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Modulation of Propofol on the Effects of Blood Pressure and Firing Activity of Related Neurons in the Medulla

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Abstract

Many studies have demonstrated that the ventrolateral medulla (VLM) plays an important role in the maintenance of systemic arterial pressure (SAP) and vascular tone. The VLM is divided into rostral (RVLM) and caudal (CVLM) portions which play opposing roles in regulating cardiovascular functions. The purposes of this study are to explore the relationship of fibers projecting between the RVLM and CVLM, and to investigate the effect of propofol (PPF, 2 mg/kg), an anesthetic agent, on modulating their neuronal firing rate (NFR). Forty-four adult cats were anaesthetized intraperitoneally with urethane (400 mg/kg) and α-chloralose (40 mg/kg). The femoral artery was cannulated to allow monitoring of SAP and heart rate (HR). The femoral vein was cannulated for intravenous drug administration. Microinjection of glutamate (Glu, 3.0 nmol/30 nl), kynurenic acid (Kyn, 3.0 nmol/30 nl), γ-aminobutyric acid (GABA, 4.0 nmol/30 nl), or bicuculline (Bicu, 4.0 nmol/30 nl) into the RVLM produced SAP increases or decreases, but did not significantly change the NFR in the CVLM. This occurred even after intravenous administration of PPF. This shows that there are few fiber projections from the RVLM to the CVLM. Conversely, microinjection of Glu, Kyn, GABA or Bicu into the CVLM produced SAP changes, and the NFR in the RVLM was significantly changed. These changes were more significant after intravenous administration of PPF. These results show that there are more fibers projecting from the CVLM to the RVLM and fewer fibers projecting from the RVLM to the CVLM to affect the SAP and its NFR.

Key Words: caudal ventrolateral medulla, heart rate, propofol, glutamate, rostral ventrolateral medulla, systemic arterial pressure

Introduction

The ventrolateral medulla (VLM) plays an important role in the generation, maintenance and reflex control of sympathetic vasomotor tone (4). The VLM is divided into rostral (RVLM) and caudal (CVLM) portions. The RVLM contains sympathetic premotor neurons responsible for maintaining tonic excitation of the sympathetic preganglionic neurons involved in cardiovascular regulation, while the CVLM, a depressor area, is involved in reflex regulation of systemic arterial pressure (SAP) (4). It is generally believed that the central circuitry involving baroreceptor-mediated control of sympathetic outflow comprises an excitatory projection from the nucleus tractus solitarii (NTS) to the CVLM (5, 11). The latter provides inhibitory projections to the RVLM which sends excitatory projections to preganglionic sympathetic vasomotor neurons (19).

Glutamate (Glu) is an excitatory neurotrans-

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mitter while kynurenic acid (Kyn) is a broad-spectrum Glu receptor antagonist (2). Microinjection of Glu into the RVLM produced an SAP increase, while microinjection of Glu into the CVLM produced an SAP decrease (22). Kyn blocked the responses of SAP and vertebral nerve activity from the RVLM induced by Glu (23). Moreover, microinjection of γ-aminobutyric acid (GABA) into the RVLM produced a decrease in SAP while microinjection of GABA antagonist bicuculline (Bicu) produced an increase in SAP. On the other hand, microinjection of GABA into the CVLM produced an increase in SAP while microinjection of Bicu produced a decrease in SAP (1, 16).

Propofol (PPF), a general anesthetic agent, is administered intravenously. It can be used also as a sedative agent with the advantages of rapid onset and effective and rapid recovery (14, 20). In a previous study, we found that PPF (1, 2, 4 mg/kg) dose-dependently inhibited the neuronal firing rate (NFR) in the RVLM and CVLM resulting in hypotension and bradycardia (24-26).

The purposes of this study are to study the effect of Glu, Kyn, GABA and Bicu on the cardiovascular and NFR, to explore the relationship of fibers projecting between the RVLM and CVLM, and to evaluate the modulating effect of PPF (2 mg/kg) on their NFR.

Materials and Methods

Animals

Forty-four adult cats of either sex, weighing 2.4-3.6 kg, were anesthetized intraperitoneally with urethane (400 mg/kg) and α-chloralose (40 mg/kg). All experimental procedures were carried out under the guidelines of the National Science Council. General procedures included cannulation of the right femoral artery and vein for monitoring SAP, mean SAP (MSAP) and heart rate (HR), and for drug injection, respectively. Tracheal intubation for artificial ventilation was performed to maintain the end-tidal CO_2 concentration at 4%. The body temperature was maintained at 37.5°C.

Brain Stimulation

The head of each cat was fixed in a David-Kopf stereotaxic apparatus. The dorsal surface of the brain stem was exposed and the obex was used as the reference point. Two areas in the medulla, namely the RVLM and CVLM, were stimulated. The stereotaxic coordinates of these structures were: RVLM, 3.5-5.0 mm rostral to the obex, 3.0-4.5 mm lateral to the midline, and 3.5-4.5 mm ventral to the dorsal surface of the medulla; CVLM, 1.0 mm rostral to the posterior obex, 2.8-4.2 mm lateral to the midline, and 3.0-4.5 mm ventral to the dorsal surface of the medulla.

Chemical stimulation was accomplished through a one-barrel micropipette (outside tip diameter of 10-20 μm) inclined at 34° from the stereotaxic frame. The micropipette contained Glu (Sigma, 3.0 nmol/30 nl), GABA (Sigma, 4.0 nmol/30 nl), Bicu (Sigma, 4.0 nmol/30 nl) in saline, and Kyn (Sigma, 3.0 nmol/30 nl) in sodium bicarbonate with 0.1% pontamine sky blue (Sigma) at pH 7.4. The other end of each barrel was connected to a pneumatic pressure system (PPS-2, PPM-2, Medical Systems Corp., Great Neck, NY, USA) for injection under a microscope (Wild M650) fitted with a reticule. Control injection of the vehicle alone did not produce any discernible effects.

Recording of Neuronal Firings

Initially, extracellular recordings of spontaneous NFR in the RVLM or CVLM were allowed to stabilize for 10 min. Then, the chemicals were microinjected slowly into the same side of the CVLM or RVLM. The NFR in the RVLM or CVLM was recorded by a metal electrode and then amplified through a preamplifier (Neurolog system, NL 104, Digitimer, Welwy Garden City, UK) coupled to a filter (NL 126, bandwidth frequency 5Hz-3kHz) and displayed on an oscilloscope (4050, Gould). Signals were trans-mitted to a window discriminator (WPI 121) to remove background noise. Spikes above the low level of the window discriminator were converted to transistor-transistor logic pulses (TTL, 5 V, 1 ms) with the window discriminator, and then integrated using an integrator (sample/hold, Gould) with a reset time of 1 s.

The NFR was measured in hertz (Hz). The absolute value of the NFR was calibrated by a series of pulses (5 V, 1 ms) generated from a function generator (Tektronix, FG 507). All data were recorded and stored on a PowerLab system coupled with chart software (AD Instruments) and a polygraph recorder (ES1000, Gould) coupled with a tape recorder system (Neuro Data DR-890, Sony slv-400) for later analysis.

Histology

At the end of each experiment, the animal was euthanized by an overdose of pentobarbital. The brain was removed and immersed in 10% formalin-saline for 8 h. After fixation, frozen transverse sections (50 μm) of the brain were stained with Cresyl violet to identify the injection sites.

Statistical Analysis

The procedures of this study were firstly, microinjecting Glu, Kyn, GABA, or Bicu into the RVLM and CVLM and then measuring the responses of SAP,

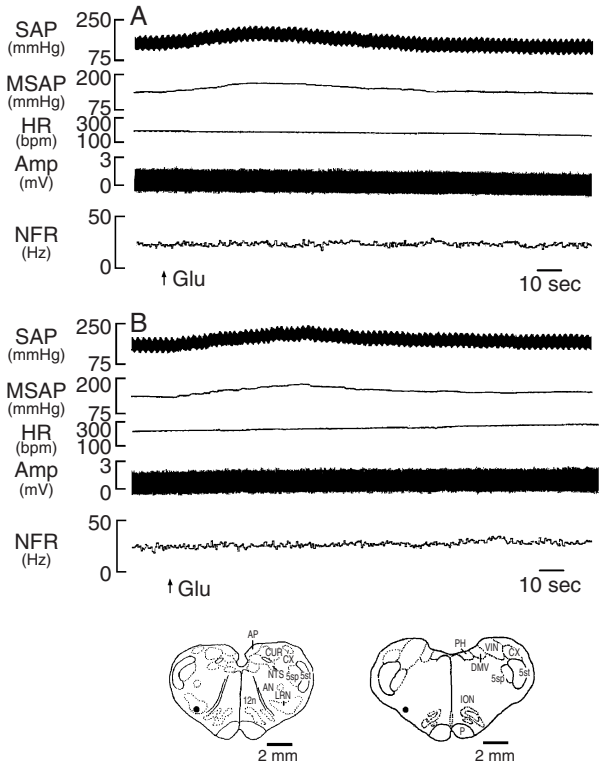

Fig. 1. A. Effects on SAP, HR, and NFR in the CVLM of a microinjection of Glu (3.0 nmol/30 nl) into the RVLM. B. Thirty minutes after intravenous PPF (2 mg/kg) the effects on SAP, HR, and NFR in the CVLM of a microinjection of Glu (3.0 nmol/30 nl) into the RVLM again. The bottom shows a section of the CVLM (left) and the RVLM (right). Tracings from top to bottom are: SAP, systemic arterial pressure; MSAP, mean SAP; HR, heart rate; Amp, amplitude of neuronal firing activity; NFR, frequency of neuronal firing rate from the CVLM; bpm, beats per minute. Arrowheads (↑) under the tracings indicate the time of applying the microinjection. Bar (—) indicates the time. A dot (•) in the brain drawing shows the site of drug stimulation or recording. Abbreviations: AN, nucleus of ambiguous; AP, area postrema; CUR, cuneate nucleus; CX, external cuneate nucleus; DMV, dorsomotor nucleus of vagus; ION, inferior olivary nucleus; LRN, lateral reticular nucleus; NTS, nucleus tractus solitarius; P, pyramidal tract; VIN, inferior vestibular nucleus; 5sp, spinal trigeminal nucleus; 5st, spinal trigeminal tract; 12N, hypoglossal nucleus. Note that microinjection of Glu into the RVLM produced an increase in SAP while the NFR in the CVLM did not show significant change.

HR, and NFR. Secondly, after intravenous administration of PPF, the first step was repeated and the responses measured again. All data are presented as means ± standard error of mean (SEM). Changes in maximal responses induced by microinjection of drugs into the RVLM or CVLM were analyzed by the paired Student *t*-test after drug microinjection. Differences

Table 1. The effects on MSAP, HR and NFR in the CVLM of microinjections with Glu (3.0 nmol/30 nl), Kyn (3.0 nmol/30 nl), GABA (4.0 nmol/30 nl), or bicuculline (4.0 nmol/30 nl) into the RVLM

	MSAP (mmHg)	HR (bpm)	NFR (Hz) from CVLM
Control	125.7 ± 8.7	213.4 ± 6.3	35.3 ± 7.4 (n = 54)
Glu	163.4 ± 9.4*	193.5 ± 7.4	32.4 ± 6.8 (n = 13)
Kyn	116.3 ± 7.2	206.4 ± 9.1	37.8 ± 5.9 (n = 15)
GABA	94.3 ± 8.5*	197.2 ± 5.7	34.6 ± 5.8 (n = 12)
Bicu	135.2 ± 8.4	210.6 ± 9.7	31.2 ± 4.7 (n = 14)

Abbreviations: MSAP, mean systemic arterial pressure; HR, heart rate; NFR: neuronal firing rate. Values are means ± SEM, n = no. in each group; *, $P < 0.05$ when compared with the control.

Table 2. Thirty minutes after intravenous PPF (2 mg/kg) the effects on MSAP, HR, and NFR of the CVLM of microinjection of Glu (3.0 nmol/30 nl), Kyn (3.0 nmol/30 nl), GABA (4.0 nmol/30 nl) or Bicu (4.0 nmol/30 nl) into the RVLM

	MSAP (mmHg)	HR (bpm)	NFR (Hz) from CVLM
Control	115.7 ± 7.5	204.5 ± 8.3	28.4 ± 5.6 (n = 54)
Glu	145.4 ± 6.8*	183.2 ± 6.4*	31.3 ± 6.7 (n = 12)
Kyn	96.4 ± 4.3*	194.4 ± 8.3	30.4 ± 5.8 (n = 15)
GABA	84.2 ± 5.5*	197.3 ± 7.7	26.3 ± 6.2 (n = 13)
Bicu	135.2 ± 6.3*	187.6 ± 8.6*	26.1 ± 5.7 (n = 14)

Values are means ± SEM, n = no. in each group; *, $P < 0.05$ when compared with the control.

of *$P < 0.05$ were considered to be significant. All nonsignificant changes are designated NS.

Results

Effects on SAP and NFR in the CVLM of Microinjection of Drugs in the RVLM

In 6 animals, microinjection of Glu (3.0 nmol/30 nl) into the RVLM produced an increase in MSAP (from 125.7 ± 8.7 mmHg to 163.4 ± 9.4 mmHg, $P < 0.05$, n = 13) with little change of the NFR in the CVLM (from 35.3 ± 7.4 Hz to 32.4 ± 6.8 Hz, n = 13, NS) (Fig. 1, Table 1). Thirty min after intravenous PPF (2 mg/kg), the NFR in the CVLM was decreased (from 35.3 ± 7.4 Hz to 28.4 ± 5.6 Hz, $P < 0.05$, n = 54). At this time, microinjection of Glu (3 nmol/30 nl) into the RVLM again produced an increase in MSAP (from 115.7 ± 7.5 mmHg to 145.4 ± 6.8 mmHg, $P < 0.05$, n = 12) but did not significantly affect the NFR

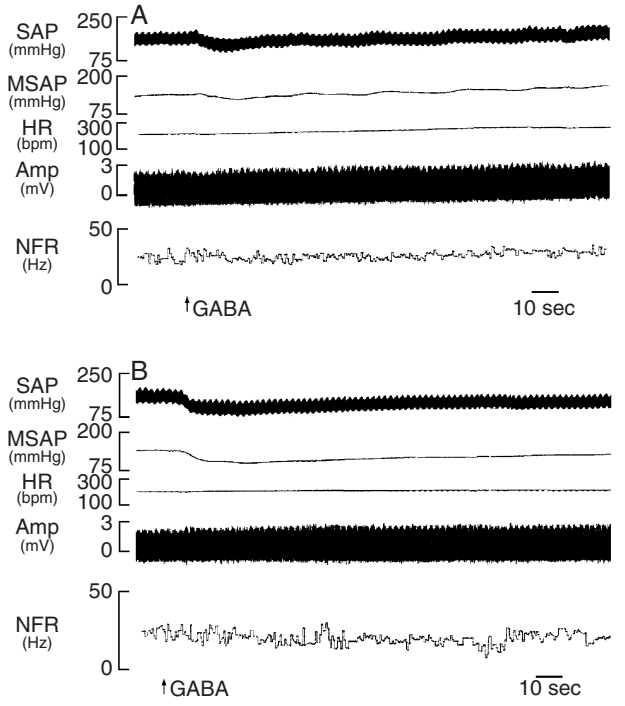

Fig. 2. A. Effects on SAP, HR, and NFR in the CVLM when GABA (4.0 nmol/30 nl) was microinjected into the RVLM. B. Thirty minutes after intravenous PPF (2 mg/kg), the effects on SAP, HR and NFR in the CVLM when GABA (4.0 nmol/30 nl) was microinjected into the RVLM again. Note that microinjection of GABA into the RVLM produced a decrease in SAP while the NFR in the CVLM did not show significant change.

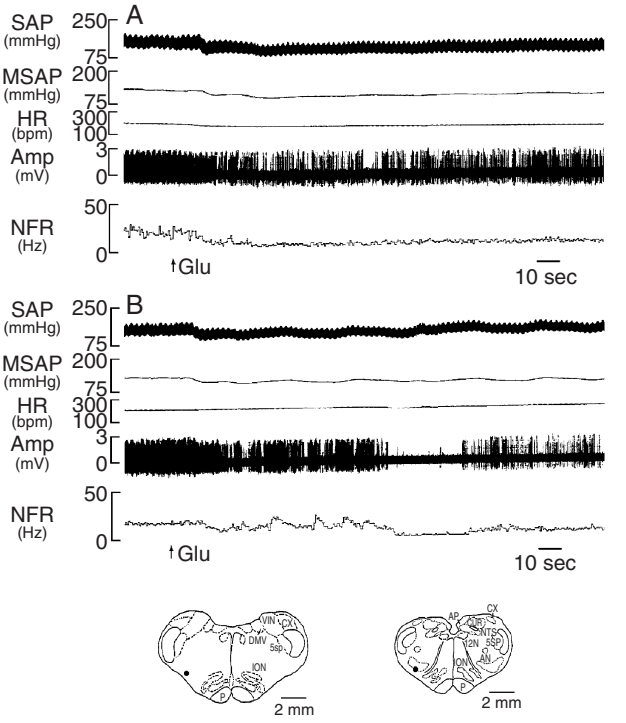

Fig. 3. A. Effects on SAP, HR, and NFR in the RVLM when Glu (3.0 nmol/30 nl) was microinjected into the CVLM. B. Thirty minutes after intravenous PPF (2 mg/kg) the effects on SAP, HR, and NFR in the RVLM when Glu (3.0 nmol/30 nl) was microinjected into the RVLM again. The brain sections at the bottom show the sites of microinjection in the RVLM (left) and CVLM (right). Note that microinjection of Glu into the CVLM produced decreases in SAP and NFR in the RVLM. After intravenous PPF, the decrease became more pronounced.

in the CVLM (from 28.4 ± 5.6 Hz to 31.3 ± 6.7 Hz, n = 12, NS) (Table 2).

In 6 animals, microinjection of Kyn (3.0 nmol/30 nl), a Glu antagonist, into the RVLM produced a small decrease in MSAP (from 125.7 ± 8.7 mmHg to 116.3 ± 7.2 mmHg, n = 15, NS). The NFR in the CVLM, however, was not affected (from 35.3 ± 7.4 Hz to 37.8 ± 5.9 Hz, n = 15, NS) (Table 1). Thirty min after intravenous PPF (2 mg/kg), microinjection of Kyn (3.0 nmol/30 nl) into the RVLM again produced a decrease in MSAP (from 115.7 ± 7.5 mmHg to 96.4 ± 4.3 mmHg, $P < 0.05$, n = 15), but did not significantly affect the NFR rate in the CVLM (from 28.4 ± 5.6 Hz to 30.4 ± 5.8 Hz, n = 15, NS) (Table 2).

In 5 animals, microinjection of GABA (4.0 nmol/30 nl) into the RVLM produced a small decrease in MSAP (from 125.7 ± 8.7 mmHg to 94.3 ± 8.5 mmHg, $P < 0.05$, n = 12), but no significant change of NFR in the CVLM (from 35.3 ± 7.4 Hz to 34.6 ± 5.8 Hz, n = 12, NS) (Fig. 2, Table 1). Thirty min after intravenous PPF (2 mg/kg), microinjection of GABA (4.0 nmol/30 nl) into the RVLM again produced a decrease in MSAP (from 115.7 ± 7.5 mmHg to 84.2 (5.5 mmHg, $P < 0.05$, n = 13), and slightly decreased the NFR (from 28.4 ± 5.6 Hz to 26.3 ± 6.2 Hz, n = 13, NS) in the CVLM (Table 2).

In 6 animals, microinjection of Bicu (4.0 nmol/30 nl), a GABA antagonist, into the RVLM produced a small increase in MSAP (from 125.7 ± 8.7 mmHg to 135.2 ± 8.4 mmHg, n = 14, NS), while the NFR in the CVLM was not significantly affected (from 35.3 ± 7.4 Hz to 31.2 ± 4.7 Hz, n = 14, NS) (Table 1). Thirty min after intravenous PPF (2 mg/kg), microinjection of Bicu (4.0 nmol/30 nl) into the RVLM again produced an increase in SAP (from 115.7 ± 7.5 mmHg to 135.2 ± 6.3 mmHg, $P < 0.05$, n = 14), and only slightly decreased the NFR (from 28.4 ± 5.6 Hz to 26.1 ± 5.7 Hz, n = 14, NS) in the CVLM (Table 2).

Effects on SAP and NFR in the RVLM of Microinjection of Drugs in the CVLM

In 5 animals, microinjection of Glu (3.0 nmol/30 nl) into the CVLM produced decreases in MSAP (from 125.7 ± 8.7 mmHg to 84.3 ± 6.4 mmHg, $P <$

Table 3. The effects on MSAP, HR, and NFR in the RVLM of microinjection of Glu (3.0 nmol/30 nl), Kyn (3.0 nmol/30 nl), GABA (4.0 nmol/30 nl), or Bicu (4.0 nmol/30 nl) into the CVLM

	MSAP (mmHg)	HR (bpm)	NFR (Hz) from RVLM
Control	125.7 ± 8.7	213.4 ± 6.2	31.5 ± 7.4 (n = 56)
Glu	84.3 ± 6.4*	192.3 ± 8.5*	22.3 ± 4.2* (n = 13)
Kyn	136.2 ± 9.2	202.3 ± 7.3	38.7 ± 7.6* (n = 12)
GABA	145.6 ± 7.4*	192.4 ± 5.4*	48.4 ± 8.5* (n = 16)
Bicu	114.3 ± 6.7	206.2 ± 9.4	23.4 ± 6.4* (n = 15)

Values are means ± SD, n = no. in each group; *, $P < 0.05$ when compared with the control.

Table 4. Thirty min after intravenous PPF (2 mg/kg) the effects on MSAP, HR, and NFR in the RVLM of microinjection of Glu (3.0 nmol/30 nl), Kyn (3.0 nmol/30 nl), GABA (4.0 nmol/30 nl), or Bicu (4.0 nmol/30 nl) into the CVLM

	MSAP (mmHg)	HR (bpm)	NFR (Hz) from RVLM
Control	116.2 ± 6.5	203.2 ± 7.3	28.4 ± 5.3 (n = 56)
Glu	86.3 ± 4.6*	187.2 ± 6.5*	18.4 ± 3.4* (n = 13)
Kynurenic acid	123.5 ± 7.5*	190.4 ± 7.3	33.7 ± 7.6 (n = 12)
GABA	135.3 ± 5.4*	193.5 ± 8.6	38.4 ± 8.5* (n = 16)
Bicuculline	93.2 ± 6.6*	185.6 ± 7.2*	16.4 ± 5.4* (n=15)

Values are means ± SD, n = no. in each group; *, $P < 0.05$ when compared with the control.

0.05, n = 13) and NFR in the RVLM (from 31.5 ± 7.4 Hz to 22.3 ± 4.2 Hz, $P < 0.05$, n = 13, Fig. 3, Table 3). Thirty min after intravenous PPF (2 mg/kg), the NFR in the RVLM was slightly decreased (from 31.5 ± 7.4 Hz to 28.4 ± 5.3 Hz, n = 56, NS), but microinjection of Glu (3.0 nmol/30 nl) into the CVLM after the procedure again produced a significant decrease in MSAP (from 116.2 ± 6.5 mmHg to 86.3 ± 4.6 mmHg, $P < 0.05$, n = 13) and NFR (from 28.4 ± 5.3 Hz to 18.4 ± 3.4 Hz, $P < 0.05$, n = 13) in the RVLM (Table 4).

In 5 animals, microinjection of Kyn (3.0 nmol/30 nl) into the CVLM produced a small increase in MSAP (from 125.7 ± 8.7 mmHg to 136.2 ± 9.2 mmHg, n = 12, NS) and a significant increase in NFR in the RVLM (from 31.5 ± 7.4 Hz to 38.7 ± 7.6 Hz, $P < 0.05$, n = 12, Table 3). Thirty min after intravenous PPF (2 mg/kg), the NFR of the RVLM decreased slightly (from 31.5 ± 7.4 Hz to 28.4 ± 5.3 Hz, n = 56, NS) while microinjection of Kyn (3.0 nmol/30 nl) into the CVLM again produced increases in MSAP (from 116.2 ± 6.5 mmHg to 123.5 ± 7.5 mmHg, n = 12, NS) and NFR (from 28.4 ± 5.3 Hz to 33.7 ± 7.6 Hz, $P < 0.05$, n = 12) in the RVLM (Table 4).

In 6 animals, microinjection of GABA (4.0 nmol/30 nl) into the CVLM produced increases in MSAP (from 125.7 ± 8.7 mmHg to 145.6 ± 7.4 mmHg, $P < 0.05$, n = 16) and NFR (from 31.5 ± 7.4 Hz to 48.4 ± 8.5 Hz, $P < 0.05$, n = 16) in the RVLM (Fig. 4, Table 3). Thirty min after intravenous PPF (2 mg/kg), the MSAP (from 116.2 ± 6.5 mmHg to 135.3 ± 5.4 mmHg, $P < 0.05$, n = 16) and NFR in the RVLM (from 28.4 ± 5.3 Hz to 38.4 ± 8.5 Hz, $P < 0.05$, n = 16) were significantly increased when GABA (4.0 nmol/30 nl) was microinjected into the CVLM again (Table 4).

In 5 animals, microinjection of Bicu (4.0 nmol/30 nl) into the CVLM produced decreases in MSAP (from 125.7 ± 8.7 mmHg to 114.3 ± 6.7 mmHg, n = 15, NS) and NFR (from 31.5 ± 7.4 Hz to 23.4 ± 6.4 Hz,

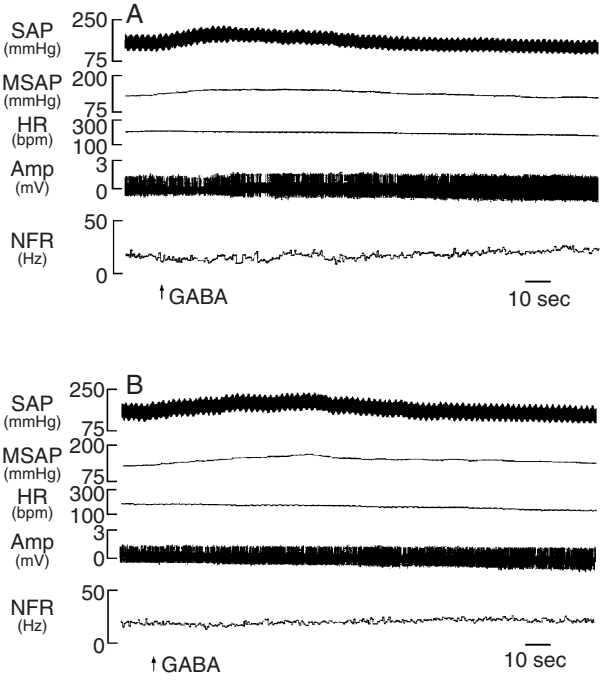

Fig. 4. A. Effects on SAP, HR, and NFR in the RVLM when GABA was microinjected (4.0 nmol/30 nl) into the CVLM. B. Thirty min after intravenous PPF (2 mg/kg) the effects on SAP, HR, and NFR in the RVLM when GABA (4.0 nmol/30 nl) was microinjected into the RVLM again. Note that microinjection of GABA into the CVLM produced similar increases of SAP and NFR in the RVLM.

$P < 0.05$, n = 15) in the RVLM (Table 3). Thirty min after intravenous PPF (2 mg/kg) both the MSAP (from 116.2 ± 6.5 mmHg to 93.2 ± 6.6 mmHg, $P < 0.05$, n = 15) and NFR (from 28.4 ± 5.3 Hz to 16.4 ± 5.4 Hz, $P < 0.05$, n = 15) in the RVLM were significantly decreased when Bicu (4.0 nmol/30 nl) was microinjected into the CVLM again (Table 4).

Discussion

Major findings of this study are that microinjections of Glu and its antagonist Kyn, and GABA and its antagonist Bicu into the RVLM produced SAP changes, while the NFR in the CVLM was not significantly changed even after administration of the intravenous anesthetic agent PPF. This suggests that there are few fibers projecting from the RVLM to the CVLM. On the contrary, microinjection of Glu, Kyn, GABA or Bicu into the CVLM produced SAP changes, while the NFR in the RVLM was significantly reduced and the reduction was more pronounced after intravenous PPF. This suggests that there are more fiber projections from the CVLM to the RVLM affecting SAP. This is consistent with the anatomical studies that neurons within the CVLM receiving multiple inputs from the NTS inhibit sympathoexcitatory neurons in the RVLM (11, 15, 18).

Neural structures responsible for the maintenance of vasomotor tone through the regulation of sympathetic outflow activity are located mainly in the medullary region (4). The RVLM area is a major source of sympathetic vasomotor drive that provides an excitatory bulbospinal pathway to the sympathetic preganglionic cells in the intermediolateral column of the spinal cord (4). The RVLM plays an important role in the maintenance of sympathetic tone and SAP (6, 17).

The CVLM plays a significant role in the inhibitory regulation of sympathetic nerve activity and SAP (3, 9). Depressor neurons in this region form a serial link in the central baroreceptor-vasomotor pathway, constituting an inhibitory connection between the NTS and sympathoexcitatory bulbospinal neurons in the RVLM (13, 15). Microinjection of Glu into the CVLM elicits decreases in SAP and HR together with mesenteric and hindquarter vascular resistance (21). In this study, microinjection of Glu into the CVLM produced decreases in SAP and HR associated with the decrease of NFR in the RVLM.

The CVLM contains A1 epinephrine neurons in the lateral reticular nucleus and plays an important role in cardiovascular regulation (8). Microinjection of Glu into the CVLM produced decreases in SAP and sympathetic nerve activity (SNA), while microinjection of the inhibitory neurotransmitter GABA into the CVLM produced increases in SAP and SNA. Functionally, the CVLM is divided into two different areas: the rostral CVLM is responsible for the transmission of the baroreflex and the function of SNA, while the caudal CVLM is responsible for the inhibition of SAP, and SNA independent of the baroreflex (3, 12).

Neurons in the CVLM directly inhibit the NFR in the RVLM through their axons. This results in a decrease of SNA from the preganglion, resulting in sympathetic inhibition. Thus, the CVLM plays an important role in sympathetic inhibition.

Microinjection of Glu into the RVLM produced an increase in SAP. Conversely, Kyn produced an SAP decrease. On the other hand, microinjection of GABA into the RVLM produced a SAP decrease while Bicu produced a SAP increase. The present study shows that microinjection of Glu, Kyn, GABA or Bicu into the RVLM produced changes in SAP but did not significantly affect the NFR in the CVLM. Even 30 min after intravenous PPF (2 mg/kg), microinjection of Glu, Kyn, GABA or Bicu into the RVLM did not affect the NFR in the CVLM. This may suggest that there are few or no nerve fiber projections from the RVLM to the CVLM affecting SAP.

Microinjection of Glu into the CVLM produced a SAP decrease associated with a decrease of NFR in the RVLM. The depressor mechanism may first excite the parasympathetic neurons in the CVLM and then inhibit the sympathetic neurons in the RVLM through GABA inhibition (10, 13, 18). On the other hand, microinjection of Kyn into the CVLM produced increases in SAP and NFR in the RVLM. The pressor mechanism may inhibit the parasympathetic neurons in the CVLM, thus indirectly elevating the activity of sympathetic neurons in the RVLM. By the same mechanism, microinjection of GABA into the CVLM produced increases in SAP and NFR in the RVLM by inhibiting the parasympathetic neurons in the CVLM. Conversely, microinjection of Bicu into the CVLM induced decreases in SAP and NFR in the RVLM. These results show that microinjection of Glu, Kyn, GABA or Bicu into the CVLM produced changes in SAP and NFR in the RVLM. On the other hand, 30 min after intravenous PPF that produced a small decrease in NFR, microinjection of Glu, Kyn, GABA or Bicu into the CVLM again produced changes in SAP associated with a significant decrease or increase in NFR in the RVLM. Such results suggest that the CVLM may have sufficient fiber projections to the RVLM to affect SAP, consistent with many studies from electrophysiology, pharmacology, and anatomy (7, 13, 26).

PPF is an anesthetic agent that enters the whole body including the brain through the circulation and results in a SAP decrease coincidental with a small decrease in the NFR in the RVLM and the CVLM. Previous reports showed that PPF produced inhibition of NFR in the brain (24-26). In other words, PPF effects general inhibitions not involving signal transmission between CVLM and RVLM neurons to affect SAP. For this reason, PPF appears to be an anesthetic agent of choice in studying neural transmission.

In summary, although microinjections of Glu,

Kyn, GABA or Bicu into the RVLM produced SAP changes, the NFR in the CVLM was not significantly changed even after administration of the intravenous anesthetic agent PPF. On the other hand, although microinjections of Glu, Kyn, GABA or Bicu into the CVLM also produced SAP changes, the NFR in the RVLM was significantly reduced and the reduction was more pronounced after intravenous PPF. This suggests that more fibers project from the CVLM to the RVLM, but few fibers projecting from the RVLM to the CVLM affect SAP and its NFR.

Acknowledgments

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