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# Dopaminergic Modulation of Renin Activity and Aldosterone and Prolactin Secretion in the Spontaneously Hypertensive Rat (40923)[1]

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*Abstract.* The effect of metoclopramide, a dopamine antagonist, and L-dopa on plasma aldosterone (PA), plasma renin activity (PRA), and plasma prolactin (PRL) was studied in eight spontaneously hypertensive rats (SHR) and eight Wistar–Kyoto normotensive rats (WKY). Basal PRL levels were greater ($P < 0.005$) in the SHR (24.3 ± 1.0 ng/ml) than in the WKY (13.7 ± 0.7 ng/ml). Baseline PA in the SHR (49.9 ± 7.2 ng/dl), although higher, were not statistically different from those in the WKY (38.0 ± 7.0 ng/dl). Basal PRA in the SHR (11.0 ± 0.6 ng/ml $hr^{-1}$) was not different from that of WKY (11.4 ± 0.8 ng/ml $hr^{-1}$). Although both groups of rats displayed significant PA, PRA, and PRL responses to metoclopramide the responses were greater ($P < 0.01$) in the SHR. These responses to metoclopramide remained exaggerated even after the rats were pretreated with L-dopa. However, administration of L-dopa resulted in similar suppression of all three hormones in the SHR and in the WKY. These findings suggest that there is altered dopaminergic modulation of secretion of PA, PRA, and PRL in the SHR. Alterations in peripheral and central dopamine control of hormone secretion may play a role in the pathogenesis of essential hypertension in the SHR.

Spontaneously hypertensive rats (SHR) are regarded as a good animal model for the investigation of human essential hypertension (1, 2). Hypertension in SHR is hemodynamically similar to essential hypertension, both resulting ultimately from increased peripheral vascular resistance. Various pathogenesis mechanisms of hypertension in this model have been studied. Alterations in central neurotransmitters and the hypothalamic–pituitary axis have been described (3–5). There is evidence of heightened sympathoadrenal activity, particularly at 1–3 months of age when blood pressure in these animals is rising rapidly (6–8). There is also evidence that exaggerated cardiovascular and hormonal responses to environmental stimuli may play a role in development of hypertension in SHR (5, 8, 9).

Levodopa and the dopamine agonist bromocriptine have been reported to cause significant depression of blood pressure in human essential hypertension (10, 11) and in SHR (12, 13). It was concluded that the hypotensive mechanism of dopamine agonists involved a central effect of depressing sympathetic nerve activity or prolactin secretion (11, 12). Recent studies in the rat (14), and in man (15–18) suggest that there is dopaminergic modulation of aldosterone secretion. In order to investigate a possible alteration in dopaminergic control of aldosterone secretion in SHR, we have compared the effects of metoclopramide, a dopamine antagonist (19), on plasma renin activity (PRA) and plasma aldosterone (PA) in SHR and Kyoto–Wistar controls. We have also studied the effect of preadministration of levodopa on metoclopramide-induced changes in PRA and PA in both groups of rats.

*Materials and methods.* Spontaneously hypertensive (SHR) and normotensive male rats weighing 200–225 g were maintained at 23° on a light–dark cycle of 14:10, fed Purina rat chow, and watered *ad libitum*. A 25-cm polyethylene catheter (PE 50) was inserted into the left common carotid artery under Nembutal anesthesia as previously described (5). The catheters were exteriorized and kept patent by flushing with heparinized saline. Studies were conducted 48 hr after surgery, all samples were 200 μl, and volume was maintained with 0.9%

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saline replacement. Hormone levels were measured in response to a 200 $\mu$l intraarterial bolus of 0.9% saline, or of 200 $\mu$g/kg metoclopramide, or of 30 mg/kg L-dopa, or metoclopramide in combination with L-dopa given 30 min prior to metoclopramide. Collections were made at −30, 0, 5, 10, 15, 30, and 45 min.

PRA and PA were performed by RIA as previously described using [$^{125}$I]iodoangiotensin I and [$^{3}$H]aldosterone obtained from New England Nuclear Corporation, Boston, Mass. (20, 21). The coefficients of variation were 6% within assay and 15% interassay for PRA and 6% within assay and 14% interassay for PA. Plasma PRL was measured by double-antibody RIA using reagents provided by NIAMDD with PRL RP-1 serving as the reference preparation (5). Potassium was measured by atomic absorption spectrophotometry. Hormonal responses to metoclopramide and L-dopa were evaluated with paired *t* tests and group comparisons were made by multivariant analysis (22).

Mean arterial blood pressures were measured using a physiograph pressure transducer with recorder. These measurements were performed at times of blood sampling after administration of metoclopramide.

*Results.* Mean arterial blood pressure (MAP) prior to metoclopramide administration was greater ($P < 0.001$) in the SHR (161 ± 20 mm Hg) than for the Wistar–Kyoto rats (108 ± 8 mm). The MAP in both groups of rats did not change significantly from 5 through 45 min after metoclopramide. Baseline PA in the SHR (49.9 ± 7.2 ng/dl), although higher, was not statistically different from baseline values in the normotensives (38.7 ± 7.0 ng/dl) (Fig. 1). At sampling times 5 through 45 min after metoclopramide administration the PA was elevated ($P < 0.005$) above the baseline values in both groups (Fig. 1). There was no significant increase in PA in either groups after the sham (saline) injection and blood sampling with volume (saline) replacement (Fig. 1). There were significantly greater ($P < 0.01$) PA responses in the SHR than the normotensives at 15, 30, and 45 min after metoclopramide.

Baseline PRA in the SHR (11.0 ± 0.6 ng/ml hr$^{-1}$) (Fig. 2). Injection of a bolus of saline (sham) did not significantly increase PRA in either group. PRA after metoclopramide was elevated($P < 0.01$) above baseline values in the SHR at 10 min and in

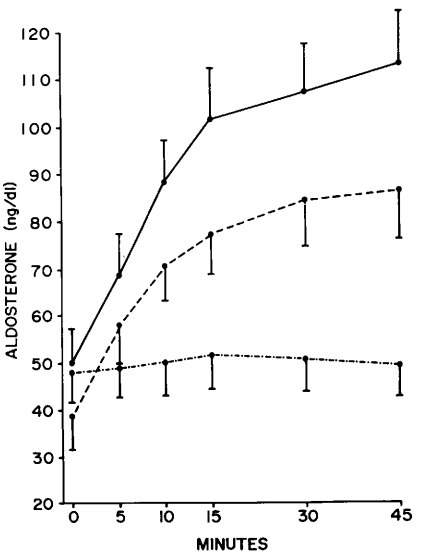


FIG. 1. Mean plasma aldosterone response to metoclopramide in eight SHR (——) and in eight normotensive Wistar–Kyoto rats (– – –), and to a sham (saline) injection in eight SHR (– · –). Vertical bars represent SEM.

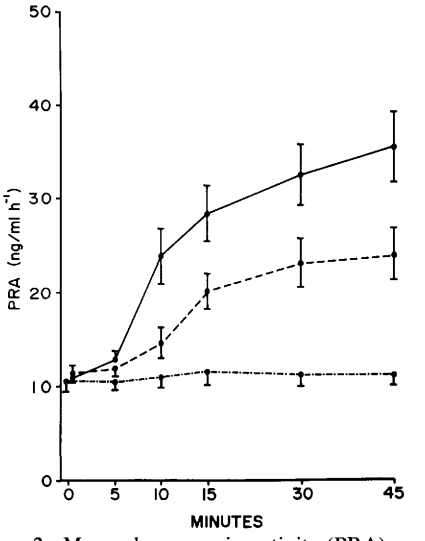


FIG. 2. Mean plasma renin activity (PRA) response to metoclopramide in eight SHR (——) and in eight normotensive Wistar–Kyoto rats, and to a sham (saline) injection in eight SHR (– · –). Vertical bars represent SEM.

both groups at 15, 30, and 45 min. The PRA response to metoclopramide was greater ($P < 0.01$) for the SHR than for the Wistar normotensives at 10 through 45 min.

Baseline PRL was higher ($P < 0.005$) in the SHR (24.3 ± 1.0 ng/ml) than the Wistar normotensives (10.4 ± 0.7 ng/ml) (Fig. 3). There was a significant ($P < 0.05$) PRL elevation in both groups at 5 min, and maximal PRL responses in the SHR (71.8 ± 8.1 ng/ml) and the controls (35.0 ± 4.6 ng/ml) occurred at 10 min after metoclopramide administration. Prolactin responses to metoclopramide were similar for the SHR and the controls at all sampling times from 5 through 45 min after metoclopramide.

Administration of L-dopa depressed PA in both groups of rats from 5 through 45 min and the suppression was similar in both groups (Fig. 4). PRA suppression was also similar for both groups. However, PRA was not suppressed until 10 min after L-dopa administration in the two groups. In both groups PRL was suppressed to approximately 50% of baseline values at 15 min and remained 50% suppressed through 45 min following L-dopa administration.

Plasma aldosterone, PRA, and PRL were suppressed 30 min after L-dopa administration (Table I). Preadministration of L-dopa

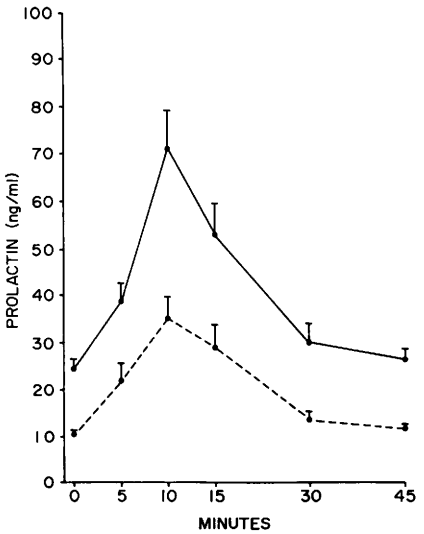


FIG. 3. Mean prolactin responses to metoclopramide in eight SHR (——) and in eight normotensive Wistar–Kyoto rats (– – –). Vertical bars represent SEM.

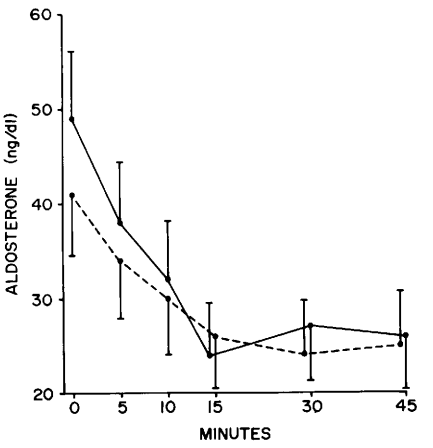


FIG. 4. Mean plasma aldosterone responses to L-dopa in eight SHR (——) and eight normotensive Wistar–Kyoto rats (– – –). Vertical bars represent SEM.

significantly ($P < 0.05$) blunted the metoclopramide-induced PRA response to metoclopramide (Table I, Fig. 2). In contrast, the PA response to metoclopramide after L-dopa was not significantly different from metoclopramide alone (Table I, Fig. 1). During L-dopa treatment, the SHR manifested greater ($P < 0.05$) PA and PRA responses to metoclopramide than the Wistar normotensives. The PRL responses to metoclopramide was blunted ($P < 0.001$) in both groups at each sampling interval from 5 through 45 min following preadministration of L-dopa (Table I, Fig. 3). The PRL response to metoclopramide remained similar in the two groups after L-dopa pretreatment. Potassium levels did not change after administration of metoclopramide or L-dopa.

*Discussion.* In this investigation, blockade of dopamine receptors by metoclopramide resulted in a prompt and marked increase in plasma aldosterone in both SHR and Wistar normotensive rats. This PA response preceded increases in PRA and paralled increases in plasma PRL. However, it is unlikely that the rise in PRL stimulated aldosterone secretion since metoclopramide can increase PA in hypophysectomized subjects (16). Our observation that PA elevations after metoclopramide and depressions after L-dopa oc-

TABLE I. MEAN (±SEM) PLASMA ALDOSTERONE, PRA, AND PLASMA PRL RESPONSE TO METOCLOPRAMIDE (GIVEN AT 0 TIME AFTER PREADMINISTRATION OF L-DOPA 30 min PRIOR TO METOCLOPRAMIDE) IN EIGHT SPONTANEOUSLY HYPERTENSIVE RATS (SHR) AND EIGHT WISTAR NORMOTENSIVES

| SHR | Min | −30 | 0 | 5 | 10 | 15 | 30 | 45 |
|---|---|---|---|---|---|---|---|---|
| Aldosterone (ng/dl) | | 50.0 ± 7.4 | 40.6 ± .2 | 58.8 ± 8.8 | 80.5 ± 9.6 | 103.0 ± 10.8 | 112.0 ± 11.4 | 112.4 ± 11.4 |
| PRA (ng/ml hr$^{-1}$) | | 10.7 ± 0.9 | 8.6 ± 1.0 | 10.6 ± 1.1 | 15.9 ± 1.6 | 17.7 ± 1.8 | 19.1 ± 2.2 | 21.2 ± 2.0 |
| PRL (ng/ml) | | 26.8 ± 1.3 | 17.2 ± 1.4 | 22.5 ± 1.5 | 29.0 ± 1.4 | 37.2 ± 3.1 | 40.5 ± 4.1 | 45.1 ± 5.4 |
| Normotensives | | | | | | | | |
| Aldosterone (ng/dl) | | 37.8 ± 7.2 | 28.4 ± 5.2 | 43.2 ± 7.3 | 61.8 ± 8.9 | 74.4 ± 8.9 | 84.4 ± 10.0 | 86.8 ± 10.0 |
| PRA (ng/ml hr$^{-1}$) | | 10.8 ± 0.8 | 8.4 ± 0.7 | 9.9 ± 1.2 | 11.4 ± 1.4 | 13.2 ± 1.6 | 13.2 ± 1.6 | 13.2 ± 1.5 |
| PRL (ng/ml) | | 13.7 ± 1.1 | 9.5 ± 0.8 | 3.7 ± 0.5 | 4.5 ± 0.6 | 10.0 ± 1.0 | 12.3 ± 1.1 | 12.9 ± 1.2 |

curred prior to changes in PRA suggests that dopaminergic control of aldosterone occurs independent of the renin–angiotensin system. Recent *in vitro* studies have demonstrated that dopamine has a direct effect on adrenal cells since it inhibited angiotensin-stimulated aldosterone biosynthesis (23). The more delayed effect of dopamine agonists and antagonists on PRA may reflect an indirect dopaminergic control mechanism for renin secretion. The decrease in PRA in response to L-dopa can be blocked by acute renal sympathetic denervation (24). L-Dopa administration results in a reduction in efferent sympathetic nervous activity, presumably due to an increase in central nervous system (CNS) catecholamine content (6). These findings suggest that dopaminergic control of renin secretion may be modulated through alterations in sympathetic outflow from the CNS.

The results of the present study suggest that dopaminergic control of both renin and aldosterone secretion is altered in the SHR. Compared to normotensive Wistar controls the SHR display exaggerated rises in PRA and PA after dopamine antagonism with metoclopramide. It is well established that the noradrenergic component of the sympathetic nervous system increases renin secretion, probably by stimulation of intrarenal $\beta$-adrenoreceptors (25). Similarly, recent evidence has been presented that both norepinephrine and epinephrine increase aldosterone secretion by stimulation of both $\alpha$- and $\beta$-adrenoreceptors (26). Thus, it appears that the dopaminergic and noradrenergic components of the sympathetic nervous system act as opposing influences in the control of renin and aldosterone secretion. In the SHR with its greater sympathetic nervous system activity, removal of the dopaminergic control after metoclopramide administration would allow unopposed stimulation of PRA and PA by the overactive noradrenergic component of the sympathetic nervous system. Alternatively, exaggerated PRA and PA responses to a dopamine antagonist such as metoclopramide may reflect greater sensitivity to the effects of dopamine in the SHR. A greater sensitivity to dopamine could result from

decreased levels of dopamine and lesser occupancy of dopamine receptors centrally and at the adrenal glomerulosa. However, our observation that L-dopa depressed PRA and PA to the same extent in both groups of rats would be against the latter explanation.

The basal PA levels were slightly higher in the SHR, which is in agreement with another recent report (9). However, there was no statistical difference in these levels because of the small numbers of animals in each group. These slightly higher levels of PA, despite normal PRA, could be explained on the basis of relatively greater counterregulatory effects of the dopaminergic component of the sympathetic nervous system on renin release in the SHR. Age-related reductions in PRA in the SHR could also be explained by a compensatory increase in tonic inhibitory dopaminergic control in renin secretion in the older SHR. Thus, the high PRA in the early stages of development of hypertension in the SHR (27) could reflect generalized increases in sympathetic nervous activity. The normal to decreased PRA values noted in the SHR after development of sustained hypertention (27) may be related to the evolution of relatively greater tonic inhibitory dopaminergic control of renin secretion.

Higher basal PRL levels have been previously observed in the SHR and in patients with essential hypertension (4, 5, 7). As previously proposed, the hyperprolactinemic state in the SHR probably reflects decreased dopaminergic activity at the hypothalamic level (5). It is unlikely that elevated prolactin levels result in the altered aldosterone and renin secretion in response to dopamine antagonists. Rather, as previously proposed, hyperprolactinemia is probably a marker of altered central dopaminergic activity. The role of altered dopaminergic activity in the development of hypertension in the SHR remains to be elucidated. However, the results of a recent study demonstrate that treatment of SHR with bromocriptine for 3 weeks results in a 30% reduction in blood pressure from hypertensive to normotensive levels (13). It was proposed by these investigators that the reduction in blood pressure resulted from depression of the elevated PRL levels in the SHR. However, the results of the present study suggest that dopamine may partly exert its vasodepressor effects by tonically inhibiting both renin and aldosterone secretion in the SHR.

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