of the A1 group. The term CVLM still includes the A1 noradrenergic cell group, but now it is generally accepted that A1 neurons are not part of the neural circuit involved in the baroreceptor-mediated vasomotor tone regulation. A1 cells project directly to diencephalic nuclei, including the paraventricular nucleus of the hypothalamus, the supraoptic nucleus, and the median preoptic nucleus.38

Anatomical studies also indicated that the CVLM receives numerous afferents from the NTS areas that receive primary baroreceptor afferent fibers. This information, with the observation that the CVLM is a vasodepressor area, led to the hypothesis that the CVLM is a relay station in the baroreceptor reflex arch. However, initial studies on the role of the CVLM in these responses produced contradictory results. Using restricted microinjections of kainic acid in the rat CVLM, Cravo et al39 demonstrated that the controversy could be attributed to heterogeneity within the CVLM. Blockade of baroreceptor reflexes are consistently obtained after lesions involving an area extending from 0.5 to 1.5 mm rostral to the calamus scriptorium. In addition, the CVLM exerts a tonic sympathoinhibition independent of baroreceptor input, because lesions in the CVLM increase sympathetic nerve activity in baroreceptor-denervated rats.39

Extracellular recordings confirmed that neurons within the rostral half of the CVLM are ideal candidates for baroreceptor interneurons, ie, (1) these cells are orthodromically activated by electrical stimulation of baroreceptor afferents or increases in arterial blood pressure; (2) they project directly to the RVLM; and (3) the latency between baroreceptor stimulation and excitation of the CVLM, combined with the delay of the CVLM-RVLM connection, is about equal to the latency between baroreceptor stimulation and inhibition of the RVLM.40 Blockade of glutamatergic transmission in the CVLM abolished cardiovascular responses to baroreceptor stimulation, indicating that, similarly to what is observed in the NTS, glutamate is likely the neurotransmitter of the baroreceptor reflex pathway.41

As mentioned earlier, our knowledge about the CVLM area and its role in cardiovascular control is probably still elementary, and several questions remain unsolved. In particular, the origin of CVLM tonic sympathoinhibitory activity is not clear. Results obtained with microinjections of antagonists suggest that tonic activity in the CVLM is maintained through a combination of tonic excitatory (glutamatergic) and inhib-
itory (GABA-ergic) synapses, but the sources of these inputs remain unknown.31,41

Particularly intriguing is the finding that tonic sympathoinhibitory activity of the CVLM seems smaller in young SHR than in age-matched Wistar-Kyoto controls.42,43 This suggests that in SHR, an abnormal inhibitory activity of the CVLM would result in increased sympathetic activity and neurogenic hypertension that characterizes the initial phase of hypertension in these animals. Clearly a better understanding of the sources and mechanisms contributing to CVLM function could contribute importantly to our knowledge of the maintenance of vasomotor SNA in normal and pathological conditions, particularly in neurogenic hypertension.

**Rostral Ventrolateral Medulla**

Specific activation of RVLM neurons causes an increase in arterial pressure mediated by an increase in peripheral resistance, cardiac output, and secretion of catecholamines.44,45 Two indications concerning the involvement of RVLM neurons in the long-term regulation and maintenance of high blood pressure are known: (1) pharmacological evidence indicates that the RVLM is the site of action of centrally acting antihypertensive agents such as clonidine and moxonidine46; and (2) fulminant neurogenic hypertension in response to CVLM or NTS lesions in both cases is consequent to RVLM desinhibition.12,30

To test the hypothesis that the RVLM is the major source of sympathetic activation observed in hypertensive states, we used 2 models of experimental hypertension. The first is a Goldblatt model, in which the left renal artery was partially obstructed (2-kidney, 1-clip [2K1C]), and the other is a model in which chronic inhibition (1 week) of NO synthesis was performed to induce increase in arterial pressure.

The Goldblatt model is characterized by high levels of circulating angiotensin (Ang) II, which alter sympathetic nerve discharge by directly acting on the sympathetic nervous system. To investigate whether the increase in sympathetic activity is mediated by an increase of RVLM activity, we microinjected drugs bilaterally into the RVLM 6 weeks after partial obstruction of the left renal artery. Injection of glutamate caused a larger increase in blood pressure in 2K1C rats than in controls.47 More important, the blockade of glutamatergic synapses in the RVLM induced a decrease in blood pressure in the renovascular model but not in normotensive rats. It is conceivable that in the renovascular rats, there is a modification in the number and/or a change in the sensitivity of glutamatergic receptors in the RVLM, and these alterations may be involved in the generation and/or maintenance of high blood pressure. Interestingly, glutamatergic transmission in the RVLM may be altered in other hypertensive models as well, because Ito et al26 found that blockade of glutamatergic synapses in the RVLM reduced blood pressure in SHR.

A possible mechanism to explain the glutamatergic hyperactivity in the RVLM of renovascular rats is an action of circulating Ang II on the area postrema. From this region, glutamatergic projections to the RVLM start to be tonically active causing increase in sympathetic activity and arterial pressure.48 According to this hypothesis, in renovascular hypertension, an increase in concentration of Ang II in the blood can elevate blood pressure by causing neurogenic vasoconstriction mediated through the area postrema and RVLM.

A change in activity in >1 receptor in the RVLM may be involved in the generation and/or maintenance of renovascular hypertension, because Kubo et al49 showed an increase in cholinergic activity in RVLM neurons in renovascular hypertensive rats.

Finally, to test the effects on blood pressure of total inhibition of the RVLM, glycine was microinjected in 2K1C. This produced a hypotension very similar to that seen after injection of kynurenic acid. For comparison, a ganglion blocker, hexamethonium was intravenously injected in both groups, normotensive and hypertensive. The same response obtained with glycine was observed, showing that all sympathetic tone in both groups is originated by RVLM neurons.

The second model we used to study the contribution of the RVLM in the maintenance of hypertension was the elevation of blood pressure caused by pharmacological inhibition of NO synthase (NOS).50 It is well known that pharmacological inhibition of NOS produces acute and chronic hypertension, but the mechanisms mediating the hypertension are not completely understood. Although this hypertension was first attributed solely to inhibition of endothelial NO, more recently a large body of evidence suggests the involvement of the CNS.51

One-week treatment with Nω-nitro-L-arginine methyl ester (L-NAME) increase blood pressure to around the value observed in renovascular model. Inhibition of the RVLM by microinjection of glycine in the RVLM reduced blood pressure to about 60 to 70 mm Hg in both hypertensive and control rats. This suggests that the hypertension after chronic NOS-inhibition is mediated by an increase in the sympathetic activity driven by RVLM neurons. However, in L-NAME-treated rats, hyperactivity of the RVLM is not due to an increase in glutamatergic transmission, because chronic treatment with L-NAME did not alter the blood pressure responses to glutamate or the glutamate antagonist kynurenic acid.50

The series of experiments described above clearly shows that the sympathetic nervous system plays a major role in the maintenance of renovascular and NOS inhibition hypertension. It seems reasonable to suggest that the RVLM is the main source of this sympathetic activation. Both L-NAME and renovascular hypertension models depend on an increase in the sympathetic activity mediated by RVLM neurons. However, in the renovascular hypertensive rats, RVLM activation is due to enhanced glutamatergic transmission, whereas in the L-NAME model it is not.

Given the results from experimental models of hypertension and the data obtained in human hypertension using microneurograph and spillover of norepinephrine techniques, there is no doubt that the sympathetic influence on the cardiovascular system is often increased when blood pressure is chronically elevated. The precise mechanisms responsible for the sympathetic activation observed in hypertension remain to be determined. One well-accepted hypothesis maintains that the sympathetic activation accompanying hy-
Hypertension is in part due to an exaggerated hypothalamic drive, resulting from excessive environmental stress. This hypothesis has been tested and proven in experimental models of hypertension.52

Another hypothesis to explain the sympathetic activation in late hypertensive states is the baroreflex hypothesis.53 The sympathetic nerve responses to stimulation and deactivation of carotid baroreceptors by carotid transmural pressure alterations (neck chamber device) are similar in normotensive, essential hypertensive, and renovascular hypertensive patients. However, reflex changes in heart rate, elicited by elevation of blood pressure, are significantly attenuated in hypertensive patients.53 In those hypertensive conditions, the baroreflex is reset toward the elevated blood pressure values, which implies that rather than opposing blood pressure elevation, this mechanism acts to maintain it.

Finally, magnetic resonance imaging (MRI) studies have indicated an association between essential hypertension and neurovascular compression of the ventrolateral medulla,54 suggesting that vascular compression of the RVLM might be at least partly associated with essential hypertension. In other words, a defect in the blood supply to the RVLM, causing ischemia of this pressor area, may increase sympathetic activity and blood pressure.

Although other regions of the CNS contribute to sympathetic tone, the RVLM is the major source of this activity. By several mechanisms, some of which were discussed in this review, we suggest that an increase in the activity of these neurons may be a common mechanism involved in the maintenance of high blood pressure in different models of hypertension. The Figure summarizes the conceptual circuitry in medulla oblongata that could explain the results discussed here.

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