Decrease of cerebral 5-hydroxytryptamine by 3,4-dihydroxyphenylalanine after inhibition of extracerebral decarboxylase

SIR,—In rats, the increase of cerebral catecholamines (especially dopamine) caused by administration of 3,4-dihydroxyphenylalanine (dopa) is markedly enhanced by pretreatment with low doses (50 mg/kg) of Ro 4–4602, [N^1-(DL-seryl)-N^2-(2,3,4-trihydroxybenzyl)hydrazine], an inhibitor of decarboxylase of aromatic amino-acids. This action of Ro 4–4602 seems to be connected with a preferential inhibition of extracerebral decarboxylase. As a consequence, dopa accumulates in the blood and penetrates into the brain where decarboxylation into dopamine occurs, since cerebral decarboxylase is not markedly inhibited (Bartholini, Bates & others, 1967; Bartholini, Pletscher & Burkard, 1967; Bartholini & Pletscher, 1968).

Here, we demonstrate that simultaneously with the increase of cerebral catecholamines a marked decrease of endogenous 5-hydroxytryptamine (5-HT) takes place.

Albino rats weighing 80–100 g were given intraperitoneal injections of differing doses of L-dopa ½ hr after Ro 4–4602 also intraperitoneally. Controls received L-dopa alone. The endogenous 5-HT and 5-hydroxyindole-acetic acid (5-HIAA) of the whole brain were measured at various time intervals after dopa with spectrophotofluorimetric procedures (Bogdanski, Pletscher & others, 1956; Giacalone & Valzelli, 1966). To determine the uptake of 5-hydroxytryptophan (5-HTP) into the brain, 50 mg/kg of DL-[^{3}H]-5-hydroxytryptophan ([^{3}H]-5-HTP) (uniformly labelled; specific activity 20 μc/mg) was injected into animals pretreated with 500 mg/kg Ro 4–4602 + 500 mg/kg L-dopa, and the total radioactivity of the brain was measured after various time intervals with a liquid scintillation counter. Controls received 500 mg/kg Ro 4–4602 + [^{3}H]-5-HTP only. The large dose of Ro 4–4602 used, markedly inhibited the cerebral as well as the extracerebral decarboxylase (Burkard, Gey & Pletscher, 1962, 1964) preventing a major decarboxylation of [^{3}H]-5-HTP and of dopa.

In the brains of animals pretreated with 50 mg/kg Ro 4–4602, dopa caused

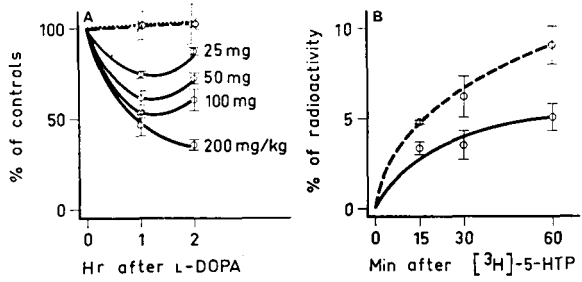

FIG. 1. A. Effect of L-dopa on the content of endogenous 5-hydroxytryptamine (5 HT) in the whole brain of rats pretreated with Ro 4–4602. – – – – 50 mg/kg Ro 4–4602 i.p. . . . . 200 mg/kg L-dopa i.p. ——— 50 mg/kg Ro 4–4602 i.p., followed by various doses of L-dopa i.p. after ½ hr. The values represent averages of 3–4 experiments ± s.e. and are indicated in % of controls (= 100 %). Absolute values of cerebral 5-HT in controls: 0·35 ± 0·02 μg/g.

B. Effect of L-dopa on the penetration of DL-[^{3}H]-5-hydroxytryptophan into the brain of rats. 50 mg/kg DL-[^{3}H]-5-hydroxytryptophan was injected i.p. 40 min after 500 mg/kg Ro 4–4602 i.p. 500 mg/kg L-dopa was administered i.p. 30 min after Ro 4–4602. ——— Ro 4–4602 + L-dopa + DL-[^{3}H]-5-hydroxytryptophan; – – – – Ro 4–4602 + DL-[^{3}H]-5-hydroxytryptophan. The values represent averages of two experiments ± s.e. and are expressed in % of the radioactivity injected per gram body weight.

a dose-dependent decrease of endogenous 5-HT (Fig. 1A). With 200 mg/kg dopa, the 5-HT rose again to normal levels after about 5 hr. Neither 50 mg/kg Ro 4–4602 nor dopa (200 mg/kg) alone significantly influenced cerebral 5-HT. Furthermore, 50 mg/kg Ro 4–4602 intraperitoneally followed by 200 mg/kg dopa by the same route elevated the endogenous 5-HIAA of brain by 125 ± 3%, but only for 1–1½ hr. Thereafter, 5-HIAA declines to normal levels. The increase of the total radioactivity in the brain caused by administration of [^{3}H]-5-HTP after 500 mg/kg Ro 4–4602 was diminished by dopa (Fig. 1B). Preliminary experiments with DL-[^{3}H]-tryptophan instead of [^{3}H]-5-HTP gave the same results.

These findings indicate that the decrease of brain 5-HT might be due to a combination of several mechanisms. The initial rise of 5-HIAA is probably caused by a displacement of the endogenous 5-HT, e.g. due to the cerebral accumulation of dopamine. Preliminary experiments with various doses of Ro 4–4602 + 200 mg/kg L-dopa confirm this view. Thus, with low doses of Ro 4–4602 (accumulation of cerebral dopa and dopamine formed by decarboxylation of dopa), the endogenous brain 5-HT decreases more markedly than after high doses of the inhibitor (accumulation of cerebral dopa only). On the other hand, the experiments with labelled 5-HTP or tryptophan indicate that dopa probably competes with the penetration of 5-HT precursors into the brain. Moreover, in the experiments with 50 mg/kg Ro 4–4602, competitive inhibition of the cerebral decarboxylation of 5-HTP by dopa (Bertler & Rosengren, 1959) must also be considered.

It has been demonstrated that an increase of cerebral 5-HT induced by 5-HTP (Udenfriend, Weissbach & Bogdanski, 1957), tremorine (Friedman, Aylesworth & Friedman, 1963), or intraventricular injection of 5-HT (Domer & Feldberg, 1960) is accompanied by tremor in animals. A decrease of cerebral 5-HT might therefore counteract tremor in Parkinsonism, whereas an increase of dopamine is thought to improve akinesia and rigidity (Barbeau, Sourkes & Murphy, 1962; Birkmayer & Hornykiewicz, 1964).

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