Antihypertensive Effect of the GABA Receptor Agonist Muscimol in Spontaneously Hypertensive Rats

Role of the Sympathoadrenal Axis

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SUMMARY. The antihypertensive action of central GABA-ergic stimulation was investigated in conscious stroke prone spontaneously hypertensive rats. Injection of the potent GABA agonist muscimol (0.01-1 Mg) into the lateral brain ventricle (icv) lowered mean arterial blood pressure (192.1 ± 8.4 mm Hg) dose-dependently in stroke prone spontaneously hypertensive rats with a maximal fall of —52.7 ± 5 mm Hg lasting for about 90 minutes. This was accompanied by bradycardia and sedation. Pretreatment with atropine (2 mg/kg, ip, or 15 µg/kg, icv) did not significantly influence the muscimol-induced fall in mean arterial pressure. In normotensive (109.3 ± 1.9 mm Hg) Wistar-Kyoto controls, the maximal decrease in mean arterial pressure was —12.1 ± 1.6 mm Hg from 109.3 ± 1.9 mm Hg, and the duration of the effect was much less than in stroke prone spontaneously hypertensive rats. Following 1 µg muscimol, icv, plasma noradrenaline did not fall significantly in stroke prone spontaneously hypertensive and Wistar-Kyoto rats, but in stroke prone spontaneously hypertensive rats, plasma adrenaline was fully suppressed (from 118.1 ± 24.2 to 22.8 ± 5.7 pg/ml) throughout the depressor response. The efferent sympathetic nervous activity as directly recorded from the n. splanchnicus was similar in conscious stroke prone spontaneously hypertensive and Wistar-Kyoto rats, and was moderately reduced in both strains by 1 µg muscimol, icv. Basal adrenal nerve activity was higher in stroke prone spontaneously hypertensive than in Wistar-Kyoto rats (14.8 ± 3.7 vs. 10.6 ± 1.7 µV, P < 0.02); it was reduced by 44% in stroke prone spontaneously hypertensive rats and only by 24% in Wistar-Kyoto rats after central muscimol administration. In contrast to muscimol, the central antihypertensive action of the α2-adrenoceptor agonist clonidine in conscious stroke prone spontaneously hypertensive rats was accompanied by similar reductions of splanchnic nerve activity (28%) and adrenal activity (25%). Our results demonstrate for the first time an increased efferent adrenal nerve activity in conscious stroke prone spontaneously hypertensive rats and a selective inhibition of the sympathoadrenal pathway by central GABA-ergic stimulation. The antihypertensive action of central GABA receptor stimulation in stroke prone spontaneously hypertensive rats is not mediated by an increase in vagal tone or a generalized reduction in sympathetic tone, but is associated with the selective suppression of sympathoadrenal activity. (Circ Res 54: 30–37, 1984)

γ-AMINOBUTYRIC ACID (GABA) is a neurotransmitter with a widespread distribution in the central nervous system. Among other actions, GABA has been shown to influence the autonomic nervous system and to alter cardiovascular function thereby (for review, see Persson, 1980a). Administration of GABA or GABA-ergic agonists such as muscimol or THIP to the brain causes a reduction in blood pressure and heart rate in various species, including man, as has been reported by several authors (Takahashi et al., 1955; Elliot and Hobbiger, 1959; Bhargava et al., 1964; Antonaccio and Taylor, 1977; Sweet et al., 1979; Williford et al., 1980a; Persson, 1980b; Gillis et al., 1982; Baum and Becker, 1982). These cardiovascular actions were found to be mediated, in most instances, by specific bicuculline- or picrotoxin-sensitive GABA receptors (Antonaccio and Taylor, 1977; Antonaccio et al., 1978; Williford et al., 1980a; Persson, 1980b). They may involve changes in central cholinergic and serotonergic activity (Persson, 1980b), and interactions with central peptidergic pressor pathways (Unger et al., 1983), as well as inhibition of somatosympathetic reflexes of the medial medullary depressor region (Taylor et al., 1982).

Sites of action include medullary regions accessible from the 4th brain ventricle (Williford et al., 1980a), the ventral medulla (Guertzenstein 1973), the nucleus ventriculares lateralis (Bousquet et al., 1981), and areas rostral to the brain stem (Antonaccio et al., 1978; Williford et al., 1980a, 1980b).

Pharmacological and neurophysiological studies...
have implicated a reduced sympathetic outflow, and an increased vagal tone in the mediation of the cardiovascular effects, following central GABA-ergic stimulation (see Persson, 1980a). Unfortunately, most of these data were obtained in anesthetized animals, which leave doubts as to their pathophysiological significance, in view of the well-known effects of anesthesia on autonomic nervous system function and blood pressure control. Furthermore, little is known concerning the blood pressure-lowering actions of GABA-ergic stimulation in hypertension.

This study was therefore designed, first, to investigate the intracerebroventricular (icv) actions of the GABA agonist muscimol on blood pressure and heart rate in conscious spontaneously hypertensive rats (SHRSP), a model of hypertension frequently reported to be associated with enhanced sympathetic activity (Hallbäck, 1975; Judy et al., 1976; Schömig et al., 1978; Bunag and Takeda, 1979; Thoren and Lundin, 1983).

Second, peripheral effector systems, such as sympatheoneuronal, sympathoadrenal, and vagal pathways, were studied for their respective roles in mediating the muscimol-induced cardiovascular changes in conscious SHRSP and normotensive Wistar-Kyoto controls (WKY). This was done by measurements of plasma catecholamine concentrations and direct recording of efferent sympathetic nervous activity in splanchnic and adrenal nerves, and by pharmacological interference with the vagal system.

In addition, changes in blood pressure and efferent sympathetic nerve activity produced by muscimol were compared with those produced by the centrally acting α2-adrenoceptor agonist clonidine, in order to determine the specificity of the GABA receptor-mediated effects.

**Methods**

**Experimental Animals and Procedures**

All experiments were done in conscious male 6- to 10-month-old SHRSP, and in age- and sex-matched WKY, bred in Heidelberg since 1975. Animals were kept under controlled temperature, humidity, and light period. For icv injections, chronic cannulas (PP20, Portex Corp.) were implanted into the lateral brain ventricle 1 week before, and arterial and venous catheters (PP10 in PP50, and PP10) were inserted into the femoral artery and vein, 1 or 2 days before the acute experiments. The surgical procedures have been described elsewhere in detail (Unger et al., 1981). Measurements of mean arterial blood pressure (MAP) and heart rate were performed via the arterial line, with a Statham P23Db pressure transducer, Gould Brush pressure computer, and Gould Brush 2400 recorder.

**Measurement of Sympathetic Nerve Activity**

For measurements of efferent sympathetic nerve activity, chronic bipolar electrodes were implanted on the splanchnic and adrenal nerves under barbiturate anesthesia 1 or 2 days before recording. The surgical procedures and the method of nerve recording were adapted from the methods described by Ricksten and Thoren (1980).

The rats were anesthetized by Methohexital (Eli-Lilly, 10 mg/kg, iv). Repeated iv injections of Methohexital were given during the surgical procedure when necessary. The area of the left splanchnic nerve, including the celiac ganglion, the renal artery, and the adrenal gland, was exposed retroperitoneally via a flank incision.

A splanchnic nerve branch between the celiac ganglion and the suprarenal plexus, as well as the adrenal nerve between the suprarenal plexus and the adrenal gland, were dissected free of fat and connective tissue over a length of approximately 8–10 mm. The nerves were placed on a thin bipolar stainless steel electrode. When an optimal signal was obtained, the nerve on the electrode was isolated with a small amount of silicone rubber (Wacker Sil-Gel 604). The transmission line to the amplifier was exteriorized via a miniature connector at the neck of the animal. The flank incision was then closed, and the rats were taken to their cages to recover from the procedure. During the surgical procedure, the rectal temperature of the animals was kept constant with a thermostatically controlled IR-heater.

Nerve potentials were amplified with a differential preamplifier with high-pass filter setting at 10 Hz and low-pass filter setting at 3 kHz. The signals were amplified again, then rectified and passed to a ratemeter with a time constant of 5 seconds. Mean rectified nervous activity, MAP, and heart rate were displayed on a Gould Brush 2400 recorder. The analog nervous signal could continuously be controlled on a monitor and an audio amplifier. The zero noise was expressed as the post-mortal activity 90 minutes after death. The animals were challenged with intravenous injections of 1 μg noradrenaline and 5 μg/min sodium nitroprusside, and only those preparations showing the appropriate sympathetic responses were used in the experiments. Animals then were placed into their home cages and were allowed 24–36 hours to recover from surgery before the experiments were performed. At this time, the rats had resumed their regular eating, drinking and grooming habits, and did not exhibit any signs of stress or pain.

**Experiment 1: Effects of Various icv Doses of Muscimol on Blood Pressure and Heart Rate in SHRSP and WKY**

SHRSP (n = 13) and WKY (n = 12) were injected icv with 0.01–0.1–1 μg muscimol. Injections were started with the lowest dose after 1 hour for stabilization of blood pressure and heart rate, and the next dose was given when blood pressure and heart rate had returned to control levels. The minimum interval between injections was 30 minutes; injection volume was 5 μl (1 μl drug flushed with 4 μl vehicle). Blood pressure and heart rate were recorded for 2 hours following the highest dose. An additional group of rats [SHRSP (n = 4) and WKY (n = 4)] was injected with vehicle alone at the appropriate time intervals.

**Experiment 2: Influence of Chemical Vagotomy on Blood Pressure Effects of icv Muscimol in SHRSP**

SHRSP were divided into three groups. Group one (n = 7) served as control and received an icv injection of muscimol only. Group two (n = 7) was injected icv with atropine (15 μg/kg) 5 minutes before 1 μg muscimol, icv. Group three (n = 7) was injected intraperitoneally (ip) with 2 mg/kg atropine 30 minutes before 1 μg muscimol, icv.
Experiment 3: Effect of icv Muscimol on Plasma Catecholamines in SHRSP and WKY

SHRSP (n = 10) and WKY (n = 10) were prepared with chronic brain cannulas and arterial and venous catheters. The catheters were connected to PP50 tubes, 30 cm long, which were attached to the outside of the rats’ home cages. The animals then were allowed a 1-hour rest period. One minute before and 1, 15, 45, and 90 minutes after an icv injection of 1 μg muscimol, blood (400 μl) was withdrawn from the arterial catheter into heparinized tubes. The volume was replaced simultaneously by an intravenous injection of 0.9% saline. Samples were centrifuged at 5000 g and 4°C for 10 minutes, and the plasma was deproteinized with 0.6 N HClO4. Aliquots (100 μl) were stored at -80°C and assayed within 4 weeks. Plasma contents of noradrenaline and adrenaline were assayed by a modified radioenzymatic method (Da Prada and Zürcher, 1976).

Experiment 4: Effect of icv Muscimol on Efferent Splanchnic and Adrenal Nerve Activity in SHRSP and WKY

SHRSP (n = 12) and WKY (n = 12) were divided in two groups (n = 6 each), and were prepared for recording of either splanchnic nerve activity or adrenal nerve activity, as described above. One or two days after surgery, the rats were connected to the recorders while sitting in their home cages, and after a control period of 1 hour, 1 μg muscimol was injected icv, and blood pressure, heart rate, and sympathetic nerve activity were recorded in conscious unrestrained animals.

Experiment 5: Effect of icv Muscimol on Blood Pressure in SHRSP after Unilateral Adrenalectomy Plus Contralateral Adrenal Denervation

Chronically instrumented SHRSP (n = 12) were divided in two groups (n = 6 each). In the first group, the right adrenal gland was removed and all fibers of the left adrenal nerve that could be visualized were cut at a length of 5 mm. The second group was sham-operated. One day after surgery, 1 μg muscimol was injected icv, and blood pressure was recorded as described above.

Experiment 6: Effect of icv Clonidine on Efferent Splanchnic and Adrenal Nerve Activity in Conscious SHRSP

SHRSP (n = 12) were divided into two groups (n = 6 each) and were prepared for recording of splanchnic and adrenal nerve activity as described above. One or two days later, 5 μg clonidine was injected icv, and the same parameters as in experiment 4 were measured.

Experiment 1: Effect of icv Muscimol on Blood Pressure and Heart Rate in SHRSP and WKY

In both strains, the icv injection of 0.01, 0.1, and 1 μg muscimol produced triphasic blood pressure responses (Table 1). An initial blood pressure decrease was followed by an increase and a second longer-lasting fall. At the two lower doses (0.01 and 0.1 μg), these changes were small and short-lasting, and there were no significant differences between SHRSP and WKY, except for the blood pressure increase after 0.1 μg, which was higher in SHRSP than in WKY (Table 1). It was accompanied by a moderate behavioral arousal reaction in some animals.

Following 1 μg, the initial and second blood pressure falls were significantly greater in SHRSP than in the normotensive controls. This difference was particularly pronounced in the second depressor response with respect to maximal fall and duration (Fig. 1). The blood pressure falls were accompanied by moderate and variable decreases in heart rate (−56 ± 24 beats/min in SHRSP vs. −21 ± 8 beats/min in WKY) which were not significantly different between both strains.

Most animals showed behavioral responses to this dose. An initial short excitation was followed by a

| Table 1 | Effect of icv Muscimol on Blood Pressure in Conscious SHRSP and WKY |
|-----------------|-----------------|-----------------|-----------------|
| **Muscimol, icv (μg)** | **Control MAP** | **MAP1** | **max1** |
| SHRSP | (n = 13) | 180.2 ± 9.8 | −3.9 ± 2.3 | 1.2 ± 0.4 |
| 0.01 | 180.7 ± 9.8 | −9.3 ± 2.2 | 1.6 ± 0.4 | +13.5 ± 2.9† |
| 0.1 | 192.1 ± 8.4 | −13.2 ± 2.8* | 0.8 ± 0.2 | +4.5 ± 2.0 |
| 1 | 109.6 ± 3.5 | −3.9 ± 1.5 | 2.3 ± 0.3 | +4.3 ± 2.4 |
| WKY | (n = 12) | 106.5 ± 3.0 | −7.3 ± 2.2 | 1.5 ± 0.3 |
| 0.01 | 109.3 ± 1.9 | −5.4 ± 1.8* | 0.6 ± 0.1 | +1.9 ± 0.9 |
| 0.1 | 192.1 ± 8.4 | −13.2 ± 2.8* | 0.8 ± 0.2 | +4.5 ± 2.0 |
| 1 | 109.6 ± 3.5 | −3.9 ± 1.5 | 2.3 ± 0.3 | +4.3 ± 2.4 |

Results are expressed as means ± sem.

* P < 0.05; † P < 0.001. Comparison between responses in SHRSP and WKY MAP: Mean arterial blood pressure (mmHg) MAP1–3: successive changes in MAP. For details, see text. max1–3: time of maximal blood pressure response, minutes after muscimol injection.

Drugs

Muscimol was purchased from Fluka AG, Buchs, Switzerland. The drug was made up freshly with 0.9% NaCl before use. Atropine sulfate was purchased from Sigma, München, F.R.G. and dissolved in 0.9% NaCl before use. Clonidine was obtained from Boehringer-Ingelheim, F.R.G., and dissolved in 0.9% NaCl before use.

Statistics

Means and sem are reported. The statistical evaluation was performed using Student’s t-test for paired and unpaired observations and BMDF7D analysis of variance (ANOVA) with Bonferroni’s method of multiple pairwise comparison when appropriate. Changes in plasma catecholamines (experiment 3) were statistically evaluated by a modified Kruskal-Wallis test. A significance level of P < 0.05 was accepted.

Results
long-lasting sedation which coincided with the blood pressure fall. The cardiovascular and behavioral effects of 1 μg muscimol, icv, were fully reversible. Doses between 1 and 10 μg, icv, were tested in some animals of both strains and found to produce a highly variable cardiovascular response pattern, which was dominated by toxic CNS reactions with convulsions and respiratory distress. The groups of animals injected with vehicle alone did not exhibit any significant deviations from their baseline blood pressure values of 179 ± 11 mm Hg (SHRSP) and 108 ± 6 mm Hg (WKY) throughout the experiment.

Experiment 2: Influence of Chemical Vagotomy on Blood Pressure Effects of icv Muscimol in SHRSP

The results of this experiment are shown in Table 2. Pretreatment with atropine given either icv or ip had no significant effect on the decrease of blood pressure in response to 1 μg muscimol, icv. The peripheral application of atropine raised the basal heart rate but did not influence the muscimol-induced bradycardia. Atropine given icv, on the other hand, did not influence basal heart rate significantly, but appeared to inhibit the bradycardia to muscimol, although there was a great variability in responses and the attenuation did not reach statistical significance (Table 2).

Experiment 3: Effect of icv Muscimol on Plasma Catecholamines in SHRSP and WKY

The results of this experiment are depicted in Figure 2. Control levels of noradrenaline were equal in both strains (163.0 ± 8.8 pg/ml in SHRSP vs. 173.0 ± 15.7 pg/ml in WKY), whereas adrenaline was higher in SHRSP (118.1 ± 24.2 pg/ml) than in WKY (25.8 ± 9.6 pg/ml). In WKY, 1 μg muscimol, icv, did not significantly alter plasma noradrenaline and adrenaline concentrations. In SHRSP, the same dose of the GABA agonist caused an initial short-lasting increase in plasma noradrenaline. Fifteen minutes after the muscimol injection, plasma adrenaline concentrations had fallen to 22.8 ± 5.7 pg/ml, and remained at this level throughout the experiment.

Experiment 4: Effect of icv Muscimol on Efferent Sympathetic Nerve Activity in Conscious SHRSP and WKY

In WKY, injection of 1 μg muscimol, icv, reduced splanchnic nerve activity by 32% and adrenal nerve

<table>
<thead>
<tr>
<th>Table 2</th>
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<tr>
<td><strong>Effect of Central and Peripheral Pretreatment with Atropine on Blood Pressure and Heart Rate Responses to 1 μg Muscimol, icv, in SHRSP</strong></td>
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</table>

<table>
<thead>
<tr>
<th>Control group</th>
<th>Atropine (15 μg/kg, icv)</th>
<th>Atropine (2 mg/kg, ip)</th>
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<tbody>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>Baseline</td>
<td>ΔMU</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>186.6 ± 8.2</td>
<td>-50.1 ± 5.9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>344 ± 16</td>
<td>-58 ± 26</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SEM. n = 7 per group.
* P < 0.05, when compared with baseline heart rate in control group. ΔMU = Responses to icv muscimol. Statistical analysis was performed by ANOVA, followed by Bonferroni's method of multiple pairwise comparison.
TABLE 3
Effect of icv Muscimol (1 µg) on Splanchnic and Adrenal Efferent Nerve Activity in Conscious SHRSP and WKY

<table>
<thead>
<tr>
<th></th>
<th>Basal nerve activity (µV)</th>
<th>After 1 µg muscimol, icv (µV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHRSP SNA</td>
<td>14.8 ± 3.7</td>
<td>11.5 ± 3.7†</td>
</tr>
<tr>
<td>ANA</td>
<td>25.5 ± 2.1†</td>
<td>14.2 ± 2.4†</td>
</tr>
<tr>
<td>WKY SNA</td>
<td>10.6 ± 1.7</td>
<td>7.2 ± 1.0*</td>
</tr>
<tr>
<td>ANA</td>
<td>16.5 ± 2.4†</td>
<td>12.5 ± 1.6†</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SEM. n = 6 per group.
SNA: splanchnic nerve activity; ANA: adrenal nerve activity.

* P < 0.05; † P < 0.01 when compared with basal activity before muscimol; ‡ P < 0.02 SHRSP vs. WKY.

activity by 24% (Table 3). A representative recording of adrenal nerve activity in WKY is shown in Figure 3.

In SHRSP, muscimol reduced splanchnic nerve activity by 22%. Basal adrenal nerve activity was higher than in WKY (P < 0.02) and was reduced by 44%. The decrease of adrenal nerve activity coincided with the blood pressure fall in response to muscimol, as can be seen from a representative recording in Figure 4. The muscimol-induced changes in blood pressure, heart rate, splanchnic and adrenal nerve activity in WKY and SHRSP are summarized in Figure 5.

Experiment 5: Effect of icv Muscimol on Blood Pressure in Conscious SHRSP after Unilateral Adrenalectomy Plus Contralateral Adrenal Denervation

In the sham-operated SHRSP, 1 µg muscimol, icv, reduced mean arterial blood pressure by 63.3 ± 8.3 mm Hg from a control level of 180.8 ± 6.9 mm Hg. In the group that had undergone unilateral adrenalectomy and contralateral adrenal denervation, the same dose of muscimol lowered blood pressure less

(P < 0.05); the decrease was 40.0 ± 8.8 mm Hg from a control level of 170.0 ± 6.3 mm Hg.

Experiment 6: Effect of icv Clonidine on Arterial Blood Pressure and Efferent Sympathetic Nerve Activity in Conscious SHRSP (Table 4)

The injection of 5 µg clonidine, icv, caused a fall in blood pressure similar to that produced by 1 µg muscimol, icv (20% vs. 27% reduction). The falls in heart rate were also the same in both treated groups. Clonidine reduced the splanchnic nerve activity by 28% and the adrenal nerve activity by 25%; these changes were not significantly different from each other.

Discussion

Administration of the GABA agonist muscimol into the lateral brain ventricle lowered blood pressure in a dose-dependent fashion in conscious SHRSP, and was much less effective in conscious WKY. Our results conform with those reported by Baum and Becker (1982), although the doses re-
quired in their experiments in SHR to produce similar depressor effects was higher. The triphasic responses observed in both strains with a more prominent blood pressure increase to the lowest dose (0.01 μg) of muscimol in SHRSP resemble the findings reported by Persson (1981b).

At the highest dose used (1 μg), icv muscimol lowered both blood pressure and heart rate in SHRSP and WKY. The changes in heart rate coincided with the fall in blood pressure; they were, however, quite variable and, statistically, there was no difference between SHRSP and WKY, despite the much greater blood pressure falls in the hypertensive animals. Therefore, it appears unlikely that the observed bradycardia contributed substantially to the depressor action of muscimol in SHRSP. This is also supported by the fact that central and peripheral pretreatment with the muscarinic receptor antagonist atropine did not significantly attenuate the depressor effects, but reduced the heart rate responses to muscimol in SHRSP.

Lack of a vagal contribution to the depressor effects of central GABA-ergic stimulation has also been demonstrated by Williford et al. (1980a) in anesthetized cats. The authors found that bilateral vagotomy had no effect on the cardiovascular responses to muscimol. On the other hand, stellate gangliectomy prevented the decrease in heart rate without attenuating the depressor responses to muscimol, suggesting that the bradycardic and depressor responses were independently mediated. Similar results were obtained by Persson (1980b), who studied the effect of combined peripheral vagal and sympathetic inhibition on the centrally evoked cardiovascular responses to GABA in conscious rats. Pretreatment with propranolol plus atropine completely prevented the bradycardia without affecting the depressor response, whereas either pretreatment alone was without effect on the cardiovascular responses to GABA.

Spontaneously hypertensive rats have repeatedly been shown to exhibit an increased sympathetic tone (Bunag and Takeda, 1979; Thoren and Lundin, 1983) and/or a sympathetic hyperreactivity to various stimuli (Hallbäck, 1975; McCarty and Kopin, 1978; Kvetnansky et al., 1979; Bunag and Takeda, 1979; Kubo, 1979; Dietz et al., 1982), although it remains controversial whether this is reflected by altered plasma catecholamines under basal conditions (McCarty and Kopin, 1978; Schömig et al., 1978).

When examining the effect of central GABA-ergic stimulation on plasma catecholamines in conscious SHRSP and WKY, we found increased basal adrenaline levels in the SHRSP, but no difference in circulating noradrenaline levels between both strains. This finding is at variance with previous reports, since, if anything, increased circulating noradrenaline, but not adrenaline levels, have been reported in SHRSP (e.g., Schömig et al., 1978). In the present experiments, special attention was given to prevent any environmental disturbances. The animals had been handled during the week before the experiment, they were allowed 1 hour rest in a quiet room before the first blood sampling, and blood was withdrawn through the catheter from outside the cage, unnoticed by the animals. It is therefore difficult to attribute the elevated basal adrenaline levels in SHRSP to an overreaction to external stimuli. The discrepancy between our observation and some others reported in the literature may be explained in part by the effect of age on adrenal medullary activity in SHR. Thus, Nagatsu et al. (1971) have reported, that the increased sympathetic neuronal activity in young SHR decreases during development and establishment of hypertension, whereas the adrenal medullary activity is increased in adult SHR. The plasma catecholamine pattern of increased adrenaline and normal noradrenaline levels observed here in SHRSP has also been reported in patients with essential hypertension (Bühler et al., 1982). A possible contribution of adrenaline to enhanced vasoconstriction in hypertension is outlined below.

Central administration of muscimol affected neither plasma noradrenaline nor adrenaline concentrations in WKY, indicating that there was no gross reduction of sympathoneuronal or sympathoadrenal activity. This corresponds to the moderate cardiovascular changes seen in these animals. In the SHRSP, however, there was a significant rise in plasma noradrenaline and a slight increase of plasma adrenaline within the first minute after the muscimol injection coinciding with the initial short-lasting blood pressure increase. Then, plasma noradrenaline returned to basal levels while plasma adrenaline fell precipitously and remained low for the rest of the experiment. The reduction in plasma catecholamine levels is consistent with the sympatho-vascular changes seen in SHRSP following muscimol administration.
adrenaline 15 minutes after the muscimol injection coincided with the maximal blood pressure decrease in SHRSP (Table 1).

It is interesting, in this respect, that the systemic injection of large doses of muscimol in SHR (4 mg/kg, ia) was reported to be followed by a moderate increase in plasma noradrenaline levels and a marked increase in plasma adrenaline levels, together with a slight fall in blood pressure (Feuerstein et al., 1981). The more than thousandfold difference in antihypertensive doses between the peripheral (Feuerstein et al., 1981) and central route of application (Baum and Becker, 1982; results reported here) point to a central and not peripheral target site for the antihypertensive action of muscimol in SHR.

The increase of plasma catecholamines in these experiments appears to be a rather unspecific effect unrelated to the depressor action of muscimol, since it also accompanied the pressor effects of the systematically injected GABA receptor antagonist picROTOXIN.

In our study, the marked fall of plasma adrenaline without a concomitant change in noradrenaline was unexpected, since it argues against a generalized decrease in sympathetic outflow in response to central GABA-ergic stimulation as was suggested by several previous reports. However, Baum and Becker (1982) have already shown, that—under icv treatment with depressor doses of muscimol in conscious SHR—the compensatory adjustments to upright tilt were almost unaffected, suggesting a selective inhibition of the sympathetic system by central GABA-ergic stimulation with the reflex activity being still intact.

Our results point to a selective reduction of sympathetic traffic to the adrenal gland with subsequently reduced adrenaline release. This was confirmed when we examined the changes in efferent sympathetic nervous activity in splanchnic and adrenal nerves following the central application of muscimol in conscious WKY and SHRSP. In both strains, the basal splanchnic nerve activities were statistically not different from each other, and the reduction after icv muscimol was even greater in the WKY (32%) than in SHRSP (22%). In contrast, the adrenal nerve activity was significantly higher in the SHRSP under basal conditions, and was reduced almost twice as much by icv muscimol in SHRSP than in WKY (44% vs. 24%). The increased basal adrenal nerve activity in conscious SHRSP corresponds to the increased basal adrenaline levels. We cannot entirely exclude, at this point, that our results have been influenced in part by recording from a different number of nerve fibers in SHRSP, when compared to WKY, though this is unlikely by individual and group comparison. Our findings of selectively increased nerve activity in SHRSP are supported, however, by earlier reports of a higher sympathetic drive to splanchnic and renal but not to lumbar areas, as recorded from multifiber nerve branches as well as from single nerve fibers in awake and anesthetized SHR (for review, see Thoren and Lundin, 1983).

The finding that the depressor action of central GABA-ergic stimulation in SHRSP was associated with a reduction of sympathoadrenal tone is strengthened by our findings that unilateral adrenalectomy combined with adrenal denervation of the other side in SHRSP reduced the antihypertensive action of icv muscimol (24% blood pressure fall after 1 μg muscimol in the denervated group, vs. 34% in the sham-operated group).

It is known that circulating adrenaline can exert a facilitatory action on neurogenic vasoconstriction by stimulating presynaptic β-receptors (Langer et al., 1980) and, as suggested by Majewski and Rand (1981) and Bühler et al. (1982), this mechanism may contribute to the pathogenesis of hypertension to a greater extent than previously thought.

If one assumes, from the present experiments, a causal relationship between the blood pressure reduction and the reduced sympathoadrenal tone, our results would favor a role of circulating adrenaline in maintaining elevated blood pressure in certain types of hypertension that are associated with increased sympathetic activity such as genetic hypertension in the rat.

In contrast to the GABA-ergic receptor stimulation by muscimol, the antihypertensive action of the centrally active α2-adrenoceptor agonist clonidine appears to go along with a more generalized reduction of sympathetic tone. Our results confirm and extend a recent report by Togashi (1983) by demonstrating a similar reduction of splanchnic and adrenal efferent sympathetic activity following icv injection of clonidine in the hypertensive animals.

In conclusion, we have shown that the sympathoadrenal axis of the autonomic nervous system is stimulated in adult SHRSP, and that central GABA-ergic stimulation by icv muscimol reduces blood pressure to a much greater extent in conscious SHRSP than in normotensive WKY controls. In contrast to clonidine, this centrally mediated depressor action does not seem to involve a generalized reduction of sympathetic activity, but is associated with a selective reduction of sympathoadrenal tone and is independent of the simultaneously occurring reduction in heart rate. The results warrant further investigation of the role of sympathoadrenal pathways in blood pressure regulation.

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INDEX TERMS: GABA • Muscimol • Clonidine • Blood pressure • Spontaneously hypertensive rat • Sympathetic nervous system • Adrenal nerve activity
Antihypertensive effect of the GABA receptor agonist muscimol in spontaneously hypertensive rats. Role of the sympathoadrenal axis.

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