PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 180, 277–283 (1985)

# Enhanced Depressor Effect of Muscimol in the DOCA/NaCl Hypertensive Rat: Evidence for Altered GABAergic Activity in Brain[1] (42176)

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*Abstract.* To elucidate the role of the central γ-aminobutyric acid (GABA) system in the maintenance of deoxycorticosterone (DOCA)NaCl hypertension, the responses of mean arterial pressure (MAP), plasma norepinephrine (NE), and epinephrine (EP) to intracerebroventricular (ICV) administration of muscimol, a GABA agonist, and the responses of MAP to bicuculline, a GABA antagonist, and to clonidine, an $\alpha_2$-adrenoceptor agonist known to lower blood pressure by inhibiting sympathetic tone, were examined in conscious, unrestrained 4 week DOCA/NaCl hypertensive rats and age-matched uninephrectomized control rats. Muscimol (50–1000 ng/300 g, ICV) caused dose-dependent decreases in MAP which were greater in DOCA/NaCl rats than in controls. Basal plasma NE and EP were significantly higher in DOCA/NaCl rats than in controls. Muscimol (1000 ng/300 g, ICV) induced decreases in plasma EP which were greater in DOCA/NaCl rats than in controls without changing NE levels in either group. Bicuculline (3 μg/300 g, ICV) caused increases in MAP which were the same in both groups. The depressor response to clonidine (5 μg/300 g) was greater in DOCA/NaCl rats than in controls. These results suggest that the activity of the central GABAergic system is altered in the rat with established DOCA/NaCl hypertension and that the alteration in central GABAergic function may be related to the increased sympathoadrenal activity and the maintenance of hypertension in this model. 

It has been reported that γ-aminobutyric acid (GABA) and GABA receptor agonists, such as muscimol (1), decrease blood pressure, while GABA receptor antagonists, such as bicuculline (1), increase blood pressure after either systemic or intracerebroventricular (ICV) administration to normotensive animals and the spontaneously hypertensive rat (SHR) of the Okamoto strain (2–8). GABA agonists and antagonists are supposed to act in the central nervous system by altering vasomotor center tone and sympathetic outflow (7–9).

Several lines of evidence indicate that sympathetic nervous system activity is increased in rats with established deoxycorticosterone acetate (DOCA)/NaCl hypertension. Increased turnover of norepinephrine (NE) in peripheral organs (10) and elevation of plasma NE levels (11, 12) and urinary excretion of NE and its metabolites (13) have been reported in the established phase (4–7 weeks) of DOCA/NaCl hypertension. Further, it has recently been demonstrated (14) that daily intraperitoneal injection of valproic acid, an inhibitor of GABA breakdown in the brain, prevents the development of DOCA/NaCl hypertension in rat. The role of the central GABAergic system in modulating increased sympathetic nervous system activity and thus in maintaining established DOCA/NaCl hypertension has not yet been examined. To elucidate the role of the central GABAergic system in DOCA/NaCl hypertensive rats, we examine the effect of ICV administration of the GABA agonist muscimol and the GABA antagonist bicuculline on blood pressure in conscious, unrestrained DOCA/NaCl hypertensive rats and age-matched uninephrectomized control rats. The effect of muscimol on sympathetic nervous system activity was assessed by assay of plasma catecholamines. In addition, we compared the depressor action of muscimol with that of the $\alpha_2$-adrenoceptor agonist clonidine, an agent known to lower blood pressure by inhibiting sympathetic tone.

**Methods.** Male Sprague–Dawley rats (Charles River Breeding Laboratories, Wilmington, Mass.) were subjected to unilateral nephrectomy at 4 weeks of age, and 2 weeks were allowed for compensatory hypertrophy

[1] This work was supported in part by USPHS Grant HL-22544, HL-07457, HL-00707, and by Grant-in-Aid 76-777 of the American Heart Association.



0037-9727/85 $1.50

to take place. The rats were divided into two groups at 6 weeks of age. One group (DOCA/NaCl rats) was implanted subcutaneously with Silastic strips (Silicone rubber, Dow-Corning, Midland, Mich.) containing 200 mg/kg of DOCA and given 1% saline to drink *ad libitum*. The second group (control rats) received a sham-operation and were given tap water to drink *ad libitum*. Throughout the study, animals were housed in a room with constant temperature (24°C), humidity (60 ± 5%), and photoperiod (12 hr on and 12 hr off). All acute experiments were carried out 4 weeks after the implantation of DOCA or sham operation. Rats were anesthetized with ether and weighed. Cannulas (PE-10 fused to PE-50) were inserted into the femoral artery for blood pressure monitoring. Some rats also received femoral venous cannulas for intravenous drug administration. Cannulas were filled with heparin–saline solution (500 U/ml), tunneled subcutaneously to the back, externalized between the scapulae, and fixed in position. After the implantation of chronic cannulas, animals were transferred to individual cages. On the following day, a cannula (PE-10) for intracerebroventricular drug administration was placed stereotaxically into the lateral ventricle through a hole drilled in the skull (1.5 mm lateral, 1.0 mm posterior to bregma and 4.0 mm below the surface of the skull) and fixed to the skull with screws and dental cement. After an interval of at least 24 hr experiments were carried out in conscious, unrestrained rats.

In a first series of animals, blood pressure responses to muscimol, a GABA agonist, and bicuculline, a GABA antagonist, were examined in both groups of rats. Mean arterial pressure (MAP) was continuously recorded via a Model CP-01 pressure transducer (Century Technology Company, Inglewood, Calif.) coupled to a Grass Model 5 polygraph. After MAP had stabilized, muscimol (50, 250, 500, and 1000 ng/300 g) or bicuculline (3 μg/300 g) was injected into the lateral ventricle. Muscimol (1000 ng/300 g) or bicuculline (3 μg/300 g) was also administered intravenously (IV) in a separate set of animals.

In a second series of animals, the effect of clonidine on blood pressure was examined. After MAP was stable, clonidine (5 μg/300 g) was injected into the lateral ventricle and the maximum decrease in MAP was recorded.

In a third series of animals, responses of plasma norepinephrine and epinephrine concentrations to muscimol were measured as an index of peripheral sympathetic nervous system activity. Tubing was connected with the arterial cannula and at least 1 hr was allowed to pass before the first sampling. In one group of rats, blood (0.5 ml) for catecholamine assay was collected 1 hr before and 15–20 min after injection of muscimol (1000 ng/300 g, ICV) or an equal volume of vehicle. In the other group of rats, blood (0.5 ml) was collected 5–10 and 60 min after muscimol or vehicle administration. Animals were unrestrained, and only resting animals were sampled. The blood withdrawn was immediately replaced with an equal volume of 0.9% saline and only two samples (total 1.0 ml) were obtained from each animal. All animals were sampled at the same time of the day under the same environmental conditions to avoid the influences of diurnal variation and ambient temperature on plasma catecholamines.

Blood samples for catecholamines were collected in iced tubes containing EGTA (90 mg/ml) and glutathione (60 mg/ml). Blood was immediately centrifuged at 4°C. Plasma was stored at −80°C until assay. Plasma norepinephrine and epinephrine were measured by a modification of the radioenzymatic assay of Peuler and Johnson (15). Throughout these experiments, 10 μl of either drug or vehicle solution was injected with a Hamilton syringe and only one treatment was administered in each animal. At the end of each experiment, the ICV injection site was confirmed by the presence of injected dye in the appropriate ventricular cavity.

The following drugs were used: muscimol (Sigma Chemical Company, St. Louis, Mo.) was dissolved in 0.9% saline solution. Bicuculline (Sigma) was dissolved in 0.01 *N* HCl, brought to volume with 0.9% saline and the pH adjusted to 5.0–6.0 before injection. Normal (0.9%) saline was used as a vehicle control.

**Statistics.** Results were expressed as means ± SEM. Statistical evaluation of the effects of the drugs on blood pressure was made using analysis of variance (ANOVA) and Duncan's New Multiple Range test. Student's unpaired *t* test was used to compare plasma values. Significance was taken at the $P < 0.05$ level.

**Results.** Baseline MAP in 4 week DOCA/NaCl rats was significantly higher than in con-

trols (169 ± 2 mm Hg DOCA/NaCl, $n = 40$ vs 122 ± 1 mm Hg control, $n = 40$, $P < 0.01$). Body weight in DOCA/NaCl rats was less than in controls (279 ± 4 g DOCA/NaCl, $n = 40$ vs 299 ± 5 g control, $n = 40$, $P < 0.01$). ICV injection of saline vehicle (10 μl) had no effect on MAP in either group (Figs. 1 and 2). ICV administration of muscimol caused a dose-dependent decrease in MAP in DOCA/NaCl hypertensive (Fig. 1) and control rats (Fig. 2). Maximal depressor effects of muscimol were seen between 10 and 20 min after administration of the drug. The maximal depressor effect of muscimol expressed as both absolute and percentage change from baseline was significantly greater in DOCA/NaCl rats than in controls (muscimol 250 ng/300 g ICV: DOCA/NaCl vs control, absolute change, $P < 0.05$ and muscimol 500, 1000 ng/300 g ICV: DOCA/NaCl vs control, absolute as well as percentage change, $P < 0.01$, respectively, unpaired $t$ test; Fig. 3). In contrast to ICV injection, IV administration of muscimol (1000 ng/300 g) had no effect on MAP in either group.

ICV injection of bicuculline (3 μg/300 g) caused a sharp rise in MAP which had a latency of 10–30 sec, reached a maximum at 1 min and returned to preinjection levels within 5 min. The absolute and percentage change in MAP following bicuculline administration were nearly the same in both groups (Fig. 4).

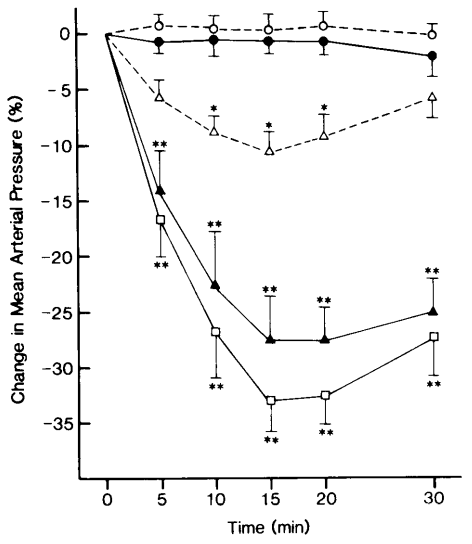


FIG. 1. Effect of muscimol on mean arterial pressure in DOCA/NaCl hypertensive rats. (○) vehicle, (●) 50 ng, (△) 250 ng, (▲) 500 ng, and (□) 1000 ng/300 g body wt of muscimol. Values represent means of eight rats in each group. Bar indicates SEM. *$P < 0.05$ and **$P < 0.01$, as compared with the control vehicle values.

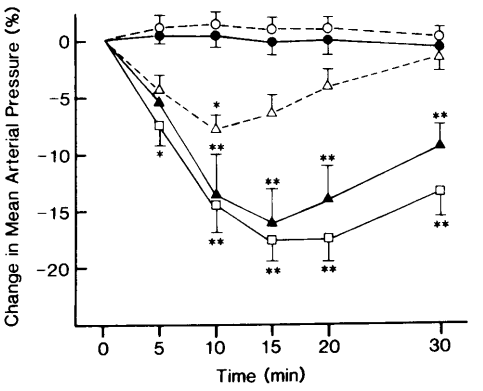


FIG. 2. Effect of muscimol on mean arterial pressure in control rats. (○) vehicle, (●) 50 ng, (△) 250 ng, (▲) 500 ng, and (□) 1000 ng/300 g body wt of muscimol. Values represent means of eight rats in each group. Bar indicates SEM. *$P < 0.05$ and **$P < 0.01$, as compared with the control vehicle values.

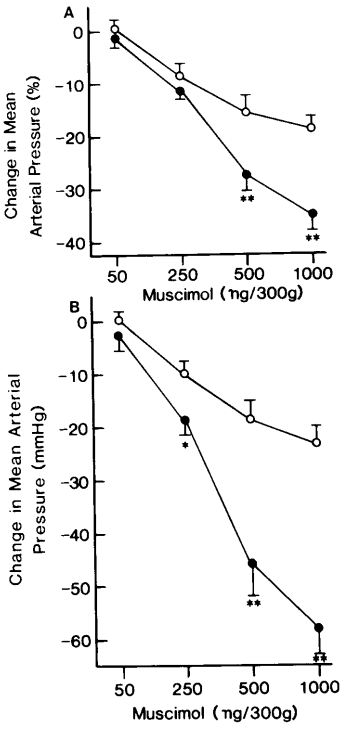


FIG. 3. Maximal percentage change (A) and absolute change (B) in mean arterial pressure with various doses of muscimol in DOCA/NaCl hypertensive rats (●) and control rats (○). Bar indicates SEM. *$P < 0.01$ and **$P < 0.05$, as compared with control rats.

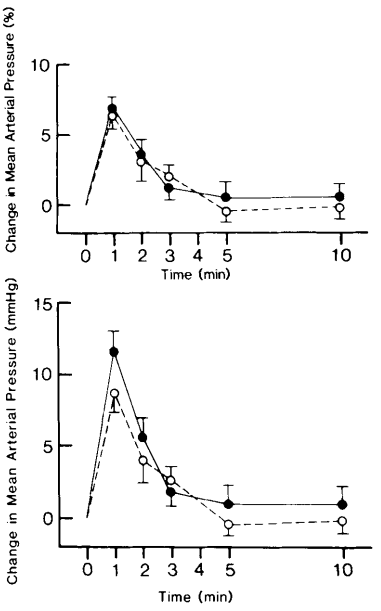


FIG. 4. Effect of bicuculline (10 μg/kg, ICV) on mean arterial pressure in DOCA/NaCl hypertensive rats (●) and control rats (○). Values represent means of eight rats in each group. Bar indicates SEM.

Higher doses of bicuculline (>6 μg/300 g), which would have been expected to produce a more marked elevation in blood pressure, could not be used because they were associated with hyperkinesis and seizure activity. In contrast to ICV injection, IV administration of bicuculline (3 μg/300 g) had no effect on MAP in either group.

Maximal percentage and absolute decreases in MAP in response to clonidine (5 μg/300 g) were significantly greater in DOCA/NaCl hypertensive rats than in controls (18.6 ± 2.4% and 30.3 ± 3.5 mm Hg in DOCA/NaCl hypertensive rats ($n = 8$) vs 10.8 ± 2.2% and 12.4 ± 2.3 mm Hg in control rats ($n = 8$), $P < 0.05$ and $P < 0.01$, unpaired $t$ test). The depressor response to 5 μg/300 g of clonidine was not significantly different than the response to 500 ng/300 g of muscimol in either the hypertensive or control group ($0.25 > P > 0.10$, ANOVA).

Baseline concentrations of plasma NE and EP in DOCA/NaCl hypertensive rats were significantly higher than in controls ($P < 0.01$ and $P < 0.05$, respectively; Table I). ICV injection of saline vehicle had no significant effect on plasma NE or EP in either group. Muscimol administration (1000 ng/300 g, ICV) did not change plasma NE levels, but significantly reduced plasma EP levels in both groups. The absolute decrease (154 ± 33 vs 49 ± 22 pg/ml: DOCA/NaCl vs control, $P < 0.05$)

TABLE I. THE EFFECT OF MUSCIMOL (1000 ng/300 g, ICV) ON PLASMA NOREPINEPHRINE AND EPINEPHRINE IN UNINEPHRECTOMIZED CONTROL RAT AND DOCA/NaCl HYPERTENSIVE RAT

| | Time (min) | | | |
|---|---|---|---|---|
| | 0 | 5 | 15 | 60 |
| Plasma norepinephrine | | | | |
| Uninephrectomized control rat | | | | |
| Vehicle | 276 ± 19 (10) | 291 ± 36 (8) | 286 ± 36 (10) | 289 ± 35 (8) |
| Muscimol | 252 ± 27 (10) | 340 ± 31 (8) | 293 ± 29 (10) | 347 ± 38 (8) |
| DOCA/NaCl hypertensive rat | | | | |
| Vehicle | 456 ± 48 (10)** | 453 ± 67 (8)* | 491 ± 57 (10)** | 438 ± 51 (8)* |
| Muscimol | 410 ± 46 (10)** | 474 ± 45 (10)* | 464 ± 44 (10)** | 423 ± 62 (10) |
| Plasma epinephrine | | | | |
| Uninephrectomized control rat | | | | |
| Vehicle | 86 ± 26 (10) | 119 ± 15 (8) | 153 ± 23 (10) | 145 ± 23 (8) |
| Muscimol | 112 ± 25 (10) | 97 ± 19 (8) | 55 ± 15 (10)†† | 107 ± 24 (8) |
| DOCA/NaCl hypertensive rat | | | | |
| Vehicle | 226 ± 46 (10)* | 192 ± 43 (8) | 279 ± 47 (10)* | 244 ± 53 (8) |
| Muscimol | 229 ± 39 (10)* | 75 ± 14 (10)† | 76 ± 18 (10)†† | 74 ± 20 (10)† |

*Note.* Results are shown as means ± SEM. Number of animals is indicated in parentheses.
* $P < 0.05$ and ** $P < 0.01$ as compared to control rat.
† $P < 0.05$ and †† $P < 0.01$ as compared to saline vehicle.

and the percentage decrease (36 ± 6 vs 16 ± 5%: DOCA/NaCl vs control, $P < 0.05$) in circulating EP from preinjection levels at 15 min after muscimol injection, a time when the depressor effect of the drug was near maximal, were significantly greater in DOCA/NaCl hypertensive rats than in controls.

**Discussion.** The present study demonstrates that injection of the GABA agonist muscimol into the lateral ventricle of the conscious, unrestrained DOCA/NaCl hypertensive rat and normotensive uninephrectomized control animals in doses which do not alter blood pressure when administered peripherally causes a dose-dependent depressor response and a fall in plasma EP. Both the depressor and the EP lowering effects of ICV muscimol and the depressor response to ICV clonidine are enhanced in the 4 week DOCA/NaCl treated animals compared to controls. Data from this and other studies indicate that the activity of the sympathetic nervous system is increased at this stage in DOCA/NaCl hypertension (10–12). Our results suggest that the increased sympathetic tone observed in rats with established DOCA/NaCl hypertension, which makes a substantial contribution to maintenance of the hypertension, may be related to altered central GABAergic activity.

The depressor action of muscimol observed in the current study appears to be a result of central GABAergic activation, as previously reported in rat and cat (9, 16), since IV injection of muscimol at the dose which gave the maximal depressor response when given ICV had no effect on MAP. Further, pretreatment with the GABA antagonist bicuculline has been reported to prevent the depressor action of muscimol in rat and cat (9, 15). Similarly, the pressor action of bicuculline administered ICV appears to result from inhibition of the central GABAergic system, since IV injection of the same dose of bicuculline had no effect on MAP. Previous studies have suggested that the GABA agonists injected into the lateral ventricle act on the hindbrain, particularly at the intermediate area on the ventral surface of the medulla oblongata, to decrease blood pressure and sympathetic outflow to the vasculature (7, 9, 17). In contrast, GABA antagonists injected into the lateral ventricle have been reported to act on the forebrain to increase blood pressure and sympathetic outflow (7, 18). Therefore, our observation that the depressor effect of muscimol is greater in DOCA/NaCl hypertensive rats than in controls gives indirect evidence that the activity of the GABAergic system in hindbrain of DOCA/NaCl hypertensive rats may be different from controls. Our observation that bicuculline gave rise to a pressor response is consistent with previous reports (7, 18). Since the dose of bicuculline which we could administer ICV in this study was limited by the development of hyperkinesis and seizures in both DOCA/NaCl treated and control rats, we could not obtain a complete set of dose–response curves for the pressor effect of this agent in conscious, freely moving rats. Therefore, our data do not rule out a differential effect of bicuculline and, therefore, different levels of activity of the GABAergic system in the forebrain of DOCA/NaCl rats vs controls.

In the current study, we observed that the depressor responses to muscimol and clonidine were enhanced to a comparable extent in DOCA/NaCl hypertensive rats compared to controls. These results are compatible with the interpretation that both agents exert their depressor effects in the DOCA/NaCl hypertensive rat, which has increased basal sympathetic activity, by decreasing sympathetic outflow.

In our experiments, ICV administration of muscimol produced a significant reduction in plasma EP in both groups, greater in DOCA/NaCl hypertensive rats than in controls, but did not alter plasma NE levels in either group. Basal levels of plasma NE and EP in DOCA/NaCl hypertensive rats were higher than in controls, suggesting that the DOCA/NaCl hypertensive rat has enhanced sympathetic nervous system activity, as previously reported (10–12). Evidence from other laboratories, including the observation of a depression in spontaneous renal and splanchnic sympathetic discharge following muscimol administration, supports the interpretation that the depressor effect of muscimol is related to a reduction in sympathetic outflow (8, 9). Our finding of unaltered plasma NE after muscimol administration does not exclude that interpretation, since plasma NE is an imperfect index of sympathetic nervous system activity (19).

The ventral surface neurons of the medulla, which represent a target area for GABA and muscimol, have been reported to connect the nucleus tractus solitarius and the cell bodies of preganglionic sympathetic neurons in the

intermediolateral cell column of the spinal cord. The adrenal medulla receives preganglionic sympathetic projections directly from cells in the intermediolateral cell column of the spinal cord (4, 7, 16). Thus the reduction in circulating epinephrine levels is most likely a direct reflection of decreased adrenal medullary discharge secondary to reduced sympathetic outflow following muscimol administration. Further, Unger *et al.* (8) reported that ICV administration of muscimol to stroke prone spontaneously hypertensive rats depressed plasma EP, but not plasma NE, and induced a greater decrease in adrenal efferent nerve activity than in splanchnic efferent nerve activity. These findings suggest that the antihypertensive action of central GABA receptor stimulation is associated with selective suppression of sympathoadrenal activity. It is likely, therefore, that the enhanced reduction in plasma EP observed after ICV administration of muscimol in DOCA/NaCl hypertensive rats compared to controls reflects a greater reduction in sympathetic outflow, which accounts for the exaggerated depressor effect of the GABA agonist in this hypertensive model.

An exaggerated depressor response to muscimol has previously been reported in a genetic model of hypertension, the spontaneously hypertensive rat of the Okamoto strain (SHR) compared to the normotensive Wistar–Kyoto (WKY) control strain (8, 20, 21). Both SHR and WKY showed increases in plasma EP and NE in association with the fall in MAP following IV administration of muscimol. The apparent inconsistency in responses of plasma catecholamines to muscimol administration between our data and those of Feuerstein *et al.* (20) may be due to differences in experimental design, such as dose and route of drug administration, and in the model of hypertension studied. The observation of an enhanced depressor response to muscimol in both the SHR and the DOCA/NaCl hypertensive rat supports the concept that GABAergic activity may be altered in more than one form of systemic hypertension. Further studies, including assessments of GABA receptor density and affinity and of GABA turnover in brain, are needed to fully assess the role of the sympathoadrenal system in the depressor response to muscimol. Such information is critical to our understanding of the role of central GABAergic pathways in the control of sympathetic outflow and, thereby, of cardiovascular homeostasis in the normal animal and in systemic hypertension.

The authors thank Ms. Cindy Yarbrough for excellent technical assistance and Ms. Vicky Chastain for her help in preparation of the manuscript.

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Received December 19, 1984. P.S.E.B.M. 1985, Vol. 180.
Accepted June 13, 1985.