Review Article

The Mechanistic Basis of Centrally Active Antihypertensive Drugs*

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ABSTRACT

Antihypertensive drugs lower arterial blood pressure by decreasing cardiac output, total peripheral resistance, or both. Most of the drugs act at the level of the heart, blood vessel, kidney, and/or the autonomic nervous system. One class selectively acts in the central nervous system. These drugs act mainly at the level of the brainstem to decrease central sympathetic outflow. Neurons in the rostral ventrolateral medullary (RVLM) pressor area are tonically active and drive the activity of sympathetic preganglionic neurons located in the intermediolateral cell column of the thoraco-lumbar spinal cord. In turn, these preganglionics then activate the postganglionic sympathetic neurons and release norepinephrine onto the heart and blood vessels to increase arterial pressure. Neurons in the RVLM are predominantly modulated by two other medullary nuclei: the nucleus of the solitary tract (involved in baro- and chemoreceptor pathways) and the caudal ventrolateral medullary (CVLM) depressor area. These three main medullary areas co-ordinate sympathetic outflow and are the targets of many centrally acting antihypertensive drugs.

Keywords: CNS acting antihypertensive drugs, Rostral ventrolateral medulla, Nucleus of the solitary tract, Clonidine, Caudal ventrolateral medulla.

INTRODUCTION

The class of centrally acting antihypertensive drugs exerts its antihypertensive effect predominantly through an action in the medulla oblongata to reduce central sympathetic outflow by acting on sympathetic centers in the medulla oblongata. This mini-review will outline the central nervous system control of sympathetic activity, which resides mainly in the medulla oblongata. The review will also delineate the mechanistic basis for the activity of currently available centrally acting antihypertensive drugs by highlighting the prototypic centrally acting antihypertensive agent, clonidine.

ANTIHYPERTENSIVE DRUG CLASSES

Arterial blood pressure is the product of cardiac output (CO) and total peripheral resistance (TPR). The CO is determined by the stroke volume (SV) multiplied by the heart rate (HR). The TPR is dependent on the diameter of resistance arterioles found throughout the vascular system. All three of these parameters: SV, HR and TPR are under the control of the sympathetic nervous system (SNS) to a great extent. Other factors controlling blood pressure include the renin-angiotensin system (RAS) as well as the parasympathetic nervous system

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(mainly via HR and myocardial contractility). Therefore, in controlling hypertension, one mechanism to lower the blood pressure is to decrease either the action of the major sympathetic neurotransmitter norepinephrine (NE) and/or the neurohormone epinephrine (E) or decrease sympathetic tone emanating from the central nervous system. Vasodilators such as prazosin decrease TPR by competitively blocking the effect of NE on vascular smooth muscle alpha-1 postsynaptic adrenergic receptors. Beta-adrenergic receptor antagonists such as metoprolol decrease CO by blocking the effect of NE and E to increase SV and HR via activation of beta-1 receptors found on the heart. Blocking beta-1 receptors also decreases the sympathetically mediated release of renin from the kidney. Renin is the enzyme that converts angiotensinogen to angiotensin I, which is then converted to angiotensin II by the enzyme angiotensin converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor as well as a stimulus for the release of the mineralocorticoid, aldosterone, from the adrenal cortex. Renin release is the rate-limiting step in the activation of the RAS.

Another mechanism to decrease the effect of the sympathetic nervous system is to deplete norepinephrine from sympathetic nerve terminals or to act as a "false transmitter" of norepinephrine. These effects lead to decreases in both CO and TPR. Agents that have this effect include guanethidine, guanadrel and reserpine. Basically, these agents are taken up by the sympathetic nerve terminal to produce their effects. These agents, although having a very potent antihypertensive effect, are poorly tolerated and produce many adverse effects in sympathectomized patients via norepinephrine depletion.

Centrally-acting antihypertensive agents act predominantly in the central nervous system to decrease central sympathetic outflow. While there are many CNS sites that control arterial blood pressure such as those in the cerebral cortex, cerebellum, hypothalamus and midbrain, the major site of action of these agents is the medulla oblongata. Within the medulla, the three main areas that control central sympathetic output are:

1. The rostral ventrolateral medulla (RVLM),
2. The caudal ventrolateral medulla (CVLM), and
3. The nucleus of the solitary tract (NTS).

MEDULLARY AREAS/NUCLEI THAT CONTROL SYMPATHETIC OUTFLOW

The role of the brainstem in the control of basal arterial blood pressure has been known for many years. It has been known that sectioning the spinal cord in animals immediately below the medulla (at a high cervical level such as C1) results in a precipitous and immediate fall in blood pressure to levels approximately 40–50 mmHg. This is the result of a loss in sympathetic tone to the heart and arterioles in the periphery. Conversely, sectioning the brain immediately rostral to medulla at the ponto-medullary junction does not affect blood pressure to any great extent. Thus, these interventions demonstrate that the sympathetic "driver" or center resides somewhere in the medulla. This effect is clearly demonstrated clinically in quadriplegic patients who sustain an injury to their cervical spinal cords. In these patients, blood pressure falls immediately to very low levels. It is interesting to note that centrally acting antihypertensive drugs do not significantly lower the pressure in quadriplegic patients, and thus are not useful to control hypertension in this patient population.

Rostral ventrolateral medulla (RVLM)

It had been known for many years that application of drugs (e.g., pentobarbital) and CNS neurotransmitters (e.g., glycine and gamma-aminobutyric acid-GABA) to the ventral surface of the medulla of animals produced profound cardiorespiratory changes.[1,2,3] In cats, application of $GABA_A$ receptor agonists such as muscimol to the Intermediate Area (Schlaefke's area) on the ventral surface of the brain produces a precipitous fall in blood pressure.[3,4] Similar studies by Sapru *et al.* in rats revealed that an area just below the Intermediate Area has profound sympathetic activity.[5] This area coincides with a group of adrenergic neurons in the rostral ventrolateral medulla called the C1 area. These neurons synthesize epinephrine, since they contain the enzyme phenylethanolamine-N-methyltransferase, which converts norepinephrine to epinephrine.[6] This area is located lateral to the rostral pole of the inferior olivary nucleus, an area near the nucleus paragigantocellularis lateralis. Despite their location near these brainstem nuclei and adrenergic cluster, this area was defined based on the function (pressor when electrically or chemically activated) and anatomical projections (containing bulbospinal neurons projecting to preganglionic sympathetic neurons located in the intermediolateral cell column at thoraco-lumbar spinal levels) - the rostral ventrolateral medulla or RVLM (Figure 1). Injection of the excitatory neurotransmitter L-glutamic acid (GA) into the RVLM has been shown to evoke dose-dependent increases in arterial blood pressure and heart rate in rats.[5] Also, injection of a retrograde neuronal tracer into the IML cell column of the spinal cord has been shown to label neuronal cell bodies in the RVLM, some of which contained epinephrine.[6] In cats, injection of GABA into this region has been shown to decrease arterial blood pressure and heart rate.[7]

Based on these data, it was hypothesized that the RVLM might be the site of action of the antihypertensive

drug clonidine. Clonidine is an alpha-2 receptor agonist, initially developed to treat nasal congestion. During clinical trials, it was found, however, to have a profound antihypertensive effect. Notably, this effect was reproduced in intact, but not in pithed animals in which the CNS has been eliminated, indicating its site of action in the CNS.

Bousquet and co-workers[8,9] demonstrated that application of clonidine to the Intermediate Area on the ventral surface of the cat medulla decreases arterial pressure. In 1981, these investigators crudely injected the drug below the Intermediate Area and also demonstrated a hypotensive effect. They believed that this effect was mediated in the lateral reticular nucleus, a nucleus in the vicinity of the RVLM in the cat. In 1988, Gatti and co-workers injected clonidine into the RVLM of cats and saw a hypotensive effect that was blocked by the alpha-2 adrenergic receptor antagonist idazoxan.

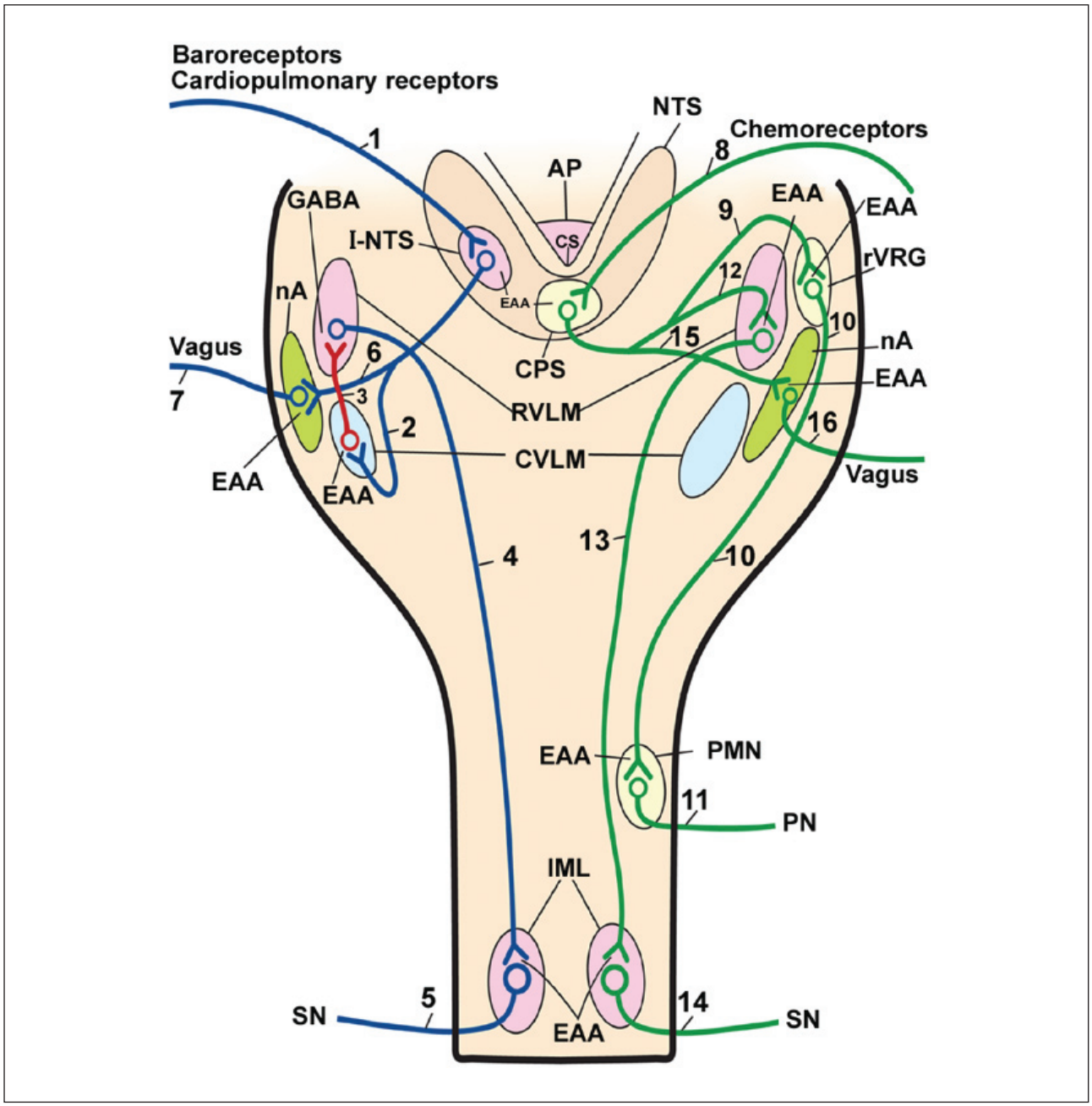

Figure 1: Representation of medullary and medullo-spinal pathways controlling central sympathetic, parasympathetic and respiratory control centers. AP, area postrema; CPS, chemoreceptor projection site; CS, calamus scriptorius; CVLM, caudal ventrolateral medullary depressor area; EAA, excitatory amino acid; GABA, gamma-aminobutyric acid; I-NTS, intermediate subnucleus of the nucleus of the solitary tract; IML, intermediolateral cell column of the thoraco-lumbar spinal cord; nA, nucleus ambiguus; NTS, nucleus tractus solitarius; PMN, phrenic motor nucleus; PN, phrenic nerve; RVLM, rostral ventrolateral medullary pressor area; rVRG, rostral ventrolateral respiratory group; SN, sympathetic nerve (permission to use figure obtained from the author[39] and publisher).

Clonidine also lowered the heart rate in these animals. In a definitive study, these investigators blocked the hypotensive effect of intravenously administered clonidine by microinjecting idazoxan into the RVLM prior to clonidine injection.[10]

Neurons in the RVLM have been extensively studied using electrophysiological and anatomical techniques. In brainstem slices, a subset of RVLM bulbospinal projecting neurons have pacemaker activity.[11] However, these same neurons are not spontaneously active when dissociated from the slice.[12] Thus, it appears that the neurons which show autoactivity rely on extracellular signals. In other words, the true pacemaker neurons appear to be activating the RVLM neurons. In addition, these neurons are influenced by baroreceptor activation. That is, when the baroreceptors are activated, these sympathoexcitatory neurons are inhibited. This effect might be both a direct input from NTS neurons in the baroreceptor reflex, or indirectly via interneurons or neurons in the caudal ventrolateral medulla (CVLM) (see below). RVLM neurons receive input from a variety of medullary, pontine and hypothalamic nuclei.[13] Finally, RVLM neurons also project to other medullary nuclei as well as rostrally to the pons and midbrain.[14] These sympathoexcitatory neurons project to the intermediolateral cell column in the spinal cord at thoraco-lumbar levels where they synapse onto sympathetic preganglionic neurons to activate them.[15,16] The neurotransmitter that underlies this effect is believed to be glutamate, although epinephrine also plays a role in this pathway. Injection of epinephrine onto the intermediolateral cell column of the thoracolumbar spinal cord has resulted in sympathoexcitatory effects mediated by alpha-1 adrenoreceptors.[17] Injection of higher concentrations of epinephrine into the IML inhibited the IML via activation of alpha-2 receptors. This effect might contribute to the sympathoinhibitory effect of clonidine in the CNS.[17] Morrison and co-workers found that there were two populations of bulbospinal projections from the RVLM to the IML.[18] One was more slowly conducting and was hypothesized to be an adrenergic pathway. The other was a rapidly conducting pathway that was hypothesized to be a glutamatergic pathway. Sundaram and co-workers demonstrated that injection of excitatory amino acids such as glutamate or aspartate into the right side of the IML at T1–3 levels of the spinal cord[19] elicits tachycardia, whereas injections into the left side elicited an increase in cardiac contractility.[19] This latter effect was blocked by prior microinjection of an antagonist of the NMDA (N-methyl-D-aspartate) receptors into the same site. A large number of neurotransmitters have been shown to regulate the activity of RVLM neurons. These include GABA, glutamic acid, acetylcholine, serotonin, corticotrophin releasing factor, oxytocin, substance P, vasopressin and orexin.[20]

The caudal ventrolateral medulla

Willette and co-workers[5] have identified a vasodepressor area in the ventrolateral medulla caudal to the RVLM and called it the caudal ventrolateral medulla (CVLM). Microinjection of glutamate into this area elicited a dose-dependent hypotension and bradycardia. Anatomically, this region is located in an area of the brainstem in a region called the A1 area, where noradrenergic neurons are located.[21] This area is located in an area ventrolateral to the nucleus ambiguus (Figure 1) adjacent but not in the lateral reticular nucleus.[5] This area does not project to the IML of the spinal cord, but it projects rostrally.[22] The RVLM and CVLM are interconnected. Injection of the $GABA_A$ receptor agonist, muscimol, into the CVLM elicits an increase in blood pressure and heart rate.[23,24] These effects were completely blocked following injection of this $GABA_A$ agonist into the RVLM. This finding demonstrated that the responses from the CVLM depended on the RVLM.[24] The RVLM neurons appear to receive tonic GABA input (from the CVLM as well as other areas) as shown by the fact that injection of bicuculline, a $GABA_A$ receptor antagonist, elicits a dose dependent increase in blood pressure.[24,25] Gatti and co-workers[26] also found that injection of bicuculline, a $GABA_A$ receptor antagonist, into the CVLM area of cats evoked hypotension and bradycardia demonstrating that the CVLM receives tonic GABAergic input. Interestingly, in this species, injection of muscimol into the CVLM, did not elicit a pressor response in contrast to what was observed in the rat. Perhaps, the CVLM in the chloralose-anesthetized cat was under maximal GABAergic inhibition; thus increasing GABA activity could not raise the pressure further.[26] Indeed, the resting arterial pressures in chloralose-anesthetized cats is usually high. Sapru and co-workers definitively showed that CVLM neurons tonically inhibit RVLM neurons via GABA. They showed that injection of bicuculline into the RVLM blocked the depressor effect of stimulating the CVLM by either bicuculline or glutamate.[25,27] Sun and Guyenet[28] have demonstrated the same results using electrophysiological techniques. They recorded from RVLM neurons and found that they were inhibited when the CVLM was activated. Moreover, other investigators found that the CVLM neurons mediated the sympathoinhibition of RVLM neurons when the NTS is activated.[29] This suggests that the inhibition of RVL neurons is mediated via activation of CVL neurons and is not a monosynaptic pathway.

Nucleus of the solitary tract

The nucleus of the solitary tract (NTS) is found bilaterally in the dorsomedial medulla. It is the primary afferent relay station in the sensory control of many autonomic

nervous system innervated organs such as the respiratory and gastrointestinal systems. In addition, the NTS is the first synapse in the control of the cardiovascular system. Specifically, baroreceptor (aortic and carotid) and chemoreceptor (aortic and carotid) afferents from the vagus (X cranial) and glossopharyngeal (XI cranial) nerves terminate in the NTS. For baroreceptors, they are activated when the blood pressure increases thereby stretching the carotid sinus and aortic arch. This leads to an increase in firing of the carotid sinus nerve (carotid baroreceptors) and/or the aortic depressor nerve (aortic baroreceptors). These afferent nerves then activate second order neurons in the NTS, which leads to sympathoinhibition to lower the arterial pressure (decrease in total peripheral resistance) and cardiac inhibition. This latter effect is the result of vagal activation which results in both bradycardia and a negative inotropic effect. Subsequently, these effects decrease cardiac output and thus the arterial blood pressure. The medullary circuits mediating these effects have been studied extensively. For the purpose of the current review, I will concentrate on sympathoinhibition.

Baro-and chemoreceptor afferent neurons that contain one process innervating the periphery (e.g., carotid sinus) and one process extending into the CNS. When these neurons are activated (for example, by stretch in the case of baroreceptors), the neurons release a neurotransmitter in the NTS. In the case of baroreceptors, these afferent terminals are believed to release glutamate in the NTS (intermediate regions).[30,31] This was based on the fact that glutamate antagonists (both NMDA and non-NMDA antagonists) block the hypotensive effect of stimulating carotid sinus nerves. Also, glutamate release increases in the NTS foIlowing carotid sinus nerve stimulation. It was initially hypothesized that second order NTS neurons in the baroreceptor reflex pathway was a GABAergic neuron that projected from the NTS directly to the RVLM to inhibit sympathoexcitatory neurons. However, it is now believed that the RVLM is inhibited by the NTS via the CVLM. As described above, the CVLM projects to the RVLM and inhibits the RVLM neurons by releasing GABA onto the sympathoexcitatory neurons. Urbanski and Sapru[32] found that when muscimol (a $GABA_A$ receptor agonist) or kynurenic acid (a non-selective ionotropic glutamate receptor antagonist) was injected into the CVLM, the depressor effect of glutamate injected into the NTS was abolished. These experiments demonstrated that the NTS sends an excitatory input into the CVLM that when stimulated, the CVLM neurons inhibit RVLM neurons. Indeed, monosynaptic (direct) pathways have been shown from NTS to the CVLM.[33] This is not to say that the NTS does not project at all to the RVLM. Again, Urbanski and Sapru[27,32] demonstrated that when muscimol (a $GABA_A$ agonist) was injected into the CVLM, injection of glutamate into the NTS elicited pressor rather than depressor effects . Thus, an excitatory input to RVLM from the NTS was unmasked when the CVLM was inhibited. Indeed, stimulation of chemoreceptor afferents (*via* an increase in plasma carbon dioxide levels or a decrease in plasma pH or plasma oxygen concentration) will activate chemoreceptor afferents running in the carotid sinus nerve. These afferents "sense" the plasma pH, carbon dioxide and oxygen tension in the carotid body. When these parameters change, the neurons are activated in a similar manner as when the baroreceptors are activated by stretching of the carotid sinus. These afferents terminate in the CNS in a specialized region of the NTS, designated the chemoreceptor projection site (CPS), an area distinct from baroreceptor termination sites. This area has also been described as the commissural subnucleus of the NTS, located in a midline area of the dorsal medulla. Excitatory amino acids also are believed to play a role in mediating this response in the CPS as blocking these receptors eliminated the pressor effect of chemoreceptor stimulation.[34] Of course, stimulation of chemoreceptors will also affect the respiratory activity. Activation of NTS second order neurons will also activate neurons in the ventral respiratory group (VRG) in the ventrolateral medulla via excitatory amino acid receptors.[35] This stimulation will eventually activate neurons in the phrenic motor nucleus to stimulate breathing. The end result is to increase respiration to decrease plasma carbon dioxide levels and increase plasma pH and oxygen levels.

A large number of receptor agonists and neurotransmitters affect arterial pressure when injected into the NTS of many species. One agent relevant to this review is the alpha-2 receptor agonist, clonidine. When injected into the NTS, clonidine reduces both arterial blood pressure and heart rate. This effect is blocked by injecting an alpha-2 receptor antagonist such as idazoxan into the NTS prior to injecting clonidine. Also, injection of alpha-2 blockers such as yohimbine blocks the depressor effect of stimulation of the aortic depressor nerve.[36] However, Punnen and Sapru[37] have demonstrated that this is not the primary site of action of this antihypertensive drug. When they injected the local anesthetic lidocaine into the NTS bilaterally, the hypotensive effect of intravenously administered clonidine was not diminished. Only injection of idazoxan into the RVLM bilaterally blocks the hypotensive effect of intravenously administered clonidine. Indeed, Sun and Guyenet[38] found that intravenously administered clonidine inhibits the slow-conducting bulbospinal neurons in the RVLM. These may be the C1 bulbospinal neurons that contain phenylethanolamine N-methyltransferase the enzymatic marker for epinephrine. A final site of

clonidine action is at sympathetic postganglionic nerve terminals at the heart. Stimulation of presynaptic alpha-2 receptors at this site results in an inhibition of NE release. This would decrease HR and contractility resulting in a decrease in cardiac output and hypotension. This last effect could contribute to a very serious adverse effect when the drug is withdrawn quickly. Chronic alpha-2 stimulation results in a down-regulation of alpha-2 presynaptic receptors on the cardiac postganglionic neuronal terminals. When the drug is withdrawn quickly, the paucity of these presynaptic autoreceptors could result in a massive release of NE and this could lead to serious life-threatening ventricular arrhythmias.

CONCLUSION

CNS acting agents such as clonidine act predominantly in the RVLM to stimulate alpha-2 adrenergic receptors found on sympathoexcitatory bulbospinal neurons. Activation of these receptors on these neurons decreases their activity and thus, in turn, decreases sympathetic activity in the periphery, most notably to the heart (to decrease HR and SV) and resistance arterioles (to decrease TPR). Both of these effects will act to decrease arterial blood pressure. These agents are very effective in reducing arterial blood pressure, because both TPR and CO are reduced. However, clinically, these agents produce sedation, which limits their usefulness. One area of future study would be to develop newer agents that act in the CNS but do not sedate the patient. Current investigations are being pursued to that end.

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