Preferential Hindquarter Vasodilation in the Hypotension Induced by GABA Injection into the Cisterna Magna of Conscious Rats

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Summary Injection of GABA into the cisterna magna of conscious rats induced a vasodilation in the hindquarter without significant change in the renal and superior mesenteric areas, when arterial pressure and heart rate markedly decreased. This circulatory change indicates that GABA decreased arterial pressure as an effect on the CNS, in particular, through a hindquarter resistance reduction, along with a bradycardia.

Key words: GABA, hemodynamics, hindquarter resistance.

Observation of the regional blood flows in animals sometimes gives information as to the cause of the accompanying change in arterial pressure. To give an example, using the electromagnetic flow probe, we could know that injection of L-arginine into the cisterna magna of conscious rats raises blood pressure [1] through regional vasoconstriction in the viscera [2]. Although GABA (γ -aminobutyric acid), an inhibitory neurotransmitter, shows depressor and bradycardic effects on central injection in conscious rats [3–5], the hemodynamic mechanism is unknown. To clarify the contribution of regional blood flows to this depressor effect of GABA, the present study was undertaken using the electromagnetic flow probe, which gives almost absolute blood flows, not their velocities.

Male Wistar rats including 7 Wistar Kyoto rats, weighing 235–390 g, were anesthetized with thiamylal sodium (50 mg/kg, i.p.) and cisternal cannulation was performed through a hole drilled into the interparietal bone. After fixation of the cannula together with two small screws to the bone using dental cement, the rat was separately kept in a transparent plastic cage covered with a metal wire top. The cage was placed in a light and dark cycle controlled room (6:00–18:00). One week or more after the operation, again under anesthesia, an electromagnetic flow probe was implanted around either the superior mesenteric artery, the left renal artery, or the terminal aorta. Polyethylene catheters were inserted into the terminal

aorta or the aortic arch, and into the right external jugular vein for measurement of arterial pressure and heart rate and intravenous injection of drugs, respectively. The distal ends of the lead wire of the probe and the catheters were led to the dorsal neck. The technical details involved are described elsewhere [2, 6].

Flow, pressure, and heart rate were observed with the rat in its home cage 2–3 d after implantation when the rat had resumed taking ample amounts of water and pellets.

Data (mean $\pm$ SE) were analyzed by group or paired *t*-test. Criterion for statistical significance was $p < 0.05$.

Figure 1 shows simultaneous recordings of (a) terminal aortic (hindquarter) flow, (b) superior mesenteric flow, and (c) renal flow when 10 μ mol of GABA was injected intracisternally. Hindquarter flow did not decrease when blood pressure

Fig. 1. Simultaneous recordings of parameters of circulation of conscious rats in cisternal injection of GABA. HR, heart rate; BP, arterial blood pressure; HQF, hindquarter blood flow; SMF, superior mesenteric blood flow; RF, renal blood flow. Ten micromols of GABA was injected at 0 in the time scale.

was lowered on GABA injection, although superior mesenteric and renal flow did decrease almost in parallel to the depressor change after GABA injection.

Figure 2 indicates the mean and standard error of arterial pressure, heart rate, and regional vascular resistance which was calculated as arterial pressure divided by regional blood flow. Arterial pressure and heart rate were gradually decreased and reached minimal values 10 min after injection and then recovered in 60 min. Of the regional vascular resistances, hindquarter resistance alone was significantly

Fig. 2. Time courses of each parameter after cisternal injection of GABA to conscious rats. The data (mean $\pm$ SE) are indicated by * $p < 0.05$ and ** $p < 0.01$ with paired t -test between the values before injection (b) and those after injection, and by the figure, $p < 0.01$, with group t -test between the values injected GABA (●) and those injected artificial cerebrospinal fluid as a control (○). The symbol of $\langle n = X \rangle$ close to the circles means the number of animals observed at or by that time. Abbreviations BP and HR are the same as in Fig. 1. HQR, hindquarter resistance; SMR, superior mesenteric resistance; RR, renal resistance.

lower 10 min after injection when blood pressure maximally decreased, while superior mesenteric and renal resistance did not change. These results indicate that intracisternal injection of GABA led to a blood pressure decrease due to vasodilation in the hindquarter, along with a concomitant decrease in heart rate.

Immediately following injection of GABA, arterial blood pressure reduced but neither heart rate nor vascular resistances did present any increase, or baroreflex response (Fig. 2). This result of the reduction in heart rate and vascular resistances rather than the increase indicates that baroreflex output did not operate immediately after injection of GABA. GABA may affect parts of the neural circuit related to baroreflex. While, 60 min after injection when blood pressure and heart rate recovered, there was a tendency to overreach the average values in resistance per cent before injection in all the three vascular beds monitored (Fig. 2). In the superior mesenteric artery, significant difference was gained between the value in GABA injection and that in control. This may be interpreted that basal tone 60 min after injection was maintained higher than before injection, since baroreflex output for the vascular beds recovered more rapidly than for heart rate.

In the pressor state induced by injection of L-arginine to the cisterna magna, hindquarter resistance does not change, while superior mesenteric and renal resistance are markedly raised [2]. In addition, intravenous injection of chlorisondamine chloride could reduce the pressor effect caused by L-arginine injection to the cisterna magna, indicating that L-arginine centrally stimulated sympathetic nerves supplying the viscera [2]. In the present study, GABA injected to the cisterna magna appeared to conversely reduce the sympathetic activity to the hindquarter region. However, the intravenous injection of a ganglion blocker, hexamethonium bromide, leads no vasodilator change in the hindquarter region of the conscious rat at rest, giving the estimation of no sympathetic tone here [7, 8]. This discrepancy may suggest a special characteristic of hindquarter vessels. Practically, in the blood pressure increase caused by intracisternal injection of L-arginine, enough amount of noradrenaline to stimulate another vascular area such as that in the hindquarter would be released from the sympathetic nervous terminals in the visceral areas to circulation, but hindquarter did not change its vascular resistance [2]. This may explain that the β_1 -receptor, which has recently been reported to be distributed in the femoral artery in rats [9, 10], plays a dilatory role against the vasoconstriction by α -receptor stimulation in the hindquarter through a similar noradrenaline release in an increase in sympathetic tone, keeping the flow unchanged due to a balance between α - and β_1 -receptors. There may be a delicate balance between α - and β_1 -receptors in the hindquarter at rest under the presence of sympathetic tone, giving apparently no change in the hindquarter resistance. Moreover, we could consider the contribution of unfound vasodilator neurons insensitive to hexamethonium bromide such as a neuron containing calcitonin gene-related peptide [11]. Exact mechanism of GABA for vasodilation in the hindquarter remains uncertain.

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REFERENCES

1. Takemoto Y: Amino acids with central pressor effect in conscious rats. *Jpn J Physiol* **40**: 561–565, 1990
2. Takemoto Y: Regional vasoconstriction and excessive grooming induced by L-arginine injection into the cisterna magna of conscious rats. *Jpn J Physiol* **43**: 389–402, 1993
3. Persson B: Cardiovascular effects of intracerebroventricular GABA, glycine and muscimol in the rat. *Naunyn-Schmiedeberg's Arch Pharmacol* **313**: 225–236, 1980
4. Wible JH Jr, DiMicco JA, and Luft FC: Hypothalamic GABA and sympathetic regulation in spontaneously hypertensive rats. *Hypertension* **14**: 623–628, 1989
5. Takemoto Y: Central depressor effects of amino acids in conscious normotensive and two-kidney, one-clip renovascular hypertensive rats. *Jpn J Physiol* **41**: 717–724, 1991
6. Kawaue Y and Iriuchijima J: Changes in cardiac output and peripheral flows on pentobarbital anesthesia in the rat. *Jpn J Physiol* **34**: 283–294, 1984
7. Iriuchijima J: Regional difference in sympathetic vasoconstrictor tone in conscious rats. *Jpn J Physiol* **35**: 1051–1063, 1985
8. Iriuchijima J: Abnormal hindquarter vasoconstrictor tone, a feature common to various kinds of hypertensive rats. *Jpn J Physiol* **38**: 545–548
9. Fujimoto S, Dohi Y, Aoki K, and Matsuda T: Altered vascular beta adrenoceptor-mediated relaxation in deoxycorticosterone-salt hypertensive rats. *J Pharmacol Exp Ther* **244**: 716–723, 1988
10. Fujimoto S, Dohi Y, Aoki K, and Matsuda T: Beta₁- and beta₂-adrenoceptor-mediated relaxation responses in peripheral arteries from spontaneously hypertensive rats at prehypertensive and early hypertensive stages. *J Hypertension* **6**: 543–550, 1988
11. Taguchi T, Kawasaki H, Imamura T, and Takasaki K: Endogenous calcitonin gene-related peptide mediates nonadrenergic noncholinergic depressor response to spinal cord stimulation in the pithed rat. *Circ Res* **71**: 357–364, 1992