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Role of Rostroventrolateral Medulla in Somatosympathetic Pressor and Depressor Response Evoked by Peripheral Nerve Stimulation

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= ABSTRACT =

The rostral ventrolateral medulla (RVLM) has been established recently as a sympathoexcitatory area. The present study was conducted to investigate whether the somatosympathetic pressor and/or depressor responses are mediated through RVLM in cats anesthetized with α-chloralose. An occipital craniectomy was performed and ventrolateral medulla were stimulated either electrically or chemically to evoke changes in arterial blood pressure. And then the effect of lesions in the ventrolateral medulla on the changes in blood pressure elicited by the peripheral nerve stimulation was observed.

Followings are the results obtained:

1) Pressor areas were found in the ventrolateral medulla, lateral reticular nucleus and rostral dorsal area.

2) Depressor areas were found mainly in the ventrolateral medulla rostral to the pressor areas.

3) Some areas showed biphasic responses: a depressor response to lower frequency and a pressor response to higher frequency stimulation.

4) After electrical lesion in pressor area in RVLM, the somatosympathetic pressor response was abolished or depressed markedly. The somatosympathetic depressor response, however, remained after the lesion.

5) Electrical lesion in the depressor area abolished somatosympathetic depressor response.

From the above results it is concluded that somatosympathetic pressor response is mediated through RVLM, while somatosympathetic depressor response is not mediated through RVLM.

Key Words: Rostroventrolateral medulla, Somatosympathetic reflex, Vasopressor area, Vasodepressor area.

INTRODUCTION

Investigators have challenged for a long time to localize the neuronal groups in brain stem which maintain the resting tone of arterial blood pressure. Although medulla oblongata has been known as a critical site of arterial blood pressure regulation for over one hundred years, the exact site was not envisaged and it was only known that the neuronal groups are located broadly from rostral to caudal medulla (Hilton, 1975). But recently numerous studies have revealed that not broad neuronal groups

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but that in rostral ventrolateral medulla (RVLM) play a critical role in maintaining the level of blood pressure (Ciriello & Calaresu, 1977; Ross et al, 1983; McAllen, 1986; Chai et al, 1988; Reis et al, 1988). Stimulation of this area by microinjection of glutamate increases blood pressure, whereas glycine decreases it. These results are due specifically to the involvement of cell bodies, rather than axons of passage (Guertzenstein, 1973; Feldberg & Guerzenstein, 1976; Willette et al, 1983; Stornetta et al, 1989). Anatomically a pathway from the RVLM to the intermediolateral nucleus (IML) of the thoracolumbar spinal cord has been demonstrated with axonal transport methods using tritiated amino acid and HRP (horseradish peroxidase) (Amendt et al, 1979; Caverson et al, 1983; Ciriello et al, 1986). By immunocytochemical labelling of adrenaline synthesizing enzyme phenylethanolamine N-methyl transferase (PNMT), it was proposed that neurons in RVLM correspond to adrenergic neurons of the C_1 group (Ross et al, 1983; Ciriello et al, 1986).

Stimulation of peripheral nerves can evoke somatosympathetic reflexes (SSR) (Johansson, 1962; Chung & Wurster, 1976; Chung et al, 1979; Kim et al, 1986). These reflexes are mediated mainly by group Aδ-fiber and unmyelinated group C-fiber (Sato & Schmidt, 1973). The well-known function of Aδ-fiber and C-fiber is related to nociception. The most important example of somatosympathetic reflex is blood pressure change. It is known that stimulation with Aδ-intensity (1 mA), low frequency (1-2 Hz) evoke depressor response, whereas stimulation with C-intensity(10 mA), high frequency (20-50 Hz) evoke pressor response (Johansson, 1962; Sato & Schmidt, 1973; Kim et al, 1986). The reflex pathway underlying the SSR was proposed to be that the afferent input travel through spinal cord to vasomotor areas in the medulla oblongata from which fibers descend to sympathetic preganglionic neurons located in intermediolateral cell column.

Although it is known that the Aδ-afferent inputs mediating depressor response ascends in spinal cord via dorsolateral funiculus (DLF) and C-afferent pressor inputs ascends via dorsolateral sulcus (DLS) area (Chung & Wurster, 1976; Chung et al, 1979), the exact location of the medullary relay neurons has not been investigated much.

In the present study, we attempted to determine whether RVLM play a role in the integration of the SSR.

METHODS

Preparation of animal

Adult cats of either sex (2-3.5 kg, body weight) were used. Animal was anesthetized with single combined dose of ketamine (Ketalar, 20 mg/kg, i.m.) and α-chloralose (60 mg/kg, i.p.). Trachea, femoral artery and vein were cannulated and used for artificial ventilation, blood pressure monitoring and intravenous injection, respectively. Animal was paralyzed by intravenous administration of pancuronium bromide (Mioblock, Organon, initial dose 0.4 mg, maintaining dose 0.4 mg/hour). The carotid sinus and vagus nerve were cut bilaterally to block the baroreflex inputs. End-expiratory CO_2 concentration was maintained at 3-4% and rectal temperature was maintained at 37± 1°C. Hartmann's solution was infused continuously throughout the experiment (10-15 ml/hour).

An occipital craniectomy was performed. To expose the floor of the fourth ventricle, the cerebellum was removed by suction. The sciatic, common peroneal and tibial nerves were isolated and exposed for electrical stimulation in the left hindlimb.

After operation the animal was mounted on a stereotaxic apparatus and mineral oil pools were made with incised skin flaps over exposed areas.

Stimulation and recording

After a recovery period of at least an hour, a specially designed needle electrode for simultaneous electrical stimulation and drug infusion (kindly borrowed from Dr. W.T. Oh) was placed at medulla using micromanipulator and lowered deep down step by step. The pressor and depressor areas were identified by stimulation of medullary sites systematically. For electrical stimulation, brief square pulses (0.1 msec, 100-200 μA, 50 Hz) were applied, and for chemical stimulation, glutamate solution (0.5 M) in a volume of 100 nl were delivered over a period of 20-30 sec using Hamilton syringe.

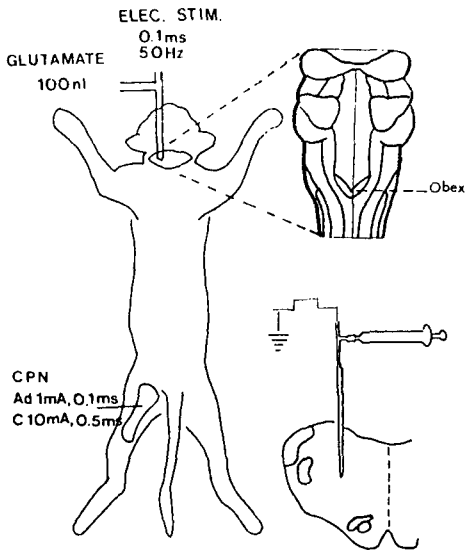

Fig. 1. A schematic diagram of experimental setup. Vasomotor areas were identified by electrical(100-200 μA, 0.1ms, 50Hz) and chemical (glutamate, 100 nl) stimulation. A specially desigend needle electrode was used for both electrical stimulation and glutamate injection. To elicit somatosympathetic pressor and depressor responses, the common peroneal nerve was stimulated electrically with varying intensities and frequencies.

Responses of the arterial blood pressure to stimulation of common peroneal nerve with Aδ-intensity (500 μA-1 mA, 0.1 msec) and C-intensity (10 mA, 0.5 msec) for 20 sec were observed as a somatosympathetic response (Fig. 1). Electrolytic lesions in RVLM were made with DC currents of 1-2 mA for 20-30 sec. Then, we compared the change in blood pressure before and after electrolytic lesion.

Histology

At the end of experiment, animal was sacrificed with excess amount of anesthetics and then brainstem was taken out and fixed in a 10% formaline solution for at least a week. After then the tissues were frozen, cut by 40 μm thickness, and stained with cresyl violet. Lesion sites maps were made using camera lucida.

RESULTS

Fig. 2 shows examples of somatosympathetic pressor and depressor responses evoked by electrical and natural mechanical stimulation. In the upper panel, a depressor response was evoked by stimulation of common peroneal nerve with low intensity (Aδ-intensity, 1 mA), low frequency (1-2 Hz) and a pressor response, by stimulation with high intensity (C-intensity, 10 mA), high frequency (20-50 Hz) in the cat. In the lower panel, the responses to noxious mechanical and chemical stimulation given to the hindlimb of a rat were shown to compare with the response of cat to electrical stimulation. As shown in the figure squeezing of deep tissue (bone, joint) evoked pressor response, whereas pinching of cutaneous tissue evoked depressor response. After hypodermal injection of formaline which is an algesic substance, a pressor response was evoked.

Figure 3 shows an example of pressor response to RVLM stimulation. The stimulation site was: 5 mm rostral to obex, 4 mm

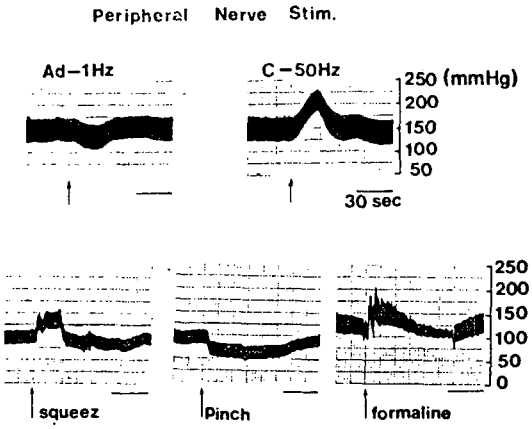

Fig. 2. An example of somatosympathetic pressor response evoked by electrical and natural stimulation. Upper panels show depressor and pressor response by electrical stimulation of common peroneal nerve of cat with low intensity(Aδ), low frequency(2Hz) and with high intensity(C), high frequency(50Hz) stimuli, respectively. Lower panels show pressor and depressor responses evoked by natural stimulation of squeezing and pinching on the hindlimb of rat, respectively as well as chemical stimulation with intradermal injection of formaline.

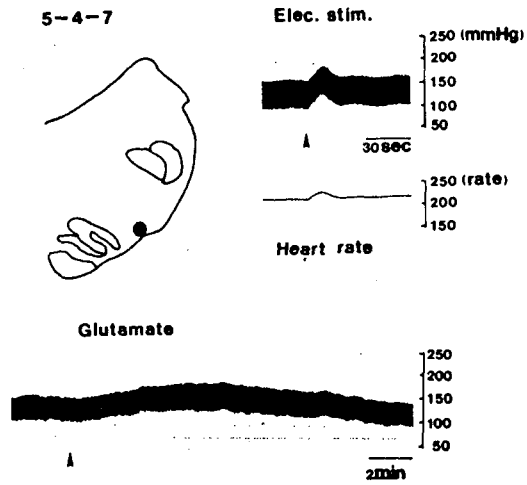

Fig. 3. An example of vasopressor area which was identified by electrical stimulation and microinjection of glutamate. Electrical stimulation evoked immediately pressor response and increased heart rate. On the other hand glutamate evoked gradual elevating pressor response. The site was at 5 mm rostral to the obex, 4 mm lateral to midline and 7 mm deep to the floor of the 4th ventricle.

lateral to midline, and 7 mm below the dorsal surface. With electrical stimulation blood pressure increased by larger than 30 mmHg, and also the heart rate increased. With microinjection of glutamate, an excitatory neurotransmitter, a gradual pressor response was evoked and maintained for longer than ten minutes. The response patterns to glutamate application were not always the same as that in the figure: in some experiments arterial blood pressure increased by glutamate initially but abruptly decreased below basal tone and then did not recover at all.

An example of depressor response to electrical stimulation and glutamate was shown in Fig. 4. The coordinates were: 4 mm rostral to obex, 4 mm lateral to midline, 4 mm below the dorsal surface. With electrical stimulation blood pressure decreased by about 40 mmHg and also the heart rate. With glutamate application, arterial blood pressure decreased slowly. In general, however, mi-croinjection of glutamate to the sites eliciting depressor response to electrical stimulation did evoke no apparent depressor response.

The distribution of pressor and depressor areas histologically identified in this experiment and compiled on to the stereotaxic map of Reinoso-Suarez's atlas from obex to 5 mm rostral was shown in Fig. 5. Pressor responses were observed mainly in three parts: the ventrolateral area, the lateral reticular nucleus, the dorsomedial area. Most of the depressor areas were overlapped

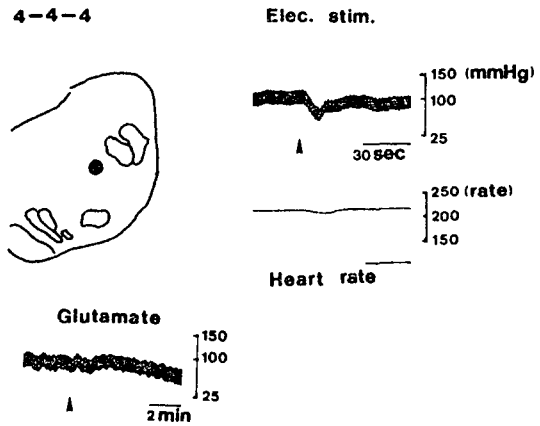

Fig. 4. An example of vasodepressor area identified by electrical stimulation and glutamate injection. Blood pressure and heart rate decreased immediately in response to electrical stimulation for 10 seconds with 100 uA, 50 Hz stimuli, while microinjection of glutamate (100 nl) elicited gradual decrease in blood pressure. This site was at 4 mm rostral to the obex, 4 mm lateral to midline and 4 mm deep to the floor of 4th ventricle. Arrows indicate the times of stimulation.

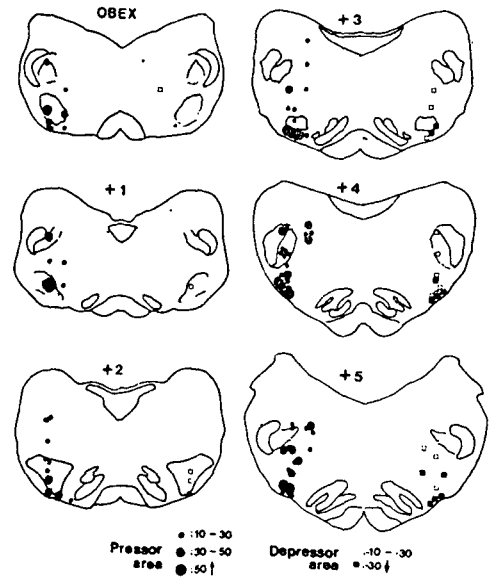

Fig. 5. Distribution of pressor and depressor sites in ventrolateral meulla. In left panel, pressor sites and in right panel, depressor sites were compiled on the map of the sterotaxic atlas of Reinoso-Suarez(1961). The positive numbers indicate the rostrocaudal medullary sections rostrally upto 5 mm from the obex. Pressor areas were found in the ventrolateral medulla, lateral reticular nucleus and rostral dorsomedial medulla, while depressor areas are found mainly in the rostral ventrolateral area.

with those of pressor areas; They were located mainly in rostral ventrolateral area and sometimes in dorsomedial area.

In some experiment a biphasic response pattern to electrical stimulation with different frequency. Such an example was shown in Fig. 6. The site was 3 mm rostral to obex, 4 mm lateral to midline and 6 mm below the dorsal surface. With 50 Hz stimulation an obvious pressor response was evoked whereas with 2 Hz stimulation a depressor response was evoked.

The next step of present study was aimed to determine whether somatosympathetic reflexes were mediated by these medullary pressor and depressor areas. Fig. 7 provides an evidence for the mediation of somatosympathetic depressor response by depressor area in ventrolateral medulla. The site was 4 mm rostral to obex, 4 mm lateral to

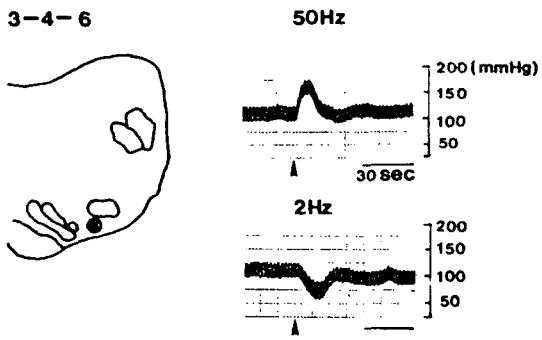

Fig. 6. An example of biphasic response to electrical stimulation of medulla with different frequency: a depressor response to lower frequency and a pressor response to higher frequency. This site was at 3 mm rostral to the obex, 4 mm lateral to midline and 6 mm deep to the floor of 4th ventricle.

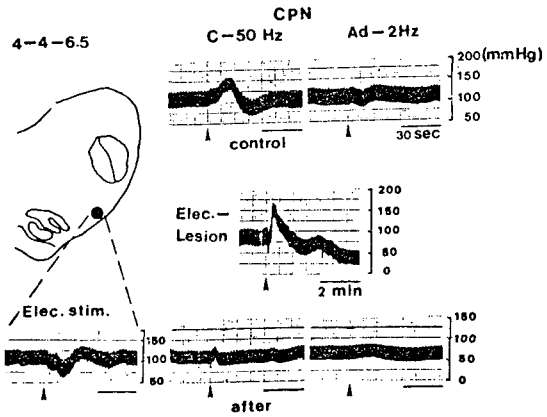

Fig. 7. Evidence for the mediation of somatosympathetic depressor response by ventrolateral medulla. The depressor area was found by electrical stimulation and somatosympathetic pressor and depressor responses were evoked by stimulation of common peroneal nerve. After electrical lesion on depressor area, the somatosympathetic depressor response was abolished but the somatosympathetic pressor response was still remained, although the size of it decreased. This site was at 4 mm rostral to the obex, 4 mm lateral to midline and 6.5 mm deep to the floor of 4th ventricle.

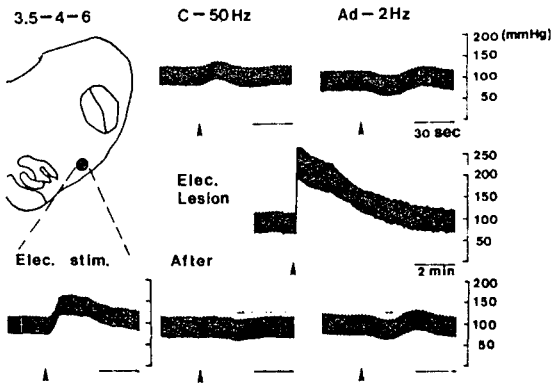

Fig. 8. Evidence for the mediation of somatosympathetic pressor response by ventrolateral medulla. The pressor area was found by electrical stimulation. Somatosympathetic pressor and depressor responses were evoked by stimulation of common peroneal nerve. After electrical lesion on a pressor area, somatosympathetic pressor response was abolished but the somatosympathetic depressor response still remained.

midline and 6.5 mm below the dorsal surface. After identifying the depressor area we evoked somatosympathetic pressor and depressor response by stimulation of the common peroneal nerve. Then electrolytic lesion was made in that site, and stimulated again the common peroneal nerve to compare the result with that before electrolytic lesion. During electrolytic lesion, slight decrease in arterial blood pressure, followed by a marked pressor response, which may be due to current spread beyond the depressor area. After lesion, the depressor somatosympathetic response changed into pressor response and the amplitude of pressor response also decreased much. In this experiment a microinjection of glutamate did not elicit apparent depressor response and the pressor response decreased after electrolytic lesion, so it is not certain whether this area mediates the somatosympathetic depressor response. But we confirmed in other experiment that depressor response remained after abolishing the pressor response by electrical lesion in pressor area. The result is shown in Fig. 8. The coordinates were: 3.5 mm rostral to obex, 4 mm lateral to midline, 4.6 mm below the dorsal surface.

DISCUSSION

The mechanism of arterial blood pressure regulation should involve modifications on activities of sympathetic preganglionic neurons located in thoracic and upper lumbar intermediolateral (IML) nucleus. Recently owing to antidromic stimulation method

and axonal transport method it has been now accepted that neurons in rostral ventrolateral portion of medulla play a critical role in determining the resting blood pressure, for such neurons project directly to the thoracolumbar IML to provide the basal tone of the sympathetic nerve discharge (Amendt et al, 1979; Caverson et al, 1983; Barman & Gebber, 1985; Ciriello, 1986; McAllen, 1986). This area overlaps the adrenaline synthesizing C1 area and also known as glycine sensitive area (Feldberg & Guertzenstein, 1976), subretrofacial nucleus (McAllen, 1986) and rostral ventrolateral medulla(RVLM). Anatomically this area is located lateral to inferior olivary nucleus, rostral to lateral reticular nucleus, ventral to retrofacial nucleus and caudal to facial nucleus (Ciriello et al, 1986). RVLM mediates baroreflex and chemoreflex (Barman & Gebber, 1980; Ciriello et al, 1986; Reis et al, 1988) and it receives inputs from hypothalamus and midbrain (Sun & Guyenet, 1986; Dampney et al, 1986). So it plays a role in arterial blood pressure regulation as an integration center.

In our experiment, we observed pressor areas in ventral medulla, lateral reticular nucleus and dorsomedial medulla. Since lateral reticular nucleus is known as exercise pressor area and dorsomedial medulla is reported to contain nerve fibers of RVLM neuron projecting to IML, our results are consistent with these results (Ciriello et al, 1977; Martin et al, 1977; Chai et al, 1988; Foreman et al, 1988).

On the contrary, depressor areas are not delineated clearly. It has been suggested that caudal ventrolateral medulla and noradrenergic A_1 area can mediate depressor responses by receiving afferents from the nucleus tractus solitarius (NTS) (Stober et al, 1986). Others suggested that depressor responses can be mediated by medullary raphe neurons which inhibits directly, not through RVLM, preganglionic sympathetic neurons in IML via secretion of serotonin (Barman & Gebber, 1989). Generally, however, it has been accepted that depressor responses are mediated by suppression of pressor areas. In our experiment, depressor areas are overlapped with pressor areas and it is located mainly in RVLM, a little in dorsomedial part including ambiguus nucleus. Since the vagi nerve were cut in the preparation of animal, we can rule out the possibility that depressor response is mediated via vagus nerve. But we can not rule out the possibility that depressor response is mediated by branch from nucleus ambiguus area to RVLM.

There were areas which showed biphasic responses to elcetrical stimulation with different frequency. We do not know the functional significance of this biphasic response. One possibility is that it may be the nerve fibers in passage since we could not evoke any response to microinjection of glutamate in these areas.

Stimulation of peripheral nerves evoke somatosympathetic reflexes (SSR). These are mediated mainly by group III, Aδ-fibers and unmyelinated group IV, C-fibers (Johansson, 1962; Sato & Schmidt, 1973). It is known that stimulation with Aδ-intensity, low frequency (1-2 Hz) evoke depressor response, whereas stimulation with C-intensity, high frequency (20-50 Hz) evoke pressor response (Chung & Wurster, 1976; Chung et al, 1979). It is generally accepted that pressor response can be mediated by sympathoexcitatory area and depressor response is resulted from suppression of sympathoexcitatory area. If RVLM known as a site of determining resting blood pressure mediate somatosympathetic pressor and depressor response, both responses should be disappeared after lesion in RVLM. In our experiment, however, somatosympathetic pressor response disappeared, whereas depressor response still existed after lesion in RVLM (Fig. 8). After lesion on depressor areas, somatosympathetic depressor response disappeared or it changed to pressor res-

ponse while pressor response still existed (Fig. 7). We are not certain that this depressor area can mediate the somatosympathetic depressor response since there is no consistent response to glutamate and pressor response after lesion of this area also decreased much together as that of depressor response. But from the above results we can suppose that somatosympathetic depressor response can be mediated by other site than sympathoexcitatory area in RVLM, since somatosympathetic pressor response but not somatosympathetic depressor response disappeared after lesion of pressor site in RVLM and sometimes depressor response was induced by microinjection of glutamate to the electrically identified depressor sites.

In conclusion, somatosympathetic pressor response is mediated through RVLM, while somatosympathetic depressor response may not be mediated through RVLM.

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