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Selective inhibition of monoamine oxidase type B by MDL 72145 increases the central effects of L-DOPA without modifying its cardiovascular effects

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1 The potential of a new, potent, irreversible and selective inhibitor of monoamine oxidase type B, (E)-2-(3,4-dimethoxyphenyl)-3-fluorallyamine (MDL 72145), to augment the effects of L-DOPA in an animal model which reproduces the biochemical defect of Parkinson's disease has been evaluated.

2 In rats bearing unilateral 6-hydroxydopamine lesions of the nigro-striatal dopamine pathways, both MDL 72145 and clorgyline, a selective inhibitor of MAO A, augmented the contralateral turning response to L-DOPA combined with carbidopa.

3 The potential of inhibitors of MAO to interact adversely in the periphery with L-DOPA was investigated in the pithed rat; L-DOPA was given either intravenously or intraduodenally.

4 Clorgyline consistently potentiated L-DOPA when given 18 h before testing. Neither MDL 72145 nor the selective inhibitor of MAO B, L-deprenyl, augmented the cardiovascular effects of intraduodenally administered L-DOPA.

5 The data provide no reason to suppose that MDL 72145 would be very different in clinical use from L-deprenyl which is both effective and well-tolerated as an adjunct to the L-DOPA-based therapy of Parkinson's disease.

Introduction

A logical approach to augmenting the therapeutic effects of L-DOPA in Parkinson's disease is to use inhibitors of monoamine oxidase (MAO) in order to decrease the metabolism of the dopamine formed centrally from the amino acid by the action of aromatic L-amino acid decarboxylase (AADC). However, inhibitors of MAO type A, or mixed type A and type B inhibitors, produce dangerous cardiovascular complications when combined with L-DOPA, despite the routine use of an inhibitor of AADC selective for the enzyme of the periphery (Birkmayer & Hornykiewicz, 1962; Riederer *et al.*, 1983; 1984). In contrast, L-deprenyl (Selegiline), a selective inhibitor of MAO B (Knoll & Magyar, 1972), does not produce cardiovascular complications when combined with L-DOPA and is proving to be a valuable adjunct to the L-DOPA therapy of Parkinson's disease (see Rinne, 1983). The exact mode of action of L-deprenyl remains, however, open to speculation since it is rapidly metabolised both in animals and man to L-amphetamine and methamphetamine (Reynolds *et al.*, 1978; Philips, 1981; Elsworth *et al.*, 1982) which may contribute, at least in part, to the clinical benefit seen with this compound (Karoum *et al.*, 1982).

We have recently described a new, potent, enzyme-activated, irreversible inhibitor of MAO ((*E*)-2-(3,4-dimethoxyphenyl)-3- fluoroallylamine hydrochloride; MDL 72145) which shows considerable selectivity for MAO type B both *in vitro* and *in vivo* (Palfreyman *et al.*, 1983; Bey *et al.*, 1984a,b; Zreika *et al.*, 1984; Fozard *et al.*, 1985). Unlike L-deprenyl, MDL 72145 cannot be transformed to amphetamine (Bey *et al.*, 1984a,b) and displays no short-term, amphetamine-like pharmacological effects (Fozard *et al.*, 1985).

The primary objective of the present study was to evaluate this new inhibitor of MAO B in rats bearing lesions of one nigro-striatal dopamine tract (Ungerstedt, 1971), an animal model which reproduces the biochemical defect of Parkinson's disease. Direct comparisons have been made with the effects of clorgyline, a selective inhibitor of MAO type A (Johnston, 1968). We have further investigated the propensity of selective inhibitors of MAO to interact adversely with L-DOPA in the periphery. The proposed clinical application of MDL 72145 as an adjunct to L-DOPA-based treatment of Parkinson's

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disease would be contingent on the lack of any such interaction.

A part of this work was presented at the meeting 'Amine Oxidases: A Cambridge Workshop', held in August, 1984 and has been published in abstract form (Palfreyman *et al.* 1984).

Methods

Animals

Male Sprague-Dawley rats weighing 300–450 g were supplied by Charles River, France and housed in groups of 5, in temperature (22 ± 1°C)- and humidity-(50–55% relative humidity) controlled rooms with free access to food and water.

Lesions of the nigro-striatal dopamine tract

Rats were lesioned unilaterally in the nigrostriatal pathway with 6-hydroxydopamine (6-OHDA) under halothane/nitrous oxide/oxygen anaesthesia according to the method of Ungerstedt (1971) with the slight modifications described by Robin *et al.* (1985). After lesioning, the animals were housed singly. Approximately one month after the operation, the success of the lesion was assessed by challenging rats with a subcutaneous injection of apomorphine, 0.2 mg kg^{-1}. Rats which showed a robust contralateral rotation response (at least 150 rotations per h) were considered to have been successfully lesioned.

Groups of successfully lesioned rats were injected i.p. with MDL 72145, 2.5 mg kg^{-1}, clorgyline, 5 mg kg^{-1}, L-deprenyl, 10 mg kg^{-1} or saline, 5 ml kg^{-1}. They were immediately placed in automated rotameters and rotational behaviour recorded for 6 h. At the end of this period, the rats were decapitated and the MAO activity of the individual striata determined (see below).

In separate experiments, a group of 11 successfully lesioned rats was identified. Individual rats were randomly assigned to receive one of the following treatments, i.p.: MDL 72145, 2.5 mg kg^{-1}, clorgyline, 5 mg kg^{-1}, or saline, 5 ml kg^{-1}. One hour later all rats were injected i.p. with L-DOPA, 4 mg kg^{-1} *and* carbidopa, 2 mg kg^{-1}, and rotational behaviour recorded for the following 4 h. Two and 4 weeks later, the experiment was repeated with individual rats being crossed over to the alternative treatments.

Cardiovascular reactivity in the pithed rat

Rats were anaesthetized with pentobarbitone sodium, 60 mg kg^{-1}, i.p., pithed and set up for recording carotid arterial pressure and for intravenous injection of L-DOPA as previously described in detail (Fozard *et al.*, 1980). In some animals L-DOPA was administered via a cannula introduced into the duodenum via a small incision in the wall of the fundus region of the stomach and secured in place by a ligature which prevented passage of injected material backwards into the stomach. Rats were pretreated once, orally, with MDL 72145, 0.5 or 2.5 mg kg^{-1}, clorgyline, 5 mg kg^{-1}, L-deprenyl, 10 mg kg^{-1}, or saline, 5 ml kg^{-1}. Eighteen hours later the animals were prepared for cardiovascular recording.

Table 1 Rotational behaviour and effects on striatal monoamine oxidase (MAO) produced by inhibitors of MAO in rats lesioned unilaterally in the striatum by 6-hydroxydopamine

*Treatment**	*Dose* (mg kg^{-1})	*Rotational behaviour*† (rotations in 6 h)	*Striatal monoamine oxidase activity*‡ MAO A (% control)	MAO B (% control)
Saline	—	32 ± 12	100 ± 16	100 ± 12
L-Deprenyl	10	144 ± 54§	80 ± 14	10 ± 1§
Clorgyline¶	5	32 ± 14	1 ± 1§	120 ± 8
MDL 72145	2.5	37 ± 12	160 ± 22	5 ± 1§

Values represent means (± s.e.mean) of from 4–8 individual determinations.

*Compounds were injected i.p. and rotations recorded for the following 6 h.

†Values are the mean cumulative ipsilateral rotations for the number of individual determinations indicated. An occasional contralateral rotation was recorded during the observation period in all treatment groups including saline (data not included).

‡Measured 6 h after drug treatment.

§$P < 0.01$ that the value differs from that of the saline-treated controls (Analysis of Variance with Dunnett's t test).

¶Due to a technical problem, rotations following clorgyline were only recorded for 4 h; the response was essentially complete at this time (see Fozard *et al.*, 1985).

Determination of monoamine oxidase activity

The MAO A and MAO B activities of tissues were measured with [^{14}C]-5-hydroxytryptamine, 10 μM, and [^{14}C]-2-phenylethylamine, 5 μM, as respective substrates as described in detail by Zreika *et al.* (1984) and Fozard *et al.* (1985).

Statistical analysis

Mean values (± s.e.mean) are presented throughout. Statistical significance was determined by Analysis of Variance with Dunnett's *t* test or Student's paired *t* test as appropriate and as indicated in the text.

Materials

[^{14}C]-5-hydroxytryptamine creatinine sulphate (56 mCi mmol^{-1}) and [^{14}C-2]-phenylethylamine hydrochloride (50 mCi mmol^{-1}) were purchased from Amersham International, U.K. and N.E.N., Dreieich, West Germany, respectively. L-DOPA, 6-hydroxydopamine hydrobromide and apomorphine hydrochloride were obtained from Sigma, St Louis, U.S.A. L-Deprenyl, clorgyline hydrochloride, desmethylimipramine hydrochloride and carbidopa were, respectively, gifts from Professor J.G. Knoll (Semmelweiss University, Budapest, Hungary), May and Baker (Dagenham, U.K.), Ciba-Geigy (Basle, Switzerland) and Merck, Sharp and Dohme, Chibret (Riom, France).

Results

Effects of monoamine oxidase inhibitors alone or in combination with L-DOPA in the 6-hydroxydopamine-lesioned rat

Neither MDL 72145, 2.5 mg kg^{-1}, nor clorgyline, 5 mg kg^{-1}, injected i.p. stimulated rotational behaviour in 6-hydroxydopamine (6-OHDA)-lesioned rats; in contrast, L-deprenyl, 10 mg kg^{-1} i.p., induced vigorous ipsilateral rotations over a 4 h observation period (Table 1; Fozard *et al.*, 1985). The degree of MAO inhibition produced in the striatum by the three compounds is shown in Table 1. Consistent with their known activities, clorgyline inhibited markedly and selectively MAO A and L-deprenyl and MDL 72145 reduced, to a similar extent and with similar selectivity, MAO B.

In 6-OHDA-lesioned rats, L-DOPA, 4 mg kg^{-1} i.p., combined with carbidopa, 2 mg kg^{-1} i.p., produced contralateral rotations; the response varied markedly in individual rats ranging from less than 100 rotations to more than 2000 rotations in the 4 h observation period (Figure 1). Pretreatment for 1 h with MDL 72145, 2.5 mg kg^{-1}, or clorgyline, 5 mg kg^{-1}, consistently potentiated the L-DOPA/carbidopa combination with the mean increase being similar for each inhibitor at approximately 50% (Figure 1).

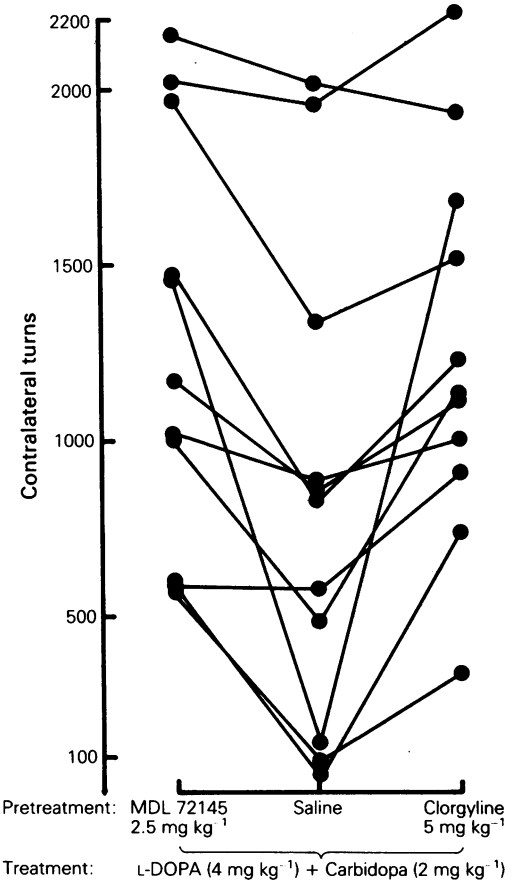

Figure 1 Rotational behaviour induced by L-DOPA combined with carbidopa in rats lesioned unilaterally in the striatum by 6-hydroxydopamine: augmentation by pretreatment with MDL 72145 or clorgyline. The monoamine oxidase (MAO) inhibitors were injected i.p. at the doses shown, 1 h before the injection of the L-DOPA/carbidopa combination. Rotations were recorded for 4 h. Each point represents the response from a single rat; each rat received all the treatments. For full details of the experimental design see 'Methods'. The mean cumulative rotations (with s.e.mean) were: 838 ± 207, 1288 ± 176 and 1256 ± 164 following saline, MDL 72145 and clorgyline respectively. Augmentation following pretreatment with MDL 72145 or clorgyline was statistically significant ($P < 0.01$, paired *t* test).

The cardiovascular effects of L-DOPA in the pithed rat: modulation by inhibitors of monoamine oxidase

Intravenous administration of L-DOPA, 1–8 mg kg^{-1}, gave dose-related increases in blood pressure and heart rate (Figure 2, control curve). Responses developed shortly after injection, reached their maximum within 2–5 min, and had generally subsided within 15 min (result not illustrated). After intraduodenal administration dose-related increases in blood pressure and heart rate were seen at doses of L-DOPA from 2–32 mg kg^{-1} (Figure 3, control curve). The onset of action was generally slow (2–3 min) and responses developed slowly to their maximum, achieved generally between 10 and 15 min after injection (result not illustrated). Responses obtained after intraduodenal injection of L-DOPA were generally more variable than those observed after intravenous injection.

The doses of the MAO inhibitors used in this phase of the study were chosen on the basis of biochemical effects reported elsewhere. At the doses used and following 18 h oral pretreatment, both L-deprenyl and MDL 72145 caused marked and selective inhibition of MAO B in a number of tissues; clorgyline caused marked and selective inhibition of MAO A (see Fozard *et al.*, 1985).

The data in Figure 2 show that clorgyline, 5 mg kg^{-1}, strongly augmented the magnitude of the blood pressure and heart rate responses to L-DOPA administered intravenously. L-Deprenyl, 10 mg kg^{-1}, in contrast, had no significant effect on the cardiovascular response to L-DOPA. Neither the 0.5 nor the 2.5 mg kg^{-1} dose of MDL 72145 augmented the heart rate increase produced by L-DOPA; the dose-response curve on blood pressure was, however, shifted dose-dependently to the left (Figure 2). When L-DOPA was given intraduodenally to rats pretreated 18 h previously with the inhibitors, clorgyline again caused marked augmentation of the cardiovascular response to L-DOPA. In contrast, neither L-deprenyl nor MDL 72145, at either dose, altered significantly the response to L-DOPA (Figure 3).

Discussion

The rat bearing unilateral lesions of the nigro-striatal dopamine pathway (Ungerstedt, 1971), has been used as a model to quantify the capacity of inhibitors of MAO to augment the central effects of L-DOPA. L-DOPA produces contralateral rotations in this model (Ungerstedt, 1971; Duvoisin & Mytilineou, 1978; Hefti *et al.*, 1980). Since the lesion produces an almost complete destruction of the nigro-striatal dopamine system (Ungerstedt, 1971; Robin *et al.*, 1985) and substantially decreases the activity of AADC (Mely *et al.*, 1984; Palfreyman *et al.*, 1985), it seems likely that L-DOPA is decarboxylated in capillaries and non-dopaminergic neurones with the dopamine formed diffusing to the supersensitive dopamine receptors on the lesioned side to produce contralateral rotations

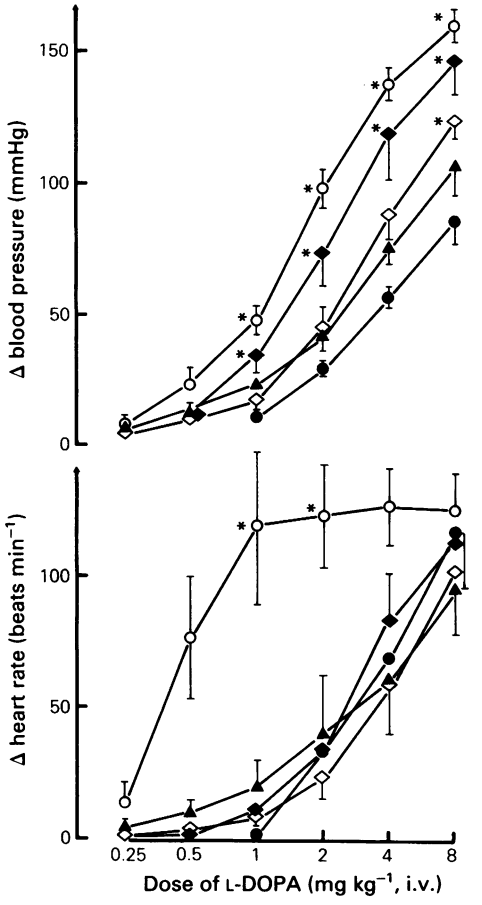

Figure 2 The effects of acute treatment with inhibitors of MAO on the cardiovascular responses to L-DOPA in the pithed rat. Animals were treated orally 18 h before the experiment with saline (●, $n = 6$), clorgyline (5 mg kg^{-1}, ○, $n = 4$), L-deprenyl (10 mg kg^{-1}, ▲, $n = 4$) or MDL 72145 (0.5 mg kg^{-1}, ◇, $n = 5$; 2.5 mg kg^{-1}, ◆, $n = 4$). L-DOPA was administered intravenously. The mean initial blood pressures and heart rates measured immediately before the injection sequence of L-DOPA were: saline 62 ± 6 mmHg and 255 ± 11 beats min^{-1}; MDL 72145, (0.5 mg kg^{-1}) 65 ± 4 mmHg and 262 ± 13 beats min^{-1}; MDL 72145 (2.5 mg kg^{-1}), 64 ± 6 mmHg and 234 ± 10 beats min^{-1}; L-deprenyl, (10 mg kg^{-1}), 63 ± 5 mmHg and 236 ± 4 beats min^{-1}; clorgyline, (5 mg kg^{-1}) 62 ± 3 mmHg and 251 ± 16 beats min^{-1}. *Indicates a significant difference from corresponding value in saline-treated group ($P < 0.05$; Analysis of Variance with Dunnett's t test).

(Hornykiewicz, 1974; Melamed *et al.*, 1980a,b; 1981; 1984). The dopamine so produced is presumably susceptible to breakdown both by non-neuronal MAO (mainly MAO B, Demarest *et al.*, 1980; Levitt *et al.*, 1982) and by MAO contained in nerves not destroyed by the lesioning procedure (MAO A and MAO B, Francis *et al.*, 1985). This reasoning would provide a ready explanation as to why the rotational behaviour induced by L-DOPA was augmented by both clorgyline and MDL 72145 and to about the same extent (Figure 1). It bears emphasis that potentiation of L-DOPA by MDL 72145 in the turning rat model may actually underestimate the potential beneficial effect of this compound in Parkinson's disease since it is known that in human brain dopamine is metabolised primarily by MAO B (Glover *et al.* 1977; Riederer *et al.*, 1981).

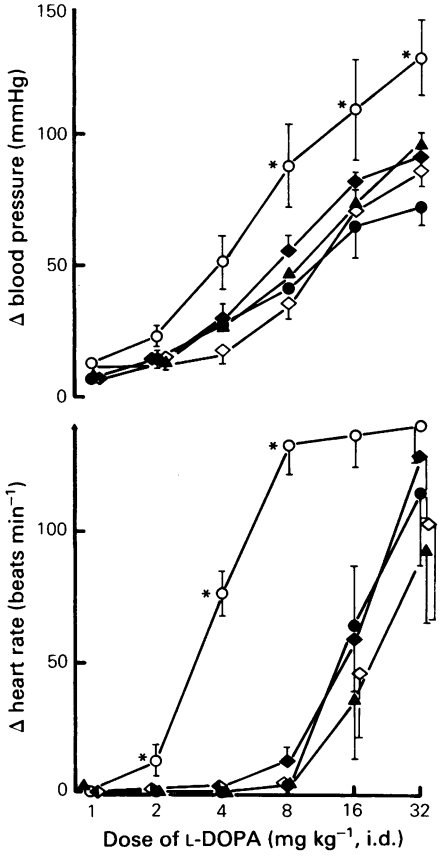

Figure 3 The effects of acute treatment with inhibitors of monoamine oxidase MAO on the cardiovascular responses to L-DOPA in the pithed rat. Animals were treated orally 18 h before the experiment with saline (●, $n = 4$), clorgyline (5 mg kg^{-1}, ○, $n = 4$), L-deprenyl (10 mg kg^{-1}, ▲, $n = 4$) or MDL 72145 (0.5 mg kg^{-1}, ◇, $n = 5$; 2.5 mg kg^{-1}, ◆, $n = 4$). L-DOPA was administered intraduodenally. The mean initial blood pressures and heart rates measured immediately before the injection sequence of L-DOPA were: saline 68 ± 5 mmHg and 257 ± 25 beats min^{-1}; MDL 72145, (0.5 mg kg^{-1}) 56 ± 2 mmHg and 244 ± 5 beats min^{-1}; MDL 72145 (2.5 mg kg^{-1}), 63 ± 3 mmHg and 216 ± 10 beats min^{-1}; L-deprenyl, (10 mg kg^{-1}), 63 ± 1 mmHg and 265 ± 15 beats min^{-1}; clorgyline, (5 mg kg^{-1}) 61 ± 3 mmHg and 298 ± 11 beats min^{-1}. *Indicates a significant difference from corresponding value in saline-treated group ($P < 0.05$; Analysis of Variance with Dunnett's t test).

A similar conclusion was reached by Heikkila *et al.* (1981) who used L-deprenyl as a selective inhibitor of MAO B. The interpretation of the effects of L-deprenyl in such studies is, however, complicated by the fact that this inhibitor is rapidly metabolised to L-amphetamine and methamphetamine (Reynolds *et al.*, 1978; Philips, 1981; Elsworth *et al.*, 1982; Karoum *et al.*, 1982) which could interact with the dopamine formed from L-DOPA or with the endogenous amine. In the case of MDL 72145, conversion to amphetamine cannot take place (Bey *et al.*, 1984a,b) and no amphetamine-like pharmacological properties have been detected (Fozard *et al.*, 1985); inhibition of MAO B is thus the most likely explanation for the observed potention of L-DOPA by MDL 72145.

Potentiation of L-DOPA by inhibitors of MAO is of considerable clinical importance in the treatment of Parkinson's disease (see Rinne, 1983). It is clear, however, that the practicality of such an approach depends on the inhibitor being free of the propensity to interact adversely in the periphery with L-DOPA. In general, selective inhibitors of MAO A and mixed type inhibitors lead to cardiovascular complications despite the L-DOPA being administered routinely with an inhibitor of the peripheral AADC (Birkmayer & Hornykiewicz, 1962; Riederer *et al.*, 1983; 1984). The potential of MDL 72145 to interact adversely with L-DOPA was investigated using the cardiovascular response to L-DOPA in the pithed rat. The pithed rat preparation was considered suitable for this purpose on three grounds; first, unlike in the anaesthetized rat, cardiovascular responses to L-DOPA are monophasic, and therefore straightforward to quantify and reasonably consistent from animal to animal; second, in the pithed rat any interaction of the MAO inhibitors with L-DOPA will be peripheral; finally, there can be no reflex compensation of any cardiovascular changes which ensures the maximum sensitivity for detection of a drug interaction. The disadvantage of using the pithed rat is that we obtain no information as to whether a combination of MDL 72145 and L-DOPA would produce centrally mediated cardiovascular effects in clinical use. However, such properties are a recognized though minor problem of treatment with carbidopa/L-DOPA combinations and do not seem to

be exacerbated by concomitant use of L-deprenyl (Rinne, 1983).

L-DOPA increased both blood pressure and heart rate in the pithed rat after either intravenous or intraduodenal administration. From the literature, such effects can be suppressed by prior treatment with inhibitors of AADC (Henning & Rubenson, 1970a,b; Eden & Nasmyth, 1974), which implicates dopamine and/or noradrenaline as the agents responsible for the cardiovascular effects. Presumably, these amines either act directly to stimulate cardiovascular adrenoceptors or, in the case of dopamine, in part indirectly by displacing noradrenaline from its stores within peripheral sympathetic nerves (Farmer, 1966; Tsai *et al.*, 1967).

Inhibitors of MAO do not generally enhance responses to agents such as noradrenaline or dopamine acting directly; these monoamines are inactivated primarily by tissue uptake and only secondarily by metabolic conversion (Iversen, 1967). The consistent potentiation of L-DOPA by clorgyline, a selective inhibitor of MAO A, would therefore most likely reflect enhancement of the indirect sympathomimetic component of the response. By inhibiting MAO A in the peripheral sympathetic neurones (Goridis & Neff, 1971; Jarrott & Iversen, 1971) not only would more noradrenaline be available for release, but the rate of metabolism of the releasing agent (presumably dopamine) by the intraneuronal enzyme would be slowed. Rubenson (1971) observed potentiation of L-DOPA by nialamide in the anaesthetized rat and offered a broadly similar interpretation of his finding.

The above interpretation of events is supported by the observation that neither L-deprenyl nor MDL 72145, in doses giving complete and selective inhibition of MAO B (Table 1; Fozard *et al.*, 1985), augmented the cardiovascular effects of L-DOPA administered intraduodenally. On the other hand, these drugs did increase the blood pressure, although not the heart rate, component of the cardiovascular response to L-DOPA given intravenously. Further studies would be required to clarify the mechanism of action of the MAO B inhibitors in this latter experimental paradigm. It remains a fact, however, that it is the oral route which is most relevant to the clinical situation and when L-DOPA is given intraduodenally, treatment with L-deprenyl or MDL 72145 did not result in potentiation. A lack of effect of these agents on L-DOPA is consistent with the fact that both L-deprenyl and MDL 72145 have a much reduced propensity to provoke the 'cheese reaction' as indicated by the response of the cardiovascular system to tyramine in animal experimental models (see Fozard *et al.*, 1985).

In conclusion, like several other inhibitors of MAO, MDL 72145 augments the central effects of L-DOPA in rats lesioned unilaterally in the nigro-striatal tract with 6-OHDA. Since, unlike L-deprenyl, MDL 72145 cannot be transformed to amphetamine and does not block the reuptake of monoamines (Bey *et al.*, 1984a,b; Zreika *et al.*, 1984; Fozard *et al.*, 1985), inhibition of MAO B is the likely explanation for the effect. In contrast, the data from the cardiovascular studies suggest that it is inhibition of the A form of MAO rather than MAO B which leads to enhancement of the cardiovascular response to intraduodenally administered L-DOPA in rats. The observations may be relevant to the fact that L-deprenyl is much better tolerated than less selective inhibitors of MAO as an adjunct to L-DOPA-based therapy of Parkinson's disease (see Rinne, 1983). Since MDL 72145 is also a selective inhibitor of MAO B and behaves similarly to L-deprenyl in this model, it seems unlikely that MDL 72145 would be any more likely than L-deprenyl to interact adversely with L-DOPA in the clinical situation.

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