The C1 Area of the Brainstem in Tonic and Reflex Control of Blood Pressure
State of the Art Lecture

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SUMMARY Recent studies have demonstrated that the neurons of the lower brainstem that are responsible for maintaining normal levels of arterial pressure reside in a specific area of the rostral ventrolateral medulla. In rat, the critical zone corresponds to a small region containing a subpopulation of the adrenergic C1 group, defined immunocytochemically by the presence of the epinephrine-synthesizing enzyme phenylethanolamine N-methyltransferase. Neurons of this region (the C1 area), possibly including the adrenergic neurons, directly innervate preganglionic neurons in the spinal cord, and are tonically active and sympathoexcitatory. The excitatory transmitter released into the spinal cord is unknown. The discharge of C1 area neurons is locked to the cardiac cycle and, in turn, leads to firing of sympathetic preganglionic neurons. The C1 area neurons are inhibited by baroreceptor input and mediate the vascular component of baroreceptor reflexes. They also mediate somatosympathetic pressor responses from skin and muscle and participate in reflex responses to hypoxia. The neurons are directly innervated by local neurons containing γ-aminobutyric acid, acetylcholine, enkephalin, and substance P, all of which modulate arterial pressure. The C1 area is the site of the hypotensive actions of clonidine. Clonidine appears to act on imidazole receptors in the C1 area to lower arterial pressure. The natural ligand for these receptors may be a newly defined substance in brain, clonidine-displacing substance. Neurons of the C1 area appear to be the critical neuronal group governing the normal resting and reflex control of arterial pressure. They may play a critical role in the maintenance of elevated arterial pressure in hypertension and as a site of action of antihypertensive drugs. (Hypertension 11 [Suppl I]: I-8–I-13, 1988)

KEY WORDS • C1 area • blood pressure • baroreceptor reflexes • clonidine • imidazole receptors

ONE of the classic problems of autonomic physiology has been the identity of those neurons of the brainstem responsible for maintaining the discharge of spinal preganglionic neurons and, hence, establishing normal resting levels of arterial pressure (AP). While it has been recognized for over 100 years that the medulla oblongata is essential for such control — since removal of the brain above the medulla has no effect on resting AP but transection at the spinomedullary junction results in its collapse — the identity of the neural group(s) responsible has long eluded detection. Indeed, the failure of investigators to replicate, by localized lesions within the medulla, the effects of spinal cord transection upon AP led to a view that the essential neurons, rather than being concentrated in a single area, were distributed throughout the brainstem.

Over the past several years, two principal lines of evidence have demonstrated that a restricted area of the medulla oblongata, specifically, a zone lying in the rostral ventrolateral quadrant (RVL), functions as a tonic vasomotor center. First, the demonstration that the application of inhibitory neurotransmitters to a restricted zone on the ventral medullary surface underlying the RVL could lower AP to spinal levels indicated the presence within that region of synapses critical for pressure control. The second was the finding that electrolytic damage to the region of the RVL not only abolished the cerebral ischemic reflex but also dropped AP to spinal levels. Supporting a role for RVL in tonic vasomotor control were observations that neurons within the area project to the intermediolateral nucleus of thoracic spinal cord, the site of origin of preganglionic sympathetic neurons.

We proposed that the overlap between the location of the cardiovascular centers in the RVL and the...
distribution of a subpopulation of catecholamine-containing neurons of the so-called adrenergic C1 group suggested a functional role for C1 neurons in cardiovascular control. The C1 group was first identified by Hökfelt et al., who demonstrated that a rostral component of the noradrenergic A1 group could be distinguished by the presence of the epinephrine-synthesizing enzyme phenylethanolamine N-methyltransferase (PNMT). In this paper we review the evidence implicating neurons of the rostral C1 area, conceivably the C1 adrenergic neurons themselves, in the resting and reflex control of AP.

**Anatomical Considerations**

The C1 area of the RVL in the rat and cat is localized within a zone lying caudal to the nucleus of the seventh nerve and rostral to most precerebellar relay neurons of the lateral reticular nucleus. It lies directly ventral to the retrofacial nucleus and is in close proximity to the ventral surface of the medulla upon which some processes of C1 cells terminate. The C1 area extends rostrocaudally as a cell column, representing a subdivision of the nucleus paragigantocellularis lateralis.

The rostral portion of the C1 area contains neurons, including those immunoreactive for PNMT, which project to the spinal cord. The C1 area is also characterized by a heavy terminal field derived from the nucleus tractus solitarii (NTS). Admixed within the C1 area are local neurons, some of which can be characterized immunocytochemically as containing γ-aminobutyric acid (GABA), or being cholinergic or enkephalinergic. Neuropeptide Y is colocalized with PNMT in some C1 neurons, while substance P, also found in the region, is only colocalized within a few PNMT-containing cells.

Ultrastructurally, the adrenergic neurons of the C1 group have several distinguishing features. They contain abundant mitochondria and not only are in proximity to capillaries but, in fact, often surround them. These features make these neurons ideal candidates as oxygen sensors, a function suggested by the importance of cells in this region in mediating the cerebral ischemic response and cerebral vasodilation in response to hypoxia.

Axons of the adrenergic neurons of the C1 area ascend dorsally through the medulla, contributing to the ascending and descending limbs of a major fiber tract, the principal tegmental adrenergic bundle (Figure 1). Local processes also project dorsally into the NTS, medially onto serotoninergic neurons of the raphe, and ventrally onto the subpial surface. It is the descending limb that appears to be of major importance in cardiovascular regulation, since these fibers project directly to the thoracic and lumbar spinal cord.

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Locations of the most active medullary pressor regions compared to locations of C1 adrenergic cells and fibers. Left side of each section: C1 neurons (solid circles) and fibers (lines) labeled with phenylethanolamine N-methyltransferase (PNMT). Right side of each section: pressor responses to electrical stimulation with 25 μA (100 Hz, 5 msec, 10-sec train). Responses between 30 and 50 mm Hg are indicated by small solid circles and those greater than 50 mm Hg are indicated by large solid circles. Responses less than 30 mm Hg or depressor responses are indicated by small dots. The location of the pressor region in the ventrolateral medulla corresponds to the location of the PNMT-labeled fiber bundle. CST = corticospinal tract, DCN = dorsal cochlear nucleus, ECN = external cuneate nucleus; ICP = inferior cerebellar peduncle; IO = inferior olive; IVN = inferior vestibular nucleus; LRN = lateral reticular nucleus; MLF = medial longitudinal fasciculus; MVN = medial vestibular nucleus; NC = nucleus cuneatus, NG = nucleus gracilis; NTS = nucleus tractus solitarii; NTSr = nucleus tractus solitarii pars rostralis; PP = nucleus prepositus; RM = raphe magnus; STN = spinal trigeminal nucleus; STT = spinal trigeminal tract; TS = tractus solitarius; VII = facial nucleus; X = dorsal motor nucleus of vagus; XII = hypoglossal nucleus. (Reprinted from Ross et al. with permission of the Society for Neuroscience.)
where they exclusively innervate neurons within auto-
nomic centers of the intermediolateral and intermedio-
medial columns bilaterally. The spinal projections of
medullary adrenergic neurons consist of both myeli-
inated and unmyelinated fibers.

Functions of C1 Neurons

Neurons of C1 Area Are Tonically Active and
Sympathoexcitatory

That neurons in the C1 area are sympathoexcitatory
has been demonstrated by the finding that chemical
stimulation in the RVL excites sympathetic pregan-
glionic neurons, elevates AP, accelerates the heart,
and releases vasopressin and adrenal catecholamines
(see Figure 1). Indeed, there is an extraordinarily
close anatomical correlation between the sites in the
medulla from which elevations of AP can be produced
and the cytochemically demonstrated distribution of
cells and fibers of the C1 group. In addition, the
finding that electrolytic lesions or chemical interfer-
ence with the activity of neurons in the C1 area results
in a collapse of AP to that produced by spinal cord
transection suggests that RVL sympathoexcitatory
neurons are tonically active.

Electrophysiology

Recent electrophysiological studies of the behavior
of neurons in the C1 area of the rat and corresponding
areas in the cat have provided some insights as to why
the cardiovascular neurons of the C1 area are so potent in regulating AP. We observed
that neurons in the RVL, antidromically driven from the
intermediolateral columns of the spinal cord, are toni-
cally active and are inhibited by baroreceptor stimula-
tion. That these cardiovascular neurons are contained
exclusively within the C1 area has been demonstrated
by marking their recording sites in sections stained for
PNMT. Correlation analysis revealed that the dis-
charges of reticulospinal neurons in the C1 area were
synchronized to the peak excitations in the tonic dis-
charge of the splanchnic sympathetic nerve both in the presence and absence of the baroreceptor input.

Thus, current evidence suggests that excitation of
neurons in the C1 area that innervate the intermedi-
olateral column determines the firing of large groups of
sympathetic preganglionic neurons. Moreover, since
C1 area vasomotor neurons are recorded at random,
the finding that the discharges of each of them are
synchronized with the activity of sympathetic nerves indicates that a large number discharge simultaneously.
This implies that the relatively massive coincident
discharge of C1 neurons results in widespread, potent,
excitatory input to preganglionic sympathetic neurons.
Withdrawal of this spinal input by lesions of the C1
area or by interruption of its spinal projection de-
creases the excitability of preganglionic neurons, re-
resulting in the silencing of preganglionic discharge and
collapse of AP. The extent to which other brain regions
can compensate for the loss of this excitatory drive to
preganglionic neurons and whether the tonic activity of
RVL-spinal sympathoexcitatory neurons is generated
by neural circuits intrinsic to the RVL or imposed on
these cells by afferent projections remain to be deter-
dined.

Role in Reflex Control of the Circulation

Not only do neurons of the C1 area participate in the
tonic regulation of AP, but they are also critical in
reflex circulatory control.

Arterial Baroreceptor Reflex

That C1 area neurons participate in baroreceptor
reflexes was initially suggested by anatomical obser-
vations that neurons in the C1 area of the RVL receive dense input from the regions of the NTS con-
taining terminals of afferent fibers from arterial baro-
ceptors and other cardiopulmonary afferents. The im-
portance of this projection in the baroreceptor reflex is
implied from the electrophysiological observations
that the probability of firing of neurons in the C1 area is
locked to the cardiac cycle and that baroreceptor input
inhibits their discharge. Direct evidence that neurons of the C1 area mediate the vasodepressor re-
sponse to baroreceptor stimulation has been demon-
strated by the findings that bilateral chemical blockade
of the C1 area, which does not affect fibers of passage,
abolishes the reflex responses to electrical stimulation
of the vagus nerve or stretch of the carotid sinus. Con-
versely, disinhibition of C1 area neurons produces
the elevations of AP elicited by withdrawal of barore-
ceptor activity. This follows, since the elevations of
AP produced by lesions of the NTS are also abolished
by interruption of synaptic transmission in the C1
zone.

Evidence therefore suggests that the baroreceptor reflex arc (Figure 2), acting upon AP, consists of a
projection from the baroreceptor afferents into the NTS which excites neurons in that nucleus. The activ-
ity along neural circuits from the NTS produces inhibi-
tion of sympathoexcitatory neurons in the C1 area that
results in withdrawal of excitatory input to pregangli-
onic sympathetic neurons and a fall of AP.

Somatosympathetic Reflexes

Another reflex that is mediated by C1 neurons is the
elevation of AP arising from pain and other receptors
on the limbs and body surface and mediated through
different fibers synapsing within the spinal cord. Stud-
ies from this laboratory demonstrated that spinal affer-
ents project directly into the C1 area from neurons
located in the dorsal horn of the spinal cord. Eleva-
tions of AP elicited from electrical stimulation of the
sural or sciatic nerves can be abolished by lesions or
chemical interference within the contralateral, but not ipsilateral, C1 area. Furthermore, RVL-spinal vas-
omotor neurons in the rat and rabbit are activated by
sciatric stimulation, demonstrating that RVL neurons
could mediate the pressor response to peripheral nerve
stimulation.
Responses to Ischemia and Hypoxia

The Cl area neurons also participate in reflex responses to reduction of blood flow and oxygen perfusion of the brain. Lesions of the Cl area in rabbit abolish the potent pressor response elicited by cerebral ischemia. More recently, we demonstrated that lesions of the area also profoundly impair the diffuse circalexions due to reductions of local blood flow or partial pressure of oxygen, or both, in such a manner as to engage various segments of the circulatory bed. That neurons of the Cl area respond to reductions of blood flow or oxygen perfusion to mediate potent cardiovascicular reflex responses. Noradrenergic input to the Cl area 17,18; it may arise from local neurons. These local neurons may, in fact, be transducers of impulses arising from elsewhere in the brainstem to mediate potent cardiovascular reflex responses. Noradrenergic input to the Cl area, possibly arising from more caudally situated interneuronal networks in the intermediolateral columns might be engaged by the descending adrenergic pathways.

Pharmacology

Classic Neurotransmitters

The Cl area of RVL is sensitive to a variety of pharmacological agents, suggesting the richness of the transmitter regulation within the area’s functional microcircuitry involved in the control of the circulation. Locally applied to RVL, GABA is a potent sympathoinhibitory agent. The fact that the local application of the GABA antagonist bicuculline results in a powerful elevation of AP and heart rate indicates that GABAergic mechanisms are tonically active. Anatomically, the presence of local GABAergic neurons, suggests strongly that GABAergic inhibition within the Cl area may arise from local neurons. These local neurons may, in fact, be transducers of impulses arising from elsewhere in the brainstem to mediate potent cardiovascular reflex responses. Noradrenergic input to the Cl area, possibly arising from more caudally situated cells, may also provide inhibition of Cl area neurons.

Excitatory neurotransmitters 5-glutamate and kainic acid elevate AP when applied to the Cl area. It has been proposed that 5-glutamate may be an important excitatory transmitter in this zone. The source of glutamatergic input to the region is unknown. Acetylcholine is also an important excitatory transmitter within the Cl area, it may arise from local neuronal perikarya within and adjacent to the Cl area. The Cl area contains muscarinic receptors that mediate the pressor response secondary to the systemic administration of physostigmine.

Clonidine and the Imidazole Receptor

Not only is the Cl area of the RVL responsive to a number of putative neurotransmitters, but it is the major site of action at which clonidine, a clinically efficacious antihypertensive agent that is an imidazole, acts to lower blood pressure. The traditional view is that clonidine lowers AP by acting as an agonist of a2-adrenergic receptors in the brain as it does in the periphery. In support has been the finding that the
clonidine analogue [3H]p-aminoclonidine ([3H]PAC) can be totally displaced from membranes of the cerebral cortex by adrenergic ligands, and [3H]PAC can be demonstrated by autoradiography to bind specifically within the RVL. 

This view, however, has been challenged on the grounds that analysis of the structural relationships of a series of imidazoles or $\alpha_2$-adrenergic agents (or both) to their hypotensive actions suggests that their blood pressure–lowering actions relate more to their imidazole structure than to interaction with $\alpha_2$-adrenergic receptors. These findings have led to a concept that clonidine acts by an interaction with imidazole-prefering receptors to lower AP in RVL.

In recent studies we examined the binding of clonidine to imidazole receptors within the Cl area of the RVL. This new class of receptors may mediate the hypotensive actions of clonidine. We have found that in membranes of the bovine RVL: 1) [3H]PAC binds to local membranes; 2) only 70% of the binding is displacable by norepinephrine and other $\alpha_2$-adrenergic ligands; 3) the remaining 30% is displaced by imidazole-like substances with high selectivity; 4) the imidazole binding sites for clonidine are not localized to the cerebral cortex, thereby explaining why others, using the cerebral cortex as a test tissue, concluded that clonidine binds exclusively to $\alpha_2$-adrenergic receptors in brain; 5) the imidazole receptors are distinct from histamine receptors; and 6) the relationship between the hypotensive action of clonidine and allied substances relates more to their binding to imidazole than to $\alpha_2$-adrenergic receptors. 

The question then arises: What is the natural ligand of the imidazole receptors? It is not histamine, the principal bioactive imidazole, since neither histamine of the imidazole receptors? It is not histamine, the clonidine-displacing substance, termed a noncatecholamine of low molecular weight. That clonidine acts by an interaction with imidazole-preferring receptors to lower AP in RVL.

It will be fascinating to determine whether variations in its concentration will relate to variations in blood pressure control in animals or humans with hypertensive disease.

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