Pulsatile Compression of the Rostral Ventrolateral Medulla in Hypertension

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Abstract The rostral ventrolateral medulla (RVLM) has been known to be a major regulating center of sympathetic and cardiovascular activities. An association between essential hypertension and neurovascular compression of the RVLM has been reported in clinical observations, including magnetic resonance imaging (MRI) studies. To confirm this relationship, we performed experiments to investigate whether pulsatile compression of the RVLM would increase arterial pressure and to elucidate the mechanism of the pressor response in rats. Sympathetic nerve activity, arterial pressure, heart rate, and plasma levels of epinephrine and norepinephrine were increased by pulsatile compression of the RVLM. The pressor response was abolished by intravenous treatment with hexamethonium or RVLM injection of kainic acid. In summary, the results from the MRI studies suggest that neurovascular compression of the RVLM is, at least in part, causally related to essential hypertension. This was supported by the results from experimental studies using rats indicating that pulsatile compression of the RVLM increases arterial pressure by enhancing sympathetic outflow (Hypertension. 1997;29[part 2]:514-518.)

Key Words • rostral ventrolateral medulla • neurovascular compression • magnetic resonance imaging • pulsatile compression • neurogenic hypertension • essential hypertension • sympathetic nerve activity

The rostral ventrolateral medulla (RVLM) contains neurons that are considered to be an origin of tonic sympathetic discharge and a major center regulating sympathetic and cardiovascular activities. Chemical or electrical stimulation of the RVLM increases sympathetic nerve activities to elevate blood pressure, while its destruction causes hypotension. Since the report by Jannetta and Gendell, it has been shown that posterior inferior cerebellar artery, anterior inferior cerebellar artery, and vertebral artery occasionally compress the medulla oblongata and that patients with essential hypertension are associated with neurovascular compression of the ventrolateral medulla at the root-entry zone of glossopharyngeal and vagus nerves (ie, the RVLM) in clinical observations including magnetic resonance imaging (MRI) studies. To confirm this relationship, we performed MRI using a high-resolution 512×512 matrix, a newly developed magnetic device, in patients with essential and secondary hypertension and in normotensive subjects. Jannetta et al also reported blood pressure elevation by pulsatile compression of the RVLM in an experimental baboon model. However, the mechanism of the development of hypertension was not investigated precisely. Therefore, we performed experimental studies to investigate whether pulsatile compression of the RVLM would increase arterial pressure and to determine the underlying mechanism of the pressor response in rats.

Methods

Clinical Studies

Nineteen patients with essential hypertension (8 women), 9 patients with secondary hypertension (3 women), and 16 normotensive subjects (5 women) were recruited. The present studies were approved by the ethics committee of Kyoto Prefectural University of Medicine. Informed consent was obtained from all subjects. In the secondary hypertension group, there were 6 patients with renal hypertension, 2 patients with primary aldosteronism, and 1 patient with pheochromocytoma. The mean age was not significantly different among the three groups (59±11, 53±18, and 49±13 years, respectively). All hypertension patients were receiving antihypertensive drugs. The duration of hypertension (147±114 versus 137±122 months), the blood pressure level (136±117/77±11 versus 140±127/8±9 mm Hg), left ventricular mass calculated using echocardiograms (279±66 versus 269±102 g), and stage of the “classification of hypertension by extent of organ damage” were not significantly different between the two hypertension groups.

MRI studies were performed on these subjects with an SMT-150X (1.5 T, Shimadzu) Proton density-weighted fast SE images (repetition time/echo time, 5000/23 ms) were obtained in axial and coronal views. To obtain high-quality images, a high-resolution (0.4×0.4 mm/pixel) 512×512 matrix with 3-mm slice thickness was used. Two neuroradiologists, unaware of each subject's medical history, assessed all the MRI scans to determine whether there was neurovascular compression of the retro-olivary
sulcus of the medulla oblongata at the level of the root-entry zone of the glossopharyngeal and the vagus nerves, assumed to be the surface of RVLM.18 Compression was recognized when contact and depression of the RVLM was observed in the axial or coronal view.

**Experimental Studies**

All experiments were carried out acutely in male Wistar rats weighing between 300 and 400 g purchased from Charles River Breeding Laboratories (Kanagawa, Japan). Animal care and procedures conformed to the position of the American Heart Association on research animal use. After anesthetized with urethane (100 mg/100 g IP), each rat was mounted on a stereotaxic apparatus (David Kopf Instruments) in the supine position. The lower trachea was cannulated, and the rats were artificially ventilated at a rate of 60 breaths/min with a respirator (Ealing Co, Ltd.) and were paralyzed with decamethonium bromide (0.2 mg/100 g IV).

Catheters were inserted separately in the right femoral artery for recording arterial pressure and heart rate and in the right femoral vein for drug injections. The splanchnic nerve was placed over a bipolar stainless steel electrode, and spike potentials were amplified and counted as described in detail elsewhere.19 The ventral surface of the medulla oblongata was then exposed by occipital craniotomy. The RVLM was identified by the pressor response of more than 25 mm Hg of mean arterial pressure by microinjection of L-glutamate monosodium (300 ng, 100 nL saline).20,21

A polyurethane cannula (outer diameter: 1.5 mm) was connected to a computer-controlled pneumatic pump,21 and a rubber membrane was stuck to the opposite end. By pumping air triggered with or without electrocardiogram (ECG), the membrane pulsed and the pressure wave inside the cannula became like that of an arterial pressure wave. The duration of air compression was set to be 50 ms. The rubber membrane of the cannula was lowered to the ventral surface of the medulla oblongata 1 mm dorsally from the line of the dura mater. Changes of arterial pressure, heart rate, and sympathetic nerve activity by pulsatile compression of the RVLM were monitored under several conditions: (1) ECG-triggered pulsatile compression of the RVLM (peak value of the pressure inside the cannula: 300 mm Hg); (2) ECG-triggered pulsatile compression of regions around the RVLM (peak value of the pressure inside the cannula: 300 mm Hg); (3) ECG-triggered pulsatile compression of the RVLM at various strengths (ie, peak value of the pressure inside the cannula: 0, 100, 200, and 300 mm Hg); (4) pulsatile compression of the RVLM at various rates (ie, 0, 100, 200, 300, and 400 cycles/min; peak value of the pressure inside the cannula: 300 mm Hg); and (5) ECG-triggered pulsatile compression of the RVLM after intravenous injection with hexamethonium (2.5 mg/100 g) or RVLM injection of kainic acid (8 nmol, 100 nL saline).23-24 Furthermore, plasma levels of epinephrine and norepinephrine were measured by high-performance liquid chromatography with electrochemical detection or by radioimmunoundassay, respectively, after ECG-triggered pulsatile compression of the RVLM for 5 minutes.

**Statistical Analysis**

A χ² test was applied to determine if there were significant differences between groups in neurovascular compression. Pulsatile compression-response curve data were analyzed by ANOVA followed by Fisher's multiple-range test. Pressor responses of pulsatile compression of the RVLM after pretreatment with hexamethonium or kainic acid were compared with sham rats by nonpaired t test. Plasma levels of catecholamines were also compared with sham rats by nonpaired t test.

**Clinical Studies**

Fig 1A is a magnetic resonance image of a case with essential hypertension with neurovascular compression of the RVLM. The left vertebral artery compresses the left retro-olivary sulcus at the level of the root-entry zone of the vagus nerve (RVLM). Fig 1B is that of an essential hypertensive subject without neurovascular compression. RVLM injection of kainic acid (8 nmol, 100 nL saline).23,24 Neurovascular compression of the RVLM was observed in 14 (74%) of 19 patients with essential hypertension. In contrast, neurovascular compression was observed in only 1 (11%) of 9 patients with secondary hypertension and in only 2 (13%) of 16 normotensive subjects. The incidence of observed neurovascular compression in the essential hypertension group was significantly higher than that in the secondary hypertension group or the normotensive group (P<.01 for both groups, Fig 2).
FIG 2 Observed neurovascular compression of the rostral ventrolateral medulla using magnetic resonance imaging. EH indicates essential hypertension (n=19), SH, secondary hypertension (n=9), and NT, normotensive (n=16) \*P < 0.1

Experimental Studies

Sympathetic nerve activity (rises by \*8 \pm 1.2\%, \*P < 0.1), mean arterial pressure (from 88 \pm 22 to 105 \pm 22 mm Hg, \*P < 0.1), and heart rate (from 325 \pm 37 to 335 \pm 39 bpm, \*P < 0.1) were increased by ECG-triggered pulsatile compression of the RVLM (peak value of the pressure inside the cannula 300 mm Hg), and these changes were normalized after cessation of the compression (Fig 3). On the other hand, these changes were not induced by pulsatile compression of regions around the RVLM (1 mm lateral, 1 mm medial, and 1 mm rostral). When the frequency of the compression or the pressure inside the cannula was changed, sympathetic nerve activity, mean arterial pressure, and heart rate were increased in a frequency-related or pressure-related manner, respectively. When the peak value of the pressure inside the cannula was 0 mm Hg or the rate of the pulsatile compression was 0/mm, changes in sympathetic and cardiovascular activities were insignificant. The pressor response was abolished by ganglion blockade with hexamethonium or destruction of RVLM neurons with kainic acid (Fig 4).

Plasma levels of epinephrine and norepinephrine were significantly increased by pulsatile compression of the RVLM (Fig 5).

At the end of the experiments, 100 nL of methylene blue dye was injected into the RVLM and 150 mL of 10% phosphate-buffered formaldehyde solution was transcardially infused. Serial sections (50 \mu m) were stained with Cresyl violet and examined by light microscopy for the location of injection sites with reference to a standard rat brain atlas. The methylene blue injection sites were located ventral to the nucleus ambiguus, caudal to the facial nucleus, and rostral to the lateral reticular nucleus, which was comparable to the RVLM.

Discussion

Our results from the MRI studies suggest that neurovascular compression of the RVLM is a cause of high blood pressure at least in some patients with essential hypertension. Our results from experimental studies with rats suggest that pulsatile compression of the RVLM causes a pressor response by enhancing sympathetic outflow, supporting the presumption from the clinical studies.

Jannetta et al\(^{19}\) reported that neurovascular compression of the RVLM was found in 51 of 53 hypertensive patients and in none of the 50 normotensive patients who underwent microvascular decompression for unrelated cranial nerve dysfunction such as hemifacial spasm or trigeminal neuralgia. Since then, several observations have indicated an association between essential hypertension and neurovascular compression of the RVLM.\(^{11-16}\) In the present clinical studies as well, the incidence of observed neurovascular compression in the

Fig 3 Effects of pulsatile compression of the rostral ventrolateral medulla on cardiovascular and sympathetic activities in rats (n=20). AP indicates arterial pressure, HR, heart rate, and SNA, sympathetic nerve activity.

Fig 4 Effects of ganglion blockade (n=6) or kainic acid (n=6) on pressor response of pulsatile compression of the rostral ventrolateral medulla (RVLM) in rats \*P < 0.1 compared with sham-treated rats (n=20). AP indicates arterial pressure.

Fig 5 Effects of pulsatile compression of the rostral ventrolateral medulla on plasma levels of epinephrine (n=6) and norepinephrine (n=6) in rats \*P < 0.1, **P < 0.05.
essential hypertension group was significantly higher than that in the secondary hypertension group or the normotensive group. In general, prolonged blood pressure elevation makes arteries elongated and tortuous. Therefore, it should be discussed whether neurovascular compression of the RVLM is a result or a cause of essential hypertension. In the present studies, however, the duration of hypertension and the degree of organ damage by hypertension were not significantly different between the two hypertension groups. Thus, it is not likely that neurovascular compression of the RVLM is the natural outcome of a chronic blood pressure elevation. Accordingly, we assume that neurovascular compression of the RVLM is a cause rather than a result of high blood pressure, at least in some patients with essential hypertension from the clinical studies.

It has been reported that chemical or electrical stimulation of the RVLM increases sympathetic nerve activity to elevate blood pressure.\(^5\) In the present experimental studies, we found that pulsatile compression of the RVLM increases sympathetic and cardiovascular activities. This finding is considered to be important because it implies that physical stimulation of the RVLM also increases sympathetic nerve activity and arterial pressure. Furthermore, although we cannot assume the long-term effects of pulsatile compression of the RVLM by the present acute experimental studies, these results support our presumption from the clinical studies described above.

Whether the pressor response in the present experimental studies is due to Cushing’s response need to be discussed. Cushing’s response is now considered to be from stretching of the receptive elements under the floor of the fourth ventricle by tissue distortion, either by direct pressure or by axial displacement of the brain stem.\(^26\) In the present studies, however, the pressor response was not induced by pulsatile compression of regions around the RVLM, and it was abolished after RVLM injection of kainic acid. Accordingly, it seems to be due to specific effects to the RVLM but not to Cushing’s response. On the other hand, when the peak value of the pressure inside the cannula was mm Hg or the rate of the pulsatile compression was mm/min, sympathetic and cardiovascular activities were not significantly increased. Thus, it is likely that pulsatile compression but not nonpulsatile compression of the RVLM is important in the pressor response.

What is the mechanism of the pressor response by pulsatile compression of the RVLM? The following evidences indicate that it is via increased sympathetic nerve activity: (1) RVLM neurons are reported to project to the spinal preganglionic sympathetic neurons,\(^27\) (2) pressor response by pulsatile compression of the RVLM was accompanied by an increase of sympathetic nerve activity in the present study, (3) plasma levels of epinephrine and norepinephrine were significantly increased by pulsatile compression of the RVLM, and (4) the pressor response was abolished after ganglion blockade with intravenously injected hexamethonium.

Microvascular decompression of the RVLM has been reported to improve hypertension.\(^10\) Jannetta et al\(^9\) reported that high blood pressure returned to normal in 32 and improved in 4 of 42 patients who were treated with left microvascular decompression of the RVLM. They reported development of hypertension by pulsatile compression of the RVLM and normalization of blood pressure by cessation of the pulsatile compression in a chronic experimental baboon model as well.\(^10\) We also observed normalization of increased sympathetic and cardiovascular activities by cessation of pulsatile compression of the RVLM in the present studies, although they were carried out acutely. Collectively, it is suggested that high blood pressure by pulsatile compression of the RVLM is reversible. Therefore, it might be possible that neurovascular decompression of the RVLM is selected as a therapy in the future for those who have neurovascular compression of the RVLM and antihypertensive medicine–resistant hypertension complicated with progressive target organ diseases.

In summary, the results from the MRI studies suggest that neurovascular compression of the RVLM is, at least in part, causally related to essential hypertension. This was supported by the results from the experimental studies indicating that pulsatile compression of the RVLM increases arterial pressure by enhancing sympathetic outflow.

References
3. Ross CA, Ruggiero DA, Puck DH, Jou TH, Svec AF, Fernandez-Pardal I, Saavedra JM, Reis DJ Tonic vasomotor control by the rostral ventrolateral medulla effect of electrical or chemical stimulation of the area containing C1 adrenergic neurons on arterial pressure, heart rate, and plasma catecholamines and vasopressors J Neurosci 1984,4 474-494
5. Willette RN, Krieger AJ, Barouq PP, Supra HB Medullary gamma-aminobutyric acid (GABA) receptors and the regulation of blood pressure in the rat J Pharmacol Exp Ther 1983,226 893-899
8. Fein FM, Feshman W Neurogenic hypertension related to vascular compression of the lateral medulla Neurosurg 1980,6 615-622
17. Devereux RB, Reschke N Echocardiographic determination of left
ventricular mass in man anatomic validation of the method Circulation 1977,55 613-618

18 World Health Organization 1993 guidelines for the management of mild hypertension memorandum from a WHO/ISH meeting Bull World Health Organ 1993,71 392-403


19 Willette RN, Barcas PP, Kriegel AJ, Sapru HN Vasopressor and depressor areas in the rat medulla Neuropharmacology 1983,22 1071-1079

20 Willette RN, Pannen S, Kriegel AJ, Sapru HN Cardiovascular control by cholinergic mechanisms in the rostral ventrolateral medulla J Pharmacol Exp Ther 1984,231 457-463

21 Rogers RC An inexpensive psclolter-volume pressure ejection system Brain Res Bull 1985,15 669-671

22 Granata AR, Ruggero DA, Park DH, Joh TH, Reis DJ Brain stem area with C1 epinephrine neurons mediates baroreflex vasodepressor responses Am J Physiol 1985,248 547-557

23 Verberne AJM, Boudier HAJS Midbrain central grey regional haemodynamic control and excitatory amino acidergic mechanisms Brain Res 1991,550 86-94


25 Bell GM Intracranial disorders and hypertension In Laragh JH, Brenner BM, eds Hypertension Pathophysiology, Diagnosis, and Management New York, NY Raven Press, 1990 703-709

26 Struck AM, Sawyer WB, Platt KB, Loewy AD CNS cell groups regulating the sympathetic outflow to adrenal gland as revealed by transneuronal cell body labeling with pseudorabies virus Brain Res 1980,191 276-296

27 Brown DL, Guyenet PG Cardiovascular neurons of brain stem with projections to spinal cord Am J Physiol 1984,247 1009-1016
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