Further Studies on the Mechanisms of Blood Pressure Lowering Effect of L-DOPA and a Peripheral Decarboxylase Inhibitor in Hypertensive Rats

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Our previous results (Nakamura, Nakamura, and Mizogami: Jap J. Pharmacol 23: Suppl 17, 1973) indicated that combination of L-DOPA and a peripheral decarboxylase inhibitor (Ro 4-4602) markedly lowered the blood pressure (BP) in DOCA-salt rats (DH) more than did in spontaneously hypertensive rats and 3 types of normotensive rats: DOCA-treated rats, unilaterally nephrectomized, or untreated (N). No significant change in BP was observed in rats made hypertensive by clipping the renal artery and contralateral nephrectomy. The drugs markedly elevated dopamine and DOPA contents in the medulla-pons and dopamine contents in the hypothalamus of DH more than did in those of others. Involvement of dopaminergic neurons might be minimal, since destruction of dopaminergic neurons in the caudate nuclei with 6-hydroxydopamine did not change the fall in BP after L-DOPA and Ro 4-4602 in DH and N.

The present study was undertaken to clarify the mechanisms of fall in blood pressure of DOCA-salt hypertensive rats after L-DOPA and Ro 4-4602.

Methods: The BP was measured without anesthesia and restraint through a cannula intubated into the aorta of male Wistar rats made hypertensive by the intramuscularly given 10 mg/Kg of DOCA dissolved into dimethyl sulfoxide once a week and 0.9% NaCl solution as drinking water *ad libitum*, 1 week after uninephrectomy. For direct administration of drugs into the lateral ventricle, a cannula was implanted into the right lateral ventricle at least 1 week before the experiments. For investigating the effects on pressor response after electrical stimulation of the brainstem, the animals were anesthetized by urethane (500 mg/Kg, i.p.) and α -chloralose (50 mg/Kg, i.p.).

Results: The present studies indicated that BP lowering effect of L-DOPA (20 mg/Kg, i.p.) and Ro 4-4602 (50 mg/Kg, i.p.) in DH and normotensive rats was completely abolished by continuous infusion of phentolamine (40 μ g/10 μ l/h) or repeated administrations of diethyldithiocarbamate (200 μ g/2 μ l/15 min $\times$ 3) into the lateral ventricle through an implanted cannula. Neither phentolamine nor diethyldithiocarbamate alone exerted a change in BP.

Diethyldithiocarbamate significantly decreased norepinephrine contents in all brain regions except the caudate nucleus of both normotensive and DOCA-salt hypertensive rats. L-DOPA and Ro 4-4602 did not restore or prevent the reduction of norepinephrine levels. Direct application of Ro 4-4602 (100 μ g/10 μ l) into the lateral ventricle also prevented both blood pressure lowering effect and bradycardia after L-DOPA with blockade of peripheral decarboxylase.

Pressor responses were elicited by electrical stimulation (1 ms, 20–200 Hz, 1–2 V, 5 s) of the posterior hypothalamus, midbrain reticular formation and medulla oblongata in anesthetized normotensive and DH rats. L-DOPA and Ro 4-4602 slightly but significantly ($P < 0.05$) reduced the pressor responses in DH rats after electrical stimulation of the posterior hypothalamus and midbrain reticular formation but not of the medulla oblongata.

We failed to observe statistically significant depressor effect following local infusion of DA into areas of the medulla oblongata (2 ng/0.1 μ l/min), posterior hypothalamus (8 ng/0.1 μ l/min) or caudate nucleus (18 ng/0.1 μ l/min) in DH and normotensive rats. The doses of dopamine after its infusion for a period of 30 min were corresponded to accumulated amounts found in each area after L-DOPA and Ro 4-4602. Atropine (0.5 mg/Kg, s. c. $\times 3$) did not change the BP fall by L-DOPA and Ro 4-4602 but prevented the accompanied bradycardia.

In unanesthetized spinal rats, L-DOPA and Ro 4-4602 enhanced the bradycardia induced by electrical stimulation (5–40 Hz, 2 V, 0.1 ms) of the central cut-end of the cervical vagus but not the peripheral end. The induced bradycardia was abolished by section of the contralateral vagus.

Conclusion: The blood pressure lowering effect of L-DOPA and Ro 4-4602 in DOCA-salt hypertensive rats seemed to be induced by stimulation of α -adrenoceptor by newly formed norepinephrine from L-DOPA in the brainstem. The central vagal loop may be involved in occurrence of the bradycardia after L-DOPA and Ro 4-4602 in DOCA-salt hypertensive rats.