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Cardiovascular responses to intracerebroventricular injection of GABA in renovascular hypertensive rats

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ABSTRACT Effects of central GABAergic stimulation on cardiovascular function were evaluated in 2-kidney, 1-clip (2K1C) renovascular hypertensive rats (RVHR). Intracerebroventricular injection (icv) of GABA (100 and 200 μg) reduced blood pressure (BP) to a greater degree in RVHR as compared with sham-operated controls, and the greatest response was seen in RVHR 4 wk after operation (4 wk-RVHR). In addition, a decreased sensitivity of baroreflex was observed in 4 wk-RVHR, and was improved by icv GABA. Pretreatment with icv captopril (200 μg) only reduced BP moderately in 4 wk-RVHR, but attenuated remarkably the depressor effect of GABA. On the contrary, pretreatment with ip captopril was less effective in attenuating the depressor effect of GABA. Our results indicated that RVHR was deficient in central GABAergic inhibition on BP control, for GABAergic stimulation reduced BP to a greater degree and improves the decreased sensitivity of baroreflex in RVHR; the depressor effect of GABA is mediated, at least in part, by inhibiting brain angiotensin system.

KEY WORDS GABA; renovascular hypertension; pressoreceptors; renin-angiotensin system; captopril; brain

Since the pioneering work of Unger *et al*[1], the dysfunction of central GABAergic system in hypertension has been extensively studied[2,3]. Central injection of GABA agonist reduced blood pressure (BP) to a greater degree in spontaneously hypertensive rats (SHR) as compared with that in Wistar-Kyoto normotensive rats (WKY). However, little has been known about the brain GABA system in other types of hypertension. In this study, we tried to elucidate the central GABAergic function in renovascular hypertension and to analyze the interaction between GABA and angiotensin in brain.

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MATERIALS AND METHODS

Renovascular hypertension Sprague-Dawley rats, ♂, weighing 235 + *s* 24 g, were anesthetized with sodium pentobarbital (45 mg·kg^{-1}, ip). A silver clip (internal diameter: 0.2 mm) was put around the left kidney artery (2K1C). Sham-operated rats were used as controls. Four days later, the systolic blood pressure (SBP) of conscious rat was monitored by tail-cuff method using automatic BP and HR recorders for rats (MRS-Ⅱ, Shanghai Hypertension Research Institute). The rats with SBP > 20 kPa were chosen for the tests.

Cardiovascular effects of icv GABA Controls (sham-operated, $n = 7$) and renovascular hypertensive rats 1 (1 wk-RVHR, $n = 7$), 4 (4 wk-RVHR, $n = 7$) and 8 wk (8 wk-RVHR, $n = 6$) after operation were anesthetized with urethane (1.1 g·kg^{-1}, ip). The femoral arterial pressure and Lead I of ECG were monitored on a polygraph. The rat was mounted on a stereotaxic apparatus, GABA was injected (icv) as described previously[4]. GABA (Shanghai 3rd Pharmaceutical Factory) was dissolved in artificial cerebrospinal fluid (CSF).

Baroreflex Baroreflex sensitivity (BRS) was assessed in 4 wk-RVHR using a method[5] as follows: mean arterial pressure (MAP) and heart rate (HR) responses to bolus iv phenylephrine (1-5 μg·kg^{-1}) were monitored, and MAP and HR were allowed to return

to basal levels for 10 min before the next dose was given. Peak increase in MAP and corresponding peak decrease in HR were recorded. BRS was determined by the slope of the relationship between increases in MAP and decreases in HR. BRS was assessed 15 min after icv GABA.

Interaction with angiotensin Additional 4 wk-RVHR received pretreatment with icv captopril 200 μg or vehicle, or ip captopril 60 mg·kg^{-1}. After delaying for 45 min, GABA was similarly injected, and cardiovascular responses to GABA were monitored.

Statistical significance was evaluated by t test and regression coefficient test.

RESULTS

Hypotensive effect of icv GABA in RVHR BP of rats began to elevate noticeably 1 wk after clipping one renal artery, and continued to increase during the following weeks. After icv injection of GABA, RVHR showed greater decreases in MAP as compared with sham-operated controls, and the greatest response of GABA was found in 4 wk-RVHR. The differences among groups were more significant in a dose of 200 μg (Tab 1).

Tab 1. Peak changes of mean arterial pressure (kPa) after icv GABA in sham-operated rats and renovascular hypertensive rats 1, 4, and 8 wk after operation. $n = 6-7$, $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* **sham-operated rats.** $^dP>0.05$, $^eP<0.05$, $^fP<0.01$ *vs* **1 wk-RVHR group.**

	Baselines	100 μg	200 μg
Sham	12.4±0.8	−3.0±0.5	−4.8±0.8
1 wk-RVHR	14.9±1.2^c	−3.7±0.9^a	−6.3±0.8^c
4 wk-RVHR	18.1±1.1^{cf}	−4.3±1.1^{bd}	−8.7±1.2^{cf}
8 wk-RVHR	17.3±1.5^{cf}	−4.1±1.1^{bd}	−6.5±1.1^{cf}

Effect of icv GABA on baroreflex An impairment of baroreflex in the acute phase of renovascular hypertension was observed. BRS in 4 wk-RVHR (−0.17 bpm·kPa^{-1}) was significantly lower than in sham-operated rats (−0.33 bpm·kPa^{-1}, $P<0.01$). Pretreatment with icv GABA (200 μg), causing no remarkable change in the pressor effect of phenylephrine, enhanced the decreased BRS to −0.28 bpm·kPa^{-1} ($P<0.05$) in RVHR. However, pretreament with iv GABA of the same dose was ineffective.

Interaction between GABA and angiotensin Pretreatment with icv captopril (200 μg) slowly induced a moderate decrease in MAP, but attenuated the subsequent depressor effect of icv GABA. On the contrary, pretreatment with iv captopril at a large dose (60 mg·kg^{-1}) reduced MAP, but it was less effective in attenuating the depressor effect of icv GABA (Tab 2).

Tab 2. Influences of pretreatment with captopril (Cap) on depressor effect of GABA (200 μg, icv) in renovascular hypertensive rats. $n = 6$. $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$ *vs* **Cap ip group.**

Pretreatments	Cap 60 mg·kg^{-1} ip	Cap 200 μg icv
MAP/kPa		
Baselines	18.5±1.1	17.9±1.6^a
After Cap	10.8±1.1	12.9±1.3^b
After GABA		
Peak changes	−2.4±0.8	−1.3±0.7^b

DISCUSSION

Our findings indicate that RVHR is deficient in central GABAergic inhibition. Exogenous GABA compensate this deficency, then induce a greater depressor response in RVHR.

Brain angiotensin system is also important in the regulation of cardiovascular function[6]. Morishita *et al* reported recently that the brain angiotensin I (A I) concentration was significantly higher in 4 wk-RVHR than in con-

trol rats[7]. By pretreatment with captopril through 2 different routes, icv and ip, we found that the depressor effect of GABA was attenuated to a greater degree after inhibiting the overactivity of brain A II by captopril in RVHR. It was reported that icv GABA in normotensive rats inhibited the central actions of A II : pressor responses, drinking and release of vasopressin[8]. These results suggested that the brain angiotensin system receive GABAergic inhibition, and the unbalance of these 2 systems in RVHR may contribute to the maintenance of hypertension.

Our results are in agreement with previous reports[5] that RVHR has a decreased sensitivity of baroreflex to BP changes. Both the overactivity of angiotensin system and high BP level might be responsible for the impairment of baroreflex[9,10]. Since GABA inhibits the central actions of A II, and has a depressor effect, both these actions may contribute to its enhancing effect on baroreflex. The precise locations of deficient GABAergic inhibition remain to be further explored.

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136—138 10

肾血管性高血压大鼠脑室注射γ-氨基丁酸的心血管效应

R965.2

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A **摘要** GABA (100和200 μg, icv)在肾血管性高血压大鼠(RVHR)产生较伪手术鼠更强的降压作用, 尤术后4 wk. GABA 降压增强的大部分可被预先 icv 卡托普利所取消, 而 ip 卡托普利作用较弱. GABA icv 还明显改善 RVHR 已下降的压力感受性反射敏感性. 提示 RVHR 脑内 GABA 抑制功能不足; 外源性 GABA 降压效应增强可能与其抑制脑内血管紧张素系统有关.

关键词 γ-氨基丁酸; 肾血管性高血压; 压力感受器; 肾素-血管紧张素系统; 卡托普利; 脑