Hypotension and Hypothalamic Depression Produced by Intracerebroventricular Injections of GABA in Spontaneously Hypertensive Rats

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To determine the central effects of 4-Amino-n-butyric acid (GABA), pressor and sympathetic nerve responses to electrical stimulation of the ventromedial hypothalamus were recorded following the intracerebroventricular (ICV) injection of GABA. In normotensive Wistar rats, anesthetized with urethane, ICV injections of GABA (50–200 µg) reduced sympathetic nerve activity, arterial blood pressure, and heart rate in a dose-dependent manner. Graded electrical stimulation of the ventromedial hypothalamus (50, 100, 150 µA) increased not only mean blood pressure but also the rate of sympathetic nerve firing, and both responses were attenuated by GABA pretreatment (100, 200 µg, ICV).

In spontaneously hypertensive rats (SHR), ICV-injected GABA also reduced sympathetic and cardiovascular activity, but the magnitude of depressor responses was significantly larger in SHR than in normotensive Wister Kyoto controls (WKY). Pressor and sympathetic nerve responses elicited by ventromedial hypothalamic stimulation were initially larger in SHR than in WKY, but upon subsequent ICV injection of GABA, hypothalamic responsiveness in SHR was inhibited more prominently and became comparable to that in WKY.

These results suggest that by depressing hypothalamic function, centrally injected GABA decreases sympathetic nerve activity to thereby lower blood pressure and heart rate, and in SHR, ICV-injected GABA reversed hypothalamo-sympathetic hyperactivity and thus attenuated hypertension.

\( \gamma \text{-aminobutylic acid (GABA), a neurotransmitter widely distributed in the central nervous system} \) is known to regulate autonomic and cardiovascular activity. Central administration of GABA or the potent GABA agonist, muscimol, decreases blood pressure and heart rate in anesthetized cats or dogs, and an anesthetized or conscious rats. These cardiovascular effects are probably mediated by GABA receptors because they can be reversed by the specific GABA antagonist, bicuculline. ICV injections of GABA suppresses sympathetic outflow to the kidneys, adrenals, heart, and vasculature. Besides lowering basal blood pressure and heart rate, ICV injections of GABA attenuate the pressor effects elicited by central injections of angiotensin II or hypertonic NaCl solution and by electrical diencephalic stimulation.

Although several forebrain and hindbrain sites have been implicated in the action of GABA-ergic compounds, an important brain area

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Key Words:
GABA
SHR
Hypothalamic Stimulation

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which contains high concentrations of GABA and its synthesizing enzyme, glutamic acid decarboxylase\textsuperscript{13} and controls sympathetic outflow\textsuperscript{14} is the ventromedial hypothalamus. Electrical stimulation of the ventromedial hypothalamus consistently increases sympathetic nerve firing and blood pressure\textsuperscript{14}. Upon confirming that ICV GABA injection lowers sympathetic nerve activity, blood pressure, and heart rate in anesthetized rats, experiments were performed to determine whether ICV GABA injection lowers blood pressure by inhibiting hypothalamic responsiveness. Since spontaneously hypertensive rats (SHR) have GABA-ergic dysfunction in the hypothalamus\textsuperscript{15} and an increased sympathetic tone of hypothalamic origin,\textsuperscript{16} similar experiments were performed in SHR.

**MATERIALS AND METHODS**

The first experiments were performed on 50 male albino Wistar rats weighing 230–260g. Of these, 24 were used for recording neural and cardiovascular dose-responses to ICV injections of GABA, and 26 to determine whether hypothalamic responses would be affected by GABA pretreatment. For the second study, the effect of ICV-injected GABA on hypothalamic responsiveness was determined in male SHR and WKY (eight each) weighing 200–230g. Each rat was anesthetized with urethane (100 mg/100g, i.p.), and catheters were inserted separately into the left femoral artery for recording blood pressure and into the left femoral vein for drug injections. Pulsatile femoral pressure and sympathetic nerve activity were recorded continuously during ICV injection of GABA and following graded hypothalamic stimulation.

**Intracerebroventricular Injections and Hypothalamic Stimulation**

A guide cannula (ga. 23, stainless steel tubing) was placed in left lateral ventricle using the stereotaxic coordinates: anteroposterior 5.6, lateral 1.6, and dorsoventral 2.0\textsuperscript{17} Drugs were injected using an injection cannula (ga. 30, stainless steel tubing) that was connected to a 25 μl syringe and inserted into the guide cannula. Each injection had a volume of 5 μl, and was delivered manually in ten seconds.

For hypothalamic stimulation, a concentric stainless steel electrode, 0.5 mm in diameter (custom-made by Unique Medical, Tokyo, Japan), was placed in the ventromedial hypothalamus.

The stereotaxic coordinates were: anteroposterior 5.8, lateral 0.9, and dorsoventral −3.7\textsuperscript{17}. Hypothalamic stimulation was graded by using 5-sec trains of 50–200 μA (pulse duration, 1 ms; frequency, 100/s) biphasic currents.

**Sympathetic Nerve Recording**

For recording sympathetic nerve activity, the inferior nerve bundle entering the celiac ganglion was placed over a bipolar stainless steel electrode ( uninsulated tips 1 mm apart). Nerves and electrode tips were immersed in mineral oil. Spontaneous respiratory movements were abolished by paralyzing skeletal muscles with decamethonium bromide (0.2 mg/100g i.v.) and connecting the rat to an artificial respirator. Spike potentials were amplified (Grass P15AC amplifier Grass Medical Instrument, Quincy, Massachusetts, and biophsyio-amplifier, NEC-Sanei Instrument, Tokyo, Japan), monitored on a storage oscilloscope, and recorded continuously together with blood pressure on magnetic tape (TEAC R210B, Tokyo, Japan). To quantify nerve activity, original analog signals were played back into a inkless rectigraph (NEC-Sanei Instrument) and simultaneously fed into a spike counter (DSE 332P Biomedical System, Tokyo, Japan) whose output was recorded separately as a histogram and printed out digitally. The low-level control of the window discriminator was routinely set to filter out any background noise persisting after crushing the nerve.

**Brain Histology, Drug, and Statistics**

After each experiment, methylene blue was injected through the injection cannula, and a 0.5 mA direct current was passed through the hypothalamic electrode for 10 seconds to produce a small lesion at its tip. Through a thoracotomy, a 15-gauge needle was inserted via the left ventricle into the ascending aorta, and 10% formalin was perfused into the brain as described by Wolf\textsuperscript{18}. The whole brain was then removed and stored in formalin until sectioning. When transverse sections were compared with the atlas by Pellegrino et al.,\textsuperscript{17} the electrode tips were invariably located in the ventromedial hypothalamus adjacent to the fornix, the median forebrain bundle, and the anterior and lateral hypothalamic areas. Staining with methylene blue injected through the ventricular cannula was limited to the walls of the lateral ventricle.

For ICV injection, 4-Amino-Butyric Acid (GABA, Nakarai Chemicals Tokyo, Japan) was

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dissolved in artificial cerebrospinal fluid, and control rats were given the same volume of vehicle alone.

Data expressed as average ± SEM from more than three groups of rats were analyzed using an analysis of variance and for F ratios significant at 5% or less, differences between pairs of means were examined using Duncan's multiple range test. Results from two groups were compared using a two-tailed t-test for independent samples and differences at a 5% level (p < 0.05) or less were considered significant.

RESULTS
Cardiovascular and Sympathetic Nerve Responses to ICV Injections of GABA
In urethane-anesthetized rats mounted on the stereotaxic instrument, mean blood pressure, heart rate, and sympathetic nerve firing averaged 100 ± 3 mmHg, 371 ± 9 beats/min, and 96 ± 5 spikes/3 sec, respectively. All three measurements consistently fell following ICV injection of GABA (Fig. 1), but similar injections of the vehicle alone were ineffective. With GABA doses of 50–200 µg/rat, blood pressure fell within 10 sec to rise slightly toward preinjection level during the next 5 min, and then dropped again to maximum hypotensive levels about 10 min later (Figs. 1 and 2). Heart rates likewise fell to attain a maximum drop about 10 min after the injection (Figs. 1 and 3). These depressor and bradycardiac responses were always preceded by pronounced decreases in splanchnic sympathetic nerve firing frequency (Fig. 4). Within the dose range tested, the magnitude of all three effects was dose-dependent.

Inhibition of Hypothalamic Responsiveness by ICV-injected GABA
Because ICV injection of GABA reduced sympathetic neural firing, blood pressure, and heart rate, the following experiments were performed to determine whether cardiovascular and sympathetic responses to ventromedial hypothalamic stimulation would be affected by pretreatment with GABA. Responsiveness to hypothalamic stimulation was recorded 5 min after ICV injection of GABA (100 µg and 200 µg). ICV injection of GABA had the same baseline effects as described above. Subsequent electrical stimulation of the ventromedial hypo-

Fig. 2. Depressor responses to intracerebroventricular injection of various doses of GABA (●50, ●100, ●200 μg) and vehicle (○) in urethane anesthetized rats. Data are average changes from baselines given in the text, and expressed as averages ± SEM from six rats in each group. In comparing data from different groups, with \( f_1 = 3 \) and \( f_2 = 20 \), F ratios that are equal to or greater than 3.10 are significant at 5% while those equal to or greater than 4.94 are significant at 1%. F ratios at 0.5, 1, 2, 3, 4, 5, 10, 15, and 20 min are 9.6, 5.1, 6.0, 8.9, 10.3, 17.1, 57.5, 63.2, and 50.0, respectively.

Fig. 3. Bradycardia responses to intracerebroventricular injection of various doses of GABA (●50, ●100, ●200 μg) and vehicle (○) in urethane anesthetized rats. Data are obtained from the same rats and presented as in Fig. 2. F ratios at 0.5, 1, 2, 3, 4, 5, 10, 15, and 20 min are 8.8, 23.3, 18.3, 11.9, 12.8, 14.2, 27.4, 31.2, and 34.2, respectively.

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The 15th Conference on the Pathogenesis of Hypertension

![Neural firing responses to intracerebroventricular injection of various doses of GABA (●50, ▲100, ★200 µg) and vehicle (○) in urethane anesthetized rats. Data are obtained from the same rats and presented as in Fig. 2. F ratios at 0.5, 1, 2, 3, 4, 5, 10, 15, and 20 min are 13.8, 11.6, 8.3, 10.6, 14.9, 14.6, 25.7, 30.4, and 30.6, respectively.](image)

Fig.4. Neural firing responses to intracerebroventricular injection of various doses of GABA (●50, ▲100, ★200 µg) and vehicle (○) in urethane anesthetized rats. Data are obtained from the same rats and presented as in Fig. 2. F ratios at 0.5, 1, 2, 3, 4, 5, 10, 15, and 20 min are 13.8, 11.6, 8.3, 10.6, 14.9, 14.6, 25.7, 30.4, and 30.6, respectively.

Thalamus with graded currents increased both mean blood pressure and sympathetic neural firing, while heart rate was decreased (Fig. 5). During each 5-sec period of stimulation, neural firing accelerated immediately to attain peak increases within the first 3 sec, after which it subsided slightly, but it still stayed well above the baseline level. Attendant pressor and bradycardiac responses began soon after the neural firing increased, with the magnitude of all three effects being directly related to the current strength applied to the hypothalamus. Pressor responses were smaller in rats injected with GABA 100 µg (100 µA current stimulation) or 200 µg (50 and 100 µA current stimulation) than in vehicle-injected control rats (Table I), and corresponding increases in sympathetic nerve firing were also smaller in GABA-treated than in control rats (Table I). None of the differences in the accompanying bradycardia was significant (Table I).

Central GABA-ergic Effects on Hypothalamic Responsiveness in SHR

The foregoing results suggest that central GABA-ergic stimulation reduces sympathetic firing, blood pressure, and heart rate, and attenuates hypothalamic responsiveness. Because sympathetic hyperactivity of hypothalamic origin contributes to a blood pressure elevation in SHR, it was considered possible that cardiovascular and hypothalamic responsiveness to ICV injection of GABA would differ in SHR from those seen in WKY. Baselines for systolic, mean, and diastolic pressure (mmHg) in SHR (167 ± 3, 110 ± 2, and 86 ± 3, respectively) were much higher (p < 0.01) than in WKY (131 ± 6, 81 ± 4, 63 ± 2, respectively). None of the other differences between SHR and WKY, either in baseline for heart rate (373 ± 10 and 369 ± 4 beats/min, respectively) or sympathetic nerve firing (56 ± 7) and 46 ± 6 spikes/sec, respectively) was significant. ICV injections of GABA (100 µg and 200 µg) produced dose-dependent decreases in blood pressure, heart rate, and neural firing in both groups of rats (Table II). The magnitude of these effects was generally larger in SHR, but because of variability from rat to rat, differences were significant only in depressor responses (Table II). Although the hypotensive effects thus elicited were more marked in SHR, the remaining mean blood pressure of SHR (83 ± 3 mmHg) was still slightly higher (p < 0.05) than that of WKY (68 ± 3 mmHg) even after adminis-
tration of 200 µg GABA.

Upon electrical stimulation of the ventromedial hypothalamus, pressor and sympathetic responses before ICV injection of GABA were invariably stronger in SHR than in WKY (Table III). ICV administration of GABA attenuated sympathetic and pressor responses to electrical stimulation of the hypothalamus in both groups. However, since central GABA-ergic stimulation was more effective in SHR, the hypothalamic responsiveness of SHR, recorded 5 min after the GABA injection, proved to be similar to that of WKY (Table III).

DISCUSSION

Apart from confirming that ICV administration of GABA lowers blood pressure, heart rate, and sympathetic neural firing, our results also indicate that GABA attenuates sympathetic and pressor responses to ventromedial hypothalamic stimulation. Furthermore, we found that centrally injected GABA was much more effective in SHR.

Cardiovascular depression induced by centrally injected GABA has been ascribed to a central reduction in sympathetic outflow. Parasympathetic involvement seems unlikely because GABA effects were unaltered by either cholinergic blockade with atropine or vagotomy. The cardiovascular depressant effect of GABA was specifically mediated by a GABA receptor since the GABA agonist, muscimol, produced similar sympatho-cardiovascular effects, which were antagonized by GABA-antagonist, bicuculline or picrotoxin. In addition, ICV-injected GABA has been reported to affect central dopaminergic, serotonergic, and noradrenergic activity.

Although exact anatomical mapping of this system has not been done, GABA containing neurons are found in relatively high concentrations in brain areas known to control blood pressure, such as the hypothalamus, dorsal
TABLE I SYMPATHETIC AND CARDIOVASCULAR RESPONSES TO VENTROMEDIAL HYPOTHALAMUS STIMULATION IN URETHANE-ANESTHETIZED RATS THAT WERE INJECTED WITH VEHICLE OR GABA (100, 200 μg), ICV

<table>
<thead>
<tr>
<th>Responses</th>
<th>Current (μA)</th>
<th>Rat groups</th>
<th>F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>control</td>
<td>GABA (100 μg)</td>
<td>GABA (200 μg)</td>
</tr>
<tr>
<td>Pressor response (mmHg)</td>
<td>50</td>
<td>11 ± 3</td>
<td>2 ± 1*</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>25 ± 3</td>
<td>8 ± 4**</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>46 ± 4</td>
<td>40 ± 5</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>52 ± 3</td>
<td>56 ± 4</td>
</tr>
<tr>
<td>Sympathetic nerve (spikes/sec)</td>
<td>50</td>
<td>25 ± 2</td>
<td>3 ± 1**</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>48 ± 5</td>
<td>25 ± 6*</td>
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<tr>
<td></td>
<td>150</td>
<td>69 ± 6</td>
<td>65 ± 6</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>78 ± 5</td>
<td>86 ± 7</td>
</tr>
<tr>
<td>Bradycardia (l/min)</td>
<td>50</td>
<td>-9 ± 5</td>
<td>-1 ± 1</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>-31 ± 15</td>
<td>-8 ± 5</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>-65 ± 19</td>
<td>-17 ± 10</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>-71 ± 20</td>
<td>-48 ± 14</td>
</tr>
</tbody>
</table>

Data are average changes from baselines given in the text, and expressed as averages ± SEM from ten vehicle-injected control rats, eight 100 μg GABA-injected rats, and eight 200 μg GABA-injected rats. In comparing data from different groups, with f1 = 2 and f2 = 23, F ratios that are equal to or greater than 3.42 are significant at 5% while those equal to or greater than 5.66 are significant at 1%.

*Significantly different from control rats using Duncan's multiple range test at the 5% level.

**Significantly different from control rats using Duncan's multiple range test at the 1% level.

TABLE II CARDIOVASCULAR AND SYMPATHETIC RESPONSES TO INTRACEREBROVENTRICULAR ADMINISTRATION OF GABA IN SHR

<table>
<thead>
<tr>
<th>Responses</th>
<th>GABA dose (μg)</th>
<th>Rat groups</th>
<th>WKY</th>
<th>SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressor response (mmHg)</td>
<td>100</td>
<td>-5 ± 2</td>
<td>-11 ± 1*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>-13 ± 2</td>
<td>-27 ± 3**</td>
<td></td>
</tr>
<tr>
<td>Sympathetic nerve activity (spikes/sec)</td>
<td>100</td>
<td>-11 ± 2</td>
<td>-16 ± 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>-19 ± 2</td>
<td>-25 ± 8</td>
<td></td>
</tr>
<tr>
<td>Bradycardia (beats/min)</td>
<td>100</td>
<td>-8 ± 4</td>
<td>-15 ± 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>-19 ± 8</td>
<td>-40 ± 5</td>
<td></td>
</tr>
</tbody>
</table>

Data are obtained from eight SHR and eight WKY, and presented as in Table I. All values are average changes from baselines given in the text.

*p < 0.05 as compared with corresponding average for the control group.

**p < 0.01 as compared with corresponding average for the control group.

tegmental nucleus, and the nucleus of the solitary tract. Neurophysiological studies further suggest the forebrain or hindbrain area, neighboring the third or fourth ventricle, or cisterna magna. Medullary sites have been suggested since topical application of GABA to the ventral medulla lowers blood pressure as does injection of muscinol into the nucleus reticularis. On the other hand, several investigators have suggested more rostral sites since localized injection of the GABA antagonist, bicuculline, directly into the forebrain increases blood pressure and heart rate, and since GABA controls anterior pituitary hormone secretion via hypothalamic.
TABLE III  SYMPATHETIC AND CARDIOVASCULAR RESPONSES TO VENTROMEDIAL HYPOTHALAMUS STIMULATION IN URETHANE-ANESTHETIZED SHR BEFORE AND 5 MIN AFTER INTRACEREBROVENTRICULAR GABA INJECTION (100, 200 μg)

<table>
<thead>
<tr>
<th>Current strength (μA)</th>
<th>Pressor response (mmHg)</th>
<th>Neural firing (spikes/sec)</th>
<th>Bradycardia (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WKY</td>
<td>SHR</td>
<td>WKY</td>
</tr>
<tr>
<td><strong>Before GABA injection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>4 ± 2</td>
<td>10 ± 3</td>
<td>13 ± 3</td>
</tr>
<tr>
<td>100</td>
<td>30 ± 2</td>
<td>42 ± 3**</td>
<td>51 ± 8</td>
</tr>
<tr>
<td>150</td>
<td>38 ± 1</td>
<td>56 ± 3**</td>
<td>72 ± 10</td>
</tr>
<tr>
<td><strong>5 min after 100 μg GABA ICV injection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
<td>9 ± 2</td>
</tr>
<tr>
<td>100</td>
<td>12 ± 4</td>
<td>16 ± 1</td>
<td>39 ± 9</td>
</tr>
<tr>
<td>150</td>
<td>32 ± 4</td>
<td>48 ± 4*</td>
<td>69 ± 8</td>
</tr>
<tr>
<td><strong>5 min after 200 μg GABA ICV injection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>0 ± 0</td>
<td>-4 ± 2</td>
<td>7 ± 2</td>
</tr>
<tr>
<td>100</td>
<td>5 ± 3</td>
<td>3 ± 2</td>
<td>33 ± 5</td>
</tr>
<tr>
<td>150</td>
<td>22 ± 5</td>
<td>35 ± 3</td>
<td>62 ± 8</td>
</tr>
</tbody>
</table>

Data are obtained from the same rats and presented as in Table II.
*p < 0.05 as compared with corresponding average for the WKY group.
**p < 0.01 as compared with corresponding average for the WKY group.

function. Forebrain sites have also been implicated since ICV injection of muscimol reduces central sympathetic discharge to attenuate pressor responses elicited by electrical diencephalic stimulation. Instead of the diencephalon, we stimulated the ventromedial hypothalamus, assuming that the VMH is a major central site for regulating sympathetic activity and because the VMH contains high concentrations of GABA and its synthetic enzyme, glutamic acid decarboxylase (GAD). Some of the actions of benzodiazepines and barbiturates are also ascribed to mechanisms involving the GABA-ergic system, since these drugs have been shown to increase the affinity of the binding sites of the receptors for GABA and induce a GABA-potentiating action. As diazepam and other benzodiazepines are known to inhibit electrically evoked cardiovascular responses from the hypothalamus, our results, which show that central GABA-ergic stimulation attenuates hypothalamic responsiveness and thereby reduces sympatho-cardiovascular activity, are in accord with their findings.

Several studies have suggested that the brain GABA-system becomes altered in hypertension. Muscimol lowers blood pressure and heart rate more markedly in SHR with selective reduction of adrenal nerve activity and subconvulsive doses of picrotoxin or bicuculline, the GABA-antagonist, increase blood pressure more in SHR. Recently, Hambley et al. reported a decreased GABA receptor complex with decreased endogenous GABA levels in the hypothalamus of the SHR despite the fact that the GABA and benzodiazepine receptors in the cortex, brainstem, and cerebellum of SHR do not differ from those of WKY. We found that SHR exhibited enhanced sympathetic and pressor responses to hypothalamic stimulation. We also found that the reduction of hypothalamic responsiveness in addition to depressor responses to ICV injections of GABA were much larger in SHR. Although the baseline blood pressure of SHR after GABA injection was still slightly higher than that of WKY, GABA restored other indices for the hypothalamic-sympatho-cardiovascular function to normal. Collectively, these data suggest that GABA-ergic dysfunction in the hypothalamus of SHR results in hypothalamic hyperactivity, and that this is causally related to genetic hypertension. The remaining difference in blood pressure after GABA injection might indicate the involvement of other mechanisms in maintaining hypertension in SHR, such as increased peripheral cardiovascular reactivity.

*Japanese Circulation Journal Vol. 50, November 1986*
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