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# Mechanism underlying γ-aminobutyric acid-induced antihypertensive effect in spontaneously hypertensive rats

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**Abstract**

We examined the effects of γ-aminobutyric acid (GABA) on the blood pressure in spontaneously hypertensive rats and normotensive Wistar–Kyoto rats. A single oral administration (0.5 mg/kg) significantly lowered the systolic blood pressure in spontaneously hypertensive rats, but not in normotensive rats. In the mesenteric arterial bed, the perivascular nerve stimulation-induced increase in perfusion pressure and noradrenaline release were significantly inhibited by GABA in spontaneously hypertensive rats, but not in normotensive rats, and attenuated by the selective $GABA_B$ receptor agonist, baclofen, but not by the selective $GABA_A$ receptor agonist muscimol. The inhibitory effects of GABA on the perivascular nerve stimulation-induced increase in perfusion pressure and noradrenaline release were completely antagonized by the selective $GABA_B$ receptor antagonist, saclofen, but not by the selective $GABA_A$ receptor antagonist, bicuculline. These results suggest that, in spontaneously hypertensive rats, GABA has an antihypertensive effect due to its inhibition of noradrenaline release from sympathetic nerves in the mesenteric arterial bed via presynaptic $GABA_B$ receptors. 

*Keywords:* GABA (γ-Aminobutyric acid); Noradrenaline; Blood pressure; Mesenteric arterial bed; Perivascular nerve stimulation; Spontaneously hypertensive rat (SHR)

## 1. Introduction

γ-Aminobutyric acid (GABA), one of the major inhibitory neurotransmitters in the central nervous system (Curtis and Johnston, 1974), is also found in peripheral tissues (Erdo, 1985). It has been proposed that GABA plays an important role in the modulation of cardiovascular function (Gillis et al., 1980) by acting not only within the central nervous system but also within peripheral tissues (DeFeudis, 1982; DeFeudis et al., 1981). Indeed, GABA has been reported to reduce blood pressure in experimental animals (Takahashi et al., 1955) and humans (Elliott and Hobbiger, 1959) following its systemic or central administration, and it has been suggested that the depressor effect induced by systemic administration of GABA (Takahashi et al., 1958, Stanton, 1963) is due to the blockade of sympathetic ganglia. The blood–brain barrier is impermeable to GABA (Kuriyama and Sze, 1971), and its concentration in the brain is not changed following i.v. injection (Roberts et al., 1958; Tsukada et al., 1960; Gelder and Elliott, 1958). Thus, the antihypertensive effects seen following i.p. or i.v. administration of GABA are due to its actions within the peripheral tissues (presumably, blood vessels or autonomic nervous system). Indeed, it has been reported that GABA is able to modulate the vascular tone by suppressing the noradrenaline release in the isolated rabbit ear artery and rat kidney (Manzini et al., 1985; Monasterolo et al., 1996; Fujimura et al., 1999). However, few studies have been done about the effects of GABA on the tone of smaller vessels, such as those of rat mesenteric arterial bed. Because the mesenteric circulation of the rat receives approximately one fifth of the total cardiac output (Nichols et al., 1985), the regulation of the mesenteric arterial bed has a considerable effect on the systemic blood pressure and circulating blood volume.

Our initial aim in the present study was to determine whether GABA lowers the blood pressure in spontaneously hypertensive rats (which, to our knowledge, has not previously been investigated). Having established that it does,

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Table 1
Peripheral nerve stimulation-induced vasoconstriction and noradrenaline release in mesenteric arterial bed from spontaneously hypertensive rats and normotensive Wistar–Kyoto rats (together with resting blood pressure and body weight)

| | Spontaneously hypertensive rats ($n=6$) | Normotensive Wistar–Kyoto rats ($n=6$) |
|---|---|---|
| Body weight (g) | 330.3 ± 14.7 | 353.3 ± 14.7 |
| Resting systolic blood pressure (mm Hg) | 180.0 ± 2.7 | 123.1 ± 3.0[b] |
| Increase in perfusion pressure (mm Hg) | 14.9 ± 0.4 | 10.8 ± 1.0[b] |
| Noradrenaline release (ng/min) | 1.15 ± 0.04 | 0.78 ± 0.10[b] |

Mean ± S.E.M. The number of determinations is shown in parenthesis.
[b] $P<0.01$.

we then examined the underlying mechanisms by focusing on the effects of GABA on the tone of the resistance vessels in the mesenteric arterial bed.

## 2. Materials and methods

### 2.1. General

This study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals adopted by the Committees on the Care and Use of Laboratory Animals in the Yakult Central Institute for Microbiology and Hoshi University.

### 2.2. Animals

Male spontaneously hypertensive rats and normotensive Wistar–Kyoto rats, 13–15 weeks old, were purchased from Funabashi Farm (Chiba, Japan), the breeder for the Disease Model Cooperative Research Association (Kyoto, Japan). All animals were allowed a standard laboratory diet (MF; Oriental Yeast Industry, Tokyo, Japan) and tap water ad libitum, and were housed in groups of three with a 12-h light/dark cycle. Temperature and humidity were controlled at 24 ± 1 °C and 60 ± 5%, respectively. Rats were habituated to these conditions for at least 1 week before the blood pressure measurements or preparation of the tissue.

### 2.3. Measurement of blood pressure and heart rate

After a given rat had been in a constant temperature box kept at 37 °C for a few minutes, the systolic blood pressure and heart rate were measured by the tail-cuff method using a blood pressure analyzer (BP-98A; Softron, Tokyo, Japan) connected to a personal computer (Mebius series; Sharp, Tokyo, Japan). Each rat received either GABA (0.5 mg/kg, p.o.) dissolved in saline or saline alone.

### 2.4. Preparation of the mesenteric arterial bed

The rats were anesthetized with ether, then killed by decapitation, and the mesenteric arterial bed was rapidly dissected out and placed in oxygenated, modified Krebs–Henseleit solution (composition in mM: NaCl 118; KCl 4.7; $NaHCO_3$ 25.0; $CaCl_2$ 1.8; $NaH_2PO_4$ 1.2; $MgSO_4$ 1.2; dextrose 11.0). The mesenteric artery and vein were tied off near the cecum, and the remaining intestine was separated from the arterial bed along the intestinal wall. The mesenteric arterial bed was then perfused as described by McGregor (1965), with various modifications (Kamata et.

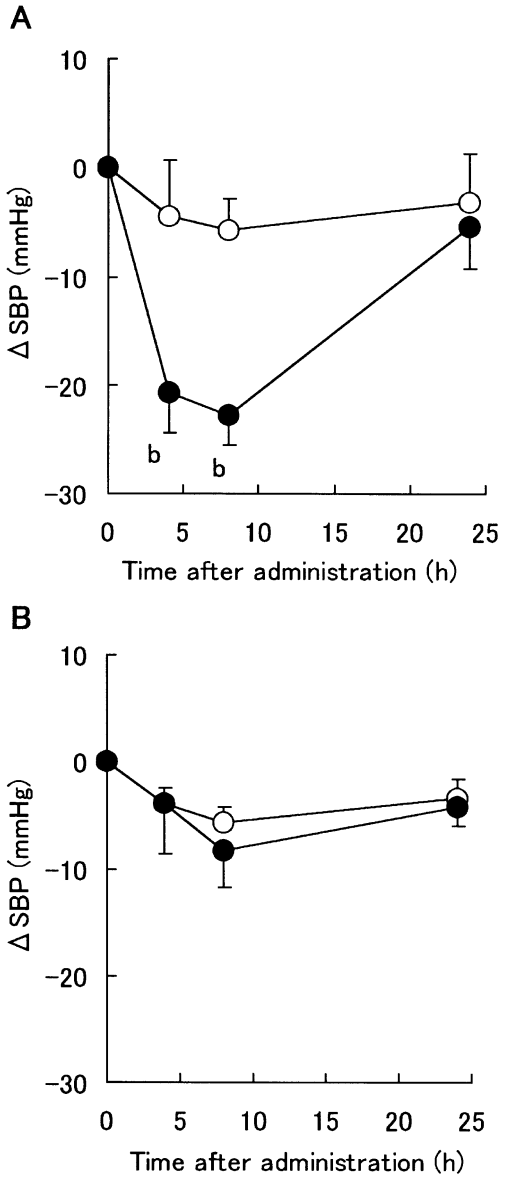


Fig. 1. Effects of a single oral administration of GABA on systolic blood pressure in spontaneously hypertensive rats (A) and normotensive Wistar–Kyoto rats (B). ΔSBP, change in systolic blood pressure. Each point represents the mean ± S.E.M. for 5–6 animals. -○-, control (saline); -●-, GABA (0.5 mg/kg, p.o.). [b]$P<0.01$ vs. control.

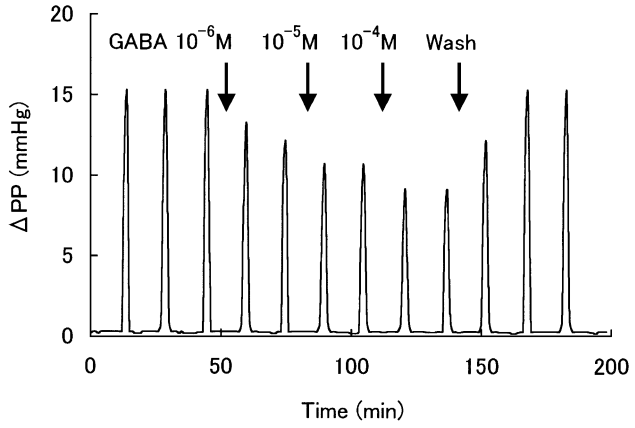


Fig. 2. Typical trace showing the effect of GABA ($10^{-6}$ to $10^{-4}$ M, at arrows) on the perivascular nerve stimulation-induced increase in perfusion pressure in mesenteric arterial bed from spontaneously hypertensive rats.

al., 1989; Abiru et. al., 1993). Warm (37 °C), oxygenated (95% $O_2$ + 5% $CO_2$) Krebs–Henseleit solution was perfused at a rate of 5 ml/min using a peristaltic pump (MasterFlex 7518-10; Cole-Palmer Instrument, IL, USA), through a cannula inserted in the superior mesenteric artery. The perfusate passed through the mesenteric arterial bed only once (i.e., it was not recirculated). Vascular responses were detected as changes in perfusion pressure, which was monitored continuously by means of a pressure transducer (TP-400 T; Nihon-Kohden, Tokyo, Japan) and recorded on a pen recorder (YEW, Type3056; Yokogawa-Electric, Tokyo, Japan). After a 60-min equilibration period, either drugs was added to the bath or the perivascular nerve was stimulated.

### 2.5. Drug application

The mesentery preparation was constricted by perfusion with a solution containing $6 \times 10^{-6}$ to $3 \times 10^{-5}$ M methoxamine, which resulted in a perfusion pressure of approximately 115–130 mm Hg, and then was maximally relaxed by means of a perfusion solution containing $3 \times 10^{-7}$ M acetylcholine.

### 2.6. Conditions used for perivascular nerve stimulation

A pair of platinum electrodes was used for perivascular nerve stimulation; one was placed where the cannula

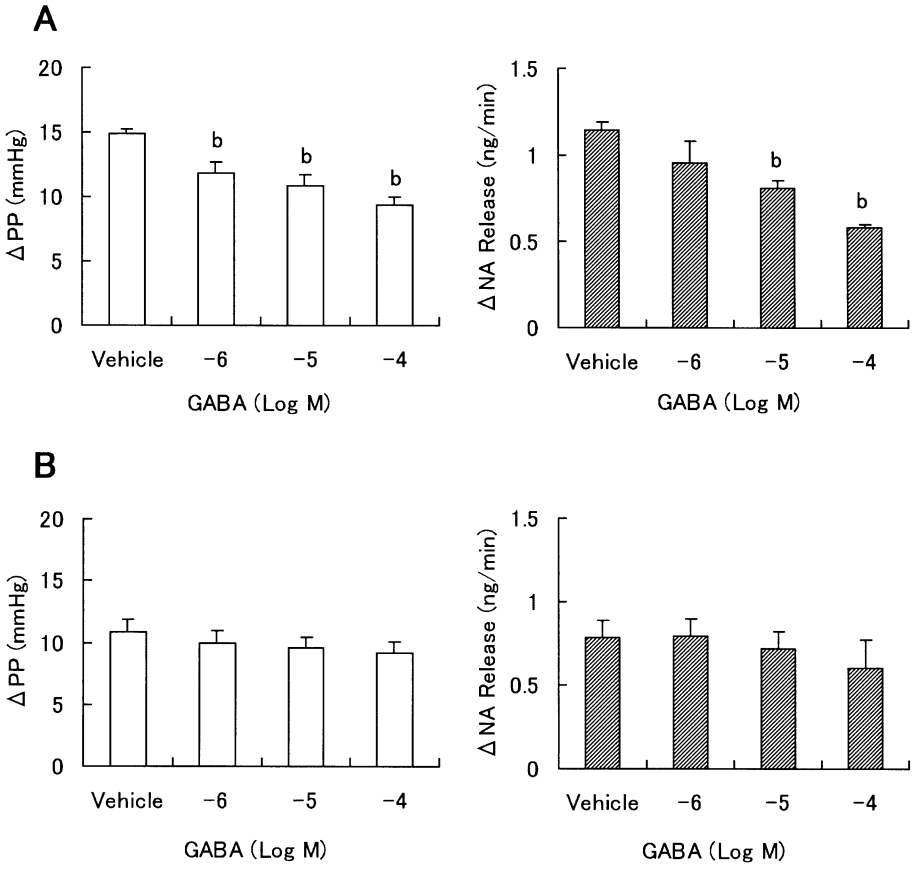


Fig. 3. Effect of GABA on the increase in perfusion pressure and noradrenaline release induced by perivascular nerve stimulation in mesenteric arterial beds from spontaneously hypertensive rats and normotensive Wistar–Kyoto rats. (A) Spontaneously hypertensive rats; (B) normotensive Wistar–Kyoto rats. Left panels, ΔPP, change in perfusion pressure; right panels, ΔNA, noradrenaline release. Each point represents the mean ± S.E.M. for 5–6 animals. $^{b}P < 0.01$ vs. vehicle.

entered the superior mesenteric artery and the other at the peripheral part of the mesenteric arterial bed. Perivascular nerve stimulation was applied at 5 Hz and 2 ms pulse duration, with 600 trains being delivered every 15 min (Electronic Stimulator, SEN-3301; Nihon-Kohden, Tokyo, Japan).

### 2.7. Drugs

γ-Amino-butyric acid (GABA), baclofen, muscimol, and methoxamine were purchased from Sigma (St. Louis, MO, USA). Saclofen hydrochloride and (−)-bicuculline methochloride were purchased from Tocris Cookson (Ballwin, MO, USA). All drugs were dissolved in distilled water.

### 2.8. Measurement of noradrenaline release

The perfusate exiting the mesenteric artery was sampled before the start of the perivascular nerve stimulation and during the last 30 s of each stimulation period. Noradrenaline was extracted from each sample by the activated alumina adsorption method, and the noradrenaline concentration was determined by high performance liquid chromatography (BAC-300 system; EICOM, Kyoto, Japan).

### 2.9. Statistical analysis

The results shown in the text and figures are expressed as the means ± S.E.M. Statistical differences were assessed with Dunnett's test. Differences were considered to be statistically significant at $P<0.05$. The data were analyzed using the SAS System Ver. 6.12 (SAS Institute, Cary, NC, USA).

## 3. Results

### 3.1. Effect of a single oral administration of GABA on the blood pressure in spontaneously hypertensive rats and normotensive Wistar–Kyoto rats

The average body weight and resting systolic blood pressure are shown for both the spontaneously hypertensive rats and normotensive Wistar–Kyoto rats in Table 1. The effects of a single oral administration of GABA (0.5 mg/kg)

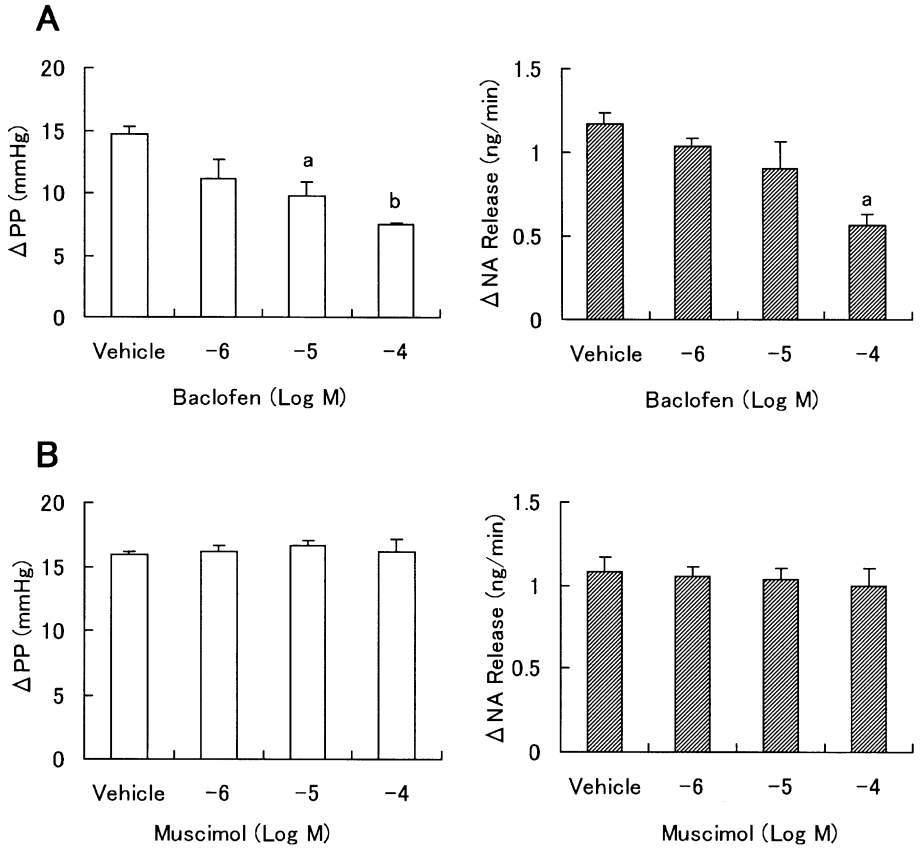


Fig. 4. Effects of baclofen and muscimol on perfusion pressure and noradrenaline release induced by perivascular nerve stimulation in mesenteric arterial bed from spontaneously hypertensive rats. (A) Effect of baclofen; (B) effect of muscimol. Other details are as in Fig. 3. Each point represents the mean ± S.E.M. for 5–6 animals. $^{a}P<0.05$, $^{b}P<0.01$ vs. vehicle.

on the systolic blood pressure in these groups are shown in Fig. 1. At 4 and 8 h after the administration, the systolic blood pressure was significantly decreased by $20.8 \pm 3.5$ ($P < 0.01$) and $22.8 \pm 2.6$ ($P < 0.01$), respectively, in spontaneously hypertensive rats, and it had returned to its initial value at 24 h after the administration. In contrast, GABA did not change the systolic blood pressure in Wistar–Kyoto rats (Fig. 1B). There were no significant changes in the heart rate following GABA administration in either group (data not shown).

### 3.2. Effect of GABA on methoxamine-induced vasoconstriction in mesenteric arterial beds

The basal perfusion pressure in the mesenteric arterial bed from spontaneously hypertensive rats was $61.2 \pm 2.5$ mm Hg ($n = 24$), and the perfusion with methoxamine ($6 \times 10^{-6}$ to $3 \times 10^{-5}$ M ) increased it to $125 \pm 4.5$ mm Hg ($n = 6$). After the tonus of the mesenteric arterial bed had been increased by methoxamine, the exposure to GABA ($10^{-6}$ to $10^{-4}$ M) did not induce any vasodilator or constrictor response. Incubating the mesenteric arterial bed with GABA ($10^{-4}$ M) did not affect the vasoconstriction induced by methoxamine; although acetylcholine ($10^{-8}$ to $3 \times 10^{-7}$ M) was still able to cause concentration-dependent vasodilatation (data not shown), suggesting that GABA did not directly affect the endothelium or smooth muscle.

### 3.3. Effects of GABA on the perivascular nerve stimulation-induced vasoconstrictor responses in mesenteric arterial

The typical effects of GABA ($10^{-6}$ to $10^{-4}$ M) on the perivascular nerve stimulation-induced increase in perfusion pressure in the mesenteric arterial bed from spontaneously hypertensive rats are shown in Fig. 2, and a summary is shown in Fig. 3. Both the increase in perfusion pressure and the noradrenaline release induced by perivascular nerve stimulation were significantly greater ($P < 0.01$) in spontaneously hypertensive rats than that in Wistar–Kyoto rats (Fig. 3 and Table 1). In spontaneously hypertensive rats, GABA at $10^{-6}$, $10^{-5}$ and $10^{-4}$ M significantly inhibited the perivascular nerve stimulation-induced increase in perfusion pressure by $20 \pm 4\%$ ($P < 0.01$), $28 \pm 5\%$ ($P < 0.01$), and $39 \pm 5\%$ ($P < 0.01$), and the induced noradrenaline release by $16 \pm 12\%$, $29 \pm 4\%$ ($P < 0.01$), and $49 \pm 2\%$ ($P < 0.01$), respectively. In contrast, there were no GABA-induced significant differences in these responses in Wistar–Kyoto rats.

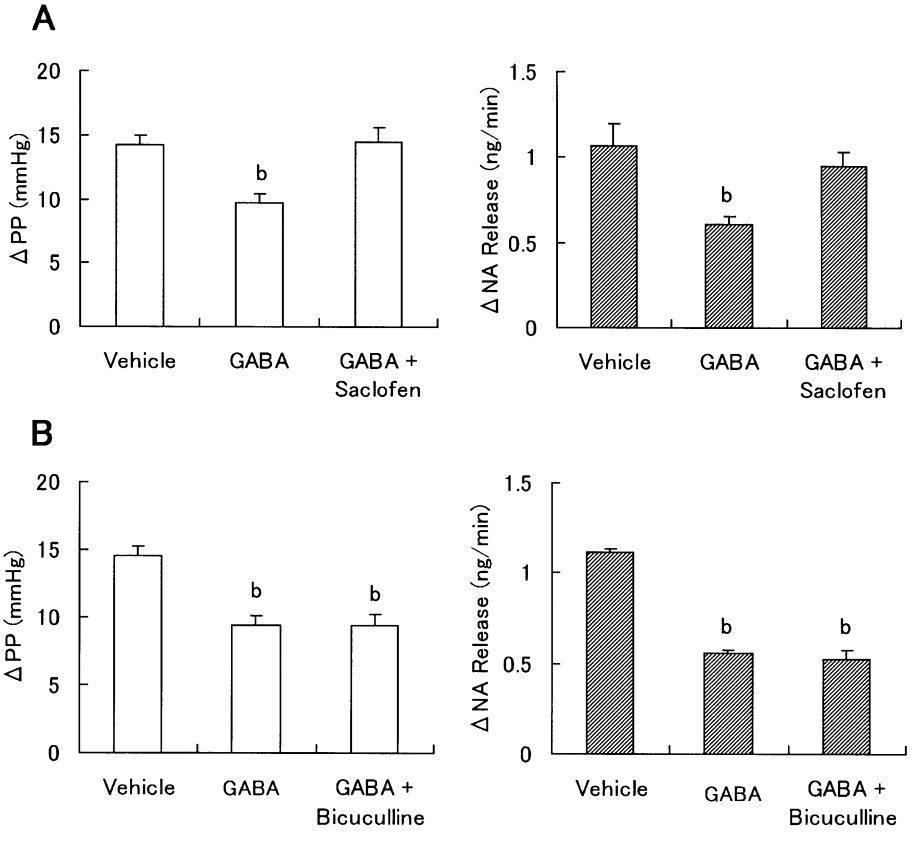


Fig. 5. Effects of saclofen and bicuculline on GABA ($10^{-4}$ M)-induced inhibition of the increase in perfusion pressure and noradrenaline release induced by perivascular nerve stimulation in mesenteric arterial bed from spontaneously hypertensive rats. (A) Effect of saclofen ($10^{-4}$ M); (B) effect of bicuculline ($10^{-4}$ M). Other details are as in Fig. 3. Each point represents the mean ± S.E.M. for 5–6 animals. $^{b}P < 0.01$ vs. vehicle.

### 3.4. Effect of GABA receptor agonists and antagonists on the perivascular nerve stimulation-induced increase in perfusion pressure in mesenteric arteries bed from spontaneously hypertensive rats

In spontaneously hypertensive rats, the $GABA_B$ receptor agonist, baclofen ($10^{-6}$ to $10^{-4}$ M), had effects quantitatively very similar to those seen with GABA itself: it inhibited the perivascular nerve stimulation-induced increase in perfusion pressure by $24 \pm 9\%$, $33 \pm 6\%$ ($P < 0.05$), and $47 \pm 6\%$ ($P < 0.01$), and the induced noradrenaline release by $15 \pm 8\%$, $29 \pm 16\%$ and $54 \pm 6\%$ ($P < 0.05$), respectively (Fig. 4A). In contrast, the $GABA_A$ receptor agonist, muscimol, did not affect these responses (Fig. 4B). The inhibitory effects of GABA ($10^{-4}$ M) on the above responses were completely antagonized by the selective $GABA_B$ receptor antagonist, saclofen ($10^{-4}$ M), but not by the selective $GABA_A$ receptor antagonist, bicuculline ($10^{-4}$ M) (Fig. 5).

## 4. Discussion

Based on the results of the present study, this is the first report that oral administration of GABA significantly lowered systemic blood pressure in spontaneously hypertensive rats, but not in normotensive Wistar–Kyoto rats. Using the mesenteric arterial bed from spontaneously hypertensive rats, we also confirmed that GABA inhibits not only the perivascular nerve stimulation-induced increase in perfusion pressure, but also the accompanying noradrenaline release. Since GABA did not produce any vasodilator response in the mesentery (a bed that makes a major contribution to blood pressure control) nor any change in heart rate, the GABA-induced antihypertensive effect may be due primarily to the inhibition of noradrenaline release from sympathetic nerve endings, and may not involve a direct effect on endothelium or smooth muscle, or an effect on the heart.

It has long been known that intravenously or orally administered GABA significantly lowers the blood pressure in animals and humans (Takahashi et al., 1955, 1958; Elliott and Hobbiger, 1959; Stanton, 1963). Moreover, there is a positive relationship between resting blood pressure and the amplitude of the GABA-induced reduction in systolic blood pressure (Giuliani et al., 1986). In line with the latter observation, our present study demonstrated that GABA lowered the blood pressure only in spontaneously hypertensive rats, not in normotensive rats, indicating that normal blood pressure is not affected by GABA. Surprisingly, to our knowledge no previous studies have investigated the effect of GABA on the blood pressure in spontaneously hypertensive rats.

Since the blood–brain barrier is impermeable to GABA (Kuriyama and Sze, 1971), the antihypertensive effect of peripherally administered GABA is due to the effects exerted in the periphery (presumably, on the blood vessels or the autonomic nervous system). Thus, we were essentially examining the peripheral effects of GABA, and we focused on the resistance vessels, specifically the mesenteric arterial bed from spontaneously hypertensive rats. Incubating the mesenteric arterial bed with GABA did not affect the vasoconstriction induced by methoxamine, suggesting that the GABA-induced antihypertensive effect in spontaneously hypertensive rats was not due to a direct effect on endothelium-dependent or -independent vasodilatation.

We now found that both the increase in perfusion pressure and the noradrenaline release induced by perivascular nerve stimulation were significantly greater in spontaneously hypertensive rats than in Wistar–Kyoto rats, strongly suggesting (i) that the increase in perfusion pressure on perivascular nerve stimulation is brought about by increased noradrenaline release and (ii) that the sympathetic nerve fibers in spontaneously hypertensive rats may be more sensitive to electrical stimulation than those in normotensive Wistar–Kyoto rats. These phenomena may have a causal relation to the hypertension of spontaneously hypertensive rats, because the mesenteric arterial bed, an assembly of resistance vessels, plays a major part in setting the level of systemic blood pressure. The increased perfusion pressure and noradrenaline release seen in the mesenteric arterial bed on perivascular nerve stimulation were selectively inhibited by GABA only when the mesentery was from a spontaneously hypertensive rat. This is consistent with our observation of an orally administered GABA-induced antihypertensive effect in spontaneously hypertensive rats, but not in normotensive Wistar–Kyoto rats. Thus, we propose that when sympathetic nerve activity is high, GABA is able to reduce the activity via the inhibition of noradrenaline release. The long-lasting antihypertensive effect of oral administration of GABA in spontaneously hypertensive rat may be due to slower absorption.

The GABA receptors involved appear to be located on sympathetic nerve endings since GABA attenuated the perivascular nerve stimulation-induced increase in perfusion pressure in the mesenteric arterial bed from spontaneously hypertensive rats, but did not affect the vasoconstriction elicited by the $\alpha_1$-adrenoceptor agonist, methoxamine. The effects produced by GABA in many kinds of peripheral tissues as well as within the central nervous system are mediated by at least two distinct receptor types, $GABA_A$ and $GABA_B$. It has been reported that GABA inhibits sympathetic neurotransmission in the rabbit ear artery through the stimulation of a prejunctional receptor of $GABA_B$ subtype (Manzini et al., 1985), and that GABA acts on presynaptic $GABA_B$ receptors to suppress neurotransmitter release (and thereby attenuate renal vasoconstriction) during the activation of the sympathetic nervous supply to the rat kidney (Monasterolo et al., 1996; Fijimura et al., 1999). In our experiment, muscimol, a selective $GABA_A$ receptor agonist (DeFeudis, 1982), did not substantially affect the perivascular nerve stimulation-induced increase in perfusion pressure in spontaneously hypertensive rats. On the other hand,

baclofen, a selective $GABA_B$ receptor agonist (Bowery, 1993), attenuated the perivascular nerve stimulation-induced increase in perfusion pressure and noradrenaline release to the same extent as did GABA itself. Furthermore, these inhibitory effects of GABA were completely antagonized by the selective $GABA_B$ receptor antagonist, saclofen (Bowery, 1993), but not by the selective $GABA_A$ receptor antagonist, bicuculline (Curtis, 1973; Kwan et al., 1996). These results strongly suggest that GABA acts on presynaptic $GABA_B$ receptors to inhibit noradrenaline release, and thus the increase in perfusion pressure, induced by perivascular nerve stimulation in the mesenteric arterial bed from spontaneously hypertensive rats.

It has been reported that baclofen has hypertensive properties after systemic or intracerebroventricular administration in rats (Persson and Henning, 1980, Crambes et al., 1996). In contrast to these reports, we found that baclofen attenuated the perivascular nerve stimulation-induced increase in perfusion pressure in the mesenteric arterial bed. These results suggest that baclofen exerts a hypertensive effect via a central action and hypotensive effect via a peripheral action

In summary and conclusion, a single oral administration of GABA significantly lowered the systemic blood pressure in spontaneously hypertensive rats, but not in normotensive Wistar–Kyoto rats. In the mesenteric arterial bed from spontaneously hypertensive rats, GABA inhibited not only the perivascular nerve stimulation-induced increase in perfusion pressure, but also the accompanying noradrenaline release. Since GABA did not produce any vasodilator response, the GABA-induced antihypertensive effect may be due to its inhibition of noradrenaline release from sympathetic nerve fibers. Our data also suggest that GABA inhibits noradrenaline release through an action on presynaptic $GABA_B$ receptors, and thus suppresses the increase in perfusion pressure induced by perivascular nerve stimulation in the mesenteric arterial bed from spontaneously hypertensive rats. On the basis of these results, we propose that GABA may be beneficial for normalizing the blood pressure when it is high.

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