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Effects of Systemic and Focal Hypoxia on the Activities of Rostral Ventrolateral Medullary Neurons in Cats

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=ABSTRACT=

Rendering the brain ischemic would evoke the cerebral ischemic reflex which is characterized by an arterial pressor response, apnea and bradycardia. Since the rostral ventrolateral medulla (RVLM) is known to play a key role in the maintenance of normal cardiopulmonary activity, during the cerebral ischemic reflex some cardiac related cells should be excited and respiration related cells inhibited. In this context, the responses of RVLM neurons to systemic and focal hypoxia were analyzed in the present study. Twenty-five adult cats of either sex were anesthetized with α-chloralose and the single neuronal activities were identified from RVLM area. For the induction of focal hypoxia in the recording site, sodium cyanide was applied iontophoretically and for systemic hypoxia the animal was ventilated with nitrogen gas for a twenty-second period. Cellular activities were analyzed in terms of their discharge pattern and responses to the hypoxia by using post-stimulus time and single-pass time histograms.

Of eighteen cardiac related cells recorded from the RVLM area, twelve cells were excited by iontophoresed sodium cyanide and of twenty-five respiration related cells, fourteen cells were excited by iontophoresed sodium cyanide. Remaining cells were either inhibited or unaffected. Eight of fifteen cells tested with iontophoresed sodium lactate were excited and remaining seven cells were inhibited. Systemic hypoxia induced by nitrogen gas inhalation elevated the arterial blood pressure, but excited, inhibited or unaffected the single neuronal activities. Some cells showed initial excitation, followed by inhibition during the systemic hypoxia. Bilateral vagotomy resulted in a decrease of arterial pressor response to the systemic hypoxia, and a slight decrease in the rhythmicity related to cardiac and/or respiratory rhythms. The single neuronal responses to either systemic or focal hypoxia were not affected qualitatively by vagotomy.

From the above results, it was concluded that the majority of the cardiac- and respiration- related neurons in the rostral ventrolateral medulla be excited by hypoxia, not through the mediation of peripheral chemoreceptors, and along with the remaining inhibited cells, all these cells be involved in the mediation of cerebral ischemic reflex.

Key Words: Rostral ventrolateral medulla (RVLM), Sodium cyanide, Nitrogen gas inhalation, Arterial blood pressure, Cardiac-related neuron, Respiration-related neuron, Vagotomy

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INTRODUCTION

It has been well known that the rostral ventrolateral medullary (RVLM) neurons send tonic excitatory influences on the spinal preganglionic sympathetic nucleus (reviewed in Spyer, 1994). The hypothesis evolved is that the tonic activity of neurons in RVLM determines the resting arterial blood pressure. An increment of this tonic activity would result in the increment of sympathetic activity and the elevation in arterial blood pressure while a decrease of the activity would result in the decrease of sympathetic activity and the depression of arterial blood pressure.

A blocking of cerebral blood flow would evoke the cerebral ischemic reflex (CIR) which consists of immediate increase in sympathetic activity, peripheral vasoconstriction, elevation in arterial blood pressure, bradycardia and apnea (Kumada et al, 1979; Dampney & Moon, 1980; Rohlicek & Polosa, 1983; Takeuchi et al, 1992). Although the exact pathways of the reflex have not been determined, according to the above hypothesis, the RVLM neurons should be involved in the reflex pathway. In experimental hypoxic conditions, changes in the neuronal activities of RVLM were reported, supporting the above hypothesis (Guyenet & Brown, 1986; Prabhakar et al, 1986; Sun et al, 1992; Sun & Reis, 1994). However, the neural basis of the reflex is not clear.

RVLM contains various kinds of neurons such as cardiac-related interneurons, respiration-related neurons (Milhorn & Eldridge, 1986; St. John et al, 1989; Duffin et al, 1995), noncardiac- and non-respration-related spontaneously active neurons, besides the sympatho-excitatory medullospinal tract cells. The responses to hypoxia were variable in these variety of neurons, which was supported in a recent study (Sun & Reis, 1993). The report, however, was not extensive one and compared the responses between cardiac-related interneurons and projection neurons.

During cerebral ischemia, brain would be rendered hypoxic and hypercapnic resulting in the accumulation of potassium ion and lactate (Lowry et al, 1964). Theoretically all these parameters would be involved in the initiation of CIR. These chemicals would activate the peripheral and/or central chemoreceptors. In general, hypoxia depresses cellular activities but the chemoreceptor activities should be increased during hypoxia. The mechanism is not clear but according to a recent hypothesis, the chemoreceptor cells in carotid body are depolarized by closing of potassium channels when the partial pressure of oxygen is lowered. Neurotransmitters would be released from the depolarized chemorecepetor cells and the nerve endings synpased with the cells will send afferent information to the center (Gonzalez et al, 1992; Archer et al, 1993).

The central chemoreceptive mechanisms are not well known. In recent studies, the activities of sympathoexcitatory neurons in RVLM were found to be increased by sodium cyanide applied iontophoretically, while those of non-specific neurons were not changed or depressed (Sun et al, 1992; Sun & Reis, 1993; 1994).

In the present study we intended to investigate the mechanisms of CIR by comparing the response of RVLM neurons to either systemic or focal hypoxia.

METHODS

Animal preparation

Tewnty-five adult cats of either sex (1.7~3.3 kg) were used. The animals were pretreated with atropine sulfate (Kwangmyung, 0.1 mg/kg, i.m.), sedated with ketamine hydrochloride (Ketalar, Yu-han, 10~20 mg/kg, i.m.) and anesthetized with α-chloralose (Sigma, 60 mg/kg, i.v.). The trachea, femoral artery and vein were cannulated for artificial ventilation, arterial blood pressure monitoring and drug injection, respectively. Pancuronium bromide

(Miobolck, Organon, initial dose 0.4 mg, maintenance dose 0.4 mg/hr) was administered intravenously to paralyze muscle. The animals were ventilated artificially and the end-tidal P_{CO_2} was maintained within 3.5~4.5% (Normocap CO_2 & O_2 monitor, Datex). Rectal temperature was maintained within 37~38°C by an electric blanket (Homeothermic Blanket Control Unit, Harvard). Hartmann solution was infused (10~15 ml/hr) throughout the experiment.

The animals were mounted on a stereotaxic frame. An occipital craniectomy was performed, and cerebellum was removed to expose the floor of the IVth ventricle. Bilateral thoracotomies were performed to reduce the respiratory movement of recording site. Electrocardiograms were obtained, using subcutaneous pin electrodes.

Iontophoresis and neural recordings

Electrodes for recording single neuronal activities and for applying various drugs were made from multibarrel capillaries (Glass 7BBL W/fil 1.0 mm, WPI). In the center barrel an 8-μm-thick carbon filament was inserted and the capillary was pull out using an electrode puller (PE-2, Narishige). The center barrel was used for recording and remaining six barrels were used for drug applications. Iontophoretic drug application was performed using iontophoresis module (S-7000, WPI). Following drugs were used: 0.2 M l-monosodium glutamate (pH 8.5), 0.8 M γ-aminobutyric acid (GABA) (pH 4.5), 0.5 M sodium cyanide (pH 8.5) and 0.3 M sodium lactate (pH 8.5). All drugs were obtained from Sigma (St.Louis, USA). One barrel was filled with 0.15 M NaCl and used for current neutralization. Holding currents were +8 nA except for GABA which was held by negative current. The recording sites were lesioned electrically by passing ±20 μA d.c. for 10 seconds each.

The obex was used as a surface landmark and electrode was placed on the dorsal surface of the medulla, 2~6 mm rostral to the obex, 3~4 mm lateral to the midline. The electrode was lowered down with a pulse motor drive (PC-5N, Narishige). Usually the single neuronal activities related to cardiac and/or respiratory cycles were picked up at depth of 3~7 mm from the dorsal surface. The electrical signals were amplified (band pass 0.3~10 KHz, gain 10,000, DAM 80, WPI), displayed on oscilloscopes and stored in a personal computer through a window discriminator (Frederick Haer & Co.) and a laboratory interface (CED 1401). For identification of cardiac-related neurons, a post R-wave histogram (500 sweeps, 1000 bins, 1ms bin width) was compiled and, for respiration-related neurons, a peak P_{CO_2} histogram (20 sweeps, 100 bins, 100 ms bin width) was compiled.

In experiments for investigating the responses of RVLM neurons to systemic hypoxia, animals were inhalated with 100% nitrogen gas for twenty seconds while monitoring the neuronal activities and arterial blood pressure. In some animals bilateral vagotomies were performed to reduce the peripheral chemoreceptor activities.

Histology and statistics

At the end of each experiment, the animal was sacrificed with sufficient dose of anesthetics. Medulla was removed and fixed in 4% formalin solution for at least a week. Frontal sections, 50 μm thickness, were obtained using a vibratome and stained with cresyl violet. The recorded sites were reconstructed by referring to the electrolytic lesions. The results were expressed as mean ±S.E. Significant differences between groups were determined by Student's *t*-test.

RESULTS

The first step of the present study was identification of spontaneously active neurons of which discharge patterns were related to cardiac and/or respiratory rhythms, and then their responses to

sodium cyanide applied iontophoretically. A total of sixty-one neuronal activities were recorded from the RVLM. Eighteen cells were cardiac-related, twenty-five were respiration-related and ten were both cardiac- and respiration-related. Remaining eight cells were neither cardiac- nor respiration-related and these cells were used as control groups (Table 1).

Effects of focal hypoxia on RVLM neuronal activities

Of eighteen cardiac-related cells, twelve cells were excited, four cells decreased and two cells not changed by sodium cyanide applied iontophoretically. Typical examples of effects of sodium cyanide

Table 1. Response patterns of single neuronal activities recorded from rostral ventrolateral medulla

	Activity change by NaCN			Total
	Increase	Decrease	No change	
Cardiac-related cells	12	4	2	18
Respiration-related cells	14	7	4	25
Cardiac- and respiration-related cells	7	1	2	10
Noncardiac- and nonrespiratory cells	3	1	4	8

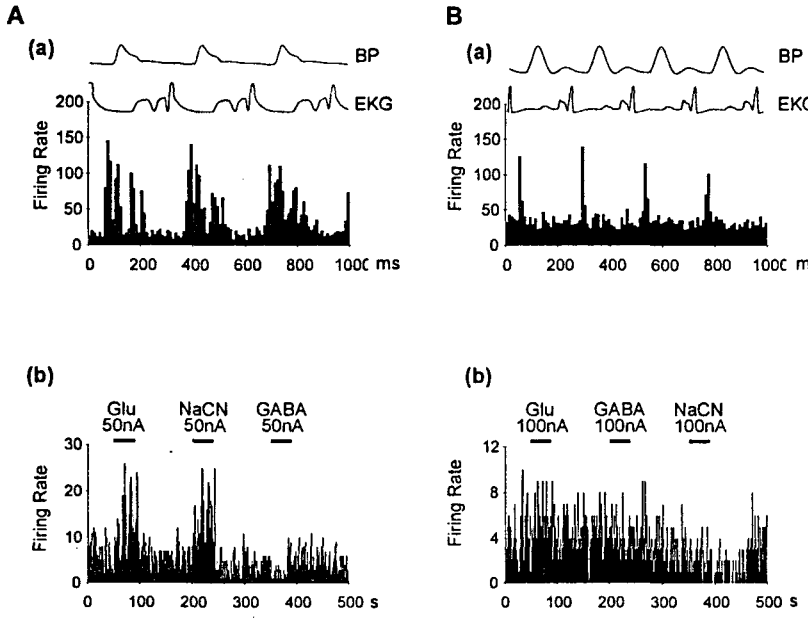


Fig. 1. Effects of sodium cyanide on cardiac-related single neuronal activities recorded from the rostral ventrolateral medulla in cats. The cardiac-related rhythmic activity was identified by compiling a post-stimulus time histogram, using R-wave as a trigger signal, from 500 sweeps of activity. The bin width was 1 msec and the bin number was 1000. Single-pass time histograms were made with 500 bins and 1 sec bin width. Drugs were iontophoretically applied to the same cell of which activity was recorded. In (A), the cell was excited by iontophoresed sodium cyanide while the cell in (B) was inhibited. Glu, sodium glutamate; NaCN, sodium cyanide; GABA, gamma aminobutyric acid; BP, arterial blood pressure; EKG, electrocardiogram; nA, nanoampere. The horizontal bars indicate the period drug was applied.

on cardiac-related single neuronal activities are shown in Fig. 1. The cell in (A) showed rhythmic activity related to cardiac cycle as one can see in upper panel (a), and its activity was increased by 50 nA-sodium cyanide current (lower panel, b). Since the activity was increased by iontophoresed glutamate and inhibited by GABA, the activity was confirmed as single neuronal activity, not as activity of a pass-bying branch. The cell in (B) was clearly a cardiac-related cell (upper panel, a), but its activity was decreased by iontophoresed sodium cyanide (lower panel, b).

Fig. 2 shows the effects of sodium cyanide on a typical respiration-related single neuronal activity. The cell in (A) showed rhythmic discharge pattern related to respiration cycle expressed by changes in carbon dioxide concentration of expired air (upper panel, a). The cell was excited by iontophoresed sodium cyanide as well as by sodium glutamate. The cell in (B) was also a respiration-related neuron but its activity was decreased by sodium cyanide and GABA, while a sodium glutamate stimulation increased its activity. Among twenty-five respiration-related neurons, fourteen were excited, seven were inhibited and four were not changed by sodium cyanide applied iontophoretically.

Fig. 3 shows the effects of sodium cyanide on single neurons showing both cardiac- and respiration-related rhythmic activities. The cell in (A) was excited by sodium cyanide and the cell in (B) inhibited. Among ten cells showing rhythmic activities related to both rhythms, seven were excited, one was inhibited and two were not changed by sodium cyanide. The results for all the cells were summarized in Table 1. As shown in the table, the majority of cardiopulmonary neurons in

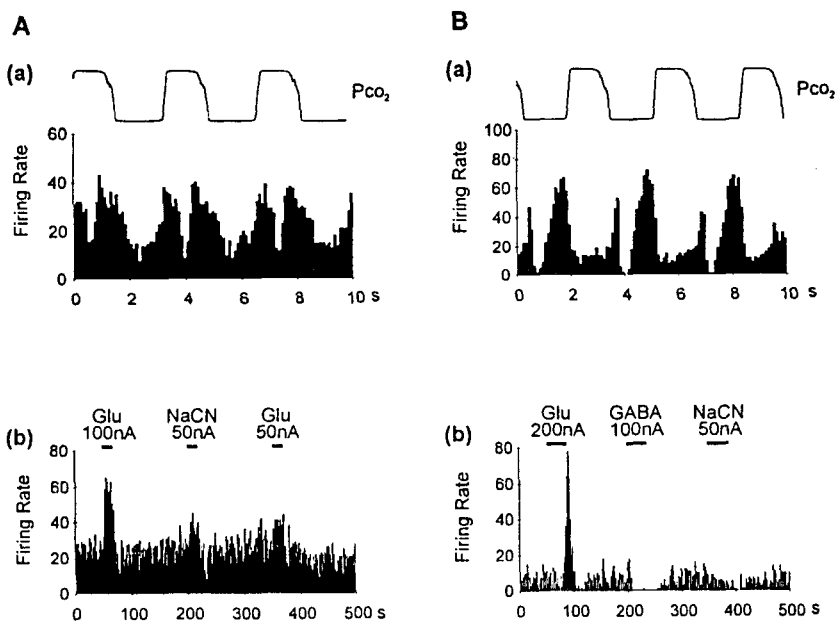


Fig. 2. Effect of sodium cyanide on respiration-related single neuronal activities recorded from the rostral ventrolateral medulla. The respiration-related activity was identified by a post stimulus time histogram complied by using the peak end tidal carbon dioxide concentration signal from the monitor as a triggering signal. Twenty sweeps were compiled with 100 bins, 100msec bin width. The cell in (A) was excited by iontophoresed sodium cyanide while the cell in (B) was inhibited.

RVLM area (62.3%) were excited by focal hypoxia induced by sodium cyanide applied iontophoretically, whereas only 37.5% of the noncardiac- and nonrespiration-related cells were excited by focal hypoxia.

One-fourth of RVLM neurons which was excitatory to hypoxia actually showed a biphasic response to iontophoretically applied sodium cyanide. Examples of such neurons are shown in Fig. 4. The cell in (A) was excited by a mild hypoxia induced by nitrogen gas inhalation (0.5 L/min). But the same cell showed initial excitation followed by inhibition by iontophoretically applied sodium cyanide (lower panel, b). The cell in (B) was excited by 100 nA glutamate and lactic acid currents. It showed marked excitation followed by complete inhibition for a couple of hundred seconds by sodium cyanide. The cell was still responsive to glutamate during depressed peroid following hypoxia.

Effects of lactic acid on RVLM neuronal activities

The next step was to compare the effects of lactic acid, one of the metabolites accumulated in the tissue during hypoxia, on RVLM neuronal activities

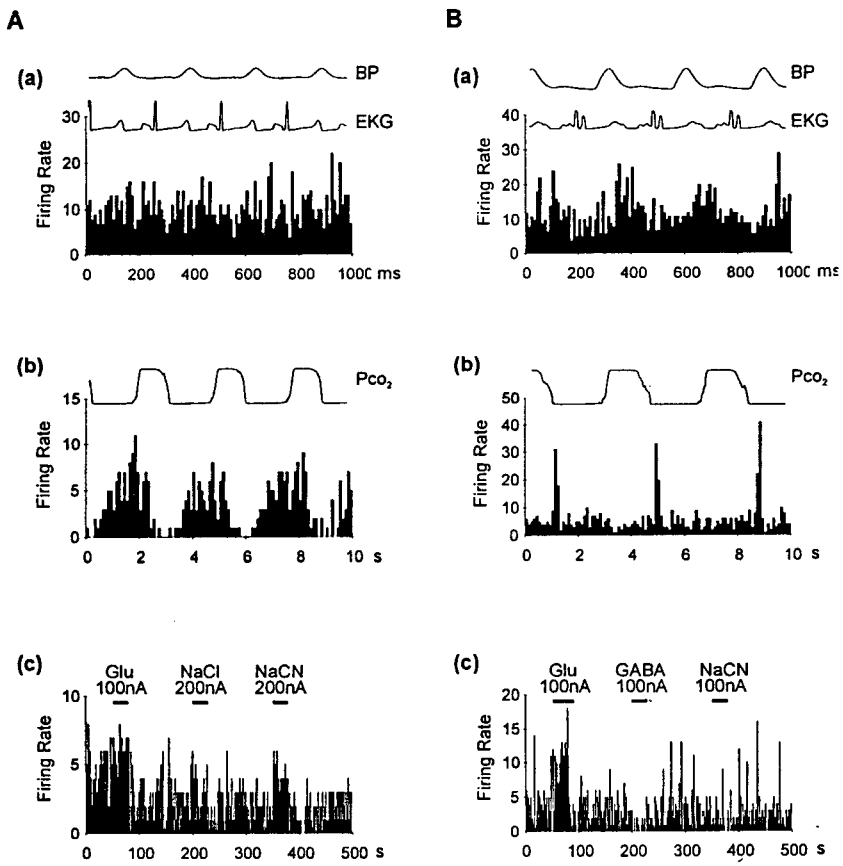


Fig. 3. Effects of sodium cyanide on both cardiac- and respiration-related single neuronal activities recorded from the rostral ventrolateral medulla. These cells had rhythmic discharge pattern related both to cardiac and respiration rhythms. The cell in (A) was excited by sodium cyanide while the cell in (B) was inhibited.

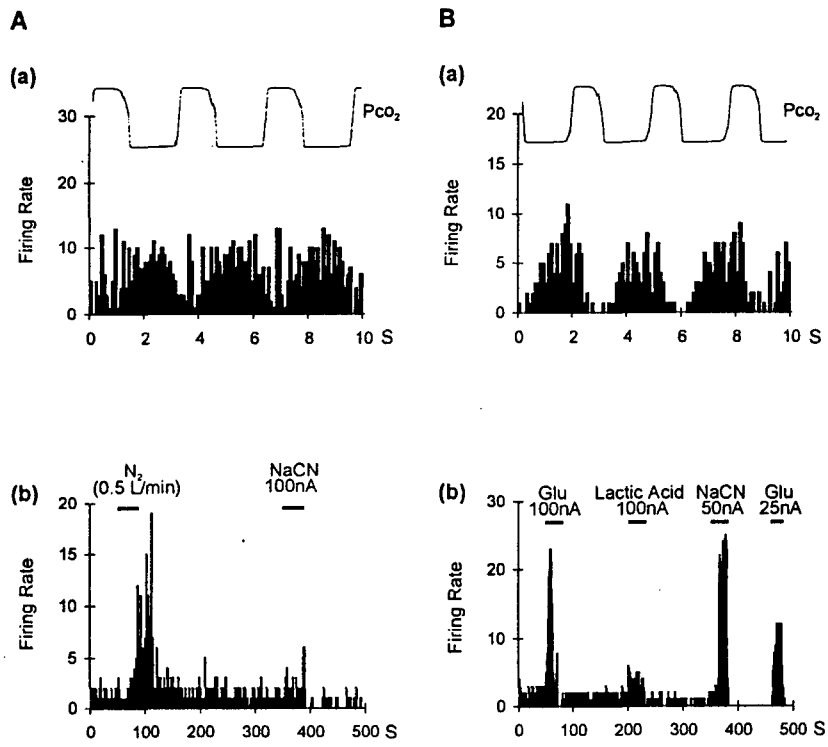
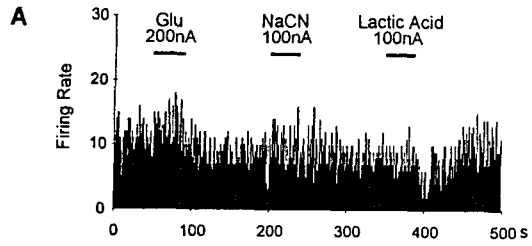


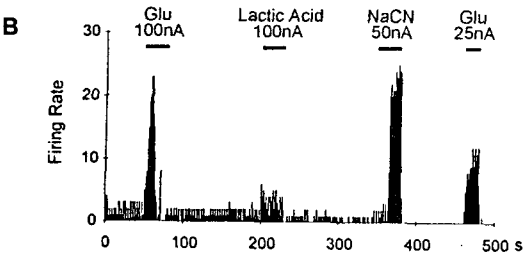
Fig. 4. Examples of single cell activities which showed a biphasic response to sodium cyanide applied iontophoretically. The cell in (A) was excited by a mild nitrogen gas inhalation-induced hypoxia. The same cell showed initial excitation, followed by inhibition by iontophoretically applied sodium cyanide. The cell in (B) was excited by lactic acid applied iontophoretically, and showed marked excitation followed by complete abolition for a couple of hundred seconds. But the cell was still responsive to glutamate.

with those of sodium cyanide. In Fig. 5, representative examples are shown. The cell in (A) decreased its activity to 100 nA lactic acid, although it was excited weakly by sodium cyanide. The cell in (B) was excited by lactic acid and also strongly excited by sodium cyanide followed by complete abolition of the activity. The cell in (B) was the same cell shown in Fig. 4. Fifteen cells were tested with lactic acid and the results were summarized in Fig. 5(C). Among them six were excited by both lactic acid and cyanide and three were depressed by both of them.

Effects of systemic hypoxia on RVLM neuronal activities

The systemic hypoxia was induced by inhalation of 100% nitrogen gas for 20 seconds and the arterial blood pressure and RVLM neuronal activities were monitored. Fig. 6 shows two examples. The cell in (A) was rendered hypoxic by inhalation of nitrogen gas with flow rate of 0.5 L/min. Its activity increased markedly during hypoxia. B cell was rendered more hypoxic than A cell and its activity increased initially, followed by complete abolition for a couple of hundred seconds even after returning to normal air breathing. Tewnty cells were in-

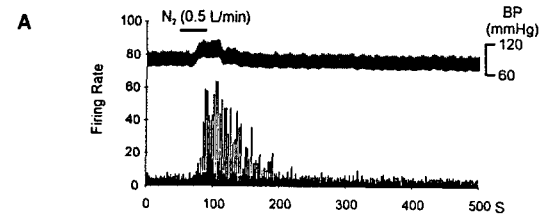


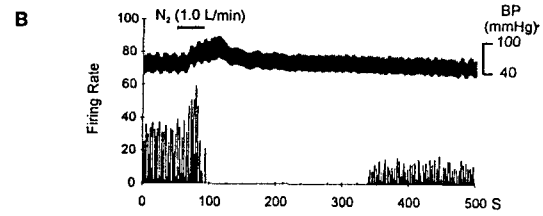


C

		Effects of lactic acid	
		Increase	Decrease
NaCN	Increase	6	4
	Decrease	2	3

Fig. 5. Effects of lactic acid on single neuronal activities recorded from the rostral ventrolateral medulla. The cell in (A) was slightly excited by sodium cyanide and inhibited by lactic acid applied iontophoretically to the recorded site. The cell in (B) was excited by lactic acid and excited markedly by sodium cyanide. The (B) cell was the same cell shown in Fig. 4. In (C), the results of fifteen cells tested with lactic acid were summarized.





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N_2	Activity Change		
	Increased	Biphasic	Decreased
0.5 L/min	6	2	2
1.0 L/min	1	4	4
2.0 L/min			1

Fig. 6. Effects of systemic hypoxia on the arterial blood pressure and single neuronal activities recorded from the rostral ventrolateral medulla. The systemic hypoxia was induced by inhalation of 100% nitrogen gas for a twenty-second period. The cell in (A) was excited during systemic hypoxia and the cell in (B) showed initial excitation, followed by inhibition. As shown in (C), the cells were excited by lower degree hypoxia and became inhibited as the degree of hypoxia increased.

vestigated and the results were summarized in Fig. 6 (C). Seven cells were inhibited by systemic hypoxia. The activities of seven cells were increased during hypoxia and remaining six showed biphasic responses. If these cells were included in excitatory cells, the proportion of RVLM neurons showing excitatory response to systemic hypoxia (13 among 20 cells) is rather similar to that of excitory neurons to focal hypoxia (33 among 51 cells). The arterial blood pressure increased markedly during systemic hypoxia, while focal hypoxia did not induce any change in arterial blood pressure.

Effects of vagotomy

Fig. 7 shows the effects of vagotomy on the arterial pressor response to nitrogen inhalation-induced hypoxia. Bilateral vagotomy reduced the arterial pressure elevation from 35.6 to 21.8 mmHg during systemic hypoxia, which was statistically significant ($n=6$, $p<0.05$). This indicates that a considerable portion of the peripheral chemoreceptor inputs was carried by vagus nerves from cervical, thoracic and abdominal glomus tissues (Howe et al, 1981; Cardenas & Zapata, 1983; Sinclair, 1986).

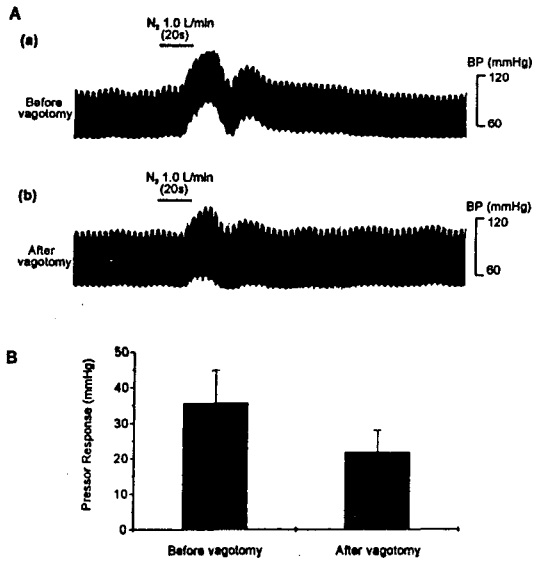

Fig. 7. Effect of vagotomy on the arterial pressor response to nitrogen inhalation-induced hypoxia. The pressor response to hypoxia was decreased from 35.6 to 21.8 mmHg after the bilateral vagotomy ($n=6$, $p<0.05$).

The response patterns of RVLM neurons to systemic hypoxia after vagotomy were not changed qualitatively as shown in Fig. 8, although the vagotomy evoked a burst-like discharge in this neuron.

DISCUSSION

In the present study we recorded single neuronal activities from RVLM using extracellular recording technique and applied drugs to the recording sites iontophoretically. For this we used a multibarrel microelectrode which consists of carbon filament-containing recording barrel, drug-containing barrels and balancing barrel. Because we only took consideration of cells which responded to iontophoretically applied glutamate, the recorded activites in the present study were not those of pass-bying fibers. In addition, since the iontophoresis of sodium chloride with negative current of the same amplitude used in cyanide or glutamate did not elicit any change in the single cell activity, the response evoked by the cyanide or glutamate was not ascribed to the negative current per se.

In general, activities of brain cells are depressed by hypoxia (Leblond & Krnjevic, 1989; Murphy & Greenfield, 1991; Luhmann & Heinemann, 1992). In the present study, less than half of the noncardiac- and nonrespiration-related neurons were depressed or showed no change during hypoxia. On the contrary, the arterial blood pressure was elevated during hypoxia, which indicates that some central neurons should be excited. In this sense the RVLM neurons are the best candidates, since RVLM area has been known to play a key role in regulation of the arterial blood pressure (Spyer, 1994). There have been many reports which indicate that RVLM neuronal activities increase during hypoxia (Kumada et al, 1979; Dampney & Moon, 1980; Guyenet & Brown, 1986; Prabhakar et al, 1986; Sun et al, 1992; Sun & Reis, 1994). Neuronal activities recorded from other areas of medulla such as nucleus of hypoglossal nerve, dorsal motor nucleus of the vagus nerve and solitary nucleus, also have been known to increase during hypoxia (Haddad & Donnely, 1989; Donnelly et al, 1992).

The cerebral ischemic reflex consists of bradycardia and apnea as well as arterial pressor response (Kumada et al, 1979; Dampney & Moon, 1980). Here the dissociating phenomena of arterial pressor response which indicates the increase in peripheral vascular tone, and a bradycardia which indicates the decrease in cardiac action suggest that the RVLM, a final common pathway of medullary sympathetic influences, would consist of functionally different subpopulation of cardiovascular neurons (Barman et al, 1984; Dampney & McAllen, 1988; Stein et al, 1989). There is a possibility that a group of RVLM neurons which influence cardiac activity would be inhibited during hypoxia, while another group of neurons which influence vasomotion would be excited by hypoxia. In addition, the activities of vasodepressor neurons would be decreased during

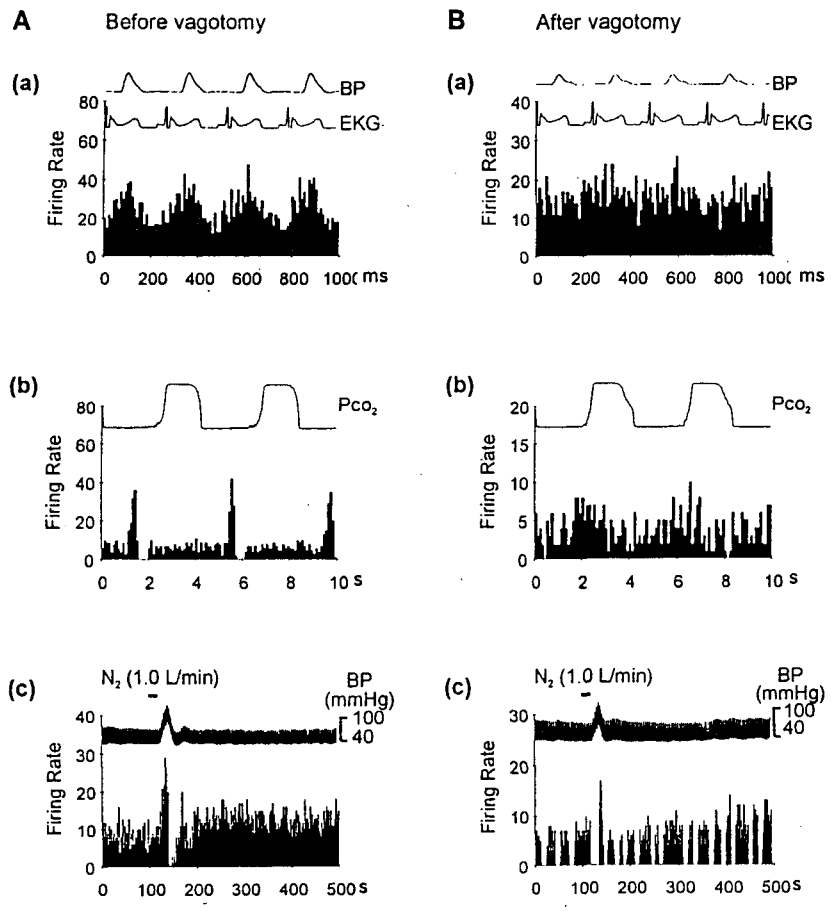

Fig. 8. Effects of the bilateral vagotomy on the single neuronal responses to the nitrogen-induced hypoxia. The cell showed cardiac- and respiration-related discharge rhythms and the rhythms were not changed qualitatively after the bilateral vagotomy. Hypoxia evoked a burst-like discharge pattern but it was not changed much by bilateral vagotomy.

hypoxia or increased during bradycardia (Morrison & Gebber, 1984; Goo et al, 1996). The vasodepressor neurons are activated by stimulation of peripheral nociceptive Aδ-nerves leading to depression of arterial blood pressure. The results of Sun & Reis (1993) who reported that cardiovascular neurons in RVLM neurons showed different responses to hypoxia, might be interpreted in this regard.

RVLM also contains respiration-related neurons (St. John et al, 1989; Duffin et al, 1995). There are several kinds of respiration-related neurons and the responses of them to hypoxia are also variable. For example, expiratory neurons would be excited during apnea due to CIR and inspiratory neurons would be depressed. To characterize the relation of neuronal activity to respiratory cycle of inspiration and expiration, the phrenic nerve activity should be recorded, but since we only intended to determine whether a neuronal activity is related to respiratory rhythm in the present study, we only recorded the fluctuation of expiratory carbon dioxide pressure.

In the present study we observed that two-thirds of cardiac-related neurons in RVLM elicited exci-

tatory response to either systemic or focal hypoxia. This made us confirm that there should be neurons which were excited during hypoxia. However, activities of the remaining one third of cardiac-related neurons were depressed during hypoxia like most noncardiac- and nonrespiration-related neurons. A considerable portion of neurons which showed excitatory responses to hypoxia eventually reduced their activities at severe or prolonged hypoxia. This suggests that there should be independent processes which are responsible for hypoxia-induced immediate excitatory responses, but severe or prolonged hypoxia will predominantly depress those processes eventually.

Three-fifth of the respiration-related neurons recorded in present study were excited and Three-tenth were depressed by hypoxia. This is essentially the same results as those of previous studies from other groups (Rohlicek & Polosa, 1983; Mitra et al, 1993; Nolan & Waldrop, 1993). The response of respiration-related neurons to hypoxia might be dependent on the types of cells. For example, at the beginning of hypoxia, the inspiratory cells might be excited and the expiratory cells inhibited. But severe or prolonged hypoxia will depress even the activities of inspiratory cell, leading to apnea.

Lactate and K ion are accumulated in the tissue during hypoxia (Lowry et al, 1964). We tested the effects of lactate on RVLM neuronal activity and observed that roughly a half of the tested cells were excited and the other half were depressed by lactic acid applied iontophoretically. This result suggests that the lactate ion does not play a major role in the response of RVLM neurons to hypoxia. The similar result was reported recently (Sun & Reis, 1994).

Bilateral vagotomy reduced the arterial pressure elevation in response to systemic hypoxia. This indicates that a considerable portion of the peripheral chemoreceptor inputs is carried by vagus nerves from cervical, thoracic and abdominal glomus tissues (Howe et al, 1981; Cardenas & Zapata, 1983; Sinclair, 1987). The response patterns of RVLM neurons to systemic hypoxia after vagotomy were not changed qualitatively, indicating that the peripheral and central responses to hypoxia might be additive.

In conclusion, the majority of the cardiac- and/or respiration-related neurons in RVLM of cats are excited centrally by hypoxia while remaining portion was depressed. The responses of all these cells should be integrated to elicit the cerebral ischemic reflex.

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