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STUDIES ON THE MECHANISMS OF L-DOPA-INDUCED DEPLETION OF 5-HYDROXYTRYPTAMINE IN THE MOUSE BRAIN

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5-HT = serotonin

Summary

The administration of L-dopa to mice causes an increase in the brain concentrations of dopa and dopamine which is related temporally to a reduction in the brain concentration of 5HT. These effects occur concurrently with a reduction in the conversion of intravenously administered ^{3}H-tryptophan to ^{3}H-5HT without an alteration in the accumulation of ^{3}H-tryptophan in the brain. The L-dopa-induced changes in the brain concentrations of dopa, dopamine and 5HT are not altered by pretreatment with drugs (imipramine, chlorimipramine, benztropine, cocaine) which inhibit the neuronal uptake of amines. Current evidence suggests that L-dopa is decarboxylated in 5HT neurons to dopamine, which displaces 5HT from intraneuronal storage sites.

Acute administration of L-dopa reduces the concentration of 5-hydroxytryptamine (5HT) in the brains of rodents (4,6). Two of the mechanisms which have been proposed to account for this action of dopa include: 1) inhibition of 5HT synthesis (5), possibly through a competition for the uptake of tryptophan (11,15), inhibition of tryptophan hydroxylase (12) or competition with 5-hydroxytryptophan for aromatic-L-amino acid decarboxylase (25), 2) displacement of 5HT by dopamine synthesized from dopa (4,6). The dopamine may be synthesized in 5HT neurons (20) or elsewhere in the brain and then taken up into 5HT neurons (8). The present report describes experiments in which the actions of L-dopa were tested 1) on the synthesis of ^{3}H-5HT from ^{3}H-tryptophan, and 2) on the whole brain concentration of 5HT in mice pretreated with drugs which reportedly block the neuronal uptake of amines.

Methods

Male ICR mice (25-30 g) obtained from Spartan Research Animals, Inc., Haslett, Mich. were used in all experiments. Mice were injected subcutaneously with an inhibitor of peripheral aromatic-L-amino acid decarboxylase, carbidopa (hydrazino-methyl-dopa, 50 mg/kg in 1% methylcellulose), 30 min before subcutaneous injections of L-dopa or saline. The mice were then sacrificed at various times thereafter. In the second experiment L-[^{3}H(G)]tryptophan (7 Ci/mmol; 0.5 μCi/g) or saline was administered intravenously 15 min prior to sacrifice. In the third experiment inhibitors of neuronal amine uptake processes (imipramine HCl; chlorimipramine HCl; cocaine HCl; benztropine mesylate) or a saline vehicle were injected intraperitoneally 15 or 30 min before the injections of L-dopa. All subcutaneous and intraperitoneal injections were made in a volume of 10 ml/kg. At the time of sacrifice mice were anesthetized with methoxyflurane and their cardiovascular systems perfused with saline through a cannula inserted into the heart. Brains were removed, homogenized in cold 0.4N perchloric acid containing 0.1% Na_2EDTA. The homogenates were