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REVIEW

The acetylenic monoamine oxidase inhibitors clorgyline, deprenyl, pargyline and J-508: their properties and applications

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The article presents a short review of some of the properties of the acetylenic inhibitors of monoamine oxidase currently under investigation: clorgyline, (−)-deprenyl, pargyline and J-508. Their substrate-selective inactivation, mechanism of inhibition, titration and pharmacology with respect to monoamine oxidase are critically discussed.

In 1968, Johnston showed that the irreversible acetylenic inhibitor clorgyline (*N*-methyl-*N*- propargyl-3-(2,4-dichlorophenoxy)-propylamine) inhibited the oxidative deamination of 5-hydroxytryptamine by rat brain monoamine oxidase (MAO, monoamine O_2: oxidoreductase (flavine containing), EC 1.4.3.4) at concentrations that were much lower than were required for the inhibition of benzylamine oxidation (Johnston 1968). When tyramine was used as substrate, a biphasic pattern of inhibition was found. Such a result has been found for a number of tissues, including the rat liver (Hall et al 1969, see Fig. 1). Johnston (1968) suggested that these results were due to the presence of two forms of monoamine oxidase, which are now generally termed MAO-A and -B, where the -A form is sensitive to inhibition by clorgyline, and the -B form more resistant to inhibition. This conclusion was reinforced by the introduction of the MAO-B selective inhibitor (−)-deprenyl (phenyl-isopropyl-methyl-propinylamine) (Knoll & Magyar 1972) and its more potent analogue J-508 (*N*-methyl-*N*-propargyl-(1-indanyl)-ammonium hydrochloride) (Knoll et al 1978). The structures of the compounds are given in Fig. 2. In addition, a variety of agents, ranging from the tricyclic noradrenaline uptake inhibitors to local anaesthetics, have been found to inhibit MAO activity in a substrate-selective manner (for review, see Fowler et al 1978).

In this article, the most commonly used substrate-selective inhibitors, the acetylenic inhibitors of which clorgyline and (−)-deprenyl are the most well known, have been reviewed with respect to their properties, since it has been these compounds that have provided the main impetus for research in MAO over the last decade.

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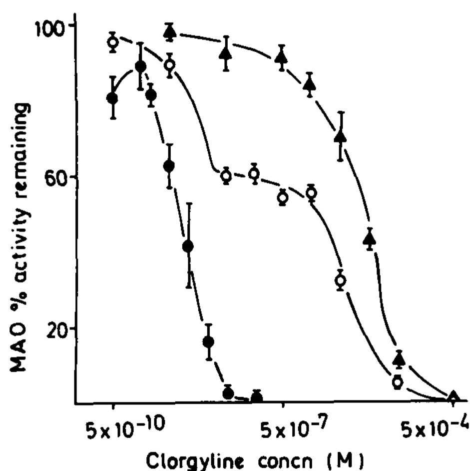
Substrate-specificity of monoamine oxidase

Most of the early studies with clorgyline and (−)-deprenyl were performed on either rat brain or liver, where it was shown that 5-hydroxytryptamine was the preferred substrate for MAO-A and benzylamine the preferred substrate for MAO-B, whilst tyramine was found to be deaminated by both enzyme forms (Johnston 1968; Hall et al 1969). However, this substrate specificity is by no means universal. In Table 1, the data published over the last ten years have been investigated in order to determine the frequency of occurrence of the metabolism of a given substrate by a given enzyme form. The 'common substrate' tyramine, for example, is in fact metabolized by both enzyme forms in only 29 out of 51 tissues (see Table 1). Most of the possible combinations of the substrate specificities of the two forms of MAO have been reported. Some examples of 'unusual' combinations towards three of the most commonly used substrates are shown in Table 2. It has been found, for both 5-HT and β-phenethylamine as substrate in a variety of tissues, that the substrate specificities of the two forms of MAO are dependent upon the concentration of substrate used to assay for enzyme activity (Kinemuchi et al 1979; Ekstedt 1979; Dial & Clarke 1979; Suzuki et al 1979; Peers et al 1980; Sourkes 1980), which, as many of the early investigations were undertaken with rather high substrate concentrations, may



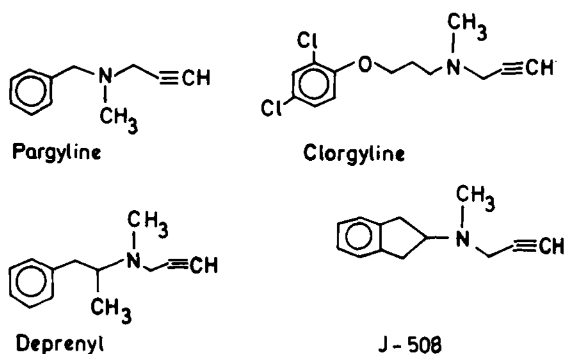


FIG. 2. The structures of the four acetylenic inhibitors of monoamine oxidase discussed in this review.

FIG. 1. The effect of clorgyline upon the in vitro deamination of 0·25 mM 5-hydroxytryptamine (●), 0·25 mM tyramine (○) and 0·15 mM benzylamine (▲) in crude homogenates of rat liver. Clorgyline was preincubated with the homogenates for 20 min at 37° before addition of substrate to assay for enzyme activity. Abscissa: molar concentration of clorgyline at preincubation; ordinate: % activity of MAO remaining. Each point represents the mean ± s.e.r. of triplicate determinations for three homogenates, each derived from the livers of two rats.

account for some, but not all, of the 'unusual' substrate specificities. Thus it is of importance to note that the two enzyme forms are defined by their inhibitor sensitivities, rather than by their substrate specificities. The two forms of MAO, defined in this manner, have been shown by a variety of biochemical techniques, including mixed substrate experiments and enzyme titration (see below), to be homogenous in the human brain (Roth 1976; Fowler et al 1980a,b), human platelet (Winter et al 1978; Fowler et al 1979a; McEntire et al 1979; Fowler & Wiberg 1980), rat heart (Fowler & Callingham 1979) and rat liver (Fowler & Oreland 1980a,b).

Mechanism of inhibition of monoamine oxidase and its application for the estimation of the number of enzyme active centres

The initial investigations into the nature of the inhibition of MAO by acetylenic inhibitors were undertaken with pargyline (*N*-methyl-*N*-benzylpropinylamine) as the inhibitor. Pargyline was found to produce irreversible inhibition of purified ox kidney MAO by acting as an electron donor, whereby reduction of the flavine prosthetic group caused, or was accompanied by, the irreversible binding step (Hellerman & Erwin 1968). Furthermore, in this tissue, the inhibitor forms a stable adduct with the flavine group (Chuang et al 1974). In the pig liver, pargyline reacts stoichiometrically with the MAO (Oreland et al 1973a) to form an adduct with the flavine group in a 1 : 1 ratio (Oreland et al 1973b). Deprenyl has also been found to react stoichiometrically with rat liver MAO (Youdim 1976). The altered fluorescence spectrum produced by the reaction between purified MAO from ox kidney and pargyline could be reproduced photochemically by the reaction between *NN*-dimethyl-2-propynylamine and flavoquinone (Zeller et al 1972).

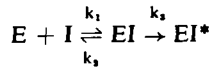
These properties of pargyline have been utilized for the development of a radioactive binding assay for the estimation of the concentration of MAO active centres in rat liver mitochondria (Parkinson & Callingham 1980), and for the identification of MAO subunits upon SDS gel electrophoresis of pargyline-treated mitochondria (see e.g. Oreland et al 1973a; McCauley 1976; Callingham & Parkinson 1979; Cawthon & Breakefield 1979).

The precise mechanism of inhibition of MAO by pargyline and its related compounds has been excellently reviewed elsewhere (Abeles & Maycock

Table 1. Variation in the substrate specificity of MAO-A and -B from tissue to tissue. The data are taken from the literature 1968–1980.

		% of tissues where substrate is oxidized by:		
Substrate	No. of tissues	MAO-A alone	MAO-A + MAO-B	MAO-B alone
5-HT	35	61	19	20
Tyramine	51	18	57	25
Dopamine	13	29	53	18
Kynuramine	39	12	63	25
β-Phenethylamine	36	6	22	72
Benzylamine	24	0	4	96

1976; Singer & Salach 1981). Briefly, the acetylenic inhibitors of MAO appear to inhibit enzyme activity by a 'suicide reaction', whereby an initial competitive interaction between inhibitor and enzyme is followed by formation of an irreversible adduct. Thus, the mode of inhibition of MAO by the acetylenic inhibitors can most simply be written:



$$E + I \underset{k_2}{\overset{k_1}{\rightleftharpoons}} EI \overset{k_3}{\rightarrow} EI^*$$

where E = enzyme, I = inhibitor, EI = reversible enzyme-inhibitor complex, and EI* = irreversible enzyme-inhibitor adduct. Within this model, it has been suggested that the MAO-A selectivity of

Table 2. The forms of MAO responsible for the oxidation of three monoamines in a variety of tissues. The references cited are given beneath the Table. Abbreviations: 5-HT, 5-hydroxytryptamine; Tyr, tyramine; PEA; β-phenethylamine; A, MAO-A; B, MAO-B; A + B, MAO-A + MAO-B.

	Form of MAO oxidizing:			
'Standard' substrate specificity	5-HT	Tyr	PEA	Ref cit.
e.g. Human brain and heart, Rat brain and liver	A	A + B	B	1–7
'Unusual' substrate specificity				
Rat Heart	A	A	A	8
Reindeer brain	A	A	A + B	9
Elk brain	A	A + B	A + B	9
Ox brain	A + B	A + B	A + B	9,10
Ox heart	A + B	A + B	B	11
Moorhen heart	B	B	A + B	12
Human platelet	B	B	B	13

References
1, Tipton et al 1973; 2, Hall et al 1969; 3, Roth 1976; 4, Parkinson & Callingham 1979; 5, Johnston 1968; 6, Yang & Neff 1973; 7, Houslay & Tipton 1974; 8, Lyles & Callingham 1979; 9, Fowler et al (1981); 10, Achee & Gabay 1977; 11, Mantle et al 1976; 12, B. A. Callingham & B. J. Browne, unpublished results; 13, Donnelly & Murphy 1977.

clorgyline and the MAO-B selectivity of deprenyl is determined by the reversible rather than the irreversible reaction (Tipton & Mantle 1981). In the case of clorgyline, the MAO selectivity could be due, at least in part, to selective partition of the lipid-soluble inhibitor into the vicinity of an enzyme active centre occluded by lipid (Houslay 1977).

Recent studies have indicated that clorgyline and (−)-deprenyl are such potent inhibitors of MAO-A and -B, respectively, that the concentrations of the free inhibitors are depleted by the formation of the EI and EI* complexes (see e.g. Fowler & Callingham 1978; Fowler et al 1980a). J-508 has also been found to inhibit the activity of MAO-B in a similar manner (Fowler et al 1979b, 1980b; Fowler & Wiberg 1980). Under conditions whereby all reactions between enzyme and inhibitor have reached completion, the inhibition of enzyme activity should be directly proportional to the inhibitor concentration used, and, in the absence of binding of the inhibitor to sites other than the active centre of the enzyme form, the concentration of the inhibitor required to produce exactly 100% inhibition of enzyme activity is equal to the concentration of available active centres of the enzyme form in the assay preparation (see Fowler & Callingham 1978, 1979). Such conditions have been determined for human brain MAO-A and -B (Fowler et al 1980a,b), human platelet MAO-B (Fowler & Wiberg 1980), human placental MAO-A (Y. Wakui, H. Kinemuchi, K. Kamijo and L. Oreland, manuscript in preparation), rat brain MAO-B (Fowler et al 1979b), rat heart MAO-A (Fowler & Callingham 1979), and rat liver MAO-A and -B (Egashira et al 1976; Fowler & Callingham 1978; Fowler & Oreland 1980a). These conditions vary considerably from tissue to tissue, and are summarized in Table 3. Titration of ox liver, rat liver and human platelet MAO by pargyline has also been reported (Hellerman & Erwin 1968; Oreland & Ekstedt 1972; Wiberg & Oreland 1976), although no adequate estimate of the degree of non-specific binding of this inhibitor was made in these studies. In a recent investigation, the concentrations of MAO-A and -B in rat liver mitochondrial membranes, estimated as described in Table 3, were found to be approximately 11 and 13 pmol mg protein^{-1}, respectively (Fowler & Oreland 1980a). These values are in good agreement with the 30 pmol mg protein^{-1} concentration of MAO-A plus MAO-B active centres found for rat liver mitochondrial membranes by a [^{3}H]pargyline binding assay (Parkinson & Callingham 1980).

In nearly all tissues examined, benzylamine is apparently a substrate for MAO-B alone (Table 1). However in the rat heart, it is a substrate for both forms of the enzyme with similar K_m values for each (Lyles & Callingham 1974, 1975). Inhibition of the enzyme activity with clorgyline indicates an A:B activity ratio of 1·25:1. However, the use of [^{3}H]-pargyline produces a concentration ratio of 19:1. These seemingly discrepant observations lead directly to the conclusion that the relative turnover rate constant for benzylamine deamination by MAO-B in the rat heart is about 15 times that for MAO-A (Parkinson et al 1980). It remains to be seen whether or not these turnover rate constants bear the same relationship in other tissues or species. It does however imply that benzylamine may possibly be deaminated by MAO-A in tissues where it is normally a substrate for MAO-B, a supposition borne out by

Table 3. Conditions required for the titration of monoamine oxidase in a variety of tissues.

Tissue/Enzyme form	Inhibitor	Minimum Preincubation time	n.s.b.	Notes
Human brain				
MAO-A	Clorgyline	180 min	0	
MAO-B	(−)-Deprenyl	180 min	+ + +	Not useful
	J-508	120 min	0	Compensate for optical activity
Human platelets				
MAO-B	J-508	90 min	+	Compensate for optical activity
	Pargyline	240 min	n.d.	
Human placenta				
MAO-A	Clorgyline	120 min	0	
Rat brain				
MAO-B	J-508	>240 min	0	Reaction not gone to completion after 240 min. Rat brain MAO-B activity decreases during long preincubation periods at 37 °C
Rat heart				
MAO-A	Clorgyline	20 min	0	
Rat liver				
MAO-A	Clorgyline	240 min	+	Not useful in crude homogenates, since clorgyline is metabolised in vitro by an SKF 525A-sensitive enzyme system
MAO-B	(−)-Deprenyl	240 min	n.d.	

Key: n.s.b. = non-specific binding, rated as: 0, no significant non-specific binding; +, non-specific binding present to a small extent; + + +, considerable non-specific binding; n.d., non-specific binding not adequately determined. The data for human platelet titration refers to isolated platelets. No information is as yet available on the titration of platelet MAO-B in samples of platelet-rich plasma. Radioactive binding assays with [^{3}H]harmaline (Nelson et al 1979b) and [^{3}H]pargyline (Parkinson & Callingham 1980) have also been described for rat brain MAO-A and rat liver MAO-A + MAO-B, respectively.

the rat liver where a component of MAO-A activity can be revealed following inhibition of MAO-B by over 95% by pretreatment with deprenyl.

The enzyme titration method, under the conditions described in Table 3, has been used to determine the maximum molecular turnover numbers of MAO-A and -B towards a variety of substrates in five tissues (see Table 4). The K_m values, but not the molecular turnover numbers are dependent upon the pH of the buffer medium in a manner consistent with the hypothesis that the unionized form of the substrate is the form preferentially metabolized by the enzyme (McEwen et al 1968; Williams 1974). In addition, both molecular turnover numbers and K_m values are increased with increasing oxygen concentration, since MAO follows a ping-pong reaction pathway (Tipton 1968; Fischer et al 1968; Oi et al 1970; Houslay & Tipton 1973; Roth 1979; Fowler & Oreland 1980a). Thus, for given pH and oxygen concentrations, the K_m and maximum molecular turnover numbers reflect the basic kinetic parameters of the enzyme forms towards their monoamine substrates, independent of the protein concentration or purity of the enzyme source tested.

Both rat heart MAO-A and human brain MAO-B activities have been found to increase with age, due entirely to an increased concentration of the respective enzyme forms, without changes in either the K_m or molecular turnover numbers towards their substrates (Fowler & Callingham 1979; Fowler et al 1980c). A similar result was found for the increased MAO-B activity of the rat brain after hemitransection (Fowler et al 1979b). Furthermore, the variation in activity of both human brain MAO-A and human platelet MAO-B from individual to individual is due also to a variation in the concentration of otherwise identical enzyme active centres (Oreland 1980; Fowler et al 1980a; Fowler & Wiberg 1980), in line with a similar finding for the variation in activity of rat brain MAO-A with age, estimated with a [^{3}H]harmaline binding assay (Nelson et al 1979a).

Thus, it would seem that, under the right conditions, the use of the acetylenic inhibitors to titrate the concentrations of MAO-A and -B can provide a simple, but effective insight into the molecular changes taking place when the activity of MAO is influenced by either physiological, pathological or biochemical factors. The interaction between MAO and the acetylenic inhibitors can also be used to titrate the inhibitor, rather than the enzyme. Such an application has been reported by Campbell et al (1979b) for the determination of the concentration of pargyline in human blood after an oral dose of this inhibitor.

Table 4. Kinetic properties of monoamine oxidase from 5 different tissues. MTN = molecular turnover number, calculated as V_{max}/concentration of appropriate enzyme form, and expressed as mol (mole enzyme form)$^{-1}$ min^{-1} (assayed at pH 7·8 and at 37 °C). The values are calculated as means ± s.e.m. for determinations under assay atmospheres of oxygen or air as appropriate. The concentrations of oxygen in the assay media were: oxygen, 1085 μM; air, 217 μM (see Fowler & Oreland 1980a).

	Kinetic parameters			
	Oxygen		Air	
	K_m (μM)	MTN	K_m (μM)	MTN
Human cerebral cortex				
5-HT (MAO-A)			35 ± 3	380 ± 20
PEA (MAO-B)	5·8 ± 0·5	1870 ± 90	1·6 ± 0·3	650 ± 20
BZ (MAO-B)	33 ± 1	960 ± 70	19 ± 1	540 ± 30
Human platelets				
PEA (MAO-B)	2·9 ± 0·1	790 ± 20	0·1 ± 0·1	150 ± 1
BZ (MAO-B)	57 ± 5	770 ± 30	26 ± 2	380 ± 20
TRYPT (MAO-B)	6·8 ± 0·8	130 ± 10	1·1 ± 0·4	40 ± 2
Human placenta				
5-HT (MAO-A)			68 ± 2	140 ± 10
Rat heart homogenates				
5-HT (MAO-A)	129 ± 43	29600 ± 2400	88 ± 37	20500 ± 2000
TYR (MAO-A)	73 ± 24	36100 ± 2000	38 ± 18	24600 ± 1100
PEA (MAO-A)	64 ± 26	5100 ± 900	38 ± 15	3400 ± 500
Rat liver mitochondria				
5-HT (MAO-A)	23 ± 3	2120 ± 170	16 ± 1	1610 ± 95
PEA (MAO-B)	20 ± 2	5390 ± 450	17 ± 2	2670 ± 170
BZ (MAO-B)	93 ± 7	3360 ± 270	60 ± 5	2140 ± 90

Key: 5-HT, 5-hydroxytryptamine; TYR, tyramine; PEA, β-phenethylamine; BZ, benzylamine; TRYPT, tryptamine. Data calculated from Fowler et al 1980a,b (human brain), Fowler & Wiberg 1980 (human platelet), Y. Wakui, H. Kinemuchi, K. Kamijo & L. Oreland, in preparation (human placenta), Fowler & Callingham 1979 (rat heart), Fowler & Oreland 1980a (rat liver).

Physiological usefulness of the acetylenic inhibitors of MAO

Clorgyline and (−)-deprenyl have been used in a number of in vivo studies. Although clorgyline appears to show some selectivity in vivo, this selectivity is not as marked as in vitro (Bevan-Jones et al 1972; Christmas et al 1972; Yang & Neff 1974). However, such selectivity as is can be retained even after repeated administration of clorgyline, provided that the doses given are sufficiently low (Campbell et al 1979a). Deprenyl has been shown to be selective in vivo, albeit not as selective as in vitro (Prozialek & Vogel 1978), and retains its substrate-selectivity after repeated doses (Ekstedt et al 1979), although this latter finding has been disputed (Waldmeier & Felner 1978). Pargyline does not show any pronounced MAO-B selectivity in vivo, particularly after repeated treatment (Fuller et al 1978; Campbell et al 1979a), although selectivity can be produced in vivo by prior protection of the MAO-A form with a reversible MAO-A selective inhibitor, such as harmaline (Fuller et al 1978; for review see Fuller 1978). Little is known, however, about the metabolism of these compounds, although deprenyl has been shown to be metabolized in vivo to methamphetamine and amphetamine (Reynolds et al 1978), and clorgyline has been found to be metabolized in vitro in the rat liver by an enzyme system sensitive to inhibition by SKF 525A (Fowler 1980).

The clinical usefulness of the acetylenic inhibitors of MAO currently available is limited. At present, only deprenyl, which appears to be without the 'cheese' effect often associated with MAO inhibitors (Knoll 1976; Elsworth et al 1978) is starting to be used clinically for its potentiating properties of the antikinetic effect of L-dopa in patients with Parkinson's disease (Birkmeyer et al 1975; Youdim et al 1979; Streifler et al 1980). Initial studies, however, have also indicated that clorgyline (but not (−)-deprenyl nor pargyline) may be of use for the treatment of certain depressive illnesses (Murphy et al 1979; Mendis et al 1981).

The acetylenic inhibitors of MAO have been used with some success in experiments where the effect of accumulation of monoamines upon a variety of physiological and behavioural parameters has been studied. For example, selective in vivo inhibition of brain MAO-A by low doses of clorgyline (or

Lilly 51641*, also a selective MAO-A inhibitor) decreases the incidence of stereotyped jumping behaviour produced by naloxone in mice rendered dependent upon morphine. This modification in the abstinence syndrome is not found when either MAO-B alone, or both forms of the enzyme are inhibited (Garzon et al 1979). It is to be hoped that studies of this type will further our knowledge of the function of the two forms of MAO in the brain.

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* *N*-[2-(*o*-Chlorphenoxy)ethyl]cyclopropylamine MCL.

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