

# Pressor Response to Compression of the Ventrolateral Medulla Mediated by Glutamate Receptors

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**Abstract**—The rostral ventrolateral medulla (RVLM) is considered a major center for the regulation of sympathetic and cardiovascular activities. Several clinical studies have indicated a possible causal relationship between neurovascular contact of the left RVLM and essential hypertension, and some investigators have suggested that the left RVLM is more sensitive to pulsatile compression than the right RVLM. Previously, we reported that pulsatile compression of the RVLM elevates arterial pressure by enhancing sympathetic outflow in rats; however, we have not investigated the laterality of the responses to the compression. In addition, it remains to be elucidated whether RVLM neurons are activated by compression and, if so, how they are activated. Therefore, we performed compression experiments in rats to investigate these issues. Pulsatile compression was performed on the unilateral RVLM with a pulsating probe in anesthetized and artificially ventilated rats. Pulsatile compression of the unilateral RVLM increased arterial pressure, heart rate, and sympathetic nerve activity. The pressor response to compression was inhibited significantly after local microinjection of glutamate receptor antagonists. Pulsatile compression of the RVLM increased Fos immunoreactivity, a marker of neuronal activation, within the nuclei of postsynaptic RVLM neurons. All results were observed symmetrically. The data indicate that the responses to pulsatile compression of the unilateral RVLM are similar on both sides. They also suggest that pulsatile compression of the RVLM increases sympathetic and cardiovascular activities by activating postsynaptic RVLM neurons through the stimulation of the local glutamate receptors in rats. (*Hypertension*. 1999;33:1207-1213.)

**Key Words:** neurons ■ receptors, glutamate ■ ventrolateral medulla ■ sympathetic nervous system ■ arterial pressure

The rostral ventrolateral medulla (RVLM) contains neurons that are the major tonic source of supraspinal sympathoexcitatory outflow<sup>1,2</sup>; thus, this area is considered an important center that regulates sympathetic and cardiovascular activities.

It has been reported that the posterior inferior cerebellar artery, anterior inferior cerebellar artery, or vertebral artery occasionally compresses the medulla oblongata in humans. Several clinical and necropsy studies have indicated a possible association between essential hypertension and neurovascular contact of the ventrolateral medulla at the root-entry zone of the glossopharyngeal and vagus nerves (ie, at the RVLM).<sup>3-5</sup> We reported previously that the incidence of observed neurovascular contact of the RVLM in an essential hypertension group was significantly higher than that in a secondary hypertension group or a normotensive group by use of MRI with a high-resolution matrix.<sup>6,7</sup> Thus, we hypothesized that neurovascular contact of the RVLM might be, at least in part, causally related to essential hypertension.

It has been shown that microvascular decompression of the RVLM on the left but not the right side improves hyperten-

sion.<sup>3</sup> Thus, it was hypothesized that the medulla oblongata has an increased sensitivity to pulsatile compression on the left side because the major portion of the afferent inputs from the myocardial receptors in the left ventricle and atrium to the nucleus tractus solitarius (NTS) are conducted by the left vagus nerve.<sup>3,8</sup> However, cardiopulmonary deafferentation does not induce sustained arterial pressure (AP) elevation<sup>9</sup> and RVLM is not considered to be functionally asymmetrical. Therefore, it remains unclear whether the left RVLM is more sensitive to physical contact than the right RVLM.

Previously, we found that pulsatile compression of the RVLM increases AP and heart rate (HR) by enhancing sympathetic outflow in rats.<sup>7</sup> We also reported that the pressor response to pulsatile compression of the RVLM disappeared after destruction of the RVLM neurons, and the pressor response was not observed by pulsatile compression of regions around the RVLM, which indicated that the pressor response to compression may be due to effects on the RVLM.<sup>7</sup> However, in that study we did not determine whether the RVLM neurons were activated by the compression and, if so, how they were activated.

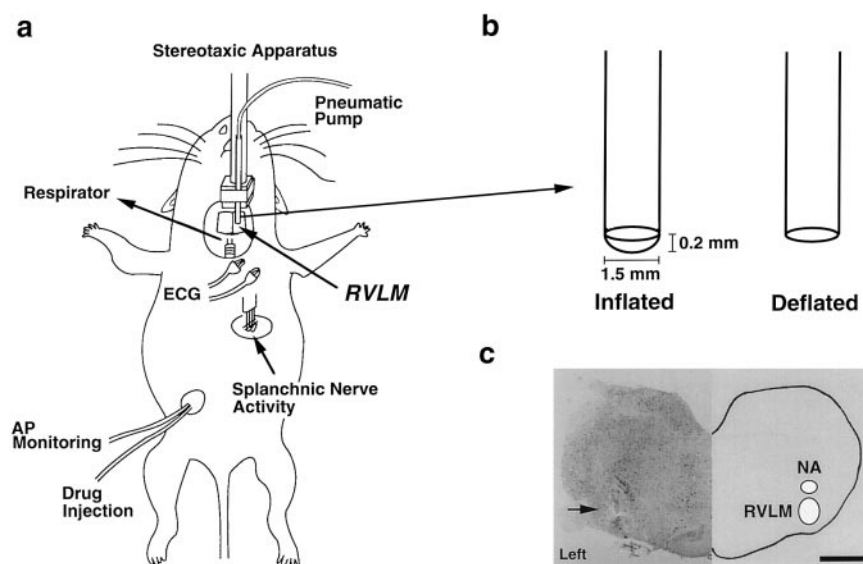
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**Figure 1.** a, Schematic drawing of the equipment for pulsatile compression of the RVLM. b, Schematic drawing of the tip of the polyurethane cannula. The rubber membrane at the tip of the cannula pulsates with a computer-controlled pneumatic pump. c, Photomicrograph of a transverse section of the medulla oblongata stained with cresyl violet. Evans blue injection site was located ventral to the NA, caudal to the facial nucleus, and rostral to the rostral end of the lateral reticular nucleus. This was comparable to the RVLM. Bar=1 mm.

Accordingly, when performing these experiments, we had 2 objectives: to determine whether responses to pulsatile compression of the left RVLM are greater than those of the right RVLM and to examine whether RVLM neurons are activated by pulsatile compression of the RVLM. We also examined whether the response to compression is mediated by glutamate receptor stimulation in rats.

## Methods

### General Surgical Procedures

All experiments were performed in male Wistar rats (Charles River Breeding Laboratories, Kanagawa, Japan) that weighed between 300 and 400 g. Animal care and procedures were approved by the Experimental Animal Care Committee of the Kyoto Prefectural University of Medicine, Japan. The rats were anesthetized with urethane (100 mg per 100 g IP). Anesthetic was supplemented (10 to 30 mg per 100 g IP) as dictated by the presence of corneal reflex and/or cardiovascular responses to surgical procedures. Each rat was mounted on a stereotaxic apparatus<sup>10,11</sup> (David Kopf Instruments) in the supine position (Figure 1a). The lower trachea was cannulated, and the rat was artificially ventilated at a rate of 60 breaths/min with a respirator (Ealing Co, Ltd) and paralyzed with decamethonium bromide (0.2 mg per 100 g IV).

Catheters were inserted separately into the right femoral artery for recording AP and HR and into the right femoral vein for drug injection. To record sympathetic nerve activity (SNA), the splanchnic nerve was placed over a bipolar stainless steel electrode and spike potentials were amplified and counted as described by Sasaki et al.<sup>12</sup>

The upper trachea, esophagus, and surrounding musculature were excised. The bilateral lungus capitis muscles were removed to expose the occipital foramen and the basal aspect of the occipital bone. The ventral surface of the medulla oblongata was then exposed. The RVLM was identified by a pressor response of >25 mmHg mean AP after microinjection of L-glutamic acid monosodium salt (2 nmol per 100 nL saline) with the stereotaxic apparatus. The coordinates for the RVLM were located 3.5 to 4.7 mm rostral to the most caudal aspect of the occipital foramen, 1.7 to 2.1 mm lateral to the midline, and 0.5 to 0.8 mm below the ventral surface of the medulla oblongata.

### Microinjection Procedures

We used glass micropipettes with tip diameters of 50  $\mu$ m for microinjections. Microinjections were made unilaterally during a 30-second period with a computer-controlled pneumatic pump.<sup>13</sup>

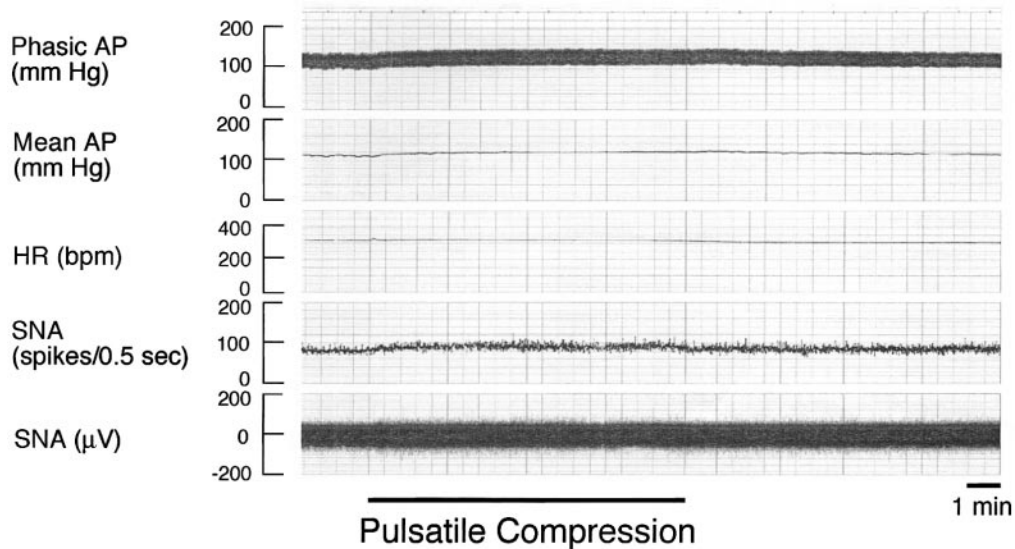
The injection volume was measured by observing the movement of the fluid meniscus along a reticule under a microscope.

### General Experimental Procedures

A polyurethane cannula with an outer diameter of 1.5 mm (Figure 1a and 1b) was connected to the pneumatic pump, and a rubber membrane was attached to the opposite end of the cannula. By pumping air triggered by ECG monitorings, the membrane pulsated (Figure 1b), and the pressure wave inside the cannula mimicked an intra-arterial pressure wave. The peak value of the pressure inside the cannula was set at 300 mmHg because of low compliance of the rubber membrane compared with that of the arterial wall. The duration of air compression was set at 50 milliseconds. The rubber membrane moved 0.2 mm in response to the pressure. With the use of the stereotaxic apparatus, the cannula was compressed to the ventral surface of the RVLM 1 mm dorsally. Changes in AP, HR, and splanchnic SNA by pulsatile compression of the unilateral RVLM were monitored for 10 minutes (left side or right side). After full recovery from the first experiment with a waiting period of at least 30 minutes, a second experiment on the opposite side was performed.

### Effects of Glutamate Receptor Antagonists on the Pressor Response to Pulsatile Compression of the RVLM

To investigate the roles of glutamate receptors in the pressor response to pulsatile compression of the RVLM, responses to unilateral pulsatile compression of the RVLM for 10 minutes were compared 5 minutes after ipsilateral microinjection of a glutamate receptor antagonist in separate rats. We used the nonselective ionotropic glutamate receptor antagonist kynurenate (100 pmol, 1 nmol, 10 nmol per 50 nL saline), the NMDA receptor antagonist D-2-amino-5-phosphonovalerate (AP-5; 10 pmol, 100 pmol, 1 nmol per 50 nL saline), or the non-NMDA receptor antagonist 6-cyano-7-nitroquinoxaline 2,3-dione (CNQX; 10 pmol, 100 pmol, 1 nmol per 50 nL saline). This experiment was performed in sinoaortic denervated (SAD) rats to clarify the differences in pressor response amplitudes by removing baroreflex modulation. Sinoaortic denervation was performed according to the method of Krieger.<sup>14</sup> Briefly, the carotid sinus, aortic depressor, and superior laryngeal nerves were sectioned bilaterally. The superior cervical ganglia were removed bilaterally, and the adventitia was stripped from the carotid bifurcation. A single compound was used in each rat. After full recovery from 1 experiment with a waiting period of at least 30 minutes, experiments on the opposite side were performed, and the



**Figure 2.** Representative tracing that shows the effects of pulsatile compression of the left RVLM on cardiovascular and sympathetic activities.

order of drug injections at different doses was randomized between experiments.

### Histological Analysis for the Microinjection Sites

At the end of these experiments, 50 nL of Evans blue dye was microinjected to mark the injection site. The rats were then perfused transcardially with 100 mL of 0.9% NaCl followed by 150 mL of 10% phosphate-buffered formaldehyde. Serial 4- $\mu$ m transverse sections of the medulla oblongata were stained with cresyl violet and subjected to light microscopic examination. The microinjection sites were identified by the location of Evans blue dye and the use of the Paxinos and Watson atlas.<sup>15</sup>

### Immunohistochemistry for Fos

In the group of animals without sinoaortic denervation, immunostaining for Fos after compression of the medulla oblongata was performed. In these experiments, L-glutamate injection was not used for identification of the RVLM to avoid stimulating Fos expression. We found that pulsatile compression of the RVLM increased >10 mm Hg in this rat model,<sup>7</sup> and only the rats that showed a pressor response of >10 mm Hg after pulsatile compression of the RVLM region (ie, 3.5 to 4.7 mm rostral to the most caudal aspect of the occipital foramen and 1.7 to 2.1 mm lateral to the midline) were used for these experiments. Pulsatile compression was given on the RVLM for 5 minutes, and 90 minutes after initiation of the compression, the rats were perfused via the heart with fixative (4% formaldehyde, 0.2% picric acid in 100 mmol/L PBS, pH 7.2, 4°C). After perfusion, the medulla oblongata was removed and immersed in the fixative for 16 hours at 4°C. It was incubated in 20% sucrose solution for 48 hours at 4°C and then frozen with CO<sub>2</sub> gas. Serial 20- $\mu$ m transverse sections of the medulla oblongata were cut with a cryostat.

Free-floating sections were treated with 0.3% H<sub>2</sub>O<sub>2</sub> in PBS for 3 hours at room temperature and then washed with 0.25% Triton X-100 in phosphate-buffered saline (PBST). The sections were incubated in (1) primary anti-Fos (rabbit polyclonal, 1:5000) for 72 hours; (2) PBST for 15 minutes; (3) biotinylated anti-rabbit IgG (PK 4001 kit) for 2 hours; (4) PBST for 15 minutes; (5) avidin-biotin-peroxidase complex (PK 4001 kit) for 1 hour; (6) PBST for 15 minutes; and (7) 0.02% 3,3'-diaminobenzidine, 0.3% nickel ammonium sulfate, and 0.006% H<sub>2</sub>O<sub>2</sub> in 50 mmol/L Tris-HCl (pH 7.6) for 15 minutes. Sections were examined by light microscopy, and the locations of Fos-immunoreactive cells were estimated with the Paxinos and Watson atlas.<sup>15</sup>

### Materials

CNQX was obtained from Tocris Cookson Ltd. Anti-Fos was obtained from Oncogene Science, Inc, and the PK 4001 kit was from Vector Labs, Inc. All other reagents were from Sigma Chemical Co.

### Statistical Analysis

Values are given as mean  $\pm$  SEM. Pulsatile compression-response curve data were compared between the left and right side of the RVLM by repeated-measures ANOVA followed by Fisher's multiple-range test. Pressor responses to pulsatile compression of the RVLM after pretreatment with glutamate receptor antagonists were compared by 1-factor ANOVA followed by Fisher's multiple range test. Group-to-group comparisons were made by nonpaired Student *t* test. A *P* value <0.05 was considered statistically significant.

## Results

### Histological Analysis for the Microinjection Sites

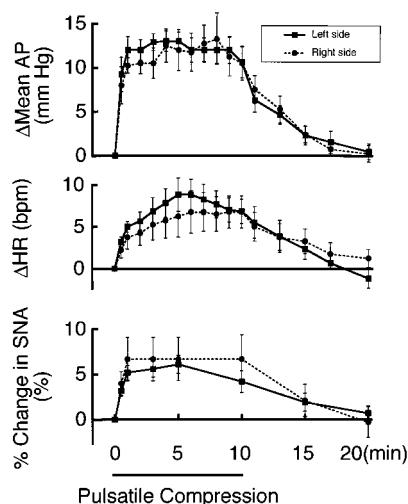
Evans blue injection sites were located ventral to the nucleus ambiguus (NA), caudal to the facial nucleus, and rostral to the rostral end of the lateral reticular nucleus, which was comparable to the RVLM (Figure 1c).

### Effects of Pulsatile Compression of the RVLM

Mean AP and HR were elevated and accompanied by an increase in SNA after pulsatile compression of the unilateral RVLM (Figures 2 and 3). The pressor response appeared within 5 seconds, plateaued 2 to 6 minutes after initiating compression, and returned to normal immediately after cessation of compression. The maximum changes and the peak latency of all parameters were similar on both sides of the RVLM (Figure 3), which indicates that the effects of pulsatile compression of the unilateral RVLM are symmetrical in rats.

### Effects of Glutamate Receptor Antagonists on the Pressor Response to Pulsatile Compression of the RVLM

With the use of SAD rats, we investigated whether the sympathetic and cardiovascular responses are mediated by activation of glutamate receptors in the RVLM. Blockade of

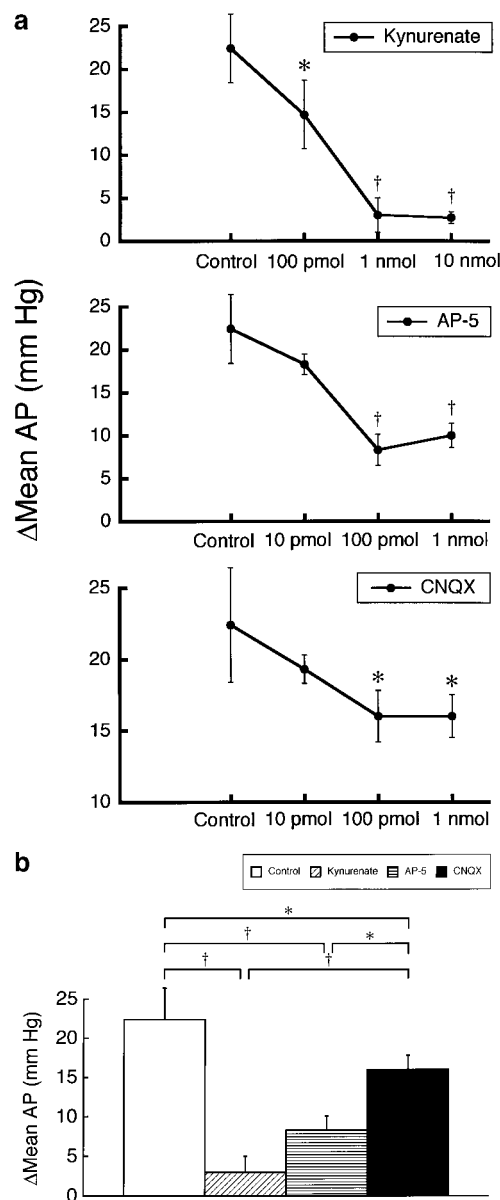


**Figure 3.** Effects of pulsatile compression of the unilateral RVLM on sympathetic and cardiovascular activities (left side,  $n=14$ ; right side,  $n=8$ ). The maximum changes and the latency to reach the peak values of all these parameters were similar in both sides of the RVLM. Bars represent SEM.

the baroreflex by sinoaortic denervation enhanced the pressor response to pulsatile compression (from  $16.8 \pm 1.3$  [non-SAD rats] to  $22.9 \pm 2.3$  mm Hg [SAD rats],  $P < 0.05$ ,  $n=10$ ). Microinjection of each glutamate receptor antagonist into the RVLM had no significant effects on baseline mean AP, HR, or SNA ( $n=10$  for all groups, data not shown). The pressor response to compression was significantly inhibited in a dose-related fashion after microinjection of each glutamate receptor antagonist. The maximum inhibitory effects were observed with 1 nmol of kynurenate, 100 pmol of AP-5, and 100 pmol of CNQX (Figure 4a). The pressor response was nearly abolished after microinjection of 1 nmol of kynurenate (Figure 4b). The response was partially but significantly reduced after microinjection of 100 pmol of AP-5 or 100 pmol of CNQX. The reduction in the pressor response after AP-5 injection was significantly greater than that after the CNQX injection. Results were similar on both sides of the RVLM ( $n=5$  for each group, data not shown). These results indicate that pulsatile compression of the RVLM increases AP by activation of both NMDA and non-NMDA receptors but primarily through activation of NMDA receptors in the RVLM. The results also suggest that the effects of glutamate receptor antagonists on the pressor responses to pulsatile compression of the RVLM are symmetrical in rats.

### Immunohistochemistry for Fos

Pulsatile compression of the RVLM increased Fos-immunoreactive neurons in the ipsilateral ventrolateral medulla (ie, ventral to the NA, caudal to the facial nucleus, and rostral to the caudal end of the lateral reticular nucleus; Figures 5a-A and 5a-B) and the rat atlas<sup>15</sup> indicates that this area includes the Evans blue microinjection site at which the compression cannula was thought to be compressed. The number of Fos-immunoreactive neurons in the ipsilateral RVLM (at the level of Figure 71 in the Paxinos and Watson atlas<sup>15</sup>) was significantly higher than in the sham-operated control rats (Figure 5b). Some Fos-positive neurons were also

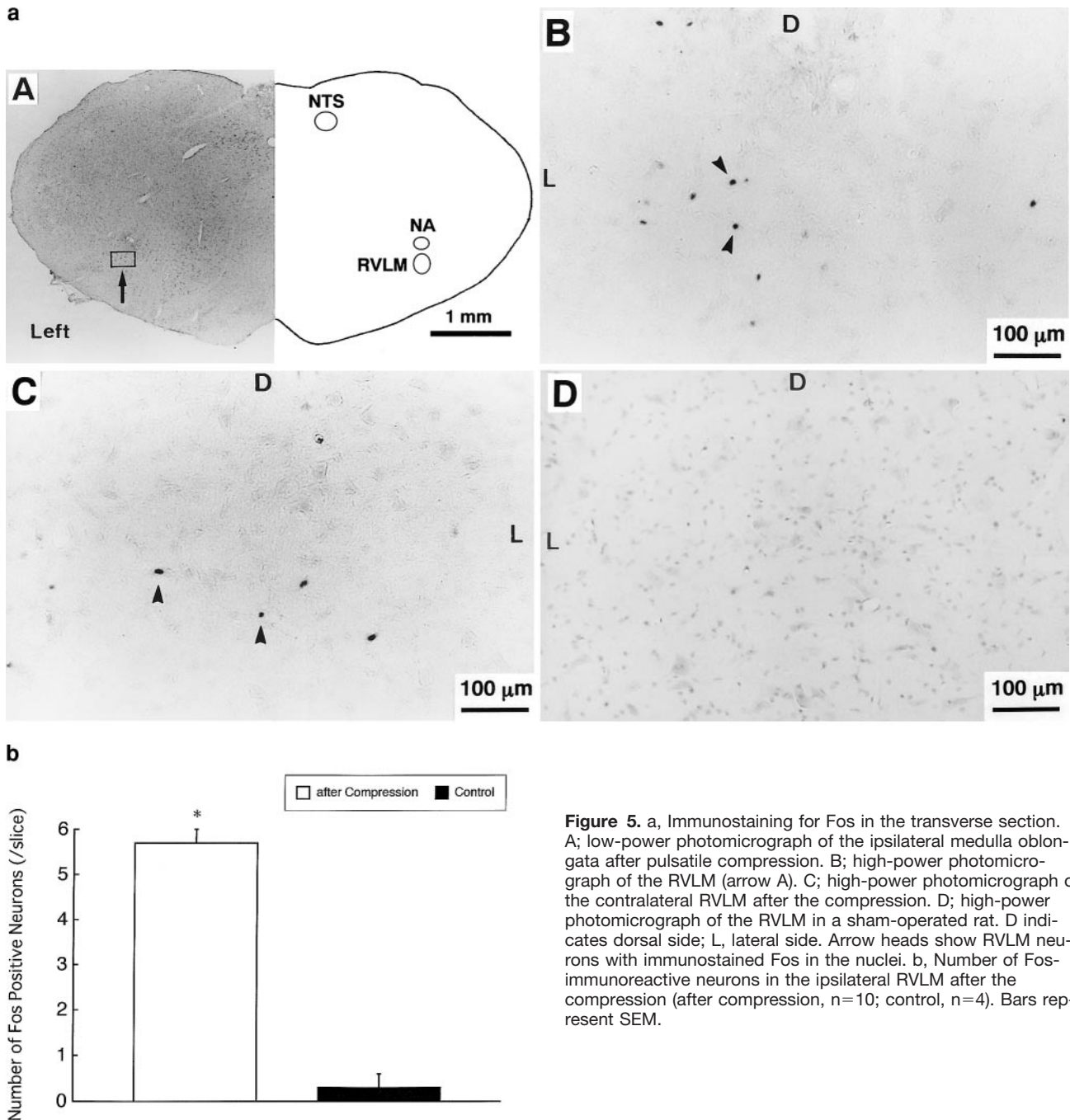


**Figure 4.** Effects of microinjection of glutamate receptor antagonists on the pressor response to pulsatile compression of ipsilateral RVLM in SAD rats. a, Dose-relation curves of the effects of glutamate receptor antagonists ( $n=10$  for all groups,  $*P < 0.05$  and  $\dagger P < 0.01$  compared with control rats). b, Comparison of the maximum effects of glutamate receptor antagonists ( $n=10$  for all groups,  $*P < 0.05$ ,  $\dagger P < 0.01$ ). Bars represent SEM.

found in the contralateral ventrolateral medulla (Figure 5a-C) and the bilateral NTS (Figure 5a-A). Pulsatile compression of regions around the RVLM (1 mm lateral, 1 mm medial, and 1 mm rostral) did not elevate the AP or produce Fos-immunoreactive neurons in the medulla oblongata (data not shown). Fos immunoreactivity was found in the nuclei of the neurons (ie, in the cell bodies of postsynaptic neurons). Fos expression was symmetrical at all these sites after compression of the ipsilateral RVLM.

### Discussion

In these short-term experiments with anesthetized rats, we found that pulsatile compression of the RVLM increased



**Figure 5.** a, Immunostaining for Fos in the transverse section. A; low-power photomicrograph of the ipsilateral medulla oblongata after pulsatile compression. B; high-power photomicrograph of the RVLM (arrow A). C; high-power photomicrograph of the contralateral RVLM after the compression. D; high-power photomicrograph of the RVLM in a sham-operated rat. D indicates dorsal side; L, lateral side. Arrow heads show RVLM neurons with immunostained Fos in the nuclei. b, Number of Fos-immunoreactive neurons in the ipsilateral RVLM after the compression (after compression,  $n=10$ ; control,  $n=4$ ). Bars represent SEM.

sympathetic and cardiovascular activities and that the pressor response was significantly inhibited after local microinjection of glutamate receptor antagonists. In addition, pulsatile compression of the RVLM increased the number of Fos-positive RVLM neurons. All results were observed symmetrically. These data indicate that the responses to pulsatile compression of the unilateral RVLM are similar on both sides and that pulsatile compression of the RVLM increases AP by activating postsynaptic RVLM neurons through stimulation of local glutamate receptors in rats.

Since the first report by Jannetta et al,<sup>3</sup> several investigators have reported a possible association between essential hypertension and neurovascular contact of the RVLM.<sup>4,5</sup>

Microvascular decompression of the RVLM on the left side but not the right side has also been reported to improve hypertension.<sup>3</sup> The medulla oblongata is also thought to be more sensitive to compression on the left versus the right side because most of the afferent inputs from the myocardial receptors in the left ventricle and atrium to the NTS are conducted by the left vagus nerve.<sup>3,8</sup> In addition, pulsatile compression of the left RVLM was reported to increase AP in an experimental baboon model.<sup>16</sup> However, cardiopulmonary deafferentation does not induce sustained AP elevation,<sup>9</sup> and RVLM is not considered to be functionally asymmetrical. In our MRI study,<sup>6</sup> we reported that neurovascular contact of the RVLM was observed in 15 of 20 (75%) patients with

essential hypertension, including 7 patients with contact on the left side, 7 patients with contact on the right side, and 1 patient with contacts on both sides, which indicates that neurovascular contact of the right RVLM might be also related to essential hypertension. Naraghi et al<sup>17</sup> reported that bilateral neurovascular contacts were observed in 6 of 15 (40%) patients with hypertension and brachydactyly. Therefore, it still has not been determined whether the left RVLM is more sensitive than the right RVLM to contact. However, in the present study, we found that pulsatile compression caused similar changes in the magnitudes and peak latencies of the sympathetic and cardiovascular activities on both sides. Fos expression in the medulla oblongata and the inhibitory effects of glutamate receptor antagonists on the pressor response to the compression were also similar on both sides. Thus, it is likely that responses to pulsatile compression of the unilateral RVLM are symmetrical. However, because the present experiments were short term and performed in anesthetized animals, it remains to be elucidated whether neurovascular contact of the right RVLM is related to essential hypertension.

L-Glutamate is hypothesized to be an excitatory neurotransmitter in the RVLM, and microinjection of L-glutamate into the RVLM rapidly increases AP, HR, and SNA.<sup>11</sup> The pressor response to pulsatile compression of the RVLM also appeared immediately after initiating compression in our rat model. Therefore, we investigated whether the pressor response to pulsatile compression of the RVLM is mediated by local glutamate receptors. The pressor response was nearly abolished after microinjection of kynurenate, a nonselective ionotropic glutamate receptor antagonist. Responses were significantly reduced not only after microinjection of the NMDA receptor antagonist AP-5 but also after injection of the non-NMDA receptor antagonist CNQX. The reduction in the pressor response after AP-5 injection was significantly greater than that after CNQX injection. Therefore, it is likely that pulsatile compression of the RVLM increases sympathetic outflow through stimulation of both NMDA and non-NMDA receptors but primarily through stimulation of NMDA receptors in the RVLM.

We have reported previously that the pressor response to pulsatile compression of the RVLM disappeared after destruction of the RVLM neurons with kainate in rats.<sup>7</sup> The pressor response was not induced by pulsatile compression of regions around the RVLM. Thus, we hypothesized that the pressor response to pulsatile compression of the RVLM was due to effects on the RVLM. However, we could not prove that the RVLM neurons were activated by compression. Neuronal excitation leads to a rapid and transient induction of *c-fos*.<sup>18</sup> Fos, the protein product of *c-fos*, is detected in neurons by immunohistochemistry 20 to 90 minutes after neuronal excitation.<sup>18,19</sup> Once expressed, Fos enters the cell nuclei and functions as a transcriptional regulator in cooperation with Jun through activator-protein-1 regulatory elements.<sup>20</sup> Electron microscopy has shown that neuronal excitation induces Fos immunoreactivity within the nuclei of neurons but not within glial or endothelial cells.<sup>21</sup> Therefore, Fos expression could be a useful marker of neuronal activation at the single cell level. In the present study, we found that

pulsatile compression of the RVLM increased the number of RVLM neurons with Fos immunoreactivity in the nuclei. Neurons having nuclei (cell bodies) in the RVLM are considered to be postsynaptic RVLM neurons. Thus, it seems that postsynaptic RVLM neurons are activated through stimulation of glutamate receptors by pulsatile compression of the RVLM. Activation of RVLM neurons is likely not to be secondary to direct activation of caudal ventrolateral medulla (CVLM) neurons and/or NTS neurons for the following reasons:

(1) pulsatile compression would not have directly activated neurons far from the compressed site because compression of regions around the RVLM did not induce Fos expression in the RVLM; (2) some pathways such as the baroreflex may be involved in this phenomenon because some neurons on both sides of the CVLM and NTS and the contralateral RVLM were also positive for Fos; and (3) direct activation of the CVLM and/or NTS would have decreased AP, HR, and SNA.<sup>2</sup>

Glutamate receptors are located principally on postsynaptic neurons in the central nervous system.<sup>22</sup> We believe that pulsatile compression of the RVLM activates postsynaptic RVLM neurons by stimulating glutamate receptors to increase SNA, AP, and HR. However, the mechanism of glutamate receptor stimulation enhancement by L-glutamate and the intracellular mechanism of neuronal excitation remains to be elucidated. Also, whether the compression affects cells other than the postsynaptic RVLM neurons (ie, presynaptic neurons and glial and endothelial cells in the RVLM) remains to be determined. Additional studies are needed to clarify the mechanism of the pressor response to the compression.

In summary, the results of our study indicate that the responses to pulsatile compression of the RVLM are symmetrical in rats. They also suggest that pulsatile compression of the RVLM activates local postsynaptic neurons through stimulation of both NMDA and non-NMDA receptors but primarily through NMDA receptors to thereby increase sympathetic and cardiovascular activities.

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