Central and Peripheral Effects of Dopamine on the Renin-Angiotensin-Aldosterone System in Conscious Rats

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To investigate the role of the central and peripheral dopaminergic systems in the control of the renin-angiotensin-aldosterone system in conscious rats, dopamine or its antagonist, metoclopramide, was injected intravenously (i.v.) and intracerebroventricularly (i.c.v.). Dopamine (100 $\mu\text{g/kg}$), when injected i.c.v., decreased plasma renin activity (PRA) and plasma aldosterone concentration (PA), while metoclopramide (50 $\mu\text{g/kg}$, i.c.v.) increased both of them. Intravenous administration of dopamine (1 $\mu\text{g/kg/min}$) did not produce significant changes in either PRA or PA. In contrast, metoclopramide (500 $\mu\text{g/kg}$, i.v.) increased PA, which was not accompanied by any change in PRA. Blood pressure was decreased by i.c.v. administration of dopamine and increased by i.c.v. injection of metoclopramide, whereas no change in blood pressure was observed when these compounds were administered i.v. Dopamine and metoclopramide, injected i.v. or i.c.v., did not produce significant changes in plasma sodium, potassium and corticosterone concentrations. These results suggest that the dopaminergic system in the brain regulates renin secretion, thereby changing PA. In contrast, dopamine receptors of the adrenal glands may inhibit aldosterone secretion, which is not mediated by changes in the renin-angiotensin system, plasma potassium and ACTH.

DURING the past few years considerable evidence has been accumulated supporting the role of dopamine as a neurotransmitter substance in the central nervous system as well as in the peripheral autonomic nervous system. However, the interaction between the dopaminergic system and the renin-angiotensin-aldosterone system is still under investigation. It was previ-

ously reported that renin secretion was increased by intravenously administered dopamine¹⁻³ but the direct effect of dopamine on renin secretion remains controversial⁴⁻⁶. In addition, recent studies have demonstrated that metoclopramide, the dopamine antagonist,^{7,8} stimulates aldosterone production in man, suggesting that dopamine participates directly in the regulation of aldosterone production⁹⁻¹¹. The dopaminergic system in the central nervous system is also involved in modulating the secretion of several hormones in a number of species,¹² but little is known concerning the role of the central dopaminergic mechanism in the regulation of the renin-angio-

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Fig.1. The effects of intravenous administration of dopamine and metoclopramide on plasma renin activity and plasma aldosterone concentration in conscious rats. The bars indicate SD. Statistical evaluation was performed with Student's t-test.

Fig.2. The effects of intracerebroventricular administration of dopamine and metoclopramide on plasma renin activity and plasma aldosterone concentration in conscious rats. The bars indicate SD. Statistical evaluation was performed with Student's t-test.

tensin-aldosterone system.

In this study, therefore, we studied the effects of intravenous (i.v.) and intracerebroventricular (i.c.v.) administrations of dopamine and metoclopramide on plasma renin activity (PRA) and plasma aldosterone concentration (PA) in conscious rats and tried to elucidate the contribution of the central and peripheral dopaminergic systems to the regulation of the renin-angiotensin-aldosterone system *in vivo*.

METHODS

All experiments were performed in male conscious unrestrained Wistar rats, weighing around 300 g. Cannulations of the lateral ventricle, carotid artery and jugular vein were performed under pentobarbital anesthesia (pentobarbital sodium, 50 mg/kg, intraperitoneally) according to the method of Hayden et al.¹³ After an interval of at least 24 hours the experiments were

started. Arterial blood pressure was recorded continuously through a catheter that had been implanted into the carotid artery with a Nihon Kodan MPU-0.5 pressure transducer coupled to a Nihon Kodan RM-25 recorder. The used drugs were dopamine hydrochloride (Sigma) and metoclopramide (Fujisawa). These drugs were dissolved or diluted in saline (0.9% w/v NaCl), and the pH and osmotic pressure of the final solutions were adjusted with 1 M NaOH and distilled water to 7.0 and 300 mOsm/L, respectively. These solutions were prepared just before injection.

Intravenous Administration. 1 µg/kg/min of dopamine was infused i.v. by a Harvard infusion pump and 500 µg/kg of metoclopramide was injected i.v. Thirty min after the injection or 30 min after the start of infusion, 1.5 ml of blood was obtained through the implanted catheter in

Fig. 3. The effects of intravenous (iv, an upper column) and intracerebroventricular (icv, a lower column) administration of dopamine and metoclopramide on plasma corticosterone concentration in conscious rats. The bars indicate SD.

the carotid artery into chilled test tubes. The volume injected or infused was always 0.3 ml. In the control rats the same volume of saline was injected i.v. 30 min before collecting the blood.

Intracerebroventricular Administration. 100 µg/kg of dopamine or 50 µg/kg of metoclopra-

mide was injected i.c.v. The volume of injection was 10 µl and the same volume of saline was injected in the control rats. Thirty min after the injection 1.5 ml of blood was collected as previously described.

Assay. Plasma renin activity (PRA) was measured by the method of Skinner,¹⁴ plasma aldosterone (PA) and corticosterone were measured by radioimmunoassay, and plasma sodium and potassium were measured with a flame photometer.

Six rats were examined in each study. Results were expressed as the mean ± SD. Comparisons were made by Student's t-test.

RESULTS

Effects of Intravenous Administration of Dopamine and Metoclopramide

Intravenous administration of dopamine did not induce significant changes in PA, and it slightly but not significantly increased PRA ($0.05 < p < 0.1$) (Fig. 1). Metoclopramide, when injected i.v., did not change PRA, whereas it significantly increased PA ($p < 0.05$). Both of these compounds did not produce significant changes in plasma sodium, potassium and corticosterone levels, as well as in blood pressure of conscious rats (the changes in mean blood pressure were less than 4 mmHg) (Fig. 3 and Table I).

Effects of Intracerebroventricular Administration of Dopamine and Metoclopramide

Intraventricular injection of dopamine decreased both PRA and PA ($p < 0.05$), while that of metoclopramide increased both PRA and PA ($p < 0.02$) (Fig. 2). These compounds, when injected i.c.v., did not produce significant change in plasma sodium, potassium and corticosterone levels (Fig. 3 and Table I). The blood pressure of

TABLE I THE EFFECTS OF INTRAVENOUS (iv) AND INTRACEREBROVENTRICULAR (icv) ADMINISTRATION OF DOPAMINE AND METOCLOPRAMIDE ON PLASMA SODIUM AND POTASSIUM LEVELS.

		Na (mEq/L)	K (mEq/L)
Control	iv	139 ± 2	4.2 ± 0.2
	icv	140 ± 2	4.1 ± 0.2
Dopamine	iv (1 µg/kg/min)	137 ± 3	4.0 ± 0.3
	icv (100 µg/kg)	139 ± 3	4.2 ± 0.2
Metoclopramide	iv (500 µg/kg)	140 ± 3	4.1 ± 0.3
	icv (50 µg/kg)	138 ± 3	4.0 ± 0.3

Values represent the mean ± SD

conscious rats was transiently but significantly decreased by dopamine, and increased by metoclopramide (the changes in mean blood pressure induced by dopamine and metoclopramide were -8 ± 3 mmHg and $+9 \pm 2$ mmHg, respectively, $p < 0.01$).

DISCUSSION

Since Ayers et al.¹ first demonstrated that dopamine was a potent stimulus for renin release in the canine model of renovascular hypertension, a lot of studies have confirmed that i.v. administration of dopamine can increase renin secretion in a number of species.^{2,3} However, since dopamine activates both alpha and beta receptors as well as specific dopamine receptors, it is still controversial whether the effect of dopamine on renin secretion is mediated by dopamine receptors or beta adrenergic receptors.⁴⁻⁶ The role of endogenous dopaminergic system in the regulation of the renin-angiotensin system *in vivo* remains also unknown. In anesthetized dogs, Otuka et al.² observed that i.v. administration of dopamine resulted in an increase in PRA but only at concentrations which produced significant increases in systemic blood pressure. Similarly Wilcox et al.³ demonstrated that dopamine could induce renin release in man when given at pressor doses. In this study we infused i.v. the subpressor dose of dopamine and found that this dose of dopamine did not produce a significant increase in PRA. Furthermore, i.v. administration of metoclopramide, the dopamine antagonist, failed to induce any change in PRA. Therefore it is suggested that dopaminergic system in the systemic circulation plays, if any, a minor role in regulation of renin secretion in conscious rats.

We observed that i.v. administration of dopamine did not affect PA in rats. In contrast to dopamine, i.v. administered metoclopramide significantly increased PA. These results are in accordance with those obtained by Carey et al.^{9,10} and Noth et al.¹¹ in man. As well as in their studies, metoclopramide did not produce significant changes in PRA, plasma Na, K and corticosterone levels, indicating that the established mediators of aldosterone secretion, angiotensin II, potassium and ACTH, are not involved in the increase in aldosterone secretion induced by metoclopramide. Our results therefore suggest that, even in rats, aldosterone secretion may be under maximum tonic dopaminergic inhibition, and that metoclopramide acts by antagonizing this tonic inhibition.

In contrast to i.v. administration, i.c.v. injection of dopamine decreased both PRA and PA in conscious rats. Blair et al.¹⁵ revealed that i.v. administration of L-dopa with prior inhibition of extracerebral dopa decarboxylase by carbidopa in dogs produced significant decreases in PRA, suggesting that catecholamine formed within the central nervous system act to lower renin secretion. In contrast to the expectation, the same laboratory reported that direct injection of dopamine into the third ventricle of dogs increased rather than decreased renin secretion.¹⁶ This result is in contrast with our findings in rats. This discrepancy is probably due to the variability in experimental procedures and in animals used.

If endogenous dopaminergic systems in the brain contribute to the regulation of the renin-angiotensin-aldosterone system, i.c.v. administration of metoclopramide, the dopamine antagonist, should change this system in a direction opposite to that produced by exogenous dopamine. As shown in Fig. 2, this is indeed the case. We observed that i.c.v. administration of metoclopramide significantly increased both PRA and PA, indicating that the dopaminergic system in the brain is involved in the regulation of the renin-angiotensin-aldosterone system in rats.

In our study, i.c.v. administration of dopamine and metoclopramide failed to change plasma Na, K and corticosterone levels. The role of catecholamines in modulating the secretion of ACTH has been investigated by numerous workers with conflicting results. Van Loon et al.¹⁷ observed that adrenergic agents inhibited the stress-induced ACTH secretion when administered i.c.v. However, Abe et al.¹⁸ reported that the i.c.v. injection of biogenic amines resulted in an enhanced ACTH secretion in anesthetized and conscious rats, and speculated that brain amines are of relatively little importance in the central regulation of ACTH secretion in rats. Although we did not measure plasma concentration of ACTH, our findings seem to indicate that, at least in the doses used in this experiment, dopamine and metoclopramide do not affect the secretion of ACTH. It is therefore suggested that the dopaminergic system in the brain can regulate PA through modulating the renin-angiotensin system.

Our data presented in this study do not clarify the mechanism how the changes in the central dopaminergic system can affect renin secretion. Our preliminary experiments, however, revealed that the pretreatment with propranolol (1 mg/kg,

i.v.) significantly attenuated the effects of metoclopramide and dopamine on PRA, indicating that the autonomic nervous system (especially peripheral beta-receptors) is involved in changes in renin secretion induced by central administration of these substances. Further studies are necessary to elucidate the precise relationship between the central dopaminergic system and the peripheral autonomic nervous system.

In conclusion, our results suggest that the dopaminergic system in the brain regulates renin secretion, thereby changing PA. In contrast, dopamine receptors of the adrenal glands may inhibit aldosterone secretion, which is not mediated by changes in the renin-angiotensin system, plasma potassium and ACTH. It is therefore suggested that not only the peripheral but also the central dopaminergic system should be considered, when the changes in the renin-angiotensin-aldosterone system are discussed *in vivo*.

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