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## Relationship between the pharmacological and biochemical properties of a monoamine oxidase inhibitor preferentially affecting 5-hydroxytryptamine oxidation

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Monoamine oxidase (MAO) present both in brain and peripheral tissues can act on various amines including noradrenaline, 5-hydroxytryptamine (5-HT) and dopamine. The majority of drugs known to inhibit MAO appear to affect equally the oxidation of these substrates. Evidence from a number of sources (Gorkin, 1963; Youdim & Sandler, 1967; Johnston, 1968; Youdim, Collins & Sandler, 1969) indicates that MAO is not a homogeneous enzyme but consists of a series of iso-enzymes with substrate specificity.

Clorgyline (M&B 9302: N-methyl-N-propargyl-3-(2,4-dichlorophenoxy)propylamine) is a compound which preferentially inhibits the oxidation of 5-HT by rat brain monoamine oxidase at concentrations which have a less marked effect on the oxidation of tyramine or of benzylamine (Johnston, 1968; Hall, Logan & Parsons, 1969).

Rats were treated with graded doses of either clorgyline, tranylcypromine, or phenelzine. The pharmacological response was measured using two tests: (i) prevention of the sedative activity of tetrabenazine in rats, and (ii) antagonism of reserpine-induced hypothermia in the rat. *In vitro* determinations were made of the degree of inhibition of the rat brain MAO using 5-HT, tyramine, and benzylamine as substrates. Changes in the brain levels of both noradrenaline and 5-HT were determined.

Clorgyline (4 mg/kg orally) produced 24% inhibition of tetrabenazine induced sedation and 53% antagonism of reserpine induced hypothermia. This dose of clorgyline produced almost complete (94%) inhibition of the oxidation of 5-HT by rat brain homogenates, 64% inhibition of the oxidation of tyramine and little or no effect on the oxidation of benzylamine. Increasing the dose of clorgyline to 8 or 16 mg/kg orally produced a progressive increase in the pharmacological response, but there was only slight further increase in the inhibition of the oxidation of 5-HT or benzylamine. There was, however, a graded increase in the inhibition of the oxidation of tyramine. Doses of clorgyline (4 to 16 mg/kg) produced increases in the brain concentrations of noradrenaline (131 to 160%) and 5-HT (137 to 165%).

With tranylcypromine and phenelzine there was little significant difference, at a particular dose level, in the degree of inhibition of the oxidation of the 5-HT, tyramine or benzylamine by rat brain tissue. Graded doses of both compounds, which produced a progressive increase in the pharmacological response, also produced increases in the inhibition of rat brain MAO and an increase in the concentrations of noradrenaline and 5-HT.

With clorgyline, there was significant correlation between the pharmacological response and inhibition of the oxidation of tyramine but not the oxidation of either benzylamine or 5-HT by rat brain tissue. Taking the data on clorgyline, tranylcypromine, and phenelzine together there was good correlation of both pharmacological responses with inhibition of the oxidation of tyramine by rat brain MAO.

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## Persistence of dose-related behaviour in mice

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Female adult mice injected with several doses of a dexamphetamine-chlordiazepoxide mixture, ratio 1 : 10 by weight, were placed singly on a horizontal wooden board with sixteen evenly spaced holes (Boissier & Simon, 1964) and their activity was assessed during 3 min by determining (1) the number of times they dipped their heads into the holes and (2) the amount of walking they did across the board.

Both forms of activity were greatly increased by moderate doses of the mixture, but with the highest dose and with most doses of the separate constituents there was little difference from saline controls. This was consistent with the effects of mixtures of amphetamine and chlordiazepoxide and of their separate constituents on the behaviour of rats in Y-mazes (Rushton & Steinberg, 1966) and also of amphetamine–amylobarbitone mixtures and their constituents on mice tested on a hole board (Joyce, Porsolt, Steinberg & Summerfield, 1968).

One week later the mice were retested on the same hole boards, but this time without any drugs or injections (Bradley, Joyce, Murphy, Nash, Porsolt, Summerfield & Twyman, 1968). The absolute amounts of both kinds of activity were now considerably lower, but the shapes of the " dose-response " curves strikingly resembled those obtained with the drugs on the first occasion.

Analogous long-term effects have previously been found with amphetamine–barbiturate mixtures in rats where a single drug experience had detectable effects on behaviour for periods of up to three months (Rushton, Steinberg & Tomkiewicz,