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Effects of Central GABA and Glutamate on Blood Pressure and Single Unit Spikes in the RVLM of Rats

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The blood pressure (BP) is regulated by the nervous system and humoral factors, such as renin-angiotensin system, vasopressin and others. In the present study, we examined the central effects of glutamate and GABA on the cardiovascular regulation by injection of these substances into the lateral ventricle and also investigated the relationship between these central effects and the action of angiotensin II (Ang). Male Sprague Dawley rats, 350~400 g, were anesthetized with urethane and instrumented with an arterial catheter for direct measurement of BP and heart rate (HR), and an guide cannula in the lateral ventricle for drug injection. A glass microelectode was inserted into the rostral ventrolateral medulla (RVLM) for recording single unit spikes. Barosensitive neurons were identified by changes of single unit spikes in RVLM following intravenous injection of nitroprusside and phenylephrine. The effects of GABA and glutamate injected into the lateral ventricle were studied in single neuronal activity of the RVLM in addition to changes in BP and heart rate, and compared the results before and after treatment with intravenous losartan, nonpeptide Ang II-type 1 receptor antagonist (1 mg/100 g BW). Intracerebroventricular administration of GABA decreased systolic blood pressure (SBP) and HR, but increased the firing rates in the RVLM. However, intracerebroventricular glutamate injection produced effects opposite to GABA. After pretreatment of intravenous losartan, the central effects of GABA on BP and firing rate in the RVLM were significantly attenuated and that of glutamate showed a tendency of attenuation. These results suggested that central GABA and glutamate regulated BP and firing rates in RVLM were inversely related to BP change. The central effects of GABA or glutamate on the autonomic nervous function were modulated by humoral factor, Ang II, by maintaining BP.

Key Words: GABA, Glutamate, Blood pressure, RVLM, Losartan

INTRODUCTION

The blood pressure (BP) is regulated by nervous system as well as humoral factors, such as renin-angiotensin system, vasopressin and others. The best known among the nervous mechanisms for BP control is by far the baroreceptor reflex. Sensory neurons from the baroreceptors are transmitted to glutamate receptors in the nucleus tractus solitarius and in the caudal ventrolateral medulla, which mediates a gamma-aminobutyric acid (GABA)ergic inhibition on the rostral ventrolateral medulla (RVLM) (Agarwal & Calaresu, 1991; Jeske et al, 1995). Neurons in the RVLM directly innervate to the preganglionic sympathetic neurons in the intermediolateral column of the spinal cord, and the activity of these bulbospinal neurons is inversely correlated with baroreceptor afferent neural activity. Therefore, the RVLM plays a central role in the neural control of the circulation (Guyenet, 1990; Dampney, 1994a). Hilton & colleagues (1983) first proposed that the RVLM is an important relay station for descending cardiovascular pathways from the hypothalamic and midbrain defense areas. There are numerous other pathways to stimulate the preganglionic sympathetic neurons in addition to this main pathway (Dampney, 1994b). Furthermore, besides the sympathoexcitatory baroreceptor reflex, parasympathetic cardioinhibitory preganglionic neurons have been shown primarily in the ventrolateral nucleus ambiguus in the case of baroreceptor vagal reflex (Stuesse & Fish, 1984).

Sun & Li (1994) demonstrated that the intracerebroventricular injection of GABA produced decreases in BP and the depressor effect of GABA was mediated, at least in part, by inhibition of brain angiotensin (Ang) system. They proposed that the deficiency of the inhibitory effect of GABA induced hypertension. Meanwhile, Maione & colleagues (1992) pointed out an increase in the central sympathetic efferent activity and in release of vasopressin after injection of NMDA into the third ventricle. Although these results suggest both central GABA and glutamate to influence sympathetic activity and BP, the exact action sites of these substances are not known.

Intracerebroventricular administration of Ang II has been

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ABBREVIATIONS: BP, blood pressure; SBP, systolic blood pressure; Ang, angiotensin II; RVLM, rostral ventrolateral medulla; HR, heart rate.

shown to increase BP (Mangiapane & Simpson, 1980; Tseng et al, 1994). Beside the central action of decrease in the sensitivity of the baroreflex (Sanderford & Bishop, 2000), Ang II acts directly on vascular smooth muscle to produce arteriolar constriction, raising BP via the Ang II type 1 receptors (AT1). Reid (1992) reported that the peripheral actions of Ang II enhanced the cardiovascular responses elicited by activation of the sympathetic nervous system.

In the present study, the central effects of GABA and glutamate on the cardiovascular regulation after injection of these substances into the lateral ventricle were examined. Considering the importance of RVLM in blood pressure regulation, single unit spike potentials of the RVLM were recorded to evaluate the central action of GABA and glutamate in addition to recording of BP. The relationship between these substances and peripheral Ang II system was also investigated.

METHODS

Animal preparation

Experiments were performed on adult male Sprague-Dawley rats weighing 350~450 g. The rats were anesthetized with an intraperitoneal injection of urethane (0.1 g/100 g i.p.). Adequacy of anesthesia was assessed by monitoring the stability of BP and heart rate (HR) and the BP responses to pinching the hind paws. Anaesthetics were supplemented when it was necessary.

The femoral artery and vein were cannulated for measurement of BP and administration of drugs, respectively. BP was monitored by a transducer (model P23XL, Ohmeda, USA), and HR was determined with an HR counter (model 7P4H, Grass, USA) triggered by the BP wave. All variables were recorded continuously on a direct-writing polygraph (model 79, Grass, USA). BP was also monitored continuously with a computer through a CED 1401 (Cambridge Electronics Design, England).

The trachea was intubated for artificial ventilation (model 683, Harvard Apparatus, England) and ventilated with a minute volume of 600~780 ml/kg oxygen-enriched room air after the animal was paralyzed with pancuronium bromide (mioblock, 0.5 mg/kg initially and 0.1 mg/kg every 60 min, i.v.) to eliminate respiratory influence on BP. Rectal temperature was kept at 38°C with a thermostatically controlled heating pad (Harvard Apparatus, England) or an infrared lamp. To check the condition of rats during entire period of experiment, electrocardiogram was monitored continuously through a oscilloscope (Narco Bio-System Inc., USA).

Operation for intracerebroventricular injection

The rats were placed on a stereotaxic frame (model 1404, David Kopf Inst., USA) with the head in a horizontal position. The scalp was longitudinally incised and skull was leveled between lambda and bregma. A 22-gauge stainless steel guide cannula was placed into the lateral ventricle through a small hole drilled in the skull (1.5 mm lateral, 0.8 mm caudal to bregma and 4.0 mm deep from the bone) according to the stereotaxic atlas of Paxinos and Watson (1986). The cannula was anchored to the skull with dental cement and a jeweler's screw. A stainless steel obturator was used to seal the cannula. The obturator was removed from the guide cannula placed into the lateral ventricle. An injector cannula connected to a 10 or 25 μl Hamilton syringe through polyethylene tube (PE-20), which was filled with the drug to be administered and the other end cut obliquely, was inserted into the lateral ventricle. The tip of the injector cannula extended 1 mm beyond the guide cannula.

The intracerebroventricular injection of glutamate (0.7 M, 2 μl, 2 min), GABA (0.1 M, 2 μl, 2 min) and losartan, a nonpeptide AT1 antagonist, (100 μg/20 μl, 10 min) was carried out slowly via a syringe (10 or 25 μl, Hamilton Co.) attached to an pump (model 22, Harvard, England) through the extension. All drugs were purchased from Sigma Chemical Co. and dissolved in 0.9% saline.

Single unit spike recordings in the RVLM

A glass microelectrode was used to record single unit activity in the RVLM. The rats were fixed in a stereotaxic apparatus. A micropositioner (Model 660, David Kopf, USA) was used to advance the electrode tip through the region of the RVLM (2.0 mm lateral to the midline, 12.0 mm caudal to the bregma and 6.5 mm below the skull) for recording. Barosensitive neurons were identified by inhibition of spontaneous firing rate after a bolus intravenous injection of phenylephrine (1 μg/100 g BW) or by the increase of firing rate after an injection of vasodilator, sodium nitroprusside (100 μg/100 g BW).

Neural signals were amplified (CyberAmp380, Axon Inst., USA) with low and high cutoff frequencies of 100 Hz and 4 kHz, respectively, and monitored on an oscilloscope (model 2205, Tektronix, USA). Neural spikes were discriminated by a time-amplitude window discriminator (model D130, Digitimer, England) and taken to the A/D converter (model 1401plus, CED, England) for continuous recording of neural activity. The ongoing neural activity was integrated at intervals of 1 s using a CED 1401 program. The baseline activity was calculated by averaging the firing rate in the 60 s period prior to administration of drugs.

Verification of intracerebroventricular cannula location

At the end of each experiment, 5 μl Evans blue dye (5%) was injected through the intracerebroventricular cannula. The position of the cannula in the lateral ventricle was confirmed by the diffusion of the dye throughout the ventricular system.

Statistical analysis

Data were expressed as mean±SE. Significant difference was considered at $p<0.05$ using the paired t-test.

RESULTS

In order to identify whether the neurons in the RVLM were barosensitive, nitroprusside or phenylephrine was injected intravenously to lower or raise the BP. A typical example of changes of BP and firing rate after nitroprusside and phenylephrine administration are shown in Fig. 1 and 2. Nitroprusside decreased arterial blood pressure and

increased firing rate through the barorecptor reflex. On the contrary, however, phenylephrine injection showed the opposite effects.

In the GABA-treated group, the basal systolic blood pressure (SBP), HR and firing rates were 106±5 mmHg, 337±10 rates/min and 12±2 spikes/s, respectively. Intracerebroventricular administration of GABA reduced peak SBP to 72±5 mmHg. However, the firing rates of baro sensitive neuron in RVLM increased significantly (Fig. 3). Intravenous injection of losartan, AT1 antagonist, alone reduced SBP from 109±3 to 89±4 mmHg, accompanied by increased number of single spike. When GABA was injected into the lateral ventricle 10 min after intravenous administration of losartan, SBP decreased to 74±4 mmHg and firing rates increased. HR was not changed significantly. These results showed that pretreatment of losartan significantly attenuated subsequent GABA-induced decrease in SBP and increase in firing rates (Fig. 3).

In the glutamate-treated group, the basal SBP, HR and firing rates were 105±1 mmHg, 330±12 rates/min and 19 ±3 spikes/s, respectively. These results were not significant different from those of the GABA group. Microinjection of glutamate into the lateral ventricle increased SBP by 40±3 mmHg and was accompanied by decrease in the firing rates (Fig. 4). Glutamate administered into the lateral ventricle after pretreatment with intravenous losartan increased SBP by 30±4 mmHg. It suggested that losartan had a tendency to attenuate subsequent glutamate-induced increase of SBP (Fig. 4).

GABA and glutamate produced significant increase in the ratio of simultaneous changes in firing rate to changes in SBP, which is an index of the baroreflex control after pretreatment with intravenous losartan (Fig. 5).

To test the effect of circulating losartan leak on the cen-

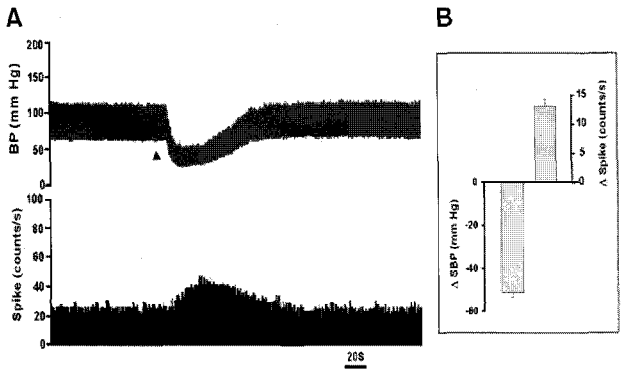

Fig. 1. A) Illustration of changes of systolic blood pressure (SBP) and single unit spike histogram, when nitroprusside (100 mg/100 g BW, indicated by filled triangle) was injected intravenously to identify cardiovascular neurons in RVLM. Bin width=1s. B) Maximum changes in SBP and single unit spike histogram of RVLM. Values are means±SE (n=20).

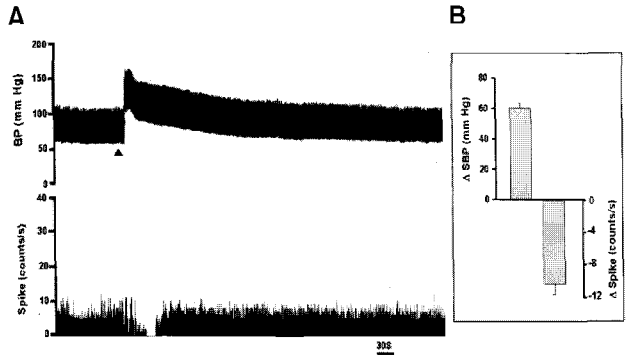

Fig. 2. A) Illustration of changes of systolic blood pressure (SBP) and single unit spike histogram, when phenylephrine (1 mg/100 g BW, indicated by filled triangle) was injected intravenously to identify cardiovascular neurons in RVLM. Bin width=1s. B) Maximum changes in SBP and single unit spike of RVLM. Values are means±SE (n=12).

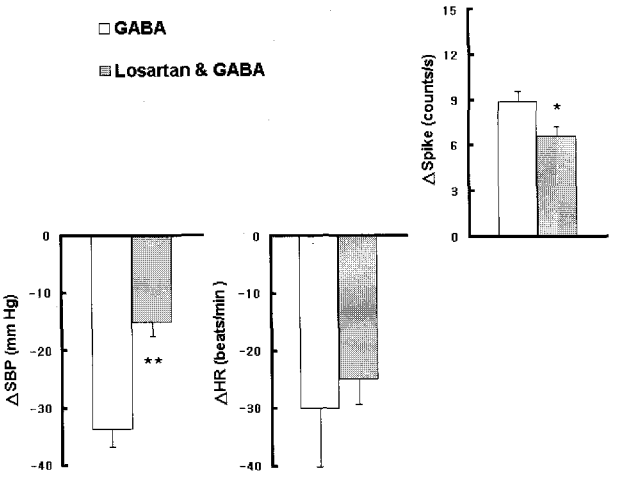

Fig. 3. Effect of intracerebroventricular GABA (0.1 M, 2 μl) on systolic blood pressure (SBP), heart rate (HR) and single unit spike of RVLM before and after intravenous injection of losartan (1 mg/100 g). Values are means±SE (n=12). *p<0.05, **p<0.01 vs. GABA.

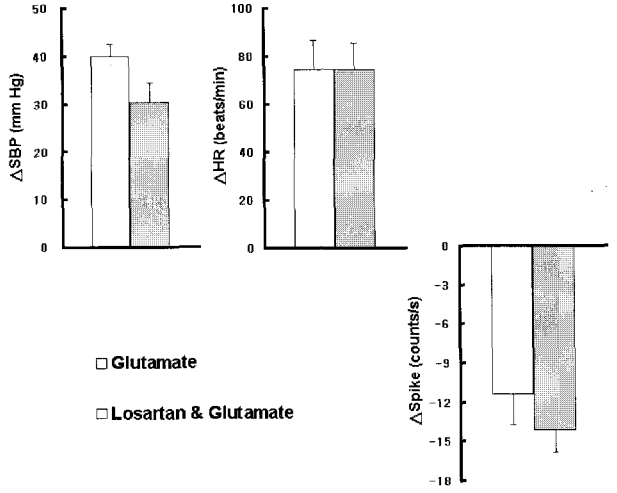

Fig. 4. Effect of intracerebroventricular glutamate (0.7 M, 2 μl) on systolic blood pressure (SBP), heart rate (HR) and single unit spike of RVLM before and after intravenous injection of losartan (1 mg/100 g). Values are means±SE (n=12).

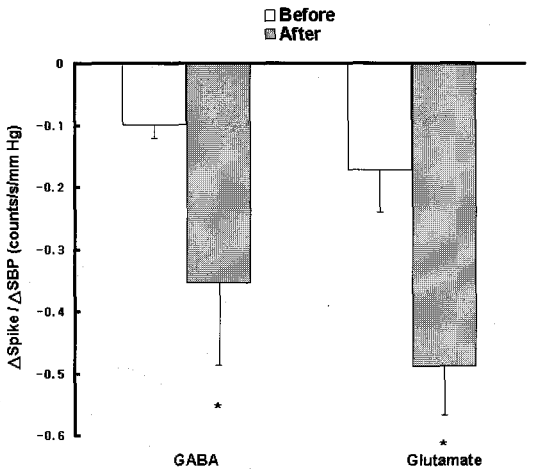

Fig. 5. Comparison of the ratio of changes in single unit spike of RVLM and systolic blood pressure (SBP) produced by intracerebroventricular injection of GABA (0.1 M, 2 μl) and glutamate (0.7 M, 2 μl) before and after intravenous injection of losartan (1 mg/100 g). Values are means±SE (n=12). *p<0.05 vs. Before.

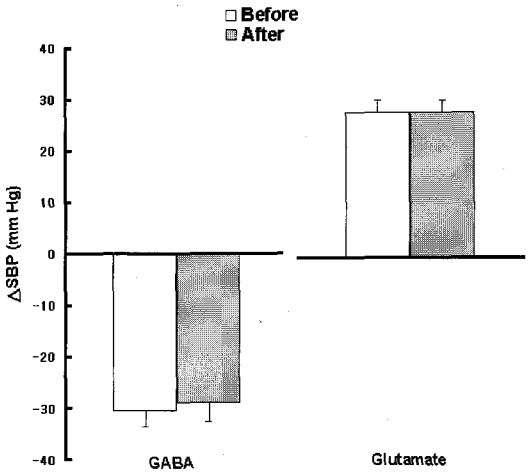

Fig. 6. Responses of systolic blood pressure (SBP) to intracerebroventricular injection of GABA (0.1 M, 2 μl, n=12) and glutamate (0.7 M, 2 μl, n=20) before and after intracerebroventricular injection of losartan (5 μg/ μl, 20 μl). Values are means±SE.

tral nervous system, we investigated the response of rats pretreated with losartan intracerebroventricularly to intracerebroventricular GABA and glutamate. There were no significant differences in SBP between the rats with and without losartan pretreatment (Fig. 6). Thus, our experiment showed no effect of intravenous injection of losartan on the central nervous system.

DISCUSSION

The aims of the present study were to determine the effects of GABA and glutamate in the lateral ventricle on BP and single unit spike in the RVLM and to explore the relationship between actions of these substances and Ang II on nervous system.

When GABA was injected into the lateral ventricle in urethane-anesthetized rats, SBP and HR decreased and firing rates in the RVLM increased. The present results are consistent with the findings of other investigators. The central injection of GABAergic agonists, muscimol, decreased BP and HR, particularly via GABA-A receptor (Persson, 1980; DiMicco et al, 1986). On the contrary, intracerebroventricular administration of bicuculline, a GABA-A antagonist, produced an increase in BP and a slight bradycardia in rats (Karson et al, 1999). However, injection of bicuculline into the region of the paraventricular nucleus produced increases in BP and HR (Martin et al, 1991). It showed that GABA may have different actions in different brain regions. The sites of GABA action in the central nervous system have been variously reported by researchers; paraventricular (Tibirica et al, 1995), anterior and ventromedial hypothalamic nuclei and nucleus tractus solitarius (Takenaka et al, 1995) and amygdala (Karson et al, 1999). Goren et al (1996) suggested that the major site of GABA action was the dorsomedial nucleus of the hypothalamus and the effect on the paraventricular or central nucleus of the amygdala was secondary to the main effect. Although the specific pathways underlying this response have not yet been identified, several possible action mechanisms have been offered, including a reduction in sympathetic tone (Unger et al, 1983a), inhibition of vasopressin release (Unger et al, 1988), and disruption of relevant peptide systems, especilally Ang II (Unger et al, 1883b; Roberts et al, 1993). Martin et al (1991) observed that GABA effects were prevented by ganglionic blockade and adrenal medullectomy, indicating a tonic inhibitory effect mediated by GABA-A receptors on the sympathetic nervous system. DiMicco & Abshire (1987) also proposed that a forebrain periventricular GABAergic system exerts a tonic inhibitory influence over the sympathetic nervous system. Therefore, the marked decreases in SBP and HR following intracerebroventricular injections of GABA in the present study might have been due to an decrease in sympathetic nervous system activity. In this point of view, Unger et al. (1983a) insisted that impairment of the central GABAergic system might play a role in maintenance of the high BP in the spontaneously hypertensive rat.

Pretreatment with intravenous losartan attenuated the SBP change induced by subsequent GABA injection into the lateral ventricle. These results are in support with Roberts et al (1993) that Ang II may modulate the actions of GABA on the SBP. Acute infusion of Ang II increases BP through peripheral angiotensin receptor-1 (Wong et al, 1993) and Ang II also exerts important actions on sympathetic nervous system (Reid, 1992; Brooks & Osborn, 1995). Reid (1992) proposed that the resetting of baroreflex control by Ang II could result from an action of the peptide on afferent, efferent, or central components of the reflex. Therefore, we suggest that losartan suppressed the action of Ang II to excite the sympathetic nervous system. The inhibitory effect of GABA on the sympathic nervous system could also be decreased considerably by the blockade action of losartan on the sympathetic nervous system.

The intracerebroventricular administration of glutamate, which has been known to be the main excitatory neurotransmitter in the mammalian central nervous system (Collingridge & Lester, 1989), markedly increased SBP and

HR and decreased firing rate. Zanzinger et al (1997) also demonstrated that intracerebroventricular injection of glutamate induced significant rises in BP, cardiac contractility and myocardial oxygen demand. Although the exact site of glutamate action in the brain stem has not been elucidated by these experiments, Dampney (1994b) suggested that glutamatergic afferents represent the majority of excitatory inputs to the RVLM from higher brain regions. This descending system can modulate the activity of the vasomotor bulbospinal neurons of the ventrolateral medulla (Chalmers & Pilowsky, 1991), which in turn modulates the activity of the sympathetic preganglionic neurones of the intermediolateral cell column in the spinal cord (Mills et al, 1990). Beside RVLM, glutamate has also other action sites. The intrathecal administration of glutamate antagonists attenuates the hypertensive response evoked by electrical stimulation of the RVLM (Mills et al, 1988).

Responses of SBP, HR and neural activity to microinjection of glutamate into the lateral ventricle were examined following intravenous injection of losartan. The pressor and sympathoexcitatory responses evoked by glutamate were attenuated by losartan. The attenuating actions of losartan seemed to be caused by the inhibitory action on the sympathetic nervous system.

In the present study, the time to show peak SBP changes did not correspond with the time that showed peak changes in firing rates after administration of GABA and glutamate into the lateral ventricle. The ratios of SBP and spikes at the time of peak SBP change showed similar appearance. Losartan increased the ratio and it seemed to be due to enhanced reflex of other areas to maintain BP in proportion to inhibition of the sympathetic system.

Losartan has been reported to be capable of entering the brain from the peripheral circulation to block the central Ang receptors (Song et al, 1991). However, in the present study there was no change of blood pressure even when losartan was intracerebroventricularly injected. This result indicated that intravenous injection of losartan did not act through Ang II receptor in the central nervous system, in agreement with Irvine & White (1997) who reported that central losartan did not produce any change in blood pressure.

In conclusion, the neural action of central GABA and glutamate together with collaboration of circulating Ang II seems to regulate arterial blood pressure.

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