Effect of the Non-N-Methyl-D-aspartate Receptor of the Glutamatergic System of the Pedunculopontine Tegmental Nucleus on Cardiovascular Responses in Normotensive and Hydralazine-Induced Hypotensive Rats

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Abstract

Background: Glutamate is an important excitatory neurotransmitter in the pedunculopontine tegmental (PPT) nucleus. The cardiovascular effect of glutamate and its non-N-methyl-D-aspartate (NMDA) receptor in the PPT is unknown; therefore, we evaluated glutamate and its non-NMDA receptor on cardiovascular parameters in normotensive and hydralazine induced hypotensive in rat.

Materials and Methods: After anesthesia, the femoral artery was cannulated for recording of cardiovascular parameters. Microinjection of drugs was done stereotaxically. L-Glutamate (L-Glu) and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) (an antagonist of nonNMDA receptor) were microinjected into the PPT in normotensive and HLZ hypotensive rats. Changes (Δ) of mean arterial pressure (MAP), systolic blood pressure (SBP), and heart rate (HR) were obtained and compared with the control group.

Results: In normotensive rats, L-Glu significantly increased SBP and MAP (P < 0.001) and decreased HR (P < 0.01), whereas CNQX alone did not significantly effect. Coinjection L-Glu + CNQX significantly attenuates the cardiovascular effect of L-Glu (P < 0.05 to P < 0.01). In hypotension induced by HLZ, SBP and MAP significantly decrease but HR did not change. In HLZ groups, L-Glu significantly improves (P < 0.05) and CNQX deteriorated hypotension induced by HLZ (P < 0.05). Coinjection of L-Glu + CNQX also attenuates the effect of L-Glu on Δ MAP and Δ SBP. In hypotension, ΔHR induced by L-Glu was significantly higher than CNQX (P < 0.01). In L-Glu + CNQX group, ΔHR also was lower than L-Glu (P < 0.05).

Conclusion: Our findings revealed that glutamatergic system of the PPT in both normotensive and hypotension induced by HLZ plays a pressor with bradycardic responses that partly mediated by non-NMDA receptor.

Keywords: Blood pressure, glutamate, hypotension, microinjection, nonN-methyl-D-aspartate receptor, pedunculopontine tegmental nucleus

INTRODUCTION

Glutamatergic system is an important excitatory system in the brain that is distributed in several brain areas and involved in functions such as memory, modulation of pain, movement, and cardiovascular regulation.¹,² The

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effect of this system is mediated by two inotropic and metabotropic receptors. The ionotropic receptors are divided into N-methyl-D-aspartate (NMDA) and nonNMDA receptors. In addition, the nonNMDA receptors also are classified into a-aminooxyacetic acid (AMPA) and kainate (KA) subtypes.

The involvement of ionotropic receptors of glutamate in central cardiovascular regulation has been well known. In rostral ventrolateral medulla (RVLM), for example, microinjection of L-glutamate (L-Glu) increased cardiovascular parameters. In the cuneiform nucleus (CnF), microinjection of glutamate also produces two long and short responses that mostly mediated by NMDA receptor. Hypotension due to hydralazine (HLZ) has also reported to increase glutamate release in several areas of the brain areas involved in cardiovascular regulation such as RVLM.

The presence of glutamate receptors in the pedunculopontine tegmental (PPT) nucleus, a mesencephalic nucleus, has also been reported. The PPT is a heterogeneous area that contains several neurons such as cholinergic, GABAergic, and glutamatergic neurons and precipitated in numerous functions such as locomotion, regulation of muscle tone, sleep, reward, control of arousal, and behavioral state as well as the regulation of autonomic responses. This region has extensive connections with different brain regions, it receives inputs from the cerebral cortex, thalamus, basal ganglia, and spinal cord, and project into various regions of the cerebral cortex, hypothalamus nuclei, reward centers, and periaqueductal gray (PAG). This nucleus also has a projection to areas involved in cardiovascular regulation. A cholinergic projection to RVLM has been proposed.

Although the effect of PPT on cardiovascular function has been reported, there are few studies about mechanisms and neurotransmitter involved in this effect of the PPT. In a previous experiment, Topchyi et al. indicated that the activation of the PPT could increase blood pressure. Our previous studies also evaluated the cardiovascular effect of cholinergic, GABAergic, and nitricergic systems of this nucleus. Microinjection of ACh into this nucleus could evoke hypotension and bradycardia that bradycardia attenuates by the antagonist of nicotinic receptor. In the previous study, we also show that the PPT is involved in hypotension induced by hemorrhage.

Glutamatergic neurons are one of the important neurons of the PPT that precipitated in several functions so microinjection of glutamate in the PPT-initiated respiratory disturbances, increases REM sleep and wakefulness, activation of electromyogram in genioglossus muscle, and increased blood pressure. Although microinjection of L-Glu elicits blood pressure but its mechanism and type of receptor that involved in this nucleus are not determined. Because glutamate involved in hypotension, the present study, the effect of L-Glu and its nonNMDA receptor on cardiovascular parameters in normotensive condition was evaluated. Due to the hypotensive effect of the PPT and also the effect of glutamate on hypotension, in another experiment, the effect of L-Glu and its nonNMDA receptor on hypotension induced by HLZ in this nucleus also was evaluated.

**Materials and Methods**

**Animals and surgery**

Forty-eight Wistar rats (250–300 g) were used in this experiment. Animals were kept in a 12 h light-dark cycle, under constant temperature (22°C ± 2°C), and were allowed free access to standard laboratory diet and water. For the recording of cardiovascular parameters, animals were anesthetized with urethane (1.5 g/kg, i. p) then a polyethylene catheter (PE-50) was inserted into the left femoral artery and parameters were recorded by a blood pressure transducer connected to Power Lab instrument (Australia). A stereotaxic apparatus did microinjection of drugs. For this purpose, a hole was drilled at coordinates of PPT nucleus (AP: -7.4 to -8.6, L: ±1.6–2.2, and H: -6.8 to -7.8 mm) from bregma according to the atlas of Paxinos. Microinjection of agonist/antagonist of the glutamate receptor into the PPT performed by a single-barreled micropipette with 40 μm diameter. The injection volume in all the groups was 150–250 ml.

The drugs included urethane, L-Glu), 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; a nonNMDA antagonist), and HLZ provided from the Sigma, USA.

The experimental groups were as follows (n = 6 in each group):

1. Control: microinjection of saline into the PPT
2. CNQX group: Microinjection of CNQX (50 nmol) into the PPT
3. L-Glu group: Microinjection of L-Glu (50 nmol) into the PPT
4. L-Glu + CNQX group: Cocominjection of Glutamate and CNQX into the PPT
5. HLZ group: Injection of HLZ intravenously (200 μg/kg)
6. CNQX + HLZ: Microinjection of CNQX into the PPT 2 min after HLZ
7. L-Glu + HLZ: Microinjection of L-Glu into the PPT 2 min after HLZ
8. L-Glu + CNQX + HLZ: Cointjection of L-Glu and CNQX into the PPT 2 min after HLZ.

**Data analysis**

Data expressed as mean ± standard error of mean; the systolic blood pressure (SBP), mean arterial pressure (MAP) and heart rate (HR) were recorded throughout of experiment. Then, changes (Δ) before and after injection of drugs were calculated in several times and compared with changes in the control group (repeated measures ANOVA). The peak changes of HR, SBP, and MAP in each group were also calculated and compared with another group. The P < 0.05 was used to indicate statistical significance.
RESULTS

Effect of saline microinjected into the pedunculopontine tegmental nucleus on cardiovascular values in normotensive rats

In this group, cardiovascular values before and after microinjection of saline were examined. Before injection, values of the MAP, SBP, and HR were 109.4 ± 1.32 mmHg, 112 ± 2 mmHg, and 337.3 ± 4.28 beats/min, respectively. However, microinjection of saline did not change those parameters than before injection (ΔMAP: −3.2 ± 0.8 mmHg, ΔSBP: −5.3 ± 1.1 mmHg, and Δ HR: −5.5 ± 2.8 beats/min).

Effect of L-Glutamate and CNQX microinjected into the pedunculopontine tegmental nucleus on cardiovascular values in normotensive rats

To determine the cardiovascular effect of L-Glu and CNQX, these agents were microinjected into the PPT and cardiovascular changes were determined. Figure 1 shows that microinjection of L-Glu alone increased Δ MAP, ΔSBP, and decreased Δ HR. Time-course changes of the Δ SBP, ΔMAP, and Δ HR in the L-Glu and CNQX groups have also shown in Figure 2. As has been showed, ΔMAP and Δ SBP in the L-Glu group significantly increased and Δ HR significantly decreased compared to the control group over time (repeated measures ANOVA, P < 0.01 to P < 0.001). Microinjection of CNQX alone specially in the first times nonsignificantly decreased both Δ MAP and Δ SBP cardiovascular parameters in comparison with the control group (repeated measures ANOVA, P > 0.05). Because this low effect of CNQX may probably due to the lack of glutamate release in anesthetic condition, in another group, CNQX with L-Glu cooinjected into the PPT and responses compared with glutamate groups. As has been shown in Figure 2, ΔMAP and Δ SBP in L-Glu + CNQX are significantly lower than glutamate group [repeated measures ANOVA, P < 0.05 Figure 2]. ΔHR in L-Glu + CNQX group was lower than L-Glu, but this effect did not significant.

Effect of glutamate and CNQX microinjected into the pedunculopontine tegmental nucleus on cardiovascular values in hypotension induced by hydralazine

In this experiment, to investigate the role of glutamate neurons of the PPT in hypotension, HLZ was systematically injected to induce hypotension, and after 2 min, L-Glu and CNQX alone and together (L-Glu + CNQX) were microinjected into the PPT, and cardiovascular responses were evaluated. Systemic injection of HLZ significantly decreased SBP, MAP with no significant effect on HR [Figure 3]. The hypotension induced by HLZ improved by microinjection of L-Glu [Figure 3] and deteriorated by CNQX. Time-course changes of the SBP, MAP, and HR in the HLZ hypotensive groups (L-Glu + HLZ, CNQX + HLZ, and L-Glu + CNQX + HLZ) are indicated in Figure 4. As is showed, ΔMAP and Δ SBP in the HLZ group were significantly decreased compared to the control group over time (repeated measures ANOVA, P < 0.001) and HR decreased but were not significant. Microinjection of L-Glu into the PPT significantly ameliorate the decreased MAP and SBP induced by HLZ over time [repeated measures ANOVA, P < 0.05 to P < 0.01, Figure 4a and b]. Microinjection CNQX could augment hypotensive effect induced by HLZ (P < 0.05) whereas Coinjection of L-Glu + CNQX significantly improved HLZ hypotensive effect in overtime[repeated measures ANOVA, P < 0.05 to P < 0.01, Figure 4]. However, these effects were not significant than L-Glu + HLZ. ΔHR in HLZ group was no significant than control, and this effect significantly deteriorated by CNQX (P < 0.05). L-Glu significantly increased bradycardia induced by HLZ group over time (repeated measures ANOVA, P < 0.05) and this effect no significantly attenuate after coinjection of L-Glu + CNQX [Figure 4c].

DISCUSSION

The result of the current study indicated that, in normotensive rats, microinjection of L-Glu into the PPT has pressor and bradycardia effect, whereas injection of CNQX did not effect. Coinjection of CNQX and L-Glu significantly attenuates cardiovascular responses induced by L-Glu. In hypotension induced by HLZ, L-Glu improved and CNXQ deteriorates cardiovascular responses. Coinjection of CNQX + L-Glu group was significantly lower than L-Glu and saline group.

The PPT is a heterogeneous nucleus that contains glutamatergic, cholinergic, and GABAergic neurons. From them, the glutamatergic system is a well-known excitatory neurotransmitter in the brain that is involved in several functions such as learning and memory, movement, sleep as well as cardiovascular regulation. The cardiovascular effect of glutamate in several brain areas has been shown, for example, microinjection of L-Glu into the RVLM, PVN,
Figure 2: Time courses changes of mean arterial pressure (ΔMAP) (a), systolic blood pressure (ΔSBP) (b) and heart rate (ΔHR) (c) after microinjection of L-Glu, CNQX, and L-Glu + CNQX into the PPT in normotensive rats. MAP and SBP in L-Glu were increased ($P < 0.01$) and HR decreased ($P < 0.01$) significantly than the control group over time ($P < 0.001$; repeated measures ANOVA). $n = 6$ Symbols are maximal changes of treated groups than the control group (independent sample $t$-test). $^{***}P < 0.001$ and $^*P < 0.01$: Compared to control. $^{+}P < 0.05$; L-Glu + CNQX: Compared to L-Glu.

Figure 3: A sample of recording of cardiovascular parameters induced by intravenous injection of hydralazine (HLZ) and L-glutamate (glut) into the PPT nucleus. Vertical lines indicate injection times

and PAG evoked cardiovascular responses and this effect was attenuated by its NMDA and non-NMDA receptors.\textsuperscript{[5,24,25]}

In line with this evidence, our results indicated that the injection of L-Glu in the PPT increased SBP and MAP and
decreased HR. The importance of the cardiovascular effect of the glutamatergic system in the PPT is unclear. However, it is reported that the PPT plays a central command, namely, it integrates the signals and modulates physiological responses during locomotion, sleep, and exercise. For example, in exercise, the regulations of blood flow in muscle are mediated by central command. Because the glutamatergic system of the PPT is involved in exercise and locomotion, we suggested at the same time, initiation of movement or exercise, it also adjusting cardiovascular responses to provide tissue blood flow in these activities. However, more studies are needed to confirm this opinion.

The glutamate pathways of PPT that precipitate in cardiovascular regulation did not determine in the present time. However, there are projections from PPT nucleus to several regions involved in cardiovascular regulation including RVLM, NTS, raphe nuclei, PAG, and parabrachial. Each one of these areas may be involved in the cardiovascular effect of PPT. In addition, it is well known that PPT has two cholinergic and noncholinergic projections. Moreover, there is evidence that noncholinergic pathway is a glutamatergic. In addition, based on electrophysiological studies, three type neurons in PPT have been identified. From them, Type I neurons are distributed in throughout of PPT and it is evident that these neurons may be form glutamatergic projections. In addition, there is a cholinergic projection from PPT to the RVLM, and a critical area in cardiovascular regulation. It is also possible that glutamate receptor presents on the cell body of these projection neurons and through these neurons play that cardiovascular effect.

In addition, the PPT and the CnF are important nuclei in the mesencephalic locomotor region. It has been reported locomotion initiated by glutamate transmission. In addition, the cardiovascular effect of CnF glutamatergic system has been shown previously. Due to the similarity between the cardiovascular effect of the CnF and the PPT and the fact that these areas are involved in locomotion, we suggested that L-Glu in these areas simultaneously with the onset of locomotion increases blood pressure to providing blood supply to the tissues. However, future studies are needed to clarify our opinion.

It is reported that nonNMDA receptor of L-Glu is present in the PPT. Therefore, in this study, probable cardiovascular effect of nonNMDA receptor of PPT was examined. According to our findings, microinjection of CNQX, a nonNMDA antagonist, into the PPT did not affect on cardiovascular parameters. Since blockade of the nonNMDA antagonist receptors alone did not produce a significant effect, we coinfected the L-Glu with CNQX to make sure that this receptor of L-Glu is present.
in the PPT area. Coinjection of L-Glu with CNQX attenuates the cardiovascular parameters evoked by L-Glu alone. These results revealed that the nonNMDA receptors are involved in cardiovascular responses of L-Glu in PPT nucleus. However, this effect of CNQX is not vigorous and did not completely abolish the effect of L-Glu and seems that the role of NMDA receptor probably is greater.

In another experiment, we evaluate the role of the glutamatergic system on cardiovascular regulation in hypotension induced by HLZ. HLZ is an antihypertensive drug that was used for several years of treatment of hypertension. The mechanism effect of this agent is not completely determined but is suggested mediated by several mechanisms including the inhibitory effect on Ca²⁺ release and prostacyclin pathway.

Our results indicate that microinjection of L-Glu could improve the cardiovascular responses induced by HLZ. However, these effects were not vigorous. In the HLZ group, HR no significantly decreased. However, this effect deteriorated by CNQX and L-Glu could increase it. In addition, coinjection of L-Glu + CNQX attenuate the effect of L-Glu on HR. Therefore, it is conceivable that in hypotension, glutamatergic system of the PPT via its non–NMDA receptor participate in the regulation of HR. The mechanism of this effect of glutamate is unknown. However, hypotension evokes both chemoreflex and baroreflex through NTS, due to the relation of PPT with NTS it is suggested that the effect of the PPT on HR may be mediated by the relation of the PPT nucleus with NTS or direct effect on the vagal system. However, the exact mechanism(s) of the PPT is unknown and future studies are needed to clarify this effect.

**Conclusion**

Our findings revealed that stimulation of the PPT with L-Glu caused a pressor effect with bradycardia responses, and this effect was partly mediated by nonNMDA receptor. Furthermore, in HLZ-induced hypotension L-Glu and nonNMDA receptor of the PPT improves hypotension but this effect is not strong.

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**Conflicts of interest**

There are no conflicts of interest.

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