A NOTE ON THE OXIDATIVE DEAMINATION OF ISOMERS OF 5-HYDROXYTRYPTAMINE AND OTHER INDOLEALKYLAMINES

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Monoamine oxidase from guinea pig tissues oxidises 4-hydroxytryptamine, 6-hydroxytryptamine and 7-hydroxytryptamine at about 50–70 per cent of the rate of 5-hydroxytryptamine. For the rat liver the relative rate of oxidation of 6-hydroxytryptamine is less. 5-Methoxytryptamine and tryptamine are substrates for amine oxidase as good as, or better than 5-hydroxytryptamine, whereas iso-5-hydroxytryptamine and iso-tryptamine are oxidised less readily than 5-hydroxytryptamine and tryptamine. 5-Hydroxy-β-hydroxy-*NN*-dimethyltryptamine(β-hydroxybufotenine) does not seem to be a substrate for amine oxidase from guinea pig kidney.

MONOAMINE oxidase (MAO) is probably the enzyme of major importance for the inactivation of 5-hydroxytryptamine (5–HT) and tryptamine in the mammalian organism. This note is intended to give a concise account of the action of MAO on the 4-, 6-, and 7-isomers of 5–HT, as well as on some other natural and synthetic indolealkylamines.

EXPERIMENTAL AND RESULTS

The MAO preparations employed in this study were obtained by homogenation, in a Waring blender, of guinea pig liver and kidney, and rat liver with 9 volumes of 0·067 M phosphate buffer at pH 7·4. Manometric determination of enzymic activity was made in a conventional Warburg apparatus at 37° and pH 7·3. The total volume of the reaction mixture in the flasks was 2·6 ml.; 2 ml. were represented by the tissue

TABLE I

ENZYMIC OXIDATION OF VARIOUS SUBSTRATES BY A GUINEA PIG LIVER HOMOGENATE. THE OXIDATION RATE IS GIVEN AS A PERCENTAGE OF THAT OF 5-HYDROXYTRYPTAMINE

Substrate	Per cent oxidation rate	Substrate	Per cent oxidation rate
5–HT	100	5-Methoxytryptamine	90
4–HT	49	Iso-5-hydroxytryptamine	10
6–HT	49	Tryptamine	118
7–HT	71	Psilocybine	0

homogenate, 0·2 ml. by a 0·01 M solution of the substrate, and 0·4 ml. by distilled water. This was eventually replaced by solutions of KCN, semicarbazide or MAO inhibitors (iproniazid, pheniprazine 2-phenylcyclopropylamine or SKF–385).

The main results are listed in the accompanying Tables I and II and in Figure 1.

Tables I and II show the enzymic oxidation of various substrates by guinea pig liver and kidney homogenates, respectively. The oxidation rate in the initial 20-minute period of observation is given as a percentage of that of 5-HT. The average oxygen consumption for 5-HT was 39 μl. using guinea pig liver homogenates, and 37 μl. using guinea pig kidney homogenates.

Three MAO inhibitors were tested on the guinea pig liver preparation using 7-HT as substrate. At final concentrations of 10^{-6} M and 10^{-5} M, β-phenylisopropylhydrazine produced, after 30 minutes, a 10 and 98 per cent inhibition of oxygen uptake, respectively; iproniazid was in-

TABLE II

ENZYMIC OXIDATION OF VARIOUS SUBSTRATES BY A GUINEA PIG KIDNEY HOMOGENATE. THE OXIDATION RATE IS GIVEN AS A PERCENTAGE OF THAT OF 5-HYDROXYTRYPTAMINE

Substrate	Per cent oxidation rate	Substrate	Per cent oxidation rate
5-HT	100	Iso-5-hydroxytryptamine	26
4-HT	48	Tryptamine	130
6-HT	54	Iso-tryptamine	22
7-HT	74	Psilocybine	5
5-Methoxytryptamine ..	94	β-Hydroxybufotenine	0

effective at a concentration of 2×10^{-5} M, but produced a 95 per cent inhibition of enzymic activity at a concentration of 2×10^{-4} M; finally, 2-phenylcyclopropylamine produced, at a concentration of 10^{-5} M a 95 per cent reduction in the oxygen consumption.

Using 5-HT and 6-HT as substrates, and homogenates of guinea pig liver and kidney as enzyme preparations, cyanide 3×10^{-3} M produced, after 10 minutes, a 20 to 40 per cent inhibition of oxygen consumption, and semicarbazide 10^{-2} M a 40 to 45 per cent reduction. It is known that these substances, while ineffective on the intracellular amine oxidase of mammalian tissue, reduce the oxygen uptake by inhibiting further oxidation of the aldehyde formed in the primary oxidation reaction. In fact, addition of cyanide and semicarbazide hindered the appearance of any coloration of the reaction mixture in the vessels (brown with 5-HT, 6-HT and 7-HT, and bluish with 4-HT).

DISCUSSION

There is no doubt that the enzyme responsible for the oxidation of the examined amines is monoamine oxidase.

It appears from the results that all isomers of 5-HT are good substrates for amine oxidase, although none of them is as good as 5-HT. On the whole, the most easily attacked, among the isomers, is 7-HT, the most resistant 6-HT. In fact, rat liver MAO oxidises 6-HT at only 15 per cent of the rate of 5-HT. 5-Methoxytryptamine also and, as known for a long time, tryptamine are excellent substrates for MAO. It is remarkable that transposition of the lateral chain to the 2-position of the indole nucleus (iso-5-hydroxytryptamine and iso-tryptamine) produces

a sharp reduction of the MAO attack. Similarly, hydroxylation of the lateral chain, at the β-position, renders bufotenine completely resistant to MAO.

Results obtained in this investigation may be of some interest because 4–HT and 6–HT are likely to be biogenic indolealkylamines, the first deriving from the decarboxylation of 4–hydroxytryptophan[1,2], the second from the hydroxylation, at the 6-position of the indole ring, of

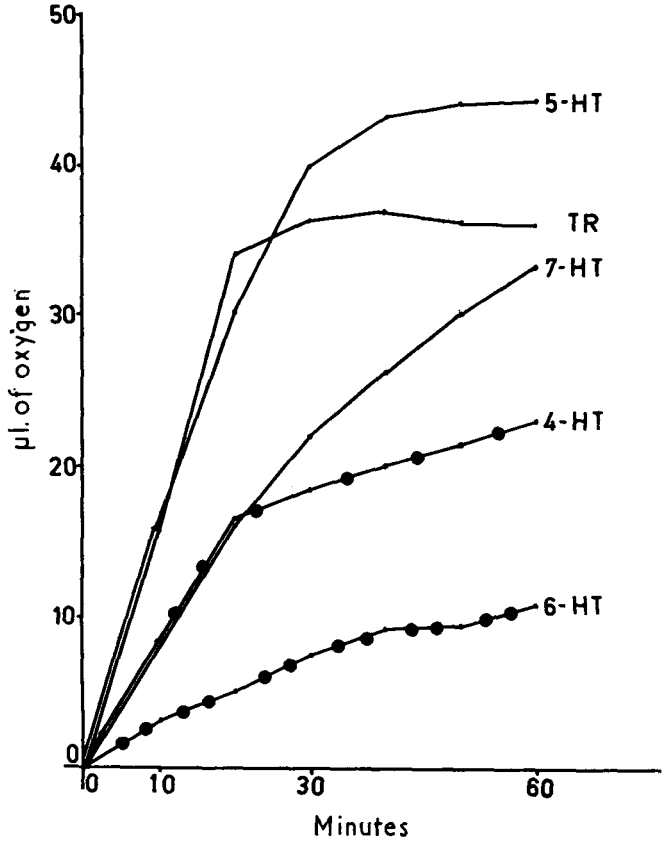

FIG. 1. Oxidation of 5-hydroxytryptamine (5–HT), 4-hydroxytryptamine (4–HT), 6-hydroxytryptamine (6–HT), 7-hydroxytryptamine (7–HT) and tryptamine (TR) by a homogenate of rat liver. Abscissa: time in minutes. Ordinate: µl. of oxygen used.

tryptamine[3], and because 5-methoxyindoleacetic acid, the deamination product of 5-methoxytryptamine, has been isolated from the bovine pineal gland[4]. Moreover, they can give a satisfactory explanation of the observation that the pharmacological actions produced *in vivo* by 4–HT and 4-hydroxytryptophan are more sustained than those produced by 5–HT and 5-hydroxytryptophan[5].

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