Brain Stem Catecholamine Mechanisms in Tonic and Reflex Control of Blood Pressure

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SUMMARY Neurons of the lower brain stem maintain resting levels of arterial pressure (AP), mediate reflex responses from cardiopulmonary receptors, and are an important site of the hypotensive actions of α2-adrenergic agonists. Details of the pathways and transmitters that mediate tonic and reflex control of AP are emerging. Afferent fibers of cardiopulmonary receptors in the ninth and tenth nerves terminate bilaterally in the nucleus of the tractus solitarius (NTS). Although some neurons contain substance P, the primary neurotransmitter appears to be the excitatory amino acid L-glutamate (L-glu). Neurons in rostral ventrolateral medulla, which most probably comprise the C1 group of epinephrine neurons, are also critical in AP control. C1 neurons project to innervate cholinergic preganglionic sympathetic neurons in the spinal cord. Stimulation of the C1 area electrically or with L-glu increases AP, while lesions or local injection of the inhibitory amino acid gamma-aminobutyric acid (GABA) lowers AP to levels comparable to spinal cord transection. Lesions of C1 neurons or their pathways abolish vasodepressor reflexes from baroreceptors and vagal afferents. In contrast, noradrenergic neurons of the caudal ventrolateral medulla, the A1 group, project rostrally to innervate, in part, vasopressin neurons of the hypothalamus. Stimulation of A1 neurons lowers AP, while lesions or GABA elevates it. We propose that C1 neurons comprise the so-called tonic vasomotor center of the brain stem and also mediate, via a projection from the NTS, the vasodepressor limb of baroreflexes. The NTS-C1 projection may be GABAergic. (Hypertension 6 (Suppl II): II-7-II-15, 1984)

KEY WORDS • adrenergic • adrenaline neurons • noradrenergic neurons • baroreceptor reflexes • blood pressure • nucleus of the tractus solitarius

It has long been recognized that neurons within the lower brain stem, which comprise the medulla oblongata and pons, are critical for the tonic and reflex regulation of systemic arterial pressure (AP).1-7 Neurons in the lower brain: (1) maintain tonic background drive to sympathetic preganglionic neurons, thereby maintaining normal resting levels of AP;8-10 (2) are the site of termination of cardiopulmonary afferents, which includes those from high and low pressure baro- and other cardiopulmonary receptors5-8; and (3) are the major targets of those centrally acting α-adrenergic agonists that act as antihypertensive agents, most notably, clonidine and α-methyldopa.9-12 Indeed that these agents, which act on receptors in the brain normally stimulated by catecholamines, produce cardiovascular actions by stimulation of baroreceptors,11, 12 raises questions about the relationship between the central networks responsible for maintaining AP and the central catecholamine neurons.

This paper reviews recent research from our laboratory directed toward clarifying the networks in the lower brain stem that are responsible for maintaining normal levels of AP and mediating baroreflex responses. Our findings suggest an important new role for catecholamine cell groups of the lower medulla in such control. We review these studies with the present knowledge of control of the circulation by the brain stem.

Nucleus of the Tractus Solitarius and Arterial Pressure

The nucleus of the tractus solitarius (NTS) is the major site of termination of afferents of the ninth and tenth cranial nerves. As such, the NTS is the major relay nucleus for information arising from baroreceptors and cardiopulmonary afferents. Interestingly, recognition that the NTS is critical for baroreceptor reflex function is relatively recent and has
been elaborated on only over the past 20 years. The evidence for its role in control of AP stems from a variety of physiological and anatomical studies.\textsuperscript{5-4} In brief: (1) The NTS has been demonstrated by retrograde transport techniques to be the site of termination of afferents that arise from cardiopulmonary receptors. (2) Neurons in the NTS can be demonstrated to respond monosynaptically to stimulation of baroreceptor afferents and also to fire in synchrony with the arterial pulse, which indicates that they are locked into the baroreceptor reflex chain. (3) Electrical stimulation of the NTS can, with stimuli of appropriate frequency, simulate the baroreceptors, while (4) lesions of the NTS have been demonstrated to abolish cardiopulmonary reflexes.\textsuperscript{13} Indeed, lesions of the NTS, produced either by destruction of local neurons or by appropriate drugs, have been shown to result in neurogenic hypertension.\textsuperscript{14, 15}

The cardiovascular portions of the NTS are abundantly innervated by inputs from a variety of brain areas as well as from branches of the ninth and tenth nerves. These areas include the area postrema, parabrachial nucleus of the pons, various monoamine brain stem nuclei of pons, paraventricular and lateral hypothalamic nuclei, amygdala, and forebrain.\textsuperscript{16-18} These areas contain a wide variety of peptide and monoamine transmitters.\textsuperscript{19} The transmitter of the primary afferent input is uncertain. Studies from this laboratory over the past several years have demonstrated that the baroreceptor response may be mediated by the excitatory amino acid L-glutamate\textsuperscript{19-23} and not by monoaminergic or cholinergic inputs,\textsuperscript{23-27} although these agents may modulate the response (as may the various peptides innervating the area). On the other hand, there is histochemical and immunocytochemical evidence that substance P also is contained in baroreceptor afferent fibers that innervate the NTS.\textsuperscript{28} Whether substance P acts to modulate baroreflex responses or to modulate them is uncertain, and the results of application of this drug locally to the NTS have been variable depending on species and investigators.\textsuperscript{29, 30}

**Ventrolateral Medulla and Cardiovascular Control**

Although neurons in the NTS relay all information arising from cardiopulmonary receptors to other centers in the brain, the pathways by which such information is relayed, particularly those that signal an inhibition of vasomotor tone — the hallmark of the baroreceptor vasodepressor response — until recently have been unknown. Attention has focused on the ventrolateral medulla as the area of importance in controlling tonic and reflex control of AP. The ventrolateral medulla can be separated into a rostral zone, the rostral ventrolateral medulla (RVL), and a caudal zone, the caudal ventrolateral medulla (CVL), which, as will be discussed, differ functionally with respect to their activities in regulating the circulation.

**Rostral Ventrolateral Medulla**

Studies have documented that bilateral lesions of the RVL,\textsuperscript{32-34} cooling of the area,\textsuperscript{35} or local application of drugs such as gamma-aminobutyric acid (GABA), phenobarbital, or clonidine,\textsuperscript{10, 36-38} reduce AP, sometimes to a magnitude comparable to that produced by spinal cord transection. In contrast, electrical stimulation or local administration of excitatory amino acids to the region has been observed to elevate AP.\textsuperscript{34} Such evidence suggests the RVL may be responsible for maintaining tonic levels of AP. The region also may mediate vasodepressor responses to baroreflex stimulation: baroreflex responses disappear after bilateral lesions of, or application of kainic acid to, the area.\textsuperscript{39, 40}

Anatomical studies have also supported the view that the RVL is important in control of AP; evidence is available that neurons in the RVL project into regions of the spinal cord that contain preganglionic autonomic neurons\textsuperscript{41-49} and that RVL receives projections from the NTS.\textsuperscript{44-47}

**Caudal Ventrolateral Medulla**

The CVL differs from the RVL with respect to its actions on AP. Electrical or chemical stimulation of neurons in the region under appropriate conditions lowered AP,\textsuperscript{43, 47} while lesions of the area resulted in elevations of AP.\textsuperscript{49-51} Neurons in the CVL do not project to the spinal cord (see next section). Thus, in functional terms, the RVL and CVL appear to have opposite actions on AP. What has not been determined are the identity of the neurons and their transmitters within each of these areas that are responsible for the cardiovascular effects. That it is different sets of catecholamine neurons within these regions that account for the functional differentiation has been suggested by some recent studies, largely from this laboratory.

**Catecholamine Neurons in Rostral Ventrolateral Medulla: C1 Group**

It has long been known that the areas of the ventrolateral medulla that have functionally been established as controlling AP contain neurons that synthesize and release catecholamines. In their pioneering studies, Dahlstrom and Fuxe\textsuperscript{52-53} described a group of fluorescent neurons in the ventrolateral medulla that were presumed on the basis of their histofluorescence to contain norepinephrine. These, the A1 neurons, were believed to project to the spinal cord.

It should be emphasized that histofluorescence cannot differentiate, with certainty, between dopamine, norepinephrine, or epinephrine. It required the introduction of immunocytochemical techniques for the localization of catecholamine biosynthetic enzymes to provide a tool that could establish which catecholamine a neuron could synthesize. Thus, neurons that contained only tyrosine hydroxylase had only the capacity for synthesizing dopamine. The presence of tyrosine hydroxylase and dopamine-β-hydroxylase indicated that the neuron could synthesize norepinephrine, while the presence of the enzyme phenylethanolamine N-methyltransferase (PNMT), the enzyme that converts norepinephrine to epinephrine, indicated that such a cell was adrenergic. In 1974 Hökfelt et al.,\textsuperscript{54} using an antibody to PNMT, discovered that a subpop-
ulation of neurons called the Cl group, which were situated in the most rostral portion of the A1 group, contained this enzyme. The ventrolateral A1 group therefore was not homogeneous, but consisted of two parts: a rostral adrenergic Cl group and a caudal noradrenergic A1 group with admixing in between.

Further evidence that the A1 and Cl neurons differ has come from examination of their projections. Using tracer techniques, it has been established that the A1 neurons do not, as first believed, project to the spinal cord but rather send their axons rostrally, innervating in large measure magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus. These neurons synthesize vasopressin and project into the posterior pituitary. In contrast, a large population of Cl neurons also send their axons caudally to innervate almost exclusively the intermediolateral column of the spinal cord (Figure 1). Indeed, the major catecholaminergic innervation of the spinal cord originating in the medulla oblongata is adrenergic.

Possible Function of Cl Adrenergic Neurons in the Tonic Control of AP

It has long been known that electrical stimulation of the RVL will elicit elevations of AP and heart rate. Whether these effects are mediated by the Cl cells in the RVL, however, remained to be established.

In a recent series of experiments by combining electrical and chemical stimulation techniques along with careful correlation with the anatomy of neurons staining for PNMT, we have demonstrated an extremely tight correlation between the responses elicited from the Cl area and the distribution of neurons and their axonal processes, which contain the enzyme PNMT. In summary, electrical stimulation of the Cl area or within the axonal pathways elicited a powerful elevation of arterial pressure and heart rate (Figure 2A). Such stimulation also elicited a release of adrenal medullary catecholamines and arginine vasopressin (AVP) from the hypothalamus. The response to electrical stimulation was dependent on the stimulus frequency in so far as the response was elicited with frequencies of more than 2 Hz and reached a maximum at stimulus frequencies greater than 100 Hz. The response was graded with respect to the stimulus intensity. The threshold for the response was less than 15 μAmp at 5 times the threshold that elicited an elevation of AP in excess of 80 mm Hg. The pressor response to electrical stimulation of the Cl area was dependent on stimulation of intrinsic neurons as elevations of AP of comparable magnitude could be elicited by the microinjection of very small amounts of the excitatory amino acid L-glutamate (L-glu) into the area. Because L-glu did not excite fibers of passage, we concluded that it was excitation of intrinsic neurons in the Cl area that caused the sympathetic neurons to discharge.

In contrast to the effects of excitation, interference with the activity of neurons in the Cl area resulted in a collapse of AP to levels comparable to those produced by spinal cord transection. Thus, small electrolytic lesions (Table 1), the introduction of tetrodotoxin (Figure 2B), or the inhibitory amino acid GABA all lowered arterial pressure. The effects of such disturbances were graded: unilateral lesions only produced partial reductions of AP. Comparable reductions of AP to those produced by lesions in the Cl cell body area could also be produced by transecting lesions in the brain stem that affect the fiber bundle stained for PNMT (unpublished observations).

These experiments therefore suggest that neurons in the RVL are tonically active and that these neurons are tonically inhibited by GABA. These studies are entirely consistent with the view that the Cl neurons of the RVL provide tonic vasomotor tone.

Role of the Cl Area in Baroreceptor Reflexes

That the RVL participates in baroreceptor reflex responses has been suggested by two lines of evidence: (1) Neurons in the RVL have been shown to be innervated by inputs from the NTS; or bilateral lesions of the RVL or the application of drugs to neurons subadjacent to it abolished vasodepressor responses elicited by electrical or natural stimulation of cardiopulmonary afferents (Table 1). Physiological studies, however, have been interpreted with difficulty because lesions or drugs may often drop blood pressure to levels below that reached by maximal stimulation of baroreceptors.

Figure 1. Autoradiographic demonstration of projections from the Cl region to the intermediolateral column (ILC). IO = inferior olive; IVN = inferior vestibular nucleus; MVN = medial vestibular nucleus; NTS = nucleus of the tractus solitarius; PP = nucleus prepositus; RPa = raphe pallidus; STN = spinal trigeminal nucleus; STT = spinal trigeminal tract. (From Ross et al.)
Figure 2a. Cardiovascular responses elicited from the C1 region in chloralose-anesthetized, paralyzed, artificially ventilated rats. A single electrode tract is seen passing through the ventrolateral medulla (right side of illustration). At each point, the animal was stimulated for 10 seconds with a square-wave pulse of 20 µAmp, 100 Hz. Note that the pressor responses are highly localized to regions that correspond with the distribution of cells labeled for phenylethanolamine N-methyltransferase (PNMT) at the same level of the brain stem (left side of illustration).

Figure 2b. Cardiovascular responses to bilateral injections of tetrodotoxin (10 pmol/100 nl saline) into the C1 area. The first injection (TTX), indicated by an arrow on the bottom of chart recording, produced a partial reduction of AP, while injection into the contralateral side (second arrow) resulted in a collapse of AP to levels comparable to that produced by subsequent spinal cord transection. CST = corticospinal tract; IO = inferior olive; IVN = inferior vestibular nucleus; MVN = medial vestibular nucleus; NA = nucleus ambiguus; NTSr = nucleus tractus solitarius pars rostralis; PP = nucleus prepositus; RPa = raphe pallidus; STN = spinal trigeminal nucleus; STT = spinal trigeminal tract; TS = tractus solitarius. (From Ross, et al.60)
TABLE 1. Effects upon Resting and Reflex Changes in Arterial Pressure and Heart Rate of Lesion(s) of C1 Area Alone or Combined with a Unilateral Lesion of the NTS*  

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Before lesion</th>
<th></th>
<th>After lesion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Vagal stimulation (mean change)</td>
<td>Control</td>
<td>Vagal stimulation (mean change)</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>MAP</td>
<td>HR</td>
<td>MAP</td>
</tr>
<tr>
<td>Bilateral C1 area lesions</td>
<td>4</td>
<td>98.5</td>
<td>380.8</td>
<td>-32.5</td>
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<tr>
<td></td>
<td>±6.2</td>
<td>±30.2</td>
<td>±2.3</td>
<td>±5.0</td>
</tr>
<tr>
<td>Contralateral NTS and ipsilateral C1 area lesions</td>
<td>4</td>
<td>96.9</td>
<td>368.0</td>
<td>-32.6</td>
</tr>
<tr>
<td></td>
<td>±6.6</td>
<td>±15.2</td>
<td>±2.5</td>
<td>±5.4</td>
</tr>
</tbody>
</table>

*From Granata et al.62 By permission of the American Heart Association

NOTES: Unilateral vagal stimulation performed with pulse of 2-msec duration, 5 Hz and 10 times threshold current intensity; 10-sec train of stimulus.

Values are expressed as means ± SEM, N = number of experiments. MAP = mean arterial pressure (mm Hg), HR = heart rate (beats/min); NTS = nucleus of the tractus solitarius.

That the C1 neurons of the RVL may mediate the baroreflex response was suggested to us by our finding that the C1 area was heavily innervated, largely unilaterally, by a projection of the cardiovascular portions of the NTS.64 To test the hypothesis that the NTS-C1 projection mediates the vasodepressor response from baroreceptor afferents, we devised an experimental model. The model has been based on the facts that the projections from cardiopulmonary afferents of the ninth and tenth nerves are distributed bilaterally; that lesions of a single C1 area only partially interfere with the magnitude of the vasodepressor response to electrical stimulation of the left vagus nerve or stretch of the left carotid sinus region; (2) the addition of a lesion of the right or left C1 area resulted in a lowering of AP to a level comparable to that of the unoperated anesthetized rat (Table 1); (3) a lesion of the left C1 area totally abolished reflex responses elicited by electrical stimulation of the left vagus nerve (Table 1) or carotid sinus (Table 2); (4) electrolytic lesion of the right NTS combined with a lesion of the right C1 area had no further effect on vasodepressor responses than did the NTS lesion alone; (5) if kainic acid was injected into the left C1 area rather than placement of an electrolytic lesion, a

TABLE 2. Effects upon Cardiovascular Responses to Carotid Sinus Stretch of Lesion(s) of C1 Area Alone or Combined with a Unilateral Lesion of the NTS*  

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Before lesion</th>
<th></th>
<th>After lesion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Carotid sinus stretch (mean change)</td>
<td>Control</td>
<td>Carotid sinus stretch (mean change)</td>
</tr>
<tr>
<td></td>
<td>MAP</td>
<td>HR</td>
<td>MAP</td>
<td>HR</td>
</tr>
<tr>
<td>Bilateral C1 area lesions</td>
<td>4</td>
<td>98.9</td>
<td>346</td>
<td>-27.8</td>
</tr>
<tr>
<td></td>
<td>±8.5</td>
<td>±20.8</td>
<td>±6.1</td>
<td>±7.1</td>
</tr>
<tr>
<td>Contralateral NTS and ipsilateral C1 area lesions</td>
<td>5</td>
<td>95.8</td>
<td>355.0</td>
<td>-29.8</td>
</tr>
<tr>
<td></td>
<td>±10.5</td>
<td>±10.1</td>
<td>±6.7</td>
<td>±7.5</td>
</tr>
</tbody>
</table>

*From Granata et al.62

*p < 0.025

Notes: The carotid sinus baroreceptors were stimulated naturally (stretched) by pulling the ligature looped around the common carotid artery downward toward the heart for 12 sec. In all cases, ipsilateral and contralateral are referred to the side of the vagal stimulation or carotid sinus stretch.

Values are expressed as mean ± SEM; N = number of experiments; MAP = mean arterial pressure (mm Hg); HR = heart rate (beats/min); NTS = nucleus of the tractus solitarius.
comparable abolition of baroreceptors was obtained, which indicated that the effects of electrolytic lesions are on neurons in the region rather than on fibers of passage. Most recently we have obtained evidence that lesions restricted to the axonal bundles of PNMT-containing fibers that project dorsally and then descend into the spinal cord produce effects comparable to those obtained with electrolytic lesions of the cell bodies (unpublished observations). These observations raise the question as to whether or not Cl neurons may be important in the expression of several forms of hypertension. That a unilateral Cl lesion reduced the significant elevation of arterial pressure produced by NTS lesions, demonstrates that its integrity is necessary for the expression of at least the neurogenic hypertension produced by bilateral lesions of the NTS (NTS hypertension).

**Contrasting Roles of A1 Neurons of the Caudal Ventrolateral Medulla in Cardiovascular Function**

Electrical stimulation of the A1 area in the rabbit or rat resulted in changes of AP that were very different from those elicited from the Cl area. Electrical stimulation of the region with low-frequency stimuli (5–15 Hz) or the microinjection of the excitatory amino acid L-glu resulted in graded reductions of AP. Electrical stimulation with higher frequencies resulted in apressor response. In the rabbit the vasodepressor response was accompanied by bradycardia; in the rat, by tachycardia.

Lesions of the A1 area produced effects entirely different from that produced by lesions of the Cl area. Thus, electrolytic lesions or the introduction of kainic acid into the A1 area of rabbit or rat resulted in elevations of AP, which led inevitably in the rat and often in the rabbit, to fulminating pulmonary edema and death. The microinjection of GABA into the A1 area also resulted in an elevation of arterial pressure.

Lesions of the A1 area, in contrast to those of the Cl area, did not substantially alter the magnitude of the vasodepressor response to maximal stimulation of vagal afferent fibers or to carotid sinus stretch. Chronically, lesions of the A1 area, however, may impair the gain of the baroreceptor reflex curve.

The hypertension produced by A1 lesions was substantially, but not totally, the result of an increase in the release of AVP from the pituitary. Thus, interference with A1 function by electrolytic lesions or kainic acid elevated AP, and the response to hypertension was significantly reduced by treatment with an AVP antagonist.

**The Neuroanatomical Substrate of the Tonic and Baroreceptor Reflex Control**

From these considerations and previous work from our laboratory, we constructed a working diagram of the neuroanatomy of the baroreceptor reflex arc (Figure 3). In brief,afferent information arising from baroreceptors projects into the NTS. From here it engages neurons that project to the Cl area; Cl neurons project...
into the intermediolateral column of the cord, with neurons of that region projecting directly to the adrenal medulla or to sympathetic ganglia, which make contact with those ganglionic neurons that innervate the blood vessels and the heart.

A provisional statement can be made about the neurochemistry of this loop. The neurotransmitter of the primary afferent fibers is still not completely established. As described previously, there is substantial evidence to suggest that these fibers may contain L-glutamate and that the release of this amino acid transmits information from baroreceptors onto neurons of the NTS. Because, however, afferent fibers contain substance P, they may exert some yet unknown function on the reflex response.

The transmitter of the NTS–Cl projection is not yet clearly established; however, the abundant evidence that (1) GABA is essential in mediating baroreceptor reflex responses on heart rate and also on blood pressure, (2) the site of action seems to be in the ventrolateral medulla, and (3) neurons in the NTS will release GABA in vitro (Meeley MP, Reis DJ, unpublished observation), makes this a reasonable candidate for this limb of the reflex arc.

Excitation of the Cl area was necessary to mediate the tonic vasomotor and reflex vasodepressor responses, and hence the transmitter in this limb could be epinephrine. Whether or not it is epinephrine that is released to act on preganglionic neurons in the spinal cord to lower arterial pressure remains to be established. That the microiontophoresis of epinephrine in the area of preganglionic neurons purportedly reduces their activity rather than elevates it is a perplexing paradox.66–67 That Cl neurons have been discovered to contain other neuropeptides, however, such as neuropeptide Y,70 raises the possibility that the release of some agent other than epinephrine may produce the effect. The transmitter from the preganglionic sympathetic neuron to the ganglion cells is presumably acetylcholine, although these neurons may contain co-transmitters, and finally, the effective transmitter released from noradrenergic neurons on blood pressure is norepinephrine.

We must emphasize that the neurochemical wiring diagram of the baroreceptor reflex arc acting on blood pressure is provisional and a working hypothesis. Sufficient surprises have emerged from studies of neurotransmitter systems over the last decade to make enthusiastic statements premature in identifying transmitter(s).

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