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EFFECT OF α-ALKYLATED TRYPTAMINE DERIVATIVES ON 5-HYDROXYTRYPTAMINE METABOLISM IN VIVO

BY

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In rats, three α-alkylated tryptamine derivatives (α-methyl, α-ethyl, and αα-dimethyltryptamine) caused alterations of 5-hydroxytryptamine metabolism typical of monoamine-oxidase inhibitors with short duration of action, viz., an increase of endogenous 5-hydroxytryptamine in brain, enhancement of the increase of 5-hydroxytryptamine in brain and heart after 5-hydroxytryptophan administration, an inhibition of the decrease in 5-hydroxytryptamine in brain induced by a benzoquinolizine derivative and of the increase induced by iproniazid. The increase after iproniazid was antagonized to the same extent by all the tryptamine derivatives and by harmaline, whereas dexamphetamine showed less effect. In the other experiments with brain, the tryptamine derivatives were less potent than harmaline, but somewhat more active than dexamphetamine. α-Methyltryptamine and α-ethyltryptamine were relatively more effective in the heart than in the brain. Among the tryptamine derivatives αα-dimethyltryptamine had the weakest activity in brain and in heart.

α-Methyltryptamine and α-ethyltryptamine (etryptamine ; Monase) inhibit monoamine oxidase both *in vitro* and *in vivo*. *In vitro*, these compounds have the same order of activity as iproniazid, but *in vivo* the inhibition is of short duration, in contrast to that caused by iproniazid (Greig, Walk & Gibbons, 1959 ; Greig, Seay & Freyburger, 1961 ; Greig & Gibbons, 1962). It has been suggested that the stimulating effect of α-methyl- and α-ethyltryptamine on the central nervous system is due to inhibition of monoamine oxidase. Other authors (Vane, Collier, Corne, Marley & Bradley, 1961 ; Parkes, Lessin & Long, 1962) doubt whether this mechanism explains entirely the central pharmacodynamic action of these compounds.

The activity of reversible monoamine-oxidase inhibitors *in vivo* is usually measured in homogenized organs, such as brain, after pretreatment of the living animals with the drugs. Enzyme inhibition determined by this method, however, does not necessarily prove a true effect *in vivo*. Thus, the α-methylated tryptamine present in the blood and in the extracellular fluid of the brain might cause or enhance inhibition of monoamine oxidase only after homogenizing the tissue, whereas *in vivo* the penetration of the drugs to the site of the enzyme (e.g., mitochondria) might be hindered.

Thus changes of monoamine content in brain might give a more reliable indication as to the action of reversible monoamine-oxidase inhibitors *in vivo* than the measurement of monoamine-oxidase activity in homogenized brain. In rat brain α-methyl- and α-ethyltryptamine are known to raise endogenous monoamines and enhance the increase in 5-hydroxytryptamine induced by administration of 5-hydroxytryptophan (Greig *et al.*, 1959 ; Greig *et al.*, 1961 ; Greig & Gibbons, 1962). The potency of these drugs, however, has so far not been ascertained for lack of comparisons with standard inhibitors.

In the present paper the effects of three α-methylated tryptamine derivatives on 5-hydroxytryptamine metabolism have been compared with those of harmaline, a potent reversible monoamine-oxidase inhibitor *in vivo*, and of dexamphetamine, which inhibits monoamine oxidase strongly *in vitro* but only slightly *in vivo*. The following changes, typical of short-acting monoamine-oxidase inhibitors, were investigated:

(*a*) Increase of endogenous 5-hydroxytryptamine in brain.

(*b*) Enhancement of the 5-hydroxytryptamine rise in brain and heart induced by 5-hydroxytryptophan.

(*c*) Reduction of the 5-hydroxytryptamine decrease in brain caused by a monoamine releaser (benzoquinolizine derivative Ro 4-1284 = 2-ethyl-1,2,3,4,6,7-hexahydro - 2 - hydroxy-3-isobutyl-9,10-dimethoxy-11*bH*-benzo[*a*]quinolizine) (Pletscher, Besendorf, Steiner & Gey, 1962).

(*d*) Antagonism against the 5-hydroxytryptamine increase in brain caused by a long-acting monoamine-oxidase inhibitor (iproniazid) (Pletscher & Besendorf, 1959).

METHODS

Wistar albino rats of 160 to 190 g, fasted for 16 hr, received various doses of α-methyl-, α-ethyl-, αα-dimethyltryptamine, harmaline, or dexamphetamine intraperitoneally, either alone or 1 hr prior to subcutaneous administration of 75 mg/kg 5-hydroxytryptophan, 10 mg/kg Ro 4-1284 or 100 mg/kg iproniazid. The animals were decapitated and the 5-hydroxytryptamine of the brain (in the experiments with 5-hydroxytryptophan also of the heart) was measured spectrophotofluorometrically (Bogdanski, Pletscher, Brodie & Udenfriend, 1956). Animals not treated with any drug, as well as others treated with either 5-hydroxytryptophan, Ro 4-1284 or iproniazid, served as controls. Preliminary investigations showed that, in agreement with Greig *et al.* (1961), α-ethyltryptamine exerted its maximal activity between 0.5 and 1.5 hr after intraperitoneal injection.

RESULTS

(1) The endogenous 5-hydroxytryptamine of the brain was raised significantly by α-methyl- and α-ethyltryptamine. Thus, 7 and 21 μM/kg respectively of the compounds caused a maximum increase which was comparable to that due to equimolar doses of harmaline. Doses of either 21 μM/kg α-ethyltryptamine or of 70 μM/kg α-methyl- and α-ethyltryptamine induced no additional rise of 5-hydroxytryptamine and were less effective than harmaline. αα-Dimethyltryptamine caused a small increase of 5-hydroxytryptamine which was significant ($P<0.01$) with 70 μM/kg of the drug only and which was less marked than that produced by harmaline. Dexamphetamine had no significant effect on the 5-hydroxytryptamine content of brain (Fig. 1).

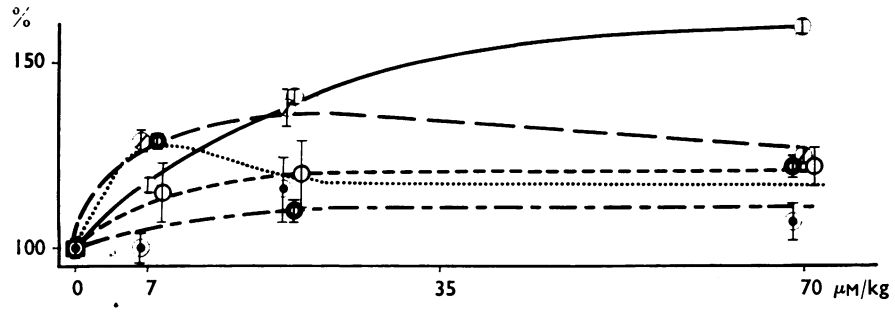

Fig. 1. Change of endogenous 5-hydroxytryptamine in brain 1.5 hr after intraperitoneal injection of ——— harmaline; — — — α-methyltryptamine; ..... α-ethyltryptamine; - - - - - ααα-dimethyltryptamine; — — — — — dexamphetamine. Ordinate: Percentage increase of 5-hydroxytryptamine compared to untreated controls (absolute 5-hydroxytryptamine values of untreated controls: 0.65±0.02 μg/g fresh brain=100±2%). Abscissa: Dose of the drugs in μM/kg. The points represent average values of 4 to 6 experiments with standard error.

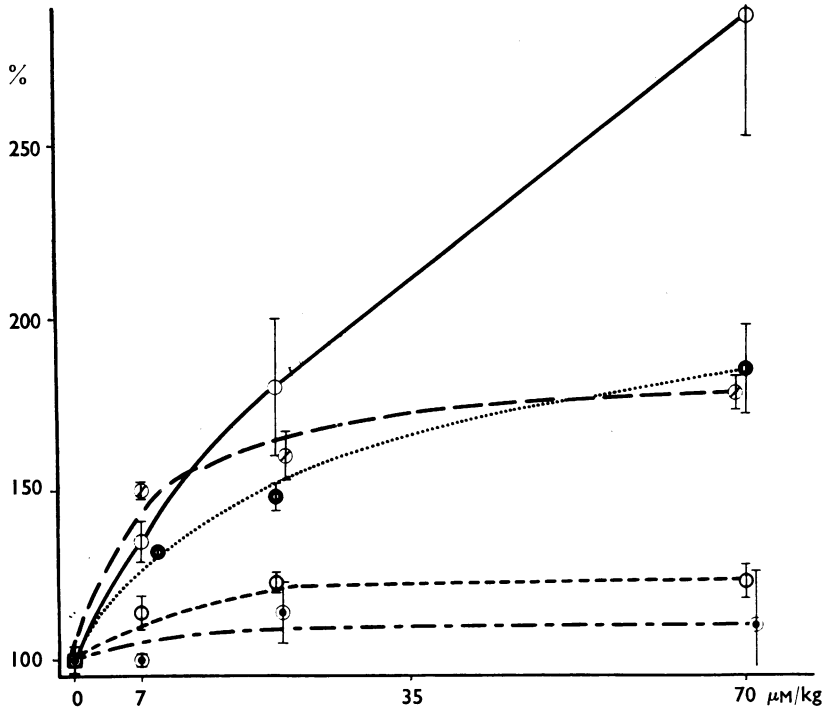

Fig. 2. Effect of the drugs on the 5-hydroxytryptophan-induced 5-hydroxytryptamine increase in brain. The drugs were administered intraperitoneally 1 hr prior to subcutaneous injection of 75 mg/kg 5-hydroxytryptophan. 5-Hydroxytryptamine determination 0.5 hr after 5-hydroxytryptophan. Ordinate: Percentage increase of 5-hydroxytryptamine compared to animals having received 5-hydroxytryptophan alone (absolute 5-hydroxytryptamine values after 5-hydroxytryptophan alone: 1.15±0.05 μg/g fresh brain=100±4%). Abscissa: Dose in μM/kg of ——— harmaline; — — — — α-methyltryptamine; ..... α-ethyltryptamine; - - - - - ααα-dimethyltryptamine; — — — — — dexamphetamine. The points represent average values of 4 to 6 experiments with standard error.

(2) The increase of 5-hydroxytryptamine in brain after 5-hydroxytryptophan administration was enhanced by the tryptamine derivatives depending on the dose of these drugs: 7 and 21 μM/kg of α-methyl- and α-ethyltryptamine had about the same activity as equimolar doses of harmaline; 70 μM/kg was considerably less active than harmaline. $\alpha\alpha$-Dimethyltryptamine and dexamphetamine enhanced the 5-hydroxytryptophan-induced rise of 5-hydroxytryptamine only slightly or not at all (Fig. 2).

(3) The increase of 5-hydroxytryptamine in the heart induced by 5-hydroxytryptophan was enhanced to about the same extent by α-methyltryptamine, α-ethyltryptamine, and harmaline. $\alpha\alpha$-Dimethyltryptamine was less active than α-methyl- and α-ethyltryptamine, and dexamphetamine had no effect (Fig. 3).

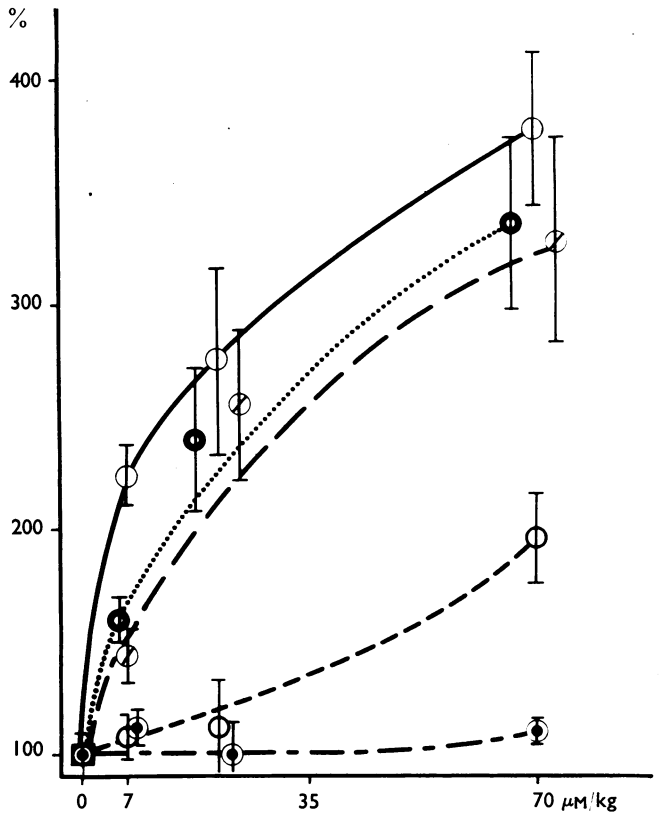

Fig. 3. Effect of the drugs on the 5-hydroxytryptophan-induced 5-hydroxytryptamine rise in the heart. The drugs were administered intraperitoneally 1 hr prior to subcutaneous injection of 75 mg/kg 5-hydroxytryptophan. Measurement of 5-hydroxytryptamine 0.5 hr after 5-hydroxytryptophan. Ordinate: Percentage increase of 5-hydroxytryptamine as compared to animals having been treated with 5-hydroxytryptophan alone (absolute 5-hydroxytryptamine val ue after 5-hydroxytryptophan alone: 2.82±0.25 μg/g fresh heart=100±9%). Abscissa: Dose in μM/kg of ——— harmaline; — — — — α-methyltryptamine; ..... α-ethyltryptamine; - - - - - $\alpha\alpha$-dimethyltryptamine; — — — — — dexamphetamine. The points represent average values of 4 to 6 animals with standard error.

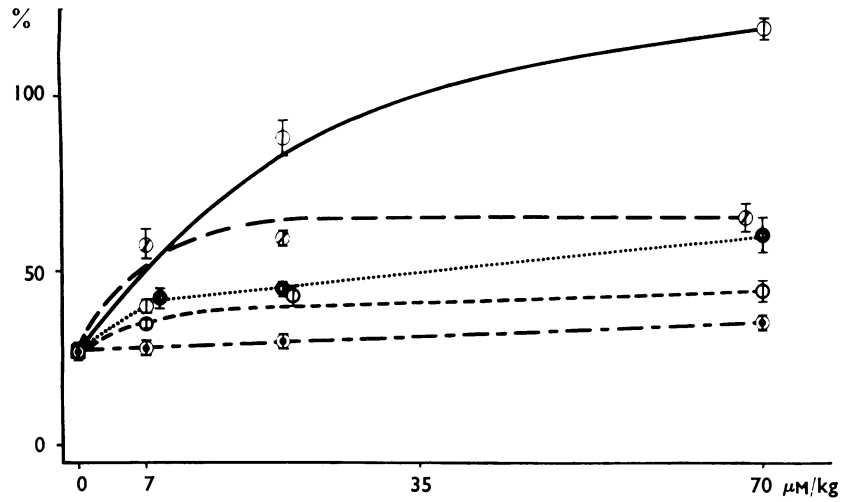

Fig. 4. Effect of the drugs on the 5-hydroxytryptamine decrease in brain induced by benzoquinolizine derivative Ro 4-1284. The drugs were administered intraperitoneally 1 hr prior to subcutaneous injection of 10 mg/kg Ro 4-1284. Determination of 5-hydroxytryptamine 0.5 hr after Ro 4-1284. Ordinate: Percentage change of 5-hydroxytryptamine as compared to untreated controls (absolute 5-hydroxytryptamine values of untreated controls: 0.65±0.02 μg/g fresh brain=100±2%). Abscissa: Dose in μM/kg of ——— harmaline; — — — — α-methyltryptamine; ..... α-ethyltryptamine; - - - - - αα-dimethyltryptamine; — — — — dexamphetamine. The points represent average values of 4 to 6 experiments with standard error.

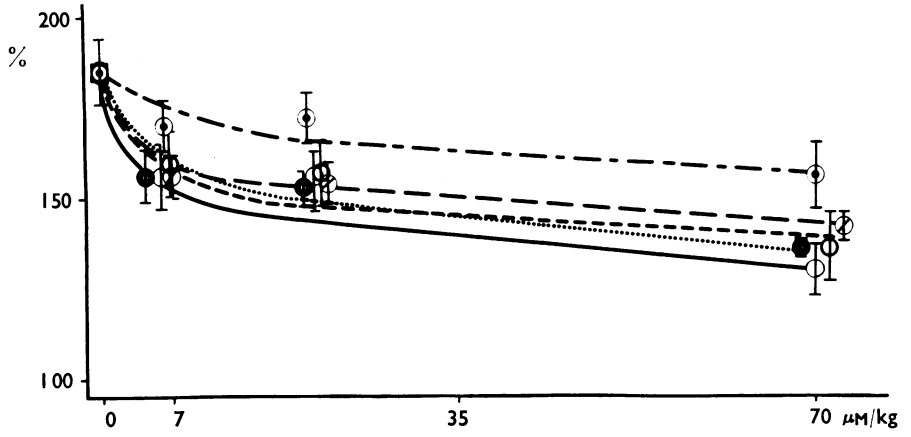

Fig. 5. Effects of the drugs on the 5-hydroxytryptamine increase in brain due to iproniazid. The drugs were administered intraperitoneally 1 hr prior to subcutaneous injection of 100 mg/kg iproniazid. Determination of 5-hydroxytryptamine 16 hr after iproniazid. Ordinate: Percentage change of 5-hydroxytryptamine as compared to untreated controls (absolute 5-hydroxytryptamine values of untreated controls: 0.65±0.02 μg/g fresh brain=100±2%). Abscissa: Dose in μM/kg of ——— harmaline; — — — — α-methyltryptamine; ..... α-ethyltryptamine; - - - - - αα-dimethyltryptamine; — — — — dexamphetamine. The points represent average values of 4 to 6 experiments with standard error.

(4) The decrease of 5-hydroxytryptamine in brain due to the benzoquinolizine derivative Ro 4-1284 was counteracted by all the tryptamine derivatives. Harmaline in doses of 21 and 70 μM/kg exerted a more marked antagonism than the tryptamines, whereas in doses of 7 μM/kg there was no significant difference. Dexamphetamine did not significantly influence the benzoquinolizine-induced decrease of 5-hydroxytryptamine (Fig. 4).

(5) The iproniazid-induced increase of 5-hydroxytryptamine in brain was counteracted to about the same extent by the three tryptamine derivatives and harmaline at all dose levels. Dexamphetamine had a significant ($P \sim 0.01$) but relatively slight effect at the highest dose level (70 μM/kg) only ; doses of 7 and 21 μM/kg were without significant influence ($P > 0.05$) (Fig. 5).

DISCUSSION

The present results show that the three α-alkylated tryptamine derivatives investigated influence the 5-hydroxytryptamine metabolism in the brain and the heart in a way typical of short-acting monoamine-oxidase inhibitors. Thus, these tryptamine derivatives increased the endogenous 5-hydroxytryptamine, they enhanced the rise of 5-hydroxytryptamine induced by 5-hydroxytryptophan, and they antagonized the decrease of 5-hydroxytryptamine induced by a benzoquinolizine derivative as well as the increase of 5-hydroxytryptamine caused by iproniazid. The tryptamine derivatives were more active than dexamphetamine, but in the brain in most respects inferior to harmaline. According to the experiments with 5-hydroxytryptophan, $\alpha\alpha$-dimethyltryptamine seems to be less effective than α-methyl- and α-ethyltryptamine. It remains unsettled why the tryptamine derivatives and harmaline showed the same potency as inhibitors of the iproniazid-induced rise of 5-hydroxytryptamine, although in all the other experiments with brain the tryptamines were less effective than the alkaloid.

It has been considered that the effects of α-alkylated tryptamines on monoamine metabolism are partly due to inhibition of decarboxylase of aromatic amino-acids, an effect which Greig *et al.* (1959) had demonstrated for α-methyltryptamine. Decarboxylase inhibition might prevent the monoamine accumulation observed after monoamine-oxidase inhibition and thus explain why the tryptamine derivatives were in most tests less active than harmaline and why an increase in the dose of α-methyl- and α-ethyltryptamine did not cause an additional rise in endogenous 5-hydroxytryptamine. However, according to previous findings by Greig *et al.* (1959) and Greig *et al.* (1961), α-ethyltryptamine did not markedly inhibit decarboxylase *in vitro* and *in vivo* ; it therefore seems unlikely that inhibition of this enzyme is important as a mechanism by which α-alkylated tryptamines interfere with monoamine metabolism. The possibility that higher doses of α-ethyltryptamine may inhibit 5-hydroxylation of tryptophan (Greig & Gibbons, 1962) remains to be proven.

In the heart, α-methyl- and α-ethyltryptamine seem to be relatively more active than in the brain: both compounds were about as potent as harmaline, and superior to dexamphetamine, in enhancing the 5-hydroxytryptophan-induced increase of 5-hydroxytryptamine. The reason for the differences between brain and heart cannot be explained.

In conclusion, in their effect on 5-hydroxytryptamine metabolism *in vivo* the three α-alkylated tryptamines are somewhat more active than dexamphetamine, but, in the brain, less potent than harmaline. It seems doubtful whether the relatively weak action of α-alkylated tryptamines on the total monoamine content of the brain can be a major contributing factor to their stimulant effect on the central nervous system.

The tryptamine derivatives were prepared by Dr B. Heath-Brown and Dr P. G. Philpott, Roche Products, Welwyn (England).

REFERENCES

BOGDANSKI, D. F., PLETSCHER, A., BRODIE, B. B. & UDENFRIEND, S. (1956). Identification and assay of serotonin in brain. *J. Pharmacol. exp. Ther.*, **117**, 82–88.

GREIG, M. E. & GIBBONS, A. J. (1962). The effect of D,L-α-ethyl-tryptamine acetate on serotonin metabolism. *Arch. int. Pharmacodyn.*, **136**, 147–152.

GREIG, M. E., SEAY, P. H. & FREYBURGER, W. A. (1961). The pharmacology of etryptamine. *J. Neuropsychiat.*, **2**, Suppl. No. 1, 131–135.

GREIG, M. E., WALK, R. A. & GIBBONS, A. J. (1959). The effect of three tryptamine derivatives on serotonin metabolism *in vitro* and *in vivo*. *J. Pharmacol. exp. Ther.*, **127**, 110–115.

PARKES, M. W., LESSIN, A. W. & LONG, R. F. (1962). In press.

PLETSCHER, A. & BESENDORF, H. (1959). Antagonism between harmaline and long-acting monoamine oxidase inhibitors concerning the effect on 5-hydroxytryptamine and norepinephrine metabolism in the brain. *Experientia*, **13**, 25–29.

PLETSCHER, A., BESENDORF, H., STEINER, F. A. & GEY, K. F. (1962). The effect of 2-hydroxybenzoquinolizines on cerebral 5-hydroxytryptamine, spontaneous locomotor activity, and ethanol hypnosis in mice. *Med. Exp.* In the press.

VANE, J. R., COLLIER, H. O. J., CORNE, S. J., MARLEY, E. & BRADLEY, P. B. (1961). Tryptamine receptors in the central nervous system. *Nature (Lond.)*, **191**, 1068–1069.