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DEPRENYL IS A SELECTIVE INHIBITOR OF BRAIN MAO-B IN THE LONG-TERM TREATMENT OF PARKINSON'S DISEASE

Deprenyl is a selective inhibitor of monoamine oxidase (MAO) type B (Knoll, 1976) that does not induce the hypertensive response to oral tyramine (Elsworth, Glover, Reynolds, Sandler, Lees, Phuapradit, Shaw, Stern & Kumar, 1978) (the 'cheese effect') which limits the use of other MAO inhibitors. It has been found to be of therapeutic benefit in Parkinson's disease when administered in conjunction with L-Dopa and a peripheral decarboxylase inhibitor (Birkmayer, Riederer, Youdim & Linauer, 1975; Birkmayer, Riederer, Ambrozi & Youdim, 1977; Lees, Shaw, Kohout, Stern, Elsworth, Sandler & Youdim, 1977). This effect is thought to be due, at least in part, to an increase in brain dopamine since MAO type B is reported to be responsible for the oxidation of this neurotransmitter in man (Glover, Sandler, Owen & Riley, 1977).

In vitro studies of deprenyl inhibition of human brain MAO show a concentration of 10^{-6} mol l⁻¹ to be selective towards the B-form, while oxidation of 5-hydroxytryptamine, and MAO-A substrate, is hardly effected (Glover *et al.*, 1977). However, recent post mortem studies have shown that *in vivo* this selectivity is less pronounced (Riederer, Youdim, Rausch, Birkmayer, Jellinger & Seemann, 1978) (see Table 1), an equivalent concentration inhibiting 5-hydroxytryptamine oxidation by approximately 70%. Indeed, a Parkinsonian patient dying from the progression of the disease after 7 days treatment with 100 mg deprenyl daily (ten-fold the normal dose) exhibited total inhibition of all MAO activity with a consequent rise in the brain levels of dopamine and 5-hydroxytryptamine (Riederer *et al.*, 1978). Thus to understand the mechanism of action of deprenyl in

Table 1 Percentage inhibition (mean $\pm$ s.e. mean) of human brain MAO after deprenyl treatment

Substrates: Treatment:	Dopamine		5-hydroxytryptamine	
	Short term	Long term	Short term	Long term
Caudate	85.6 $\pm$ 1.8	89.0	65.7 $\pm$ 5.0	70.3
Putamen	83.4 $\pm$ 2.2	89.2	61.7 $\pm$ 5.7	66.1
Pallidum	86.5 $\pm$ 1.9	90.5	70.8 $\pm$ 3.7	74.4
Thalamus	86.0 $\pm$ 4.2	77.3	50.0 $\pm$ 6.8	55.7
S. nigra	88.0 $\pm$ 2.2	88.7	74.5 $\pm$ 4.0	66.7
Raphé	86.0 $\pm$ 2.6	85.4	70.6 $\pm$ 4.1	72.3
Amygdalae	82.0 $\pm$ 2.8	85.6	70.3 $\pm$ 4.5	69.8

Short term: seven patients treated with 10 mg deprenyl for 6 ± 1.8 days.

Long term: one patient treated with 10 mg deprenyl for over 4 years.

Parkinson's disease it is important to ascertain whether or not long-term treatment with the drug involves a further loss of specificity and hence a functionally important inhibition of MAO type A.

A senile Parkinsonian patient (male, 81 years) receiving 10 mg deprenyl and levodopa as Madopar (625 mg) daily for over 4 years died from heart failure 8 h after the morning medication. Brain samples were obtained 2 h post mortem and assayed for MAO activity (Tipton & Youdim, 1976), using dopamine and 5-hydroxytryptamine as substrates. The results are shown in Table 1 and compared with the inhibition exhibited by seven patients who had short-term treatment with deprenyl (10 mg day⁻¹) before death. Full details of these patients and controls are given by Riederer *et al.* (1978).

It is notable that the inhibition of the oxidation of both amines is not significantly increased after long-term treatment with deprenyl. This suggests that the inhibitor does not further accumulate in the brain after the first few days, presumably reflecting a rapid metabolism to amphetamine and methamphetamine (Reynolds, Elsworth, Blau, Sandler, Lees & Stern, 1978). These results are consistent with those of Stern, Lees & Sandler (1978), who show no clinically

significant change in tolerance to tyramine after 18 months treatment and they serve to underline the safety of the drug in clinical practice (Birkmayer *et al.*, 1977; Lees *et al.*, 1977).

Thus we have demonstrated that long-term treatment with deprenyl does not result in a further loss of its selective inhibition of MAO. Studies are underway to assess the effect of this inhibition on the central concentrations of monoamine neurotransmitters.

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