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DEPRENYL IS METABOLIZED TO METHAMPHETAMINE AND AMPHETAMINE IN MAN

(−)-Deprenyl (Figure 1) is a monoamine oxidase (MAO) inhibitor with selective action against the B form of the enzyme (Knoll, 1976). Its administration prevents the degradation of dopamine in human brain, where this is a substrate for MAO B (Glover, Sandler, Owen & Riley, 1977); however, it leaves the peripheral mechanisms normally preventing a hypertensive response following tyramine administration intact (Elsworth, Glover, Reynolds, Sandler, Lees, Phuapradit, Shaw, Stern & Kumar, 1978), although this amine interacts adversely with all other irreversible MAO inhibitors so far described. Because of this freedom from what has come to be called the 'cheese effect', deprenyl, in combination with L-dopa, provides both a rational and safe therapy for the treatment of Parkinson's disease (Birkmayer, Riederer, Ambrozi & Youdim, 1977; Lees, Shaw, Kohout, Stern, Elsworth, Sandler & Youdim, 1977).

Little is known of the metabolism of deprenyl either in man or animals. However, by analogy with that of the not dissimilar MAO inhibitor, pargyline (N-methyl-N-propynylbenzylamine), which is metabolized in mammals to benzylamine (Edwards & Blau, 1973; Durden, Philips & Boulton, 1976), it seemed possible that deprenyl might be degraded to amphetamine. Indeed, a preliminary *in vitro* study (unpublished) showed that rat liver homogenates convert some of the drug to amphetamine and methamphetamine. We therefore sought to identify these compounds in human urine after the administration of therapeutically-active doses of (−)-deprenyl.

Urine samples (24 h) were collected from six normal male volunteers on the third day each of test and placebo administration during the course of a double-blind crossover study of the effects of (−)-deprenyl hydrochloride on sleep. The volunteers, who received either 5 or 10 mg of this drug (Table 1) in a single dose daily, were free from other medication whilst the experiment lasted.

Urine was stored at −20°C and thawed immediately before assay. Amphetamines in 0.5 ml urine were quantified after adding an internal standard, *p*-methylphenylethylamine. Samples were then subjected to acid hydrolysis (pH 1) at 100°C for 1 h to release any conjugates present. Quantification was achieved by extraction of the amines from alkaline urine into hexane, back-extraction into acid, derivatization with pentafluorobenzoyl chloride and

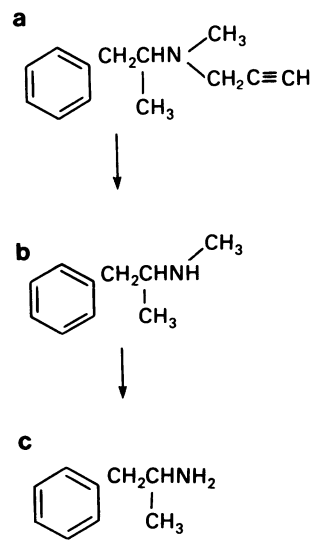

Figure 1 The structural formulae of a) deprenyl, b) methamphetamine and c) amphetamine.

gas chromatography-mass spectrometry (GC-MS) of the resultant pentafluorobenzamides (Reynolds, King, Elsworth & Sandler, unpublished observations). This method of detection involves monitoring ions of m/e 118 (corresponding to methyl-substituted phenylethyl moieties) and is specific for the two amphetamines and the internal standard used here.

Unchanged deprenyl was sought by extracting alkaline urine with ether, back-extracting into acid and re-extracting into ether after adding excess alkali. For quantification by GC-MS, this ether solution was injected directly on to a 6 ft column of PPE-21 at 200°C, monitoring the major ions associated with the mass spectrum of the drug (m/e 56 and 96).

Urinary output values of the two major metabolites of deprenyl are shown in Table 1. Substantial amounts of methamphetamine and rather less amphetamine were identified in all samples collected during drug administration but were not present in control specimens. Methamphetamine accounted for a quantitatively major proportion of the administered dose, with rather less amphetamine being excreted. The simple relationship between (−)-deprenyl and these two compounds is shown in Figure 1. It is of interest that methamphetamine output was greatest in the two most highly acid urine samples. Although this finding may have occurred by chance, it is consistent with the known effect of urinary pH on the excretion of this compound (Beckett & Rowland, 1965). Indeed, the anomalously high excretion value in subject 2 might be explicable in terms of an alkaline urine on the previous day causing relative methamphetamine retention, with later rebound.

The proportion of this amine excreted after deprenyl ingestion is comparable with that detected after an oral dose of methamphetamine itself (Beckett & Rowland, 1965). Amphetamine is probably derived from the demethylation of methamphetamine (Figure 1), although demethylation of (−)-deprenyl followed by loss of the propynyl group cannot be ruled out. Thus virtually all administered (−)-deprenyl was metabolized via methamphetamine by an as yet unknown enzymatic mechanism. A careful search for unmetabolized deprenyl proved negative, even though the method employed is sensitive down to a concentration of less than 10 ng/ml, corresponding to no more than 1% of the administered dose.

The dealkylation process seems likely to take place in the liver (Caldwell, 1976) and, because of their lipophilic nature, the amphetamines liberated into the blood stream are likely to cross the blood-brain barrier to gain access to the brain. Thus, corresponding pharmacological effects would presumably be evident if the dose were sufficiently large. It is here that an important point must be taken into account: the (−)-isomer of deprenyl possesses substantially greater MAO inhibitory action than the (+)-form (Knoll, 1976) and the former alone is now used in clinical practice. However, the central effect of (+)-amphetamine is 3–4 times larger than that of the (−)-isomer (Innes & Nickerson, 1977). Although we have not yet made direct measurements of the optical activity of the amphetamines generated from deprenyl, it seems likely that they will show the (−)-configuration, for Magyar, Vizi, Ecsery & Knoll (1967) showed that (+)-deprenyl has considerably greater amphetamine-like action than its (−)-isomer.

What is the significance of these findings in clinical practice? The therapeutically-effective dose of (−)-deprenyl given in combination with L-dopa in parkinsonism is no more than 10–15 mg (Birkmayer *et al.*, 1977; Lees *et al.*, 1977), an amount unlikely to produce any marked degree of central amphetamine-like action, although a contribution of amphetamine to the total pharmacological response cannot be ruled out. Indeed, some improvement in disability was demonstrated during a recent trial of (+)- and (−)-amphetamine in Parkinson's disease (Parkes, Tarsy, Marsden, Bovill, Phipps, Rose & Asselman, 1975); those patients on L-dopa plus amphetamine derived greater benefit than those on L-dopa or on amphetamine alone. Perhaps the benefit accruing from the L-dopa plus deprenyl treatment combination should be reassessed in the light of these considerations.

The unique lack of 'cheese effect' (Elsworth *et al.*,

Table 1 Urinary output of amphetamine and methamphetamine, the two major metabolites of deprenyl

Subject	(−)-Deprenyl HCl (mg/24 h)	Urine volume (ml)	pH	Amphetamine excretion (mg)	Amphetamine excretion Equivalent % dose	Methamphetamine excretion (mg)	Methamphetamine excretion Equivalent % dose
1	5	1435	6.4	0.48	15.8	1.67	50.2
2	5	1400	5.9	0.59	19.5	3.47	104.0
3	10	2100	6.1	1.05	17.3	3.42	51.3
4	10	1190	6.4	0.88	14.5	3.55	53.2
5	10	1280	5.8	0.67	11.1	4.98	74.6
6	10	1600	6.8	0.74	12.2	3.08	46.2
Mean					15.1		63.3

1978) of this MAO inhibitor might even be explicable in terms of the protection by chronic amphetamine treatment on the tyramine pressor response in man (Cavanaugh, Griffith & Oates, 1970). Freedom from this effect is still apparent at substantially higher deprenyl dosage (Stern, Lees & Sandler, 1978). It seems possible that such regimens will be helpful in depressive illness, if preliminary trials can be confirmed (Varga & Tringer, 1967; Mendlewicz & Youdim, 1978). If subsequent investigations show high dosage (–)-deprenyl treatment to be useful in depression, it may well be necessary to minimize the risk of adverse reactions, e.g. amphetamine psychosis (Kety, 1959), by maintaining a maximally acid urine to facilitate amphetamine excretion (Beckett & Rowland, 1965).

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Note added in proof:

The recent paper by Simpson (1978) shows (–)-deprenyl to possess indirectly acting sympathomimetic properties *in vivo*. We wish to point out that these findings are explicable in terms of the pharmacological effects of the metabolites of (–)-deprenyl.

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