Acta Zoologica Taiwanica 11(1): 17-32 (2000)

Effects of Chemical Lesioning the Dorsal or Rostral Ventrolateral Medulla on Glutamate-induced Cardiovascular Actions of the Pontine Gigantocellular Tegmental Field and Lateral Tegmental Field of the Cat

Jui-Hsiang Hsieh[1], Tung-Chin Chu[1], Chen-Tung Yen[2] and Chok-Yung Chai[3]

[1]Institute of Biomedical Engineering, Chung Yuan Christian University

[2]Department of Zoology, National Taiwan University,

[3]Institute of Biomedical Sciences, Academia Sinica

Taipei, Taiwan, Republic of China

ABSTRACT

The present project studies the effects of chemical lesioning in the dorsal medulla (DM) or rostral ventrolateral medulla (RVLM) on glutamate-induced cardiovascular action of the pontine gigantocellular tegmental field (PFTG) and lateral tegmental field (PFTL) in cats. Experiments were performed on 39 adult cats anesthetized with intraperitoneal injection of a mixture of alpha-chloralose and urethane. Systemic arterial blood pressure (SAP), heart rate (HR) and vertebral nerve sympathetic activity (VNA) were continuously monitored. Microinjections of the glutamate solution (Glu, 0.25 M of sodium glutamate dissolved in artificial cerebrospinal fluid with 0.5% pontamine sky blue) in 50- to 70- nl aliquots were made in the PFTG and PFTL. SAP, HR, and VNA were measured before and after chemical lesioning of the DM and/or RVLM and compared. The DM or the RVLM was lesioned by injection of 150-200 nl of kainic acid (24 mM) acutely. We found that when the ipsilateral DM was lesioned, microinjection of Glu into PFTG no longer elicited a pressor response. In contrast, when the contralateral DM was lesioned, the Glu-induced PFTG pressor response was little affected. Lesioning of either the ipsi- or contralateral RVLM affected the PFTG response very little. This suggests that the connection between PFTG in producing the pressor action is principally unilateral through the ipsilateral DM. When the ipsi- or contralateral DM was lesioned, injection of Glu into the PFTL no longer could elicit a depressor response. Interestingly, when either the ipsi- or contralateral RVLM was lesioned, the PFTL-induced depressor effect changed to a pressor one. These results suggest that the PFTL depressor effect is dependent on the integrity of both the DM and RVLM. Furthermore, there may be a mixture of sympathoexcitatory and parasympathoexcitatory neurons in the PFTL.

Key words: Pressor, Depressor, Blood pressor, Heart rate, Sympathetic nerve activity, Spectral analysis

INTRODUCTION

The rostral ventrolateral medulla (RVLM) has been extensively studied and is well documented for supplying a basal sympathetic tone in order to maintain systemic arterial pressure (SAP) at a proper level (Chai *et al*. 1988; Dampney1994). Similar types of experiments have shown that the dorsal medulla (DM), extending rostrally from the ventral to the vestibular nucleus and nucleus praelositus hypoglossi and caudally to the caudal part of the nucleus tractus solitarius (NTS), is also important in the integration of vasomotor

activity (Chai *et al*. 1988). In our previous studies, using excitatory amino acids as a tool (Goodchild *et al*., 1982), we demonstrated that RVLM and DM exert differential effects over sympathetic nerve activities, and that RVLM is more important than DM in tonic maintenance of the basal SAP (Su *et al.* 1989; Su *et al*., 1992). Recent reports also have demonstrated that the majority of RVLM-spinal vasomotor neurons exhibit an obvious intrinsic pacemaker activity. Such pacemaker activity does not depend on synaptic inputs (Gatti & Gillis 1991; Sun *et al*., 1988a; and Su *et al*., 1992).

In the pons, the pontine gigantocellular tegmental field (PFTG) has shown very active pressor action in response to sodium glutamate (Glu). Neurons of this region are not catecholaminergic, and they contain neither acetylcholine (ACh) nor the ACh synthetic enzyme choline acetyltransferase (Chai *et al*., 1993). The PFTG, however, contains receptors for Ach, and most of the previous studies here have concentrated on the ACh effects in the PFTG on behavior (Holmes & Jones 1994; Holmes *et al*., 1994; Lydic & Baghdoyan 1993). Thus the PFTG is referred to as cholinoceptive (Gilbert & Lydic 1994; McCarley *et al*., 1987). PFTG neurons have also been associated with rapid eye movement (REM) sleep (McCarley & Hobson 1971), which includes rapid eye movement, ponto-geniculo-occipital waves (McCarley & Ito 1983), and a suppression of postural muscle tone with superimposed distal muscle twitches (Braun & Pivik 1983; Oka *et al*., 1993).

The pontine lateral tegmental field (PFTL) has been considered a functional rather than an anatomical term, referring to some non-cardiovascular actions by other laboratories (Holstege *et al*., 1986; Tan & Holstege 1986; and Yates *et al*., 1995), although activation of this region can produce complex cardiovascular responses such as changes in blood pressure and heart rate.

From the above discussion, it is understood that both the PFTG and PFTL are active in cardiovascular actions. Unfortunately, only a few reports have dealt with their possible mechanisms. The present study is an attempt to study the relationship between these two regions with the medullary cardiovascular integrative areas, the DM and RVLM. In particular, we want to learn whether the PFTG and PFTL responses are mediated through the pressor mechanism of the DM or RVLM by lesioning the latter medullary structures using kainic acid (KA). KA is a neurotoxic analog of glutamate. When injected in nanomolar quantities into the CNS, it destroys neuronal cell bodies in the region of the injection site but leaves nerve terminals and fibers of passage intact. The selective nature of the KA lesion makes it a useful tool for the interpretation of the effects of destruction of discrete areas.

MATERIAL AND METHODS

General procedures

Thirty-nine cats of either sex (2.5-3.5 kg) were anesthetized with an intraperitoneal injection of a mixture of urethane (400 mg/kg) and a-chloralose (40 mg/kg). This regimen of anesthetics produces a stable anesthesia for at least 8 h, while the animal retains high sensitivity responsiveness to brain stimulation. The femoral artery and vein were cannulated for measurement of SAP and for administration of drugs. The trachea was intubated, and artificial ventilation was adjusted to maintain an end-tidal CO_2 level between 4% and 4.5%. The rectal temperature was kept at 37 ± 0.5 ° C with a feedback-controlled thermal blanket. The resting mean systemic arterial pressure (MSAP) was maintained above 80 mmHg, if necessary, by intravenous infusion of a 5% dextran solution (4 ml/h).

Brain stimulation and destruction

The head of the animal was fixed in a David Kopf stereotaxic instrument. Exposure of the hindbrain for stimulation of the pressor and depressor areas of the pons and medulla has been described previously (Chai *et al*., 1993). To prepare a two-barreled micropipette, two glass tubes (WPI Glass 1BBL W/Fil 1B100F-6)

were fused together using a Narishige PE-2M glass microelectrode puller, giving a tip with an outside diameter of 40-60 μM. One of the barrels was filled with 3 M NaCl and used for electrical stimulation; the other, filled with 0.25 M sodium glutamate (pH 7.4, 1% pontamine sky blue in artificial CSF) or 24 mM kainic acid (dissolved with 0.5% pontamine sky blue in artificial CSF), was for microinjection. The micropipette was inserted into the brainstem with the aid of a stereotaxic carrier inclined at an angle of 34°, using the obex as the reference point. At first, Glu was injected into the PFTG or PFTL bilaterally through the glass micropipettes. Then, kainic acid was injected into the unilateral DM or RVLM only to produce lesioning. At least a 40- min wait ensued after KA injection for the animals to return to a stable situation. Then bilateral microinjection with the same dose of Glu was made into the same sites in the PFTG or PFTL.

Neural recordings

The left vertebral sympathetic nerves were approached dorsolaterally through incisions made in the thoracic wall. Under an operating microscope, the nerves were dissected free from the surrounding connective tissues, desheathed, and cut at the distal end. A conventional electrophysiological setup and a bipolar platinum electrode were used to record and amplify the efferent whole-bundle nerve activities. This neural signal was channeled through two separate band pass filters, one for low frequency (1-30 Hz) and the other for high frequency (30-3000 Hz). The signals were monitored with an oscilloscope and stored on a tape recorder (Neuro Data DR-886) for later analysis.

Histology

At the end of each experiment the brain was processed for histological examination. The animal was sacrificed by an injection of a bolus of saturated KCl. The brain was removed and fixed in 10% formalin. Frozen sections, 50 μ thick, were cut and stained with neutral red. Injection sites were verified from the positions of the blue dye marks in the frozen section. Chemical stimulation sites were reconstructed from sections containing the electrode tracks and marks of the sky blue dye.

Data analysis

Percent changes of MSAP and heart rate (HR) in response to microinjection of Glu or KA into the pressor or depressor site were calculated by dividing the value of maximum change with the control value. Significant changes from the control level of the experimental data set were verified by Student's *t*-test. Data are presented as mean ± standard error. A *P* value less than 0.05 was considered to be statistically significant. Fast Fourier transform was performed on 40 contiguous 4-s windows in the period of the maximum effects of chemical activation of the PFTG or PFTL. Spectral analyses were done over a frequency band of 0 to 300 Hz with a resolution of 0.25 Hz/bin. All analyses were performed on SNAP MASTER software (HEM Data Corp).

RESULTS

In the present study, Glu was microinjected into the same site in the PFTG or PFTL before and after medulla oblongata cardiovascular sites were lesioned with KA. Changes in SAP, HR, and vertebral nerve activity (VNA) were studied in 39 cats. Stimulation of the PFTG by Glu in intact animal produced an increase of SAP and VNA concomitant with a decrease in HR. Table 1 summarizes the changes of SAP and HR induced by Glu stimulation of the PFTG before and after lesioning of the DM or RVLM.

Lesioning the DM or RVLM on the PFTG-induced pressor effect

In nine cats, effects of DM lesioning were tested on the Glu-induced PFTG pressor effect. A representative example is illustrated in Fig. 1. Within a few seconds after Glu injection, the SAP of the cat exhibited a rapid initial but short increase. After reaching the first peak, the SAP fell slightly, and then again increased to a

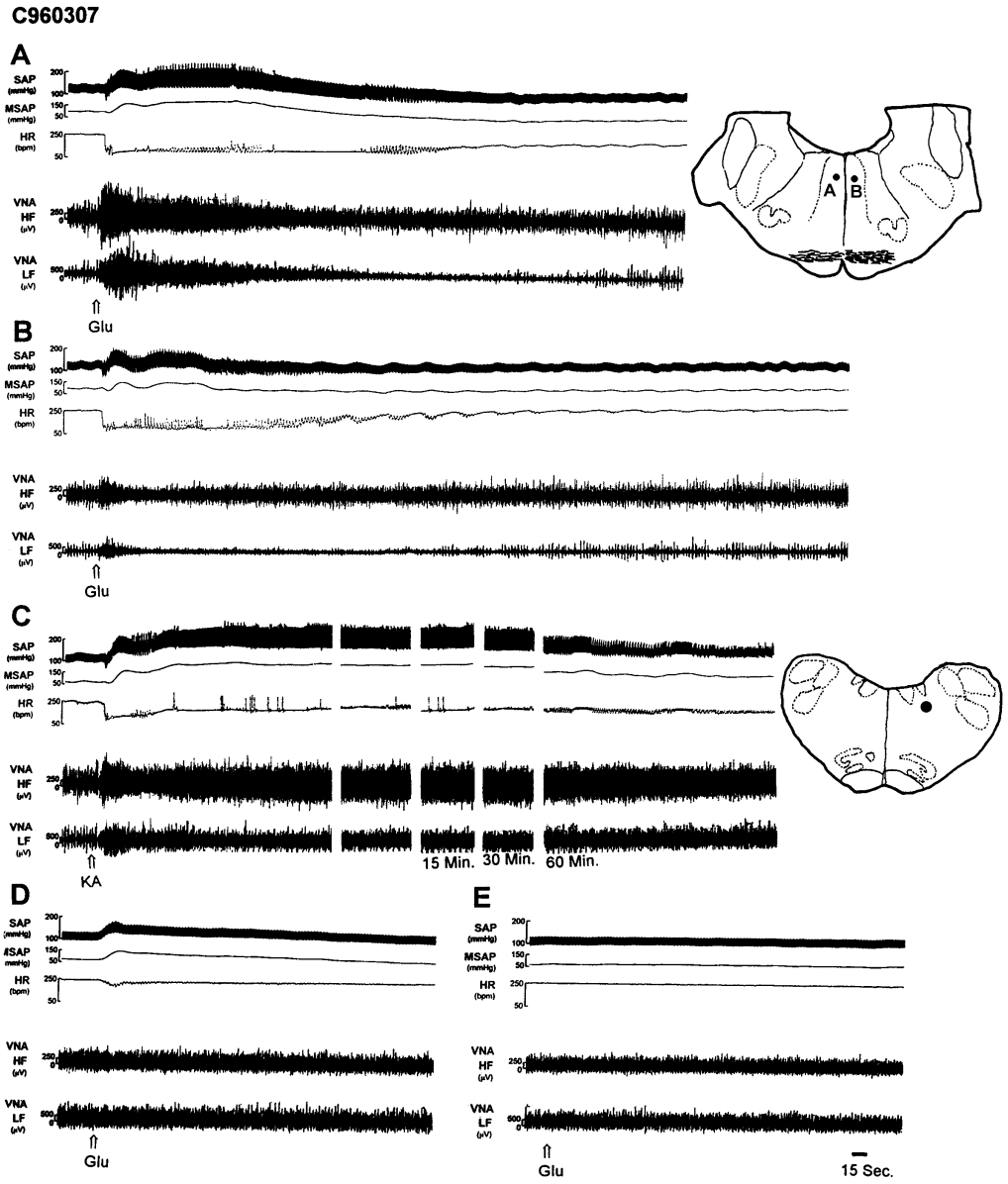

Figure 1. Lesioning of the DM attenuates the pressor responses of the PFTG induced by glutamate (Glu, 0.25 M, 70 nl) in a cat (C960307). In this and the following figures: SAP = systemic arterial pressure, MSAP = mean systemic arterial pressure, HR = heart rate, VNA = vertebral nerve activity. HF = high frequency (band pass of 10-3000 Hz), LF = low frequency (band pass of 1-30 Hz). Arrows indicate the time of Glu or KA microinjection. The solid circles in the brain drawing indicate histological verification of the injection site. A. Control responses (left PFTG) . Note that Glu in the PFTG increased SAP and VNA concomitantly with a decrease in HR. B. Control responses (right PFTG). Note that Glu in the PFTG increased SAP and VNA concomitant with a decrease in HR. C. Microinjection of KA for lesioning the DM (right) produced an increase of SAP, which returned to the resting level in about 60 min. D. Following contralateral DM lesioning, the pressor response of the left PFTG still persisted. E. After ipsilateral DM lesioning, Glu in the left PFTG no longer produced a pressor response.

Table 1. Effects of lesioning the dorsal medulla (DM) or rostral ventrolateral medulla (RVLM) on changes of blood pressure and heart rate induced by glutamate stimulation of the pontine gigantocellular tegmental field (PFTG)

	MSAP			HR		
	Resting	Stimulation (mm Hg)	Response (%)	Resting	Stimulation (BPM)	Response (%)
DM lesioning						
Ipsilateral (n = 4)						
A	110±1.9	155±4.8	41.6±6.5	185±10.9	95±10.2	-48.9±4.7
B	97.5±2.1	97.5±2.1	0.0±0.0*	142.5±16.5	142.5±16.5	-0.0±0.0*
Contralateral (n = 5)						
A	111±6.0	152±8.1	37.1±1.8	198±14.5	66±7.3	-66.6±2.6
B	92±5.0	146±2.6	61.7±10.9*	175±28.0	126±120.8	-21.7±8.8*
RVLM lesioning						
Ipsilateral (n = 4)						
A	118.7±5.7	145±8.5	21.9±1.9	203±16.7	95±4.3	-51.1±7.1
B	100±1.8	127±12.3	28.4±14.6	145±23.8	142±25.6	-3.1±2.7*
Contralateral (n = 4)						
A	125±2.5	153.7±8.5	22.8±5.7	200±19.6	113.7±25.3	-43.5±9.2
B	98.8±3.2	128.8±5.7	31.2±8.3	132±24.1	106±9.9	-13.5±9.9*

A = before lesioning; B = after lesioning; n = number of experiments; MSAP = mean systemic arterial blood pressure, in mm Hg; values are mean ± S.E.; HR = heart rate; an asterisk (*) indicates a significant difference in values between the control and after DM or RVLM lesioning tested by Student's t-test. * P <0.05.

second peak plateau. The second peak was a prolonged SAP rise. The effect was similar when either side of the PFTG was chemically stimulated (Fig. 1A and B). Lesioning of the right DM, however, affected the ipsilateral PFTG Glu effect most profoundly (Fig 1E), but did not affect the changes induced from the contralateral PFTG (Fig. 1D). When effects were pooled from nine cats, it could be seen that an ipsilateral DM lesion totally eliminated the 41.6% increase in SAP and 48.9% decrease in HR (P<0.05); whereas a contralateral DM lesion had much reduced effects (Table 1).

RVLM lesion was tested on the PFTG pressor effect in another eight cats. An example is shown in Fig. 2. Microinjection of Glu into the PFTG produced an increase in SAP and a decrease in HR, along with an increase of pulse pressure and VNA. After lesioning of the ipsilateral RVLM by KA, the responses of the SAP increase following PFTG stimulation were augmented slightly, but the bradycardiac effect was abolished. Lesioning of the contralateral RVLM had no significant effect on the PFTG-induced SAP effect; also the bradycardiac effect was minor (Table 1).

Lesioning the DM or RVLM on the PFTL-induced depressor effect

The depressor responses of microinjection of Glu in the PFTL consist of a decrease in SAP and HR, a widening of the pulse pressure and

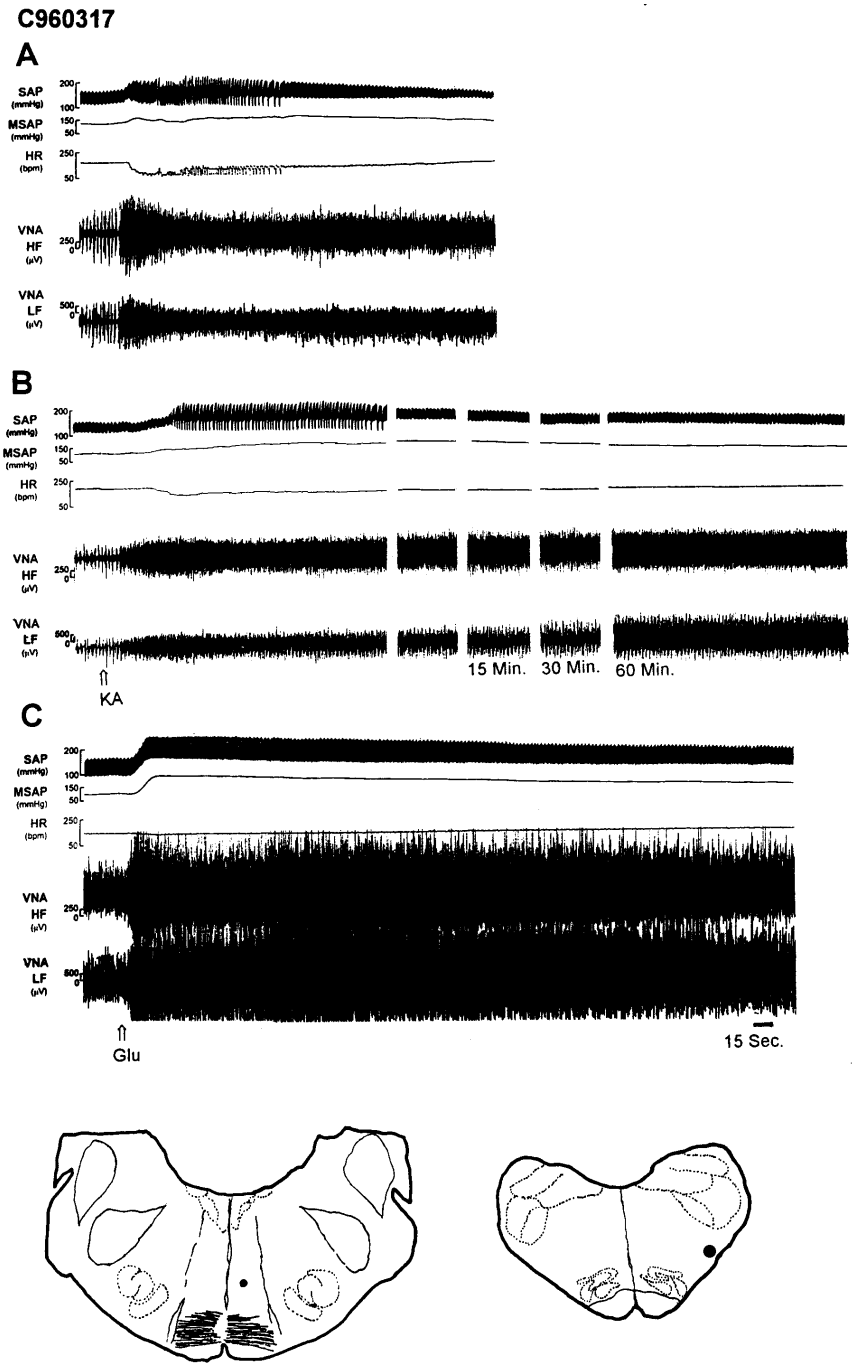

Figure 2. Effects of lesioning of the RVLM on the responses of blood pressure, heart rate, and vertebral nerve activity induced by Glu stimulation (0.25 M, 70 nl) of the PFTG in a cat (C960317). A. Microinjection of Glu in the PFTG produced an increase in SAP and a decrease in HR, accompanied by an increased pulse pressure and VNA. B. The ipsilateral RVLM was lesioned by KA. Note the initial slow hypertension and bradycardia concomitant with increased VNA. This pressor effect can last for 60 min. C. After ipsilateral RVLM lesioning, the pressor response of PFTG activation by Glu remained while the bradycardiac responses disappeared.

Table 2. Effects of DM or RVLM lesioning on the responses of blood pressure and heart rate induced by glutamate stimulation on the pontine lateral tegmental field (PLTF)

	MSAP			HR		
	Resting	Stimulation (mmHg)	Response (%)	Resting	Stimulation (BPM)	Response (%)
DM lesioning						
Ipsilateral (n = 5)						
A	122±1.6	103±2.8	-15.6±1.9	202±10.1	124±11.4	-39.2±3.1
B	104±3.5	109±3	5.1±2.6*	146±18.6	144±17.4	-0.9±0.8*
Contralateral (n = 7)						
A	121±2.1	102.9±1.9	-15.3±0.9	221±10.9	132±10.5	-39.1±5.7
B	111±4.6	112±4.9	0.6±0.5*	160±18.3	160±18.3	0.0±0.0*
RVLM lesioning						
Ipsilateral (n = 5)						
A	122±4.8	103±5.4	-15.8±1.2	204±11.2	102±19.9	-50.2±8.6
B	91±6.9	119±8.6	31.9±7.7*	140±14.9	125±9.2	-9.1±4.1*
Contralateral (n = 5)						
A	122±6.7	113±8.7	-7.8±3.7	204±7.8	74±7.3	-63.4±4.1
B	94±7.9	138±8.3	50.1±12*	149±18.2	111±11.2	-23.3±5.7*

A = before lesioning; B = after lesioning; n = number of experiments; MSAP = mean systemic arterial blood pressure, in mmHg; values are mean ± S.E.; HR = heart rate; an asterisk (*) indicates a significant difference in values between the control and after DM or RVLM lesioning tested by Student's t-test. * P <0.05.

an increase or decrease in VNA (Chai *et al.*, 1993). Table 2 summarizes the effects of DM or RVLM lesioning on the changes of SAP and HR induced by Glu stimulation of the PFTL.

An example of the effect of lesioning the DM on the PFTL-induced depressor effect is illustrated in Fig. 3. Glu microinjection into the right PFTL produced a decrease in SAP and HR. After KA lesioning of the contralateral DM, the same Glu injection in the PFTL no longer produced any SAP or HR effects. As seen in Table 2, in 12 cats, after either the contra- or ipsilateral DM lesioning by KA, the hypotension and bradycardiac effects of PTFL were completely eradicated.

Fig. 4 illustrates an example of KA lesioning of the RVLM on PFTL-induced depressor effects. A slight transient increase in SAP was seen in this example during Glu stimulation of the right PFTL followed by a more prolonged decrease in SAP. The HR decreased. Following KA lesioning of the contralateral RVLM, Glu stimulation of the PFTL produced a strong SAP increase. Table 2 summarizes the results obtained in ten cats. After either contra- or ipsilateral RVLM lesioning by KA, the 7.8% to 15.8% decrease in SAP produced by Glu stimulation in the PFTL reversed to a 31.8 to 50.1% increase instead. Slight HR decrease effects still remained after RVLM lesioning (Table 2).

Comparison of resting SAP changes following DM or RVLM lesioning by KA

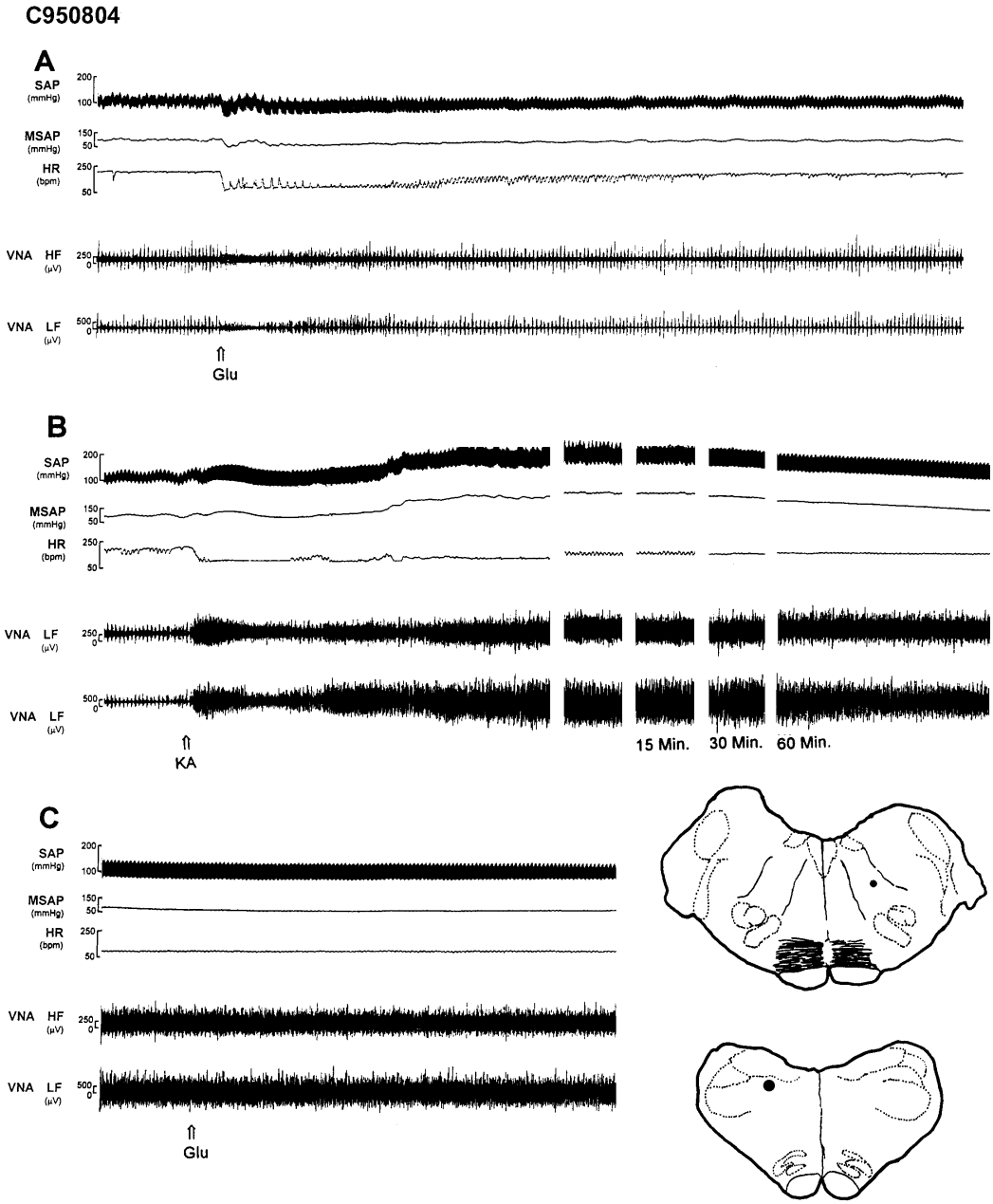

Figure 3. Lesioning of the DM attenuates the blood pressure, heart rate, and vertebral nerve activity changes induced by Glu stimulation of the PLTF in a cat (C950804). A. Microinjection of Glu (0.25 M, 70 nl) in the PLTF produced decreases in SAP and HR, and widening of the pulse pressure. B. The contralateral DM was lesioned by KA. Note that initial hypotension and bradycardia occurred concomitant with an increase in VNA. Late but long-lasting (60 min) hypertension followed. C. After lesioning of the contralateral DM, the same dose of Glu in the same site of PLTF induced no response.

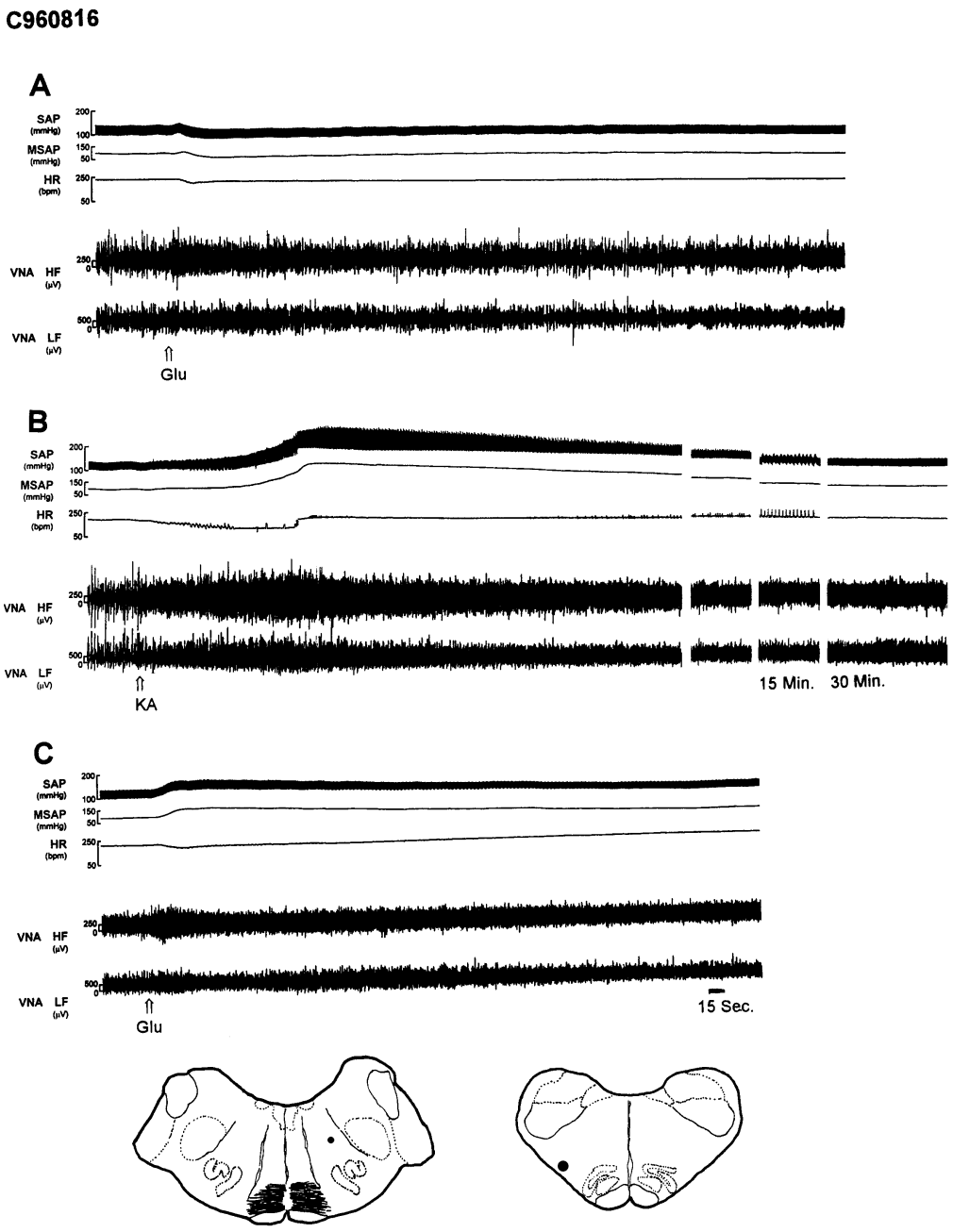

Figure 4. Lesioning of the RVLM attenuates blood pressure, heart rate, and vertebral nerve activity responses induced by Glu stimulation of the PLTF in a cat (C950816). A. Microinjection of Glu (0.25 M, 70 nl) in the PLTF produced slight decreases in SAP and HR, widening of pulse pressure, and an increase of VNA. B. The contralateral RVLM was lesioned by KA. Note the initial hypotension and bradycardia responses, followed by secondary but long-lasting (60 min) hypertension. C. After contralateral RVLM lesioning, the same dose of Glu in the same site of the PLTF changed the depressor response into a pressor response.

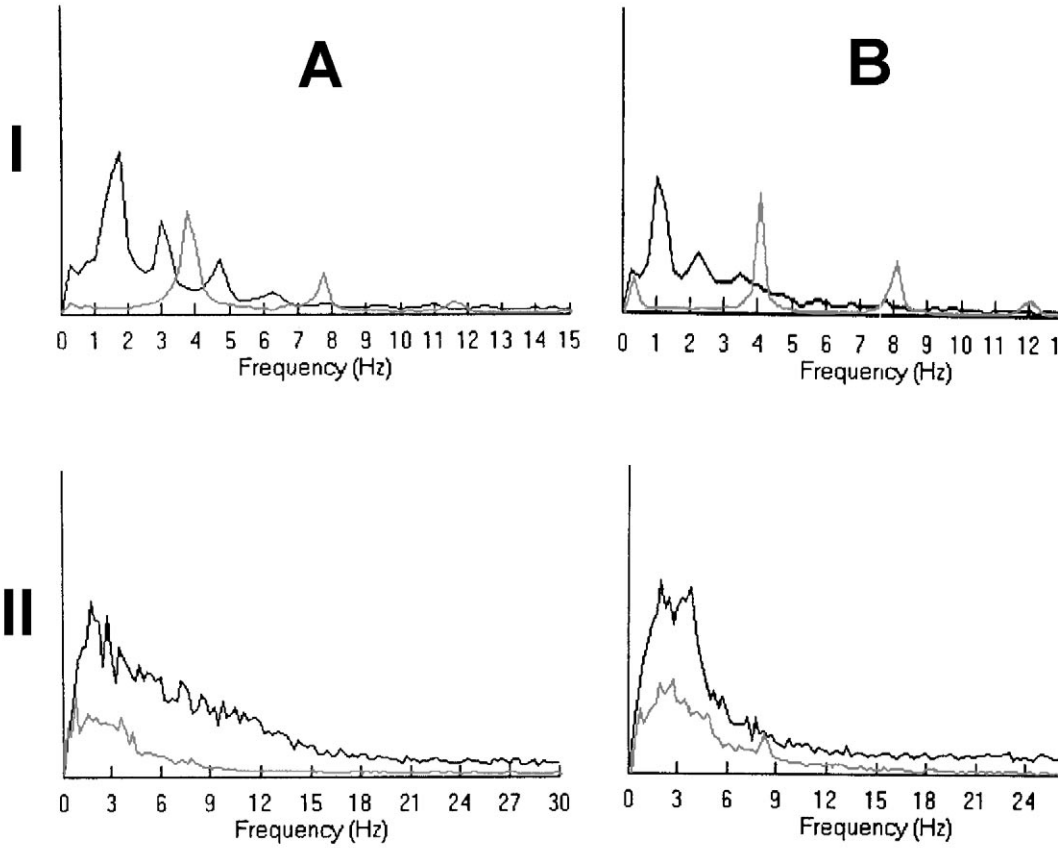

Figure 5. Change of autospectra of sympathetic vertebral nerve activity (VNA) during the Glu-induced responses of PFTG and PFTL. The gray line shows the VNA power spectra in resting conditions, and the black line shows the spectra during Glu-induced responses. A. The autospectra before and during PFTG stimulation. B. The autospectra before and during PFTL stimulation. I. Average autospectra of SAP between the frequency range 0-15 Hz. II. Average autospectra of the VNA between the frequency range 0-30 Hz. Each spectrum is the average of forty 4-s data blocks. The frequency resolution is 0.25 Hz/bin.

Differences between DM and RVLM lesioning by KA were also observed. When KA was injected into the pressor point of either the DM or RVLM, its initial excitatory effects produced increases in SAP and VNA. The magnitude of such pressor rises was slightly higher from the RVLM than from the DM. The initial rise in SAP following KA lesioning of either the DM or RVLM was followed by a fall of SAP. The magnitude of fall taken at 60 minutes after lesion was slightly higher after RVLM than after DM lesioning (Tables 1,2).

Change in power spectra of VNA during brain stimulation

In resting state, the predominant frequency of VNA was from 1 to 4 Hz. Following microinjection of Glu into the PFTG or PFTL, all components in the spectrum were greatly increased. No recognizable difference could be discerned in the spectra of VNA responses between that induced by PFTG versus the one induced by PFTL (Fig. 5).

DISCUSSION

The principle findings of the present study

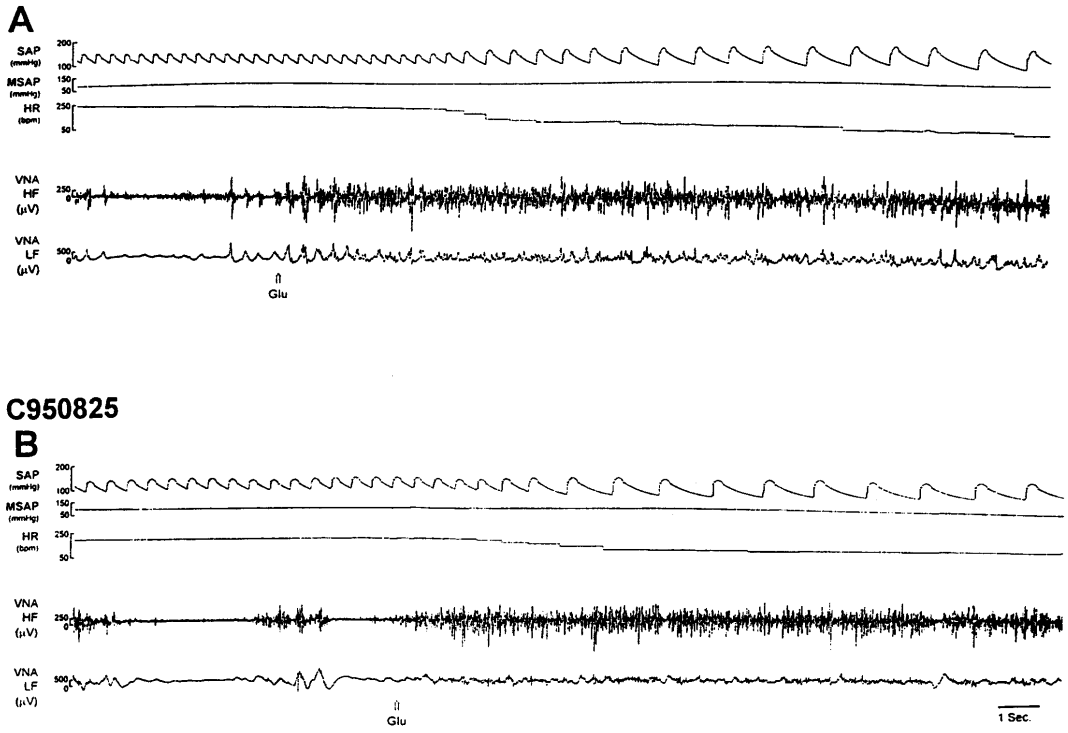

Figure 6. Fast tracings showing effects of Glu microinjection into the PFTG in a cat (C960307) and into PLTF in another (C950825). A. Responses induced by microinjection of Glu (0.25 M, 70 nl) in the PFTG. Note that the decrease of HR lagged about 3 s behind the increase of VNA. B. Responses induced by microinjection of Glu (0.25 M, 70 nl) in the PLTF. Note a shorter delay (1 s) of the HR decrease against the increase of VNA.

were that PFTG and PFTL cardiovascular effects are mediated differentially through the DM and RVLM, of which, the dorsal medulla on the ipsilateral side dominates. Through selective lesioning of either the RVLM or DM, we also uncovered additional functional organization principles of the PFTG and PFTL.

Ipsilateral DM lesioning greatly reduced or eliminated the Glu induced-pressor responses of PFTG. Contralateral DM lesioning left most of the pressor responses of PFTG unaltered. Either ipsi- or contralateral lesioning of the DM significantly attenuated the SAP and HR effects of PFTL stimulation. RVLM lesions of either side could also eliminate the depressor effects of PFTL. In fact, the PFTL-induced depressor effect was reversed to a pressor effect. In sharp contrast, RVLM lesions left the PFTG-induced pressor effects largely unaltered. Taken together, these findings indicate that the pressor responses induced from the PFTG depend largely on the neural structures of the ipsilateral DM, while the depressor responses induced from the PFTL depend on the integrity of the DM and RVLM on both sides.

Stimulation of the PFTG by Glu produced an increase of SAP and VNA concomitant with a decrease in HR. The established important cardiovascular functions of RVLM are its roles in a variety of reflexive and centrally initiated sympathetic cardiovascular responses, including the arterial baroreflex and chemoreflex (Agrawal *et al.*, 1990; Agrawal & Calaresu 1991). When the RVLM was lesioned, the function of the baroreflex was seriously affected and baroreceptor-induced bradycardia was eliminated (McAllen 1986; Dempesy *et al.*, 1993). This may explain why in the present

study after the RVLM was lesioned; the Glu-induced pressor responses of the PFTG were augmented. Although the present study provides no direct evidence showing whether the bradycardia accompanying the PFTG-induced SAP rise is an effect directly obtained by brain activation or secondarily to baroreceptor activation, based on the fact that the decrease of HR was about 3 s behind the increase of VNA (Fig. 7A), it is most likely that the PFTG produced a sympathoexcitatory effect first, causing a SAP rise, which triggered the decrease in HR through the baroreflex. Therefore, we conclude that the PFTG is a DM-dependent sympathoexcitatory area.

Stimulation of PFTL produced bradycardia, and increased VNA and hypotension immediately (Fig 7B). The patterns of the response are very similar to those of stimulation of the midbrain central tegmental field (Lin *et al.*, 1987), which is a parasympathetic cardioinhibitory area. When unilateral RVLM was lesioned, the Glu-induced depressor response of the PFTL was not only eliminated but was also converted into a response of SAP and VNA increases. A reasonable explanation is that there are both parasympathoexcitatory and sympathoexcitatory neurons colocalizing in the PFTL. Before RVLM lesioning, the parasympathoexcitatory cardioinhibitory effects are more powerful than the sympathoexcitatory ones. Thus, the overall cardiovascular responses to PFTL activation are depressor-like. RVLM lesion might either have eliminated the parasympathetic cardioinhibitory neurons in the nucleus ambiguus, or have compromised the baroreflex pathway, hence causing the overall PFTL-induced cardiovascular effects to be shifted to sympathoexcitatory. Therefore, the PFTL appears to contain a heterogeneous mixture of sympathoexcitatory and parasympathoexcitatory neurons.

Findings of a previous study have shown that the DM and RVLM exert differential effects over sympathetic nerve activity (Su *et al.*, 1992). Whether the PFTG and PFTL also exert a specific effect over the sympathetic activity was examined with power spectral analysis (Stauss *et al.*, 1995). Our results show that in the resting state, the VNA was synchronized, with a predominance of frequency in the 1 Hz to 4 Hz component. With stimulation of the PFTG or PFTL by Glu, the power was increased in all frequencies. At this moment, there are insufficient data to allow meaningful physiological interpretation.

Cardiovascular responses produced not only by RVLM-spinal vasomotor neural but also by DM-spinal vasomotor neural pathways.

As a part of a series of studies concerning the cardiovascular functional pathways in the brain stem in our laboratories, we found that the DM is an important relay of cardiovascular function. Destruction of either the DM or RVLM produces a precipitous fall of resting SAP, suggesting the participation of both nuclei in the maintenance of basal cardiovascular tone. But KA destruction within a limited area in the unilateral DM causes only a moderate fall of resting SAP, while the effects of KA lesioning in the RVLM are more serious than those in the DM. This suggests that the RVLM is more important than the DM in the tonic maintenance of the basal blood pressure level (Su *et al.*, 1989). Anatomically, when HRP was injected into the intermediolateral column of the thoracic spinal cord, where sympathetic preganglionic neurons reside, retrogradely labeled cells were found in both the DM and RVLM (Lan *et al.*, 1997). The neural structures responsible for generating sympathetic vasomotor tone are believed to be located in the medulla, since midcollicular or midbrain transection generally resulted in no marked reduction in SAP (Chai *et al.*, 1993). The neurons of the RVLM may represent the neuronal circuit relaying baroreceptor information to other neurons and providing excitatory output to the sympathetic preganglionic neurons as well (Agrawal *et al.*, 1990; Agrawal & Calaresu 1991). The present study shows that the pressor and depressor responses induced from the PFTG and PFTL depend largely on neural

structures of the DM while the RVLM has a minor role. Thus, our present study adds additional functional evidence that the DM is an important cardiovascular regulatory area in the medullary oblongata.

From studies of other laboratories, the PFTG or PFTL are believed to play an impressive role in non-cardiovascular functional regulation (Holstege *et al*., 1986; McCarley & Hobson 1971; McCarley & Ito 1983; and McCarley *et al*., 1987). For instance, the PFTL may serve as a feedback regulatory system in pain perception, receiving afferents from the spinothalamic tract, and sending efferents to neurons which form the spinothalamic tract. The PFTL not only receives fibers from the spinal cord but also from several limbic areas such as the amygdala, bed nucleus of the stria terminalis, the posterior hypothalamus, and various other hypothalamus areas (Tan & Holstege 1986). Mitani *et al.* (1988) have provided evidence showing projections of the PFTG to the bulbar reticular formation. In our previous study, however, it was shown that the pressor response to chemical stimulation of the PFTG is altered by precollicular decerebration, demonstrating that this response must be mediated by an ascending pathway (Chai *et al*., 1993). Similarly, the pathway of the depressor response evoked by stimulation of PFTL takes also an ascending pathway (Chai *et al*., 1993). It seems therefore, that the pontine PFTG and PFTL relate heavily with the rostral brain areas. Moreover, there must be several parallel cardiovascular regulatory pathways in the rostral brain areas. How these pathways are organized awaits further study.

REFERENCES

Agrawal, S. K. and F. R. Calaresu (1991) Monosynaptic connections from caudal to rostral ventrolateral medulla in the baroreceptor reflex pathway. Brain Res. 555: 70-74.

Agrawal, S. K., A. J. Gelsema, and F. R. Calaresu (1990) Inhibition of rostral VLM by baroreceptor activation is relayed through caudal VLM. Am. J. Physiol. 258: R1271-R1278.

Braun, C. M. J. and R. T. Pivik (1983) Effects of brainstem lesions on tonic immobility in the rabbit (*Oryctolagus cuniculus*). Brain Res. Bull. 10: 127-135.

Chai, C. Y., S. Y. Chen, S. D. Wang, C. J. Tseng, R. H. Lin, S. P. Mao, H. T. Horng, J. C. Liu, and J. S. Kuo (1993) Precollicular decerebration reduces the pressor responses evoked by stimulation of rostral pons but not medulla in cats. J. Auton. Nerv. Syst. 46: 147-159.

Chai, C. Y., R. H. Lin, A. M. Y. Lin, C. M. Pan, E. H. Y. Lee, and J. S. Kuo (1988) Pressor responses from electrical or glutamate stimulation of the dorsal or ventrolateral medulla. Am. J. Physiol. 255: R709-R717.

Clement, M. E. and R. B. McCall (1993) Impairment of baroreceptor reflexes following kainic acid lesions of the lateral tegmental field. Brain Res. 618: 328-332.

Dampney, R. A. L. (1994) Functional organization of central pathways regulating the cardiovascular system. Physiol. Rev. 74: 323-364.

Dempesy, C. W., D. E. Richardson, and C. J. Fontana (1993) Cardiovascular sympathoinhibitory neurons from an extended longitudinal column in cat lateral medulla. Brain Res. 603: 328-332.

Gatti, P. J. and R. A. Gillis (1991) Interaction between pressor and depressor areas in cat ventrolateral medulla. Brain Res. 552: 153-158.

Gebber, G. L. (1980) Central oscillators responsible for sympathetic nerve discharge. Am. J. Physiol. 239: H143-H155.

Gebber, G. L., S. M. Barman, and M. Zviman (1989) Sympathetic activity remains synchronized in presence of a glutamate antagonist. Am. J. Physiol. 256: R722-R732.

Gilbert, K. A. and R. Lydic (1994) Pontine cholinergic reticular mechanisms cause state-dependent changes in the discharge of parabrachial neurons. Am. J. Physiol. 266: R136-R150.

Goodchild, A. K., R. A. L. Dampney, and R. Bandler (1982) A method for evoking physiological responses by stimulation of cell bodies, but not axons of passage, within localized regions of the central nervous system. J. Neurosci. Methods. 6: 352-363.

Holmes, C. J. and B. E. Jones (1994) Importance of cholinergic, gabaergic, serotonergic and other neurons in the medial medullary reticular formation for sleep-wake states studied by cytotoxic lesions in the cat. Neuroscience 62: 1179-1200.

Holmes, C. J., L. S. Mainville, and B. E. Jones (1994) Distribution of cholinergic, gabaergic and serotonergic neurons in the medial medullary reticular formation and their projections studied by cytotoxic lesions in the cat. Neuroscience 64: 1155-1178.

Holstege, G., J. Tan, J. J. vanHam, and G. A. Graveland (1986) Anatomical observations on the afferent projections to the retractor bulbi motoneuronal cell group and other pathways possibly related to the blink reflex in the cat. Brain Res. 374: 321-334.

Ito, K. and R. W. McCarley (1987) Physiological studies of brainstem reticular connectivity. I. Responses of mPRF neurons to stimulation of bulbar reticular formation. Brain Res. 409: 97-110.

Lan, C. T., W. C. Wu, E. A. Ling, and C. Y. Chai (1997) Evidence of a direct projection from the cardiovascular-reactive dorsal medulla to the intermediolateral cell column of the spinal cord in cats as revealed by light and electron microscopy. Neuroscience 77: 521-533.

Lin, A. M. Y., C. M. Pan, Y. F. Lin, J. S. Kuo, S. H. H. Chan, and C. Y. Chai (1987) A cardioinhibitory area in the midbrain central tegmental field of cats. Brain Res. Bull. 18: 699-707.

Lydic, R. and H. A. Baghdoyan (1993) Pedunculopontine stimulation alters respiration and increases ACh release in the pontine reticular formation. Am. J. Physiol. 264: R544-R554.

Malpas, S. C. and I. Ninimiya (1992) A new approach analysis of synchronized sympathetic nerve activity. Am. J. Physiol. 263: H1311-H1317.

McAllen, R. M. (1986) Action and specificity of ventral medullary vasopressor neurons in the cat. Neuroscience 18: 51-59.

McCarley, R. W. and J. A. Hobson (1971) Single neuron activity in cat gigantocellular tegmental field: selectivity of discharge in desynchronized sleep. Science 174: 1250-1252.

McCarley, R. W. and K. Ito (1983) Intracellular evidence linking medial pontine reticular formation neurons to PGO wave generation. Brain Res. 280: 343-348.

McCarley, R. W., K. Ito, and M. L. Rodrigo-Angulo (1987) Physiological studies of brainstem reticular connectivity. II. Responses of mPRF neurons to stimulation of mesencephalic and contralateral pontine reticular formation. Brain Res. 409: 111-127.

Mitani, A., K. Ito, A. E. Hallanger, B. H. Wainer, K. Kataoka, and R. W. McCarley (1988) Cholinergic projections form the laterodorsal and pedunculopontine tegmental nuclei to the pontine gigantocellular tegmental field in the cat. Brain Res. 451: 397-402.

Mitani, A., K. Ito, Y. Matani, and R. W. McCarley (1988) Morphological and electrophysiological identification of gigantocellular tegmental field neurons with

descending projections in the cat: I. Pons. J. Comp. Neurol. 268: 527-545.

Oka, T., H. Iwakiri, and S. Mori (1993) Pontine-induced generalized suppression of postural muscle tone in a reflexively standing acute decerebrate cat. Neurosci. Res. 17: 127-140.

Stauss, H. M., R. Mrowka, B. Nafz, A. Patzak, T. Unger, and P. B. Persson (1995) Dose low frequency power of arterial blood pressure reflect sympathetic tone? J. Auton. Nerv. Syst. 54: 145-154.

Su, C. K., A. M. Y. Lin, R. H. Lin, J. S. Kuo, and C. Y. Chai (1989) Contribution between dorsal and ventrolateral regions of medulla oblongata in vasomotor function of cats. Brain Res. Bull. 23: 447-456.

Su, C. K., C. T. Yen, J. C. Hwang, C. T. Tseng, J. S. Kuo, and C. Y. Chai (1992) Differential effects on sympathetic nerve activities elicited by activation of neurons in the pressor areas of dorsal and rostral ventrolateral medulla in cats. J. Auton. Nerv. Syst., 40: 141-154.

Sun, M. K., J. T. Hackett, and P. G. Guyenet (1988) Sympathoexcitatory neurons of rostral ventrolateral medulla exhibit pacemaker properties in the presence of glutamate receptor antagonist. Brain Res. 438: 23-40.

Sun, M. K., B. S. Young, J. T. Hackett, and P. G. Guyenet (1988) Reticulospinal pacemaker neurons of the rostral ventrolateral medulla with putative sympathoexcitatory function: An intracellular study in vitro. Brain Res. 442: 229-239.

Sved, A. F. (1986) Pontine pressor sites which release vasopressin. Brain Res. 369: 143-150.

Tan, J. and G. Holstege (1986) Anatomical evidence that the pontine lateral tegmental field projects to lamina I of the caudal spinal trigeminal nucleus and spinal cord and to the Edinger-Westphal nucleus in the cat. Neurosci. Lett. 64: 317-322.

Yardley, C. P., J. M. Andrade, and L. C. Weaver (1989) Evaluation of cardiovascular control by neurons in the dorsal medulla of rats. J. Auton. Nerv. Syst. 29: 1-12.

Yates, B. J., C. D. Balaban, A. D. Miller, K. Endo, and Y. Yamaguchi (1995) Vestibular inputs to the lateral tegmental field of the cat: potential role in autonomic control. Brain Res. 689: 197-206.

Zhong, S., S. M. Barman, and G. L. Gebber (1992) Effects of brain stem lesions on 10-Hz and 2- to 6- Hz rhythms in sympathetic nerve discharge. Am. J. Physiol. 262: R1015-R1024.

(Received Mar. 20, 2000; Accepted Apr. 18, 2000)

化學性破壞貓延腦背區與腹外側區對橋腦巨大細胞被蓋區與側蓋區的心臟血管功能控制作用的影響

謝瑞香[1]，屈統郅[1]，嚴震東[2]，蔡作雍[3]

[1] 中原大學醫學工程研究所，中壢，桃園
[2] 台灣大學動物學系，台北市
[3] 中央研究院生物醫學研究所，台北市

摘 要

本研究目的在探討橋腦巨大細胞被蓋區（PFTG）及橋腦側蓋區（PFTL）調控心血管功能機制與延腦中區（DM）及腹外側區（RVLM）之間的關係。以貓為實驗動物。以尿酯及氯醛醣混合試劑腹腔醉後，記錄其血壓，心跳及椎交感神經活性。 比較海人草酸破壞同側或異側DM 或RVLM 前後以麩胺酸刺激PFTG 或PFTL所引發的心血管反應的變化。發現當以海人草酸破壞了同側的DM時， PFTG 不再能引起升壓反應；但是如果破壞異側DM ，對此升壓反應並無明顯影響。如破壞是在RVLM ，無論同側或異側，PFTG 的升壓反應反而變的比原先稍大。對於PFTL的降壓反應，當以海人草酸破壞同側或異側的DM ，均轉變為幾乎消失。當破壞同側或異側的RVLM ，PFTL 的降壓反應反而轉變為升壓。因此，我們的結論是橋腦PFTG 的升壓作用主要經由延腦同側DM 表現。橋腦PFTL 的降壓作用則需要兩側的DM 及RVLM 均保持正常，並且PFTL 中可能混有一些交感興奮性神經元。

關鍵字：升壓作用，降壓作用，心跳，交感神經活性，頻譜分析