Tryptamine and 5-hydroxytryptamine-induced hypothermia in mice

D. J. DOOLEY†, R. M. QUOCK*, *Department of Pharmacology, School of Medicine, University of Washington, Seattle Washington 98195, U.S.A.*

Various *in vitro* and *in vivo* experiments have indicated the concurrent existence of more than one receptor for tryptamine and 5-hydroxytryptamine (5-HT) (Woolley & Shaw, 1957; Winter & Gessner, 1968; Clineschimdt & Lotti, 1974; Frankhuijzen & Bonta, 1974). These studies have used differential antagonism of various pharmacological responses: vasopressor action, contraction of the rat stomach fundus preparation, tryptamine-induced forepaw clonus, and 5-HT-induced head twitch. Lessin & Parkes (1957a, b) demonstrated a dose-related hypothermia in mice following the injection of 5-HT, while Winter (1972) showed a dose-related hypothermia in rats to various tryptamine derivatives (*NN*-dimethyltryptamine, bufotenine, and 5-methoxytryptamine). It was of interest, therefore, to examine and compare the following related aspects: (1) the hypothermic effect of tryptamine and 5-HT, (2) antagonism of tryptamine and 5-HT to determine if these drugs produced hypothermia at the same receptor site(s), (3) the use of a peripheral antagonist to rule out any central contribution to the hypothermic effect, and (4) inhibition of monoamine oxidase (MAO) to determine if a prolongation of pharmacological response would occur.

Male Swiss-Webster mice (Simonsen Labs, Gilroy, California), 22–30 g, had rectal temperature measured by a heat sensitive thermistor probe. The probe was inserted to a depth of 3 cm and retained *in situ* until a constant temperature was displayed on a Model 47 Tele-Thermometer (Yellow Springs Instrument Co.). The ambient temperature was maintained at 21·0° ± 1·0°. Tryptamine hydrochloride (Regis), 5-hydroxytryptamine creatinine sulphate complex (Calbiochem), cinanserin hydrochloride (E. R. Squibb & Sons), pargyline hydrochloride (Abbot), and xylamidine tosylate (Wellcome) were all dissolved in distilled water. Methergoline (Farmitalia) was dissolved in 0·7% w/v ascorbic acid (pH = 3·8). Drugs and saline (0·9%) were injected intraperitoneally at a volume of 0·01 ml g^{-1}. All doses represent that of the salt. Temperatures were taken 30 min before and immediately before tryptamine or 5-HT injection. Pretreatment with other drugs before tryptamine or 5-HT injection occurred as follows: cinanserin/methergoline, 30 min; xylamidine, 4 h; and pargyline, 18 h. Following tryptamine or 5-HT injection, temperatures were monitored at 30 min intervals for a period of 2 h. The results were analysed using the *t*-statistic (one-tailed). The level of significance was taken at $P < 0.05$.

Tryptamine produced a dose-related hypothermia that was maximal at 30 min post-injection (Fig. 1). 5-HT, at doses of 5, 10, and 50 mg kg^{-1}, produced results similar to tryptamine as well as being in agreement with the observations of Lessin & Parkes (1957a, b). A statistical comparison of 30 min mean temperatures for both tryptamine and 5-HT doses showed a significant difference ($P < 0.01$) from other doses. All tryptamine and 5-HT doses, except the lowest doses, were statistically significant ($P < 0.01$) from the saline 30 min mean temperature. Since there was a comparable hypothermic response, the intermediate doses of tryptamine (50 mg kg^{-1} = 41 mg kg^{-1} free base) and 5-HT (10 mg kg^{-1} = 4 mg kg^{-1} free base) were chosen for the test doses in pretreatment experiments. The 30 min mean temperature was the endpoint in determining the change of hypothermic response due to antagonist or monoamine oxidase inhibitor pretreatment.

Pretreatment with xylamidine (1 mg kg^{-1}) blocked the hypothermia to tryptamine and 5-HT. Methergoline pretreatment antagonized the hypothermic effect of the two indolealkylamines at 0·05 and 1·0 mg kg^{-1} but not at 0·01 mg kg^{-1}. The methergoline solvent (ascorbic acid) had no influence on tryptamine or 5-HT hypothermia. Cinanserin blocked the hypothermia at 5·0 mg kg^{-1} while doses of 1·0 and 2·5 mg kg^{-1} were not antagonistic. Fig. 2 shows the effects of pargyline pretreatment (25 mg kg^{-1}) on the hypothermia induced by the test dose of tryptamine. The 30 min mean tempera-

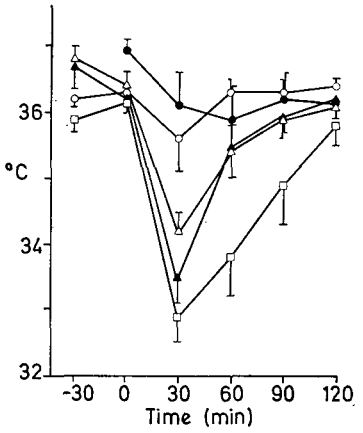

FIG. 1. Effect of tryptamine and 5-HT on the rectal temperature (°C) in mice. All drug solutions were injected intraperitoneally at zero time. Each point corresponds to the mean temperature of at least 10 animals after the injection of saline (●); tryptamine (mg kg^{-1}): 10 (○), 50 (△), 100 (□); or 5-HT (mg kg^{-1}): 10 (▲). Vertical bars indicate standard error of the mean. y axis—Rectal temp. (°C).

† Correspondence.

* Present address: Division of Pharmaceutical Sciences, School of Pharmacy, University of the Pacific, Stockton, California 95207, U.S.A.

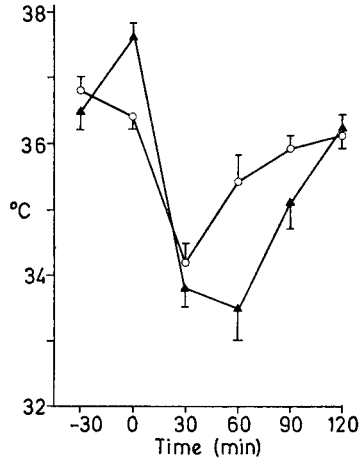

FIG. 2. Effect of tryptamine (50 mg kg^{-1}) on the rectal temperature (°C) in mice pretreated with pargyline (25 mg kg^{-1}). Each point corresponds to the mean temperature of at least 10 animals after the injection of tryptamine (○) or pargyline + tryptamine (▲). Vertical bars indicate standard error at the mean. y axis—Rectal temp. (°C).

ture for pargyline-pretreated mice was not significantly different from the test dose mice. However, for 60 and 90 min mean temperatures there was a significant difference ($P < 0.01$ and $P < 0.05$, respectively). Pargyline had no influence on hypothermia induced by the test dose of 5-HT.

These data indicate that tryptamine produces hypothermia in rodents analogous to derivatives of tryptamine (Lessin & Parkes, 1957a b; Winter, 1971, 1972). However, tryptamine was found to be less potent in terms of dose than 5-HT when inducing hypothermia. Pretreatment with xylamidine tosylate, a peripheral antagonist of 5-HT (Copp, Green, & others, 1967), indicated that the test doses of tryptamine and 5-HT were acting peripherally rather than centrally. Previously, Winter (1969, 1971, 1972) demonstrated in rats that xylamidine could antagonize the hypothermic and/or behavioural actions of certain tryptamine derivatives (5-HT, 5-methoxytryptamine, bufotenine) but not others (dimethyltryptamine, diethyltryptamine). This suggests a relation exists between the central and peripheral distribution of tryptamine-like compounds and their non-polar, lipid soluble nature.

Pretreatment with the two tryptaminergic antagonists, cinanserin and methergoline, indicated a lack of differential antagonism of tryptamine and 5-HT test dose hypothermia. Previous differential antagonism experiments have indicated that there is more than one tryptaminergic receptor centrally (Clineschmidt & Lotti, 1974) and peripherally (Winter & Gessner, 1968; Frankhuijzen & Bonta, 1974) in rats, and peripherally in dogs (Woolley & Shaw, 1957). The lack of differential antagonism in the present experiment suggests that both tryptamine and 5-HT act at the same peripheral receptor(s) mediating hypothermia.

Pargyline pretreatment prolonged the hypothermic effect to the test dose of tryptamine but not to 5-HT. It is suggested that the primary termination of action of tryptamine involves MAO while that of 5-HT involves reuptake. Weissbach, Lovenberg, & others (1961) showed in mice that iproniazid had no effect on 5-HT elimination but slowed the disappearance of tryptamine. This would indicate that 5-HT need not depend on MAO for elimination while tryptamine has less efficient alternate routes of elimination available. However, Lessin & Parkes (1957a) showed that iproniazid caused a marked potentiation and prolongation of 5-HT hypothermia in mice. Possible factors to account for the discrepancies between the present and prior experiments are the dose and pretreatment time of the MAO inhibitor, inhibition of non-MAO enzymes that can metabolize 5-HT, and/or the dose of 5-HT used.

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