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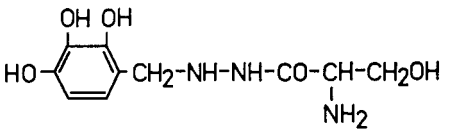
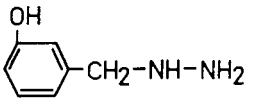
LETTERS TO THE EDITOR

Effect of various decarboxylase inhibitors on the cerebral metabolism of dihydroxyphenylalanine

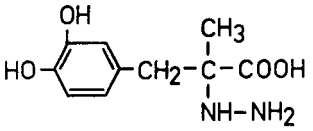
Small doses of Ro 4–4602 [*N*-(DL-seryl)-*N'*-(2,3,4-trihydroxybenzyl)hydrazine], an inhibitor of decarboxylase (DC), enhance the dopa-induced increase of catecholamines in the brain of rats. This was attributed to a poor penetration of the drug through the blood-brain barrier leading to a preferential inhibition of DC in extracerebral tissues like liver, heart and kidney. As a consequence, the concentration of administered dopa in plasma rose and the supply to the brain of this amino-acid was enhanced. This was followed by an increased formation of cerebral catecholamines and their metabolites, the phenolic carboxylic acids (Bartholini, Bates & others, 1967; Bartholini & Pletscher, 1968; Bartholini, Tissot & Pletscher, 1968; Constantinidis, Bartholini & others, 1968). We now report the effect of some other known DC inhibitors: MK485 [β-(3,4-dihydroxyphenyl)-α-hydrazino-α-methyl propionic acid]; NSD 1015 (*m*-hydroxybenzylhydrazine) and α-methyldopa.



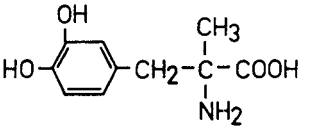
Ro 4–4602



NSD 1015



MK 485



α-methyldopa

Albino rats, 80–100 g, fasted for 16 h, were given α-methyldopa and DC inhibitors of the hydrazine type, i.e. Ro 4–4602, MK 485, NSD 1015, 30 min before 3 mg/kg of [^{14}C]dopa (specific activity 2·07 mCi/mmol), orally. The animals were decapitated 60 min after [^{14}C]dopa. Rats treated with [^{14}C]dopa alone served as controls. Three [^{14}C]catechol fractions containing the [^{14}C]amino-acids—mainly *O*-methyldopa and dopa, the [^{14}C]catecholamines—mainly dopamine and noradrenaline, and the [^{14}C]phenolic carboxylic acids—mainly homovanillic and acid dihydroxyphenylacetic acid, were isolated from two pooled brains in each experiment and measured (Bartholini & Pletscher, 1968).

All four inhibitors act similarly. They cause an enhancement of the dopa-induced rise of amino-acids, phenolic carboxylic acids and catecholamines in the brain and this is dose-dependent at lower doses. Ro 4–4602, NSD 1015 and MK 485 have a stronger effect than α-methyldopa.

The hydrazine type inhibitors also differ among themselves. Lower doses of NSD 1015 and Ro 4–4602 have a more marked effect on the catecholamine concentration than equimolar doses of MK 485. On the other hand, at higher doses, Ro 4–4602—and more so NSD 1015—contrary to MK 485, cause a reduction of the

increase of catecholamines and phenolic carboxylic acids, but not of amino-acids in the brain. This points to some penetration of NSD 1015 and Ro 4–4602 into the brain with consequent inhibition of cerebral DC. The decrease of the amino-acids after high doses of Ro 4–4602 may be explained by an inhibition of *O*-methyl transferase leading to a reduction in the content of *O*-methyldopa (Bartholini, Blum & Pletscher, 1969). This metabolite is an important component of the amino-acid fraction and, in contrast to dopa, accumulates in the brain (Bartholini & Pletscher, 1968).

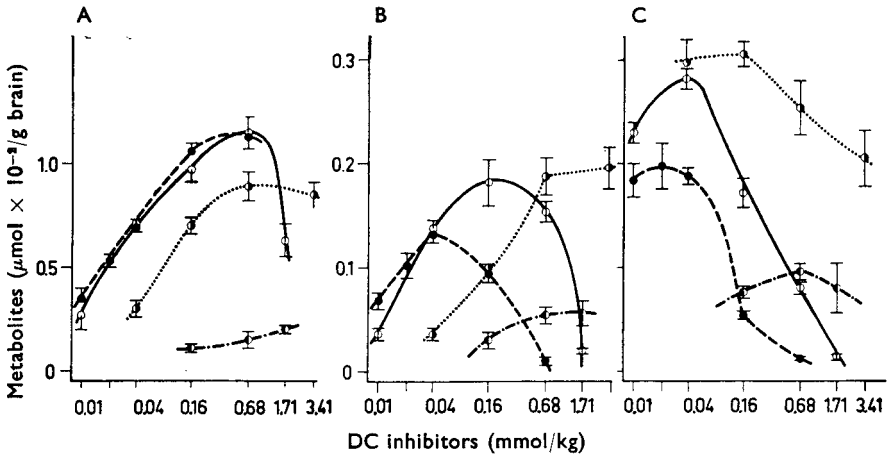


FIG. 1. Effect of the DC inhibitors (Ro 4-4602; - - - NSD 1015; . . . . MK 485; - · - α-methyldopa) on the [^{14}C]dopa-induced rise of [^{14}C]catechol metabolites in the brain of rats. A. [^{14}C]Amino-acids. B. [^{14}C]Catecholamines. C. Phenolic carboxylic acids. The inhibitors were given 30 min before 3 mg/kg [^{14}C]dopa, orally; rats were killed 60 min after [^{14}C]dopa. The points indicate averages with s.e. of 2–9 experiments. The values obtained 60 min after [^{14}C]dopa alone were (in μmol $\times$ 10^{-2}/g brain): [^{14}C]Amino-acids: 0·034 $\pm$ 0·003. [^{14}C]Catecholamines: 0·0011 $\pm$ 0·0003. [^{14}C]Phenolic carboxylic acids: 0·027 $\pm$ 0·002.

In conclusion, the four DC inhibitors may be tentatively characterized: NSD 1015 causes an inhibition of extracerebral DC, but—owing to penetration into the brain—also inhibition of the brain enzyme in low doses. Ro 4–4602 inhibits the extracerebral DC. It interferes only in high doses with the cerebral DC. MK 485 is less potent than NSD 1015 and Ro 4–4602 in inhibiting extracerebral DC, but even in high doses little appears to penetrate the brain. α-Methyldopa has only a slight effect on the extracerebral and no demonstrable effect on cerebral DC.

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