POTENTIATION OF THE EFFECT OF L-DOPA BY α-METHYLDOPA

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After preliminary administration of α-methyldopa to mice, the stereotypes induced by L-dopa were potentiated and prolonged. The ability of L-dopa to abolish catalepsy induced by reserpine and haloperidol also was potentiated. In cats, α-methyldopa potentiated the responses of the arterial blood pressure and contractions of the nictitating membrane induced by L-dopa and dopamine, if the interval between injection of the substances was 4-6 h.
KEY WORDS: *L-dopa; dopamine; α-methyldopa.*

The effectiveness of treatment of parkinsonism with L-dopa is enhanced by the use of α-methyldopa [1, 11]. Meanwhile, under experimental conditions, α-methyldopa, behaving as an inhibitor of dopa-decarboxylase and preventing the formation of dopamine from L-dopa, can abolish the vascular effects of L-dopa [3]. α-Methyldopa can pass relatively well through the blood-brain barrier so that it inhibits dopa-decarboxylase not only at the periphery, but also in brain tissue [7].

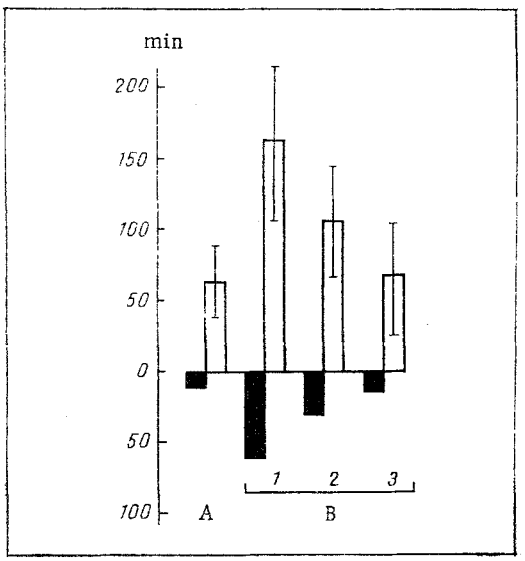

Fig. 1. Effect of α-methyldopa on latent period and duration of stereotypes induced by L-dopa. A) L-dopa 500 mg/kg; B) L-dopa 500 mg/kg after α-methyldopa 500 mg/kg. Interval between injections of drugs 30 min (1), 4 h (2), and 18 h (3). Shaded columns show mean values of latent period; unshaded columns show duration of stererotypes. Ordinate, time (in min).

The object of this investigation was to analyze the effect of α-methyldopa on central and peripheral effects of L-dopa.

EXPERIMENTAL METHOD

The effect of α-methyldopa on the duration of stereotypes induced by L-dopa in a dose of 500 mg/kg and also on the anticataleptogenic effect of L-dopa was studied in experiments on male mice weighing 20-24 g. Catalepsy was induced by reserpine or haloperidol in doses of 1.5 mg/kg. Catalepsy was evaluated quantitatively [2]. L-dopa was injected in doses of 150 and 500 mg/kg during the development of catalepsy: 4 h after injection of reserpine, and 1 h after injection of haloperidol. α-Methyldopa was injected in a dose of 500 mg/kg 30 min, and 4 and 18 h before injection of L-dopa. The choice of these times was determined by the characteristics of the pharmacodynamics of α-methyldopa: After 30 min inhibition of dopa-decarboxylase reached a maximum; after 4 h the decrease in the natural dopamine level and the accumulation of α-methyldopamine also reached a maximum. After 18 h only a small decrease in the natural noradrenalin level still remained [4]. The effect of α-methyldopa, injected 30 min before reserpine, on ED_{50} of reserpine as shown by

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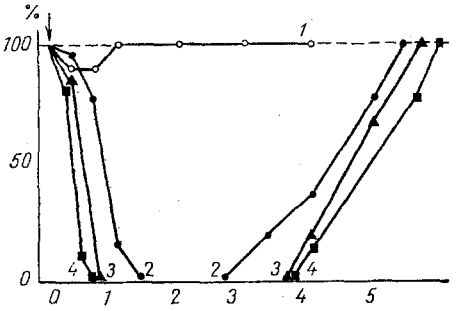

Fig. 2

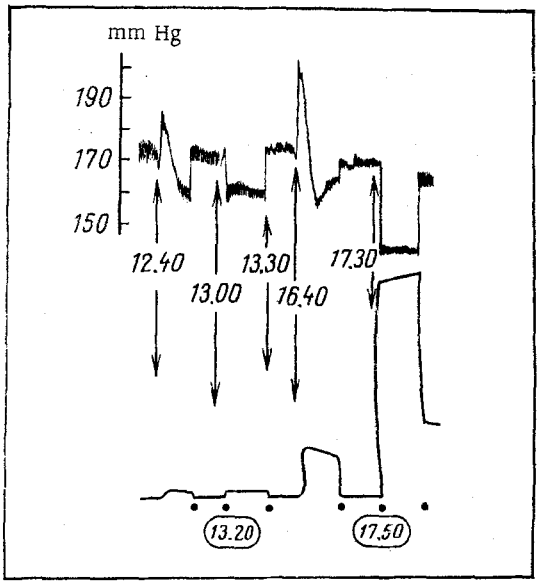

Fig. 3

Fig. 2. Effect of L-dopa and a combination of L-dopa with α-methyldopa on catalepsy induced by reserpine. Broken line shows level of catalepsy in control after injection or reserpine in a dose of 1.5 mg/kg (taken as 100%). Injection of L-dopa in a dose of 150 mg/kg 4 h after reserpine indicated by arrow. 1) Effect and duration of anticataleptogenic action of L-dopa; 2) the same after preliminary injection of α-methyldopa in a dose of 500 mg/kg 30 min after; 3) 4 h before, and 4) 18 h before injection of L-dopa. Abscissa, time (in h).

Fig. 3. Effect of α-methyldopa on reaction of arterial pressure (above) and of nictitating membrane (below) to dopamine and L-dopa. Arrows mark injection of preparations and time: 12.40 — dopamine 150 μg/kg, 13.00 — L-dopa 25 μg/kg, 13.30 — α-methyldopa 50 mg/kg, 16.40 — dopamine 150 μg/kg, 17.30 — L-dopa 25 mg/kg. Dots show times of stopping kymograph. Time of starting kymograph shown during recording effects of L-dopa.

the catalepsy test also was investigated. All preparations were injected intraperitoneally except haloperidol, which was injected subcutaneously, in volumes not exceeding 0.2 ml/10g body weight.

The effect of L-dopa and dopamine on the systemic blood pressure and tone of the nictitating membrane was assessed in experiments on cats anesthetized with urethane (500 mg/kg) and chloralose (50 mg/kg). Preganglionic fibers of the superior cervical ganglion were divided. After control intravenous injections of dopamine (50-300 μg/kg over a period of 30 sec in a volume of 0.5-1 ml) and L-dopa (10-30 mg/kg) and the return of the parameters studied to their initial level, α-methyldopa was injected intravenously (20-100 mg/kg). Injection of dopamine and L-dopa was repeated at time intervals of between 30 min and 6 h after injection of α-methyldopa. The L-dopa and α-methyldopa were dissolved before injection in 1 N HCl and neutralized with an equal volume of 1 N NaOH; the pH of the solutions injected ranged from 6 to 8.

EXPERIMENTAL RESULTS AND DISCUSSION

L-dopa, in a dose of 500 mg/kg, induced excitation in the mice 5-10 min after injection, manifested chiefly as stereotypes. The duration of the effect averaged 62 (35-89) min. α-Methyldopa under similar conditions lowered motor activity. If L-dopa was injected in a dose of 500 mg/kg 30 min after α-methyldopa in the same dose, the latent period of onset of the stereotypes was increased on the average to 1 h. However, the intensity of the subsequent stereotyped movements was increased and their mean duration was now 162 (107-217) min (Fig. 1).

α-Methyldopa in doses of 500-1000 mg/kg had a weak cataleptogenic action and potentiated the cataleptogenic action of reserpine. ED_{50} for reserpine by the test used in these experiments was 1.1 (0.9-1.3) mg/kg. After previous injection of α-methyldopa in a dose of 500 mg/kg 30 min before reserpine, ED_{50} for reserpine was reduced on average to 0.59 (0.41-0.77) mg/kg. Reserpine in a dose of 1.5 mg/kg induced catalepsy up to 24 h in duration. L-dopa in a dose of 150 mg/kg had a very weak anticataleptogenic action. After preliminary injection of α-methyldopa, the catalepsy was completely abolished in all animals (Fig. 2). L-dopa in a dose of 500 mg/kg completely abolished the catalepsy induced by reserpine. The effect lasted about 3 h. After preliminary administration of α-methyldopa the duration of the anticataleptogenic action of L-dopa was increased by 2-3 times. Haloperidol in a dose of 1.5 mg/kg induced catalepsy lasting 4-6 h, but it was more severe than the catalepsy induced by reserpine. L-dopa in a dose of 150 mg/kg had no anticataleptogenic action, but in a dose of 500 mg/kg it abolished the catalepsy in 30-40 min. After α-methyldopa, the anticataleptogenic action of L-dopa in a dose of 500 mg/kg was potentiated and prolonged.

Dopamine in a dose of 50-100 μg/kg caused a slight increase in arterial pressure and in the tone of the nictitating membrane. The effect continued for 5-10 min. In doses of 20-30 mg/kg, L-dopa initially caused elevation of the arterial pressure, which continued for a few minutes. However, the pressor response to these doses did not invariably occur, whereas the depressor response was observed constantly. It reached its maximum after 10-20 min, when it amounted to 10-40% of the initial level. The contraction of the nictitating membrane reached its maximum at this time. Doses of L-dopa equally effective with doses of dopamine on the tone of the nictitating membrane and arterial pressure were about 100-300 times greater than doses of dopamine. The duration of action of L-dopa was 1.5-2 h. Injection of α-methyldopa in doses of 20-50 mg/kg either had no effect on the arterial pressure or caused a weak pressor response (5-10% of the initial level), which could continue for 1-1.5 h. The tone of the nictitating membrane was unchanged. Injection of dopamine 30 min after α-methyldopa caused responses of the arterial pressure and nictitating membrane similar to those in the control. With an interval of 4-6 h between injections the response of the membrane was 2-3 times greater and the response of the arterial pressure 1.5-2 times greater. Injection of L-dopa 30 min after α-methyldopa caused no contraction of the nictitating membrane. The response of the arterial pressure was reduced or completely abolished. If the interval between injections was 4-6 h the response of the nictitating membrane was several times greater. The response of the arterial pressure was increased (Fig. 3). Frequently repeated injections of L-dopa in the same dose of 20-30 mg/kg at intervals of 2-2.5 h, sufficient to restore the original level, induced virtually identical changes of arterial pressure and contractions of the nictitating membrane.

These results point to the dual character of changes in the effects of L-dopa when preceded by α-methyldopa. When L-dopa was injected 30 min after α-methyldopa (at the height of inhibition of dopa-decarboxylase) the appearance of the central effects was delayed and the peripheral effects were abolished completely. A few hours after injection of α-methyldopa, after recovery of dopa-decarboxylase activity and accumulation of α-methyldopamine, the central and peripheral effects of L-dopa and also the peripheral effects of dopamine were intensified.

α-Methyldopa and α-methyldopamine had no inhibitory effect on monoamine oxidase or catechol-O-methyltransferase. Accordingly, potentiation of the action of L-dopa and dopamine by disturbances of the best-known pathways of their inactivation is improbable. Most of the dopamine formed from exogenous L-dopa is inactive [12]. One of the possible ways of rapid and very effective inactivation of exogenous catecholamines is by binding with pyridoxal phosphate to form a Schiff base [5, 8]. Not only free pyridoxal phosphate, but also the pyridoxal phosphate of many enzymes may evidently participate in this reaction [6, 9]. The α-methylated analogues of natural catecholamines also readily form Schiff bases with pyridoxal phosphate; in the case of interaction with pyridoxal phosphate of enzymes they evidently have advantages in this respect over natural catecholamines. This is shown, in particular, by the fact that in the presence of equimolar concentrations in vitro of α-methyldopa and L-dopa, no decarboxylation of L-dopa takes place [10]. Presumably α-methylated compounds, competing with natural catecholamines for pyridoxal phosphate, favor their preservation in a functionally active state. This mechanism probably lies at the basis of potentiation of the effects of L-dopa and dopamine by α-methyldopa.

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