Effect of tranylcypromine sulphate on the metabolism of [^{14}C]tyramine *in vivo* in the rat

Oxidative deamination of tyramine is decreased by the inhibition of monoamine oxidase (MAO). Tyramine is an excellent substrate of MAO and is a principal tool in the study of this enzymatic activity and inhibitors of it, yet little is known of the effects of MAO inhibition on the metabolism of tyramine to compounds other than *p*-hydroxyphenylacetic acid, the principal metabolite *in vivo* in the rat (Tacker, McIsaac & Creaven, 1970). The metabolism of other amine substrates to acidic metabolites is decreased by inhibition of MAO and metabolism by minor pathways such as *N*-acetylation and conjugation of the unchanged amine is increased (Weissbach, Lovenberg & others, 1961; Schweitzer & Friedhoff, 1966; Musacchio & Goldstein, 1967). Various authors have reported that minor metabolites of tyramine include octopamine, tyrosol, and *N*-acetyltyramine (Nakajima & Sano, 1964; Musacchio, Kopin & Weise, 1965; Tacker & others, 1970), but the effect of MAO inhibition on the formation of these metabolites *in vivo* has been studied only for octopamine (Kakimoto & Armstrong, 1962; Carlsson & Waldeck, 1964; Masuoka, Alcaraz & Hansson, 1964; Kopin, Fischer & others, 1965). Having established in some detail the metabolism of [^{14}C]tyramine in the rat *in vivo* (Tacker & others, 1970), we examined the effects of pretreatment with tranylcypromine sulphate, an inhibitor of MAO, on this metabolism.

Male Sprague–Dawley rats, 200 g, were pretreated with daily intraperitoneal injections of tranylcypromine sulphate (10 mg/kg) in saline for 4 days and 5 mg/kg on day five. [1-^{14}C]Tyramine HBr (5·3 mCi/mmol, New England Nuclear Corp.) (shown to be radiochemically pure by two-dimensional paper chromatography and autoradiography) was administered to each rat (1·9 mg/kg) intraperitoneally in saline 4 h after the final dose of tranylcypromine. The rats were housed in stainless steel metabolism cages with free access to water but not food during the first 24 h after administration of the [^{14}C]tyramine. Urine was collected at intervals until 120 h after administration of the amine, adjusted to pH 1 with 2N HCl, and stored at $-10°$. Under these conditions tyramine added to urine is unaltered.

Pretreatment with tranylcypromine decreased the oxidative metabolism of tyramine and increased the production of non-oxidative metabolites. Percentages of urinary radioactivity excreted during the first 24 h for tranylcypromine treated and control animals, respectively, were *p*-hydroxyphenylacetic acid (pHPAA) 39·7 $\pm$ 4·7, 77·0 $\pm$ 2·2; pHPAA sulphate 1·4 $\pm$ 0·5, 0·5[1]; *p*-hydroxyphenylacetyl glycine (pHPAA-glycine) 8·3 $\pm$ 0·6, 10·5 $\pm$ 0·7; pHPAA glycine sulphate 0·4 $\pm$ 0·1, 0·7 $\pm$ 0·0; TA 6·6 $\pm$ 1·6, 1·4 $\pm$ 0·3; *N*-acetyltyramine (NAT) 1·8[1], 0·2 $\pm$ 0·2; NAT glucuronide 14·5[2], 1·4 $\pm$ 0·2; tyrosol glucuronide 2·0[2], 0·1 $\pm$ 0·1; tyrosol sulphate 0·9[1], 0·6 $\pm$ 0·1; unidentified metabolite A 0·9 $\pm$ 0·4, 2·2 $\pm$ 0·2; B 0·2 $\pm$ 0·1, 0·7 $\pm$ 0·2. (Except where indicated, figures are the mean of four animals $\pm$ s.d.). An approximately tenfold increase in tyramine glucuronide was observed but complete separation and determination was not achieved. All the metabolites of [^{14}C]tyramine excreted by control animals were identified in the urine of animals pretreated with tranylcypromine. In addition, the urine from pretreated animals contained octopamine (0·8 $\pm$ 0·1%) and five other metabolites not excreted by control animals and so far unidentified.

In a further series of experiments in which another inhibitor of MAO, pargyline hydrochloride (25 mg/kg a day in four animals), was used, essentially the same results were obtained except that less free pHPAA was excreted (22·7 $\pm$ 3·9%) after treatment with pargyline and an additional unidentified metabolite was observed.

[1] Based on one animal.
[2] Based on two animals.

The decrease in pHPAA and the increase in free and conjugated tyramine were expected from the known action of both inhibitors used. The increases in pHPAA sulphate and in the sulphate and glucuronide conjugates of tyrosol were unexpected since these compounds would normally require the action of MAO for their formation. It is possible that in the absence of MAO activity, mixed function oxidases in the endoplasmic reticulum are responsible for the initial oxidation of tyramine and that this location is more favourable to subsequent conjugation of the product. Alternatively, if oxidation is slowed, conjugation could precede oxidation. Rats given tranylcypromine excreted only 17·0 $\pm$ 3·1% of the administered radioactivity in 4 h whereas control animals excreted 66·6 $\pm$ 22·5% in 3 h. However, the total amounts of radioactivity excreted in 24 h are comparable for both groups of rats (84·5 $\pm$ 9·3% of the dose excreted by tranylcypromine-pretreated animals and 96·3 $\pm$ 4·0% by control animals).

Octopamine, one of the metabolites of tyramine excreted only when MAO was inhibited, is known to have pharmacological activity. The presence of five other metabolites not found in the urine of control animals raises the possibility that one or more of these compounds could also be related to some of the effects of tryamine observed in patients receiving MAO inhibitors.

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