Dose-dependent potentiation or inhibition by Ro4-4602 of 5-HTP hyperthermia in rabbits

Horita & Hamilton (1970) observed that the slight hyperthermia produced by intravenous injection of 25 mg kg^{-1} DL-5-hydroxytryptophan (DL-5-HTP) was potentiated in 13 of 18 rabbits pretreated 30 min previously with DL-α-hydrazino-α-methyldopa (HMD; 25 mg kg^{-1} i.v.), an inhibitor of dopa-5-HTP decarboxylase; the remaining 5 animals did not respond or exhibited a slight hyperthermia.

Using a different dopa-5-HTP decarboxylase inhibitor, N^1-(DL-seryl)-N^2-(2,3,4-trihydroxybenzyl) hydrazine (Ro4-4602), we observed, on the contrary, that a dose of 100 mg kg^{-1} (i.v.) inhibited the hyperthermia produced in rabbits by injection of DL-5-HTP, 50 mg kg^{-1} (i.v.).

As a result of these conflicting observations we therefore investigated whether Ro4-4602 induces a variable effect depending on the dose used. The experiments were at 20° ± 1° with male rabbits, 2·2–2·5 kg. The Ro4-4602 and DL-5-HTP were made up in 0·9% NaCl pyrogen free, the concentration being such that the injected volume was always 1 ml kg^{-1} for each dose tested. Ro4-4602 was given intravenously at 12·5, 25, 50 and 100 mg kg^{-1}, 60 min before administration of 5-HTP (50 mg kg^{-1} i.v.) which we found, when used alone, induced a mean maximal hyperthermia of 0·6° in 45 min.

Horita & Hamilton (1970) observed a maximal hyperthermia of the same magnitude 60 min later with a dose of 25 mg kg^{-1}, while Horita & Gogerty (1958) obtained a maximal hyperthermia of about 1° within 120 min, using 50 mg kg^{-1}. With the lowest dose of Ro4-4602 tested (12·5 mg kg^{-1}), all the rabbits exhibited a potentiation of the hyperthermic effect of 5-HTP (+5°), and death ensued in less than 210 min. Administration of the highest dose of Ro4-4602 (100 mg kg^{-1}) resulted in total inhibition of the hyperthermia produced by 5-HTP, followed 60 to 75 min after injection of the

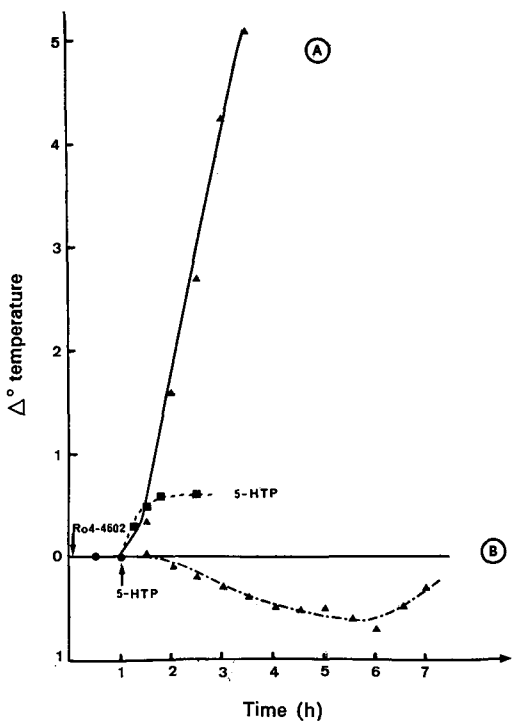

FIG. 1. Rectal temperatures of rabbits given 5-HTP alone (50 mg kg^{-1}, i.v.), or pretreated with Ro4-4602, A, 12 mg kg^{-1} i.v., or B, 100 mg kg^{-1} i.v. Drugs were given at arrows. There is significant hyperthermia when the smaller dose of Ro4-4602 is given with 5-HTP. This becomes a hypothermia when the dose of Ro4-4602 is 100 mg kg^{-1}.

5-HTP by hypothermia (Fig. 1). The injection of Ro4-4602 itself, even at the highest dose used (100 mg kg^{-1}), had no effect on the rectal temperature of the rabbit. The effects of 5-HTP on rectal temperature of the rabbit after inhibition of dopa/5-HTP decarboxylase by doses of Ro4-4602 from 12·5 — 100 mg kg^{-1} are: at 12·5 mg kg^{-1} deaths 4/4, hyperthermia 4/4; at 25 mg kg^{-1} the figures were 1/4, 2/4 and 2 with slight hypothermia, at 50 mg kg^{-1} 1/5, 1/5, 4/5, for the three parameters and at 100 mg kg^{-1} 0/4 deaths and 3/4 with slight hypothermia, one animal showing no change. The following points are worth noting: 1. The progressive decrease both in the number of rabbits responding by potentiation of the hyperthermia, and in the mortality rate. 2. The progressive increase in the number of rabbits exhibiting hypothermia, which was about $-1°$; it appeared to be more prolonged in duration after 25 mg kg^{-1} than after 50 or 100 mg kg^{-1} of Ro4-4602.

We suggest that these findings can be interpreted as follows. At the lowest dose tested, Ro4-4602 inhibits mainly the peripheral decarboxylases, allowing an increased amount of 5-HTP to reach the brain where it is decarboxylated, thereby liberating a large quantity of 5-HT to give a marked hyperthermic effect. Banerjee, Burks & others (1970) and Jacob, Girault & Peindaries (1972) have in fact shown that in the rabbit 5-HT is hyperthermic at high concentrations whether injected intraventricularly or directly into the hypothalamus. The decrease in mortality, and in occurrence and degree of hyperthermia which was observed with increasing doses of Ro4-4602, may be attributable to intracerebral penetration of the inhibitor at these dose levels; this would result in a decreased cerebral metabolism of 5-HTP, and no increase in the cerebral levels of 5-HT. Bartholini, Da Prada & Pletscher (1968) have previously shown that Ro4-4602 crosses the blood brain barrier in the rat at high concentrations.

The hypothermia observed after administration of the highest dose of Ro4-4602 followed by 5-HTP may be attributable to the hypothermic action of low doses of 5-HT (Cooper, Cranston & Honour, 1965; Takashima, 1962; Weber & Angell, 1967). This does not exclude the possible intervention of dopamine, since the cerebral synthesis of dopamine is altered in the presence of excess 5-HTP which competes with dopa in the decarboxylation process (Bertler & Rosengren, 1959; Johnson, Kim & Boukma, 1968; Ng, Chase & others, 1972); this results in the synthesis of 5-HT in dopaminergic structures (Butcher, Engel & Fuxe, 1971; Fuxe, Butcher & Engel, 1972) and liberation of catecholamines; Ro4-4602 could inhibit this synthesis of 5-HT in such dopaminergic structures, which may be involved in thermoregulation.

Institut de Pharmacologie,
21, rue de l'Ecole-de-Médecine,
75270 Paris Cedex 06, France.

C. GARDEY-LEVASSORT
P. LECHAT

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