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Tyramine-induced noradrenaline release from rat brain slices: prevention by (−)-deprenyl

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1 Clorgyline (1 and 10 μM) and (+)-deprenyl (10 μM) both significantly potentiated the tyramine (100 μM)-induced release of [^{3}H]-noradrenaline from rat cerebral cortex slices. (−)-Deprenyl (50 μM) significantly reduced it, while lower concentrations had no effect on noradrenaline release. However, in combination, 1 μM (−)-deprenyl blocked the release-facilitating action of 1 μM clorgyline, and 10 μM (−)-deprenyl that of 10 μM (+)-deprenyl.

2 Low concentrations of (+)- and (−)-deprenyl (1 and 10 μM), both selectively inhibited phenylethylamine oxidation by monoamine oxidase B. Higher concentrations of (−)-deprenyl (20 and 50 μM) also inhibited 5-hydroxytryptamine oxidation by monoamine oxidase A. Clorgyline (1 and 10 μM) inhibited both enzymes. Thus, the effects of these drugs on noradrenaline-release cannot be explained solely in terms of irreversible inhibition of monoamine oxidase A and B, and other possible mechanisms are discussed.

3 If the brain-slice model faithfully mirrors the sequence of events manifesting peripherally as the tyramine hypertensive response ('cheese effect'), then it is possible that low doses of (−)-deprenyl, administered with antidepressant monoamine oxidase inhibitors, can prevent this adverse reaction.

Introduction

There is good evidence that the monoamine oxidase (MAO) inhibiting drugs can be effective antidepressants (e.g. Paykel, Rowan, Parker & Bhat, 1982). Even so, clinicians are reluctant to use them because of one major adverse reaction, the 'cheese effect', a hypertensive crisis which supervenes when patients taking these drugs eat tyramine-containing foods, particularly cheese (Blackwell & Mabbitt, 1965).

The mechanism by which ingested tyramine induces a pressor response is complex and the MAO-inhibiting drugs probably act at more than one site. The amine firstly traverses the intestinal wall, where a proportion is inactivated, before entering the blood stream (Garcha, Imrie, Marley & Thomas, 1983). Among its sites of uptake are peripheral noradrenergic nerves, where it probably releases noradrenaline (NA) from its storage vesicles into the cytoplasm, and thence into the synaptic cleft (Trendelenburg, 1979). Such cytoplasmic release would explain why MAO inhibitors have little effect on nerve stimulation-induced release of NA (Paton, 1976). The released NA then acts on receptors in blood vessels, inducing a pressor response of a magnitude depending on the rapidity of its reuptake and inactivation.

Although a facilitated NA release of this kind may result, in some measure, from retarded oxidative deamination of tyramine in both gut wall and sympathetic nerve endings, recent data indicate that this is unlikely to be the whole explanation of the effect of the MAO inhibitors. It has been shown that clorgyline, the selective MAO-A inhibitor, causes a large 'cheese effect' in man (Lader, Sakalis & Tansella, 1970), whereas (−)-deprenyl, the MAO-B inhibitor, used at selective doses (10 mg), causes virtually none (Elsworth, Glover, Reynolds, Sandler, Lees, Phuapradit, Shaw, Stern & Kumar, 1978). Tyramine, in man, is a substrate for both forms (Tipton, Houslay & Mantle, 1976). Whilst it may have been reasonable to suppose (Knoll & Magyar, 1972) that the safety of (−)-deprenyl was due to its inability to block the tyramine-inactivating gut MAO-A (Squires, 1972) barrier, we now know that in man pretreated with clorgyline, intravenous tyramine still provokes the 'cheese effect' (Pickar, Cohen, Jimerson & Murphy, 1981). Also relevant are our recent experiments in the pig (Sandler, Glover, Ashford & Esmail, 1980) where, apart from MAO-A in the gut wall (Squires, 1972), tyramine oxidation is catalyzed almost wholly

by MAO-B. Despite a marginal inhibitory effect only on extraintestinal MAO-B, clorgyline still potentiated the pressor response to intravenous tyramine unequivocally, whereas (−)-deprenyl, with its very substantial degree of such MAO inhibition, did not (Sandler *et al.*, 1980). Thus, at least one component of the 'cheese effect' is independent of the inhibition of tyramine oxidation. If, as some evidence suggests (Neff & Fuentes, 1976), MAO in sympathetic nerve terminals is of the A variety, clorgyline pretreatment would allow cytoplasmic NA to accumulate. It is also possible, however, that clorgyline and the non-selective MAO inhibitors have some futher action not possessed by (−)-deprenyl, of directly facilitating NA release (Sandler *et al.*, 1980). Its possession would not preclude the existence of a NA release-inhibiting action of (−)-deprenyl.

In this study, we have examined rat brain cortical slices as a model system to study tyramine-induced NA release and have used the preparation to investigate the effects of clorgyline and of (+)- and (−)-deprenyl.

Methods

Superfusion release studies

The basic method used to study the drug-induced release of radioactive transmitters from superfused rat cerebral slices has been described previously (Kerwin & Pycock, 1979). Male or female Porton rats weighing approximately 200 g were used in all experiments. Animals were killed by cervical dislocation, the brains removed and areas of frontoparietal cortical region dissected away over ice. Tissue was chopped in two directions at 0.2 mm intervals with a McIlwain tissue chopper.

Cortical slices were preincubated at 37°C for 20 min in 95% O_2:5% CO_2 bubbled through Krebs–Ringer bicarbonate buffer (pH 7.4) containing ^{3}H-labelled NA (sp.act. 9 Ci mmol^{-1}, Amersham International) in a final concentration of 10^{-8} M. The buffer contained 0.1% (w/v) ascorbic acid to inhibit NA oxidation. The prelabelled tissue was transferred to perspex superfusion chambers (~5 mg tissue per chamber) and superfused with buffer (containing MAO inhibitors in different concentrations) at a rate of 0.5 ml min^{-1}. Following a washout period of 30 min, 1 ml fractions were collected every 2 min and the radioactivity in each fraction was determined before or after the addition of potassium chloride (50 mM) or tyramine hydrochloride (0.1–100 μM, Sigma) to the perfusate for 8 min.

Samples of released radioactivity, with the different drug combinations used, were run on thin layer chromatographic plates, and at least 80 to 85% of radioactivity chromatographed with authentic [^{3}H]-NA.

Results are expressed as a release rate constant,

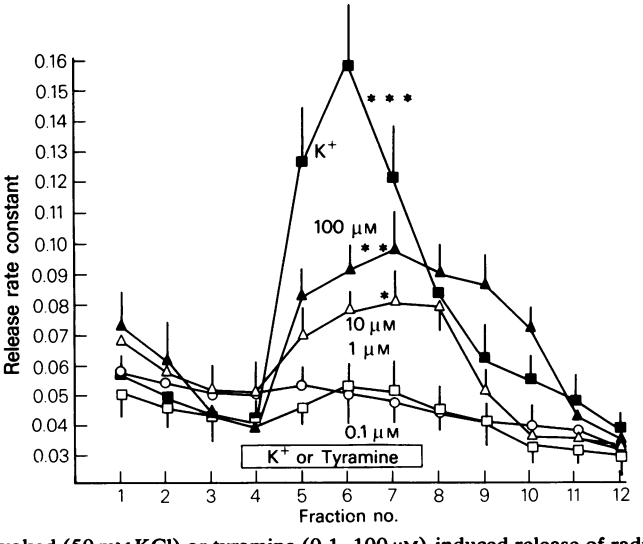

Figure 1 Potassium-evoked (50 mM KCl) or tyramine (0.1–100 μM)-induced release of radioactivity from superfused slices of rat cerebral cortex prelabelled *in vitro* with 10^{-8} M [^{3}H]-noradrenaline. Potassium chloride or drugs were added to the perfusate for 8 min (as indicated by the bar) 38 min after the start of superfusion. In all cases, Krebs-Ringer bicarbonate buffer contained 10 μM pargyline. The results are shown as a release rate constant derived from the recovered radioactivity in each fraction and expressed as a percentage of the total radioactivity remaining in the tissue at that instant. Each point is the mean of 4 or 8 determinations: vertical bars indicate 1 s.e.mean (shown in one direction only): 50 mM KCl (■); tyramine 0.1 μM (○), 1 μM (□), 10 μM (△) and 100 μM (▲).

the amount of radioactivity released per min being expressed as a percentage of radioactivity remaining in the tissue at that time. The amount of radioactivity released by tyramine in the presence or absence of various MAO inhibitors has been compared statistically using Student's *t* test.

Monoamine oxidase activity

MAO activity was assayed in tissue slices which had been perfused by buffer, with or without inhibitors, as in the release experiments. The tissue slices were homogenized in 10 mM phosphate buffer, pH 7.4, approximately 10% (w/v). MAO-A was assayed using [^{14}C]-5-hydroxytryptamine (5-HT) (final concentration, 360 μM) and MAO-B, using [^{14}C]-phenylethylamine (PEA) (final concentration, 30 μM). The procedures used were as described by Lewinsohn, Glover & Sandler (1980). Protein was assayed by the method of Lowry, Rosebrough, Farr & Randall (1951). Clorgyline was kindly provided by May & Baker Ltd., Dagenham, Essex, and (−)-deprenyl and (+)-deprenyl by Prof. J. Knoll, Budapest.

Results

Potassium and tyramine-induced release of [^{3}H]-noradrenaline

A depolarizing stimulus (50 mM KCl) increased the rate of efflux of [^{3}H]-NA from prelabelled cortical slices superfused with Krebs buffer containing pargyline hydrochloride (10 μM, Sigma) ($P<0.001$, Figure 1). Similarly tyramine, in concentrations of 10 and 100 μM, produced a dose-related increase in efflux of [^{3}H]-NA from prelabelled cortical slices superfused with Krebs buffer containing pargyline ($P<0.05$; $P<0.01$ respectively, Figure 1). Lower doses of tyramine (0.1 and 1 μM) had no significant effect on [^{3}H]-NA release. In all subsequent experiments, 100 μM tyramine was employed as the standard releasing dose.

Effect of stereoisomers of deprenyl on tyramine-induced release of [^{3}H]-noradrenaline

The effect of 1 and 10 μM concentrations of (+)- and (−)-deprenyl added to the superfusion buffer on tyramine (100 μM)-induced release of [^{3}H]-NA are illustrated in Figure 2. Neither 1 μM nor 10 μM (−)-deprenyl had any significant effect on the increased efflux of [^{3}H]-NA evoked by 100 μM tyramine, although 10 μM (−)-deprenyl tended to decrease the release of radiolabelled NA induced by tyramine. In contrast, both 1 μM and 10 μM (+)-deprenyl enhanced tyramine-induced release of [^{3}H]-NA, the increase in the presence of 10 μM (+)-deprenyl being statistically significant ($P<0.01$). In addition, both concentrations of (+)-deprenyl enhanced the spontaneous efflux of radiolabelled NA from cortical slices, the effect of 10 μM (+)-deprenyl being statistically significant ($P<0.05$).

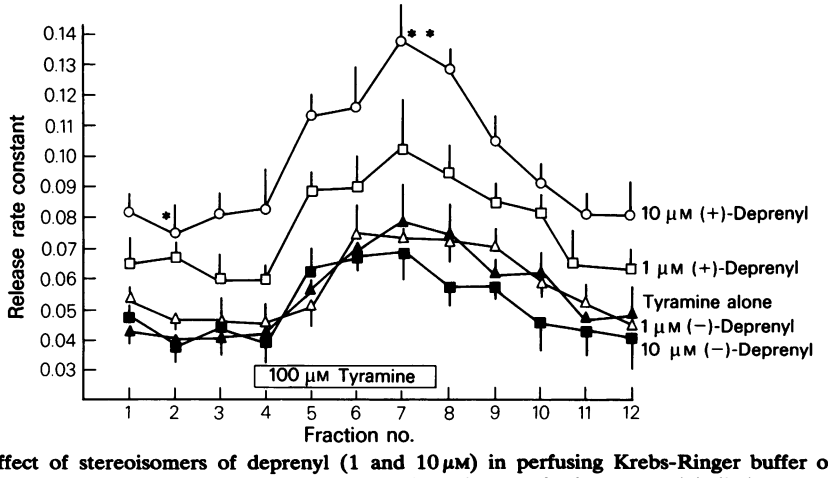

Figure 2 Effect of stereoisomers of deprenyl (1 and 10 μM) in perfusing Krebs-Ringer buffer on tyramine (100 μM)-induced release of radioactivity from perfused slices of rat cerebral cortex prelabelled *in vitro* with 10^{-8} M [^{3}H]-noradrenaline. Deprenyl was present in the superfusing buffer at all times; tyramine was added for 8 min (as indicated by the bar), 38 min after the start of superfusion. The results are expressed as a release rate constant, as explained in the legend to Figure 1. Each point is the mean of 4–8 determinations: vertical bars indicate 1 s.e.mean. Tyramine alone (▲); (+)-deprenyl 1 μM (□) and 10 μM (○); (−)-deprenyl 1 μM (△) and 10 μM (■). Statistical significance from tyramine(alone)-induced release indicated by $*P<0.05$; $**P<0.01$ (Student's *t* test).

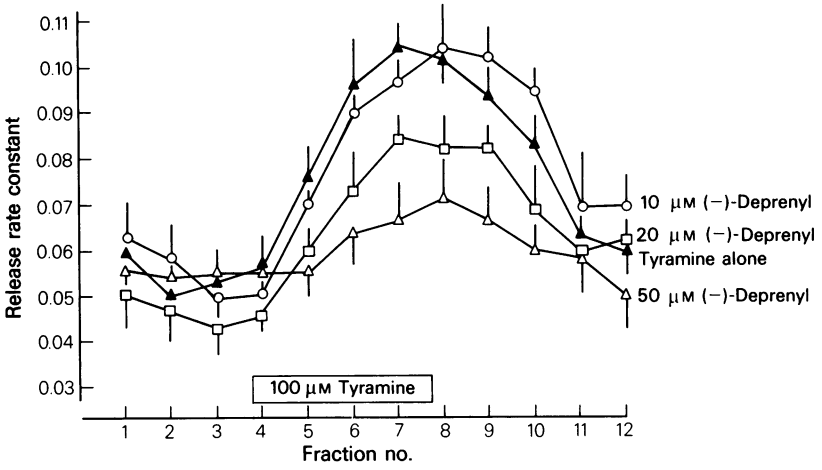

Figure 3 Effect of varying concentrations of (−)-deprenyl in perfusing buffer on tyramine (100 μM)-induced release of radioactivity from superfused slices of rat cerebral cortex prelabelled *in vitro* with 10^{-8} M [^{3}H]-noradrenaline. For experimental details and expression of results see legend to Figure 1. Each point is the mean of 6 observations: vertical bars indicate 1 s.e.mean. Tyramine alone (△); (−)-deprenyl 10 μM (○), 20 μM (□) and 50 μM (△). Statistical significance for tyramine(alone)-induced release indicated by $^*P < 0.05$ (Student's *t* test).

Varying concentrations of (−)-deprenyl on tyramine-induced release of [^{3}H]-noradrenaline

As noted above, 10 μM (−)-deprenyl in the perfusing Krebs solution had no significant effect on either spontaneous release of [^{3}H]-NA or on tyramine (100 μM)-induced release of [^{3}H]-transmitter (Figure 2). However, increasing concentrations of (−)-deprenyl lowered the ability of tyramine to release [^{3}H]-NA from cortical slices; 50 μM (−)-deprenyl significantly reduced tyramine-induced release of radiolabelled neurotransmitter ($P < 0.05$; Figure 3). A smaller concentration (20 μM) of (−)-deprenyl reduced the releasing ability of tyramine but this effect did not reach a level of statistical significance ($P < 0.1$; Figure 3).

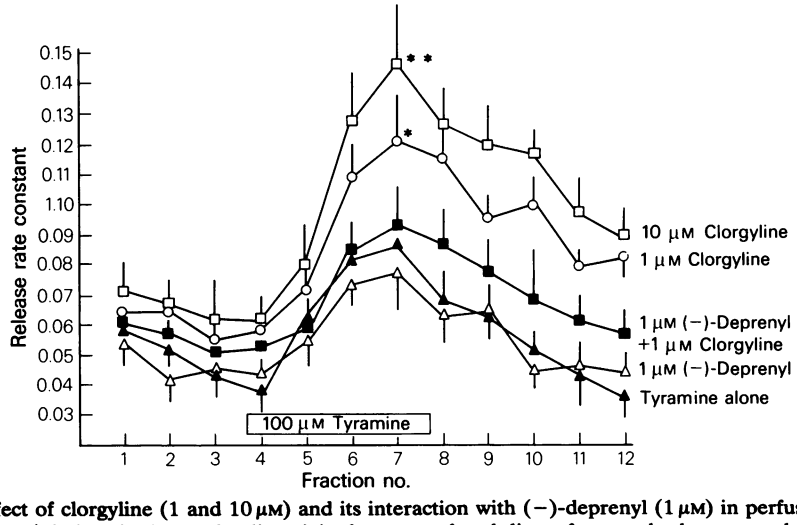

Figure 4 Effect of clorgyline (1 and 10 μM) and its interaction with (−)-deprenyl (1 μM) in perfusing buffer on tyramine (100 μM)-induced release of radioactivity from superfused slices of rat cerebral cortex prelabelled *in vitro* with 10^{-8} M [^{3}H]-noradrenaline. For experimental details and expression of results see legend to Figure 1. Each point is the mean of 4–6 observations; vertical bars denote 1 s.e.mean: tyramine alone (▲); clorgyline 1 μM (○) and 10 μM (□); (−)-deprenyl 1 μM (△) and (−)-deprenyl 1 μM in combination with clorgyline 1 μM (■). Statistical significance from tyramine(alone)-induced release indicated by $^*P < 0.05$; $^{**}P < 0.01$ (Student's *t* test).

Effect of clorgyline on tyramine-induced release of [^{3}H]-noradrenaline and its interaction with (−)-deprenyl

Addition of clorgyline (1 and 10 μM) to the perfusing buffer significantly enhanced the [^{3}H]-NA-releasing action of 100 μM tyramine ($P<0.05$ and $P<0.01$ respectively; Figure 4), although this drug, unlike (+)-deprenyl, had no effect on spontaneous release of [^{3}H]-NA. Addition of 1 μM (−)-deprenyl, a concentration which on its own has no significant effect on this releasing action of tyramine (Figure 1), blocked the enhancing effect of 1 μM clorgyline; the combination of 1 μM (−)-deprenyl and 1 μM clorgyline showing a release profile indistinguishable from that of 100 μM tyramine alone (Figure 4).

Combinations of the stereoisomers of deprenyl on tyramine-induced release of [^{3}H]-noradrenaline

(+)-Deprenyl (10 μM) significantly enhanced tyramine (100 μM)-induced release of [^{3}H]-NA from cortical slices ($P<0.01$), whereas (−)-deprenyl (10 μM) had no effect on the sympathomimetic action of tyramine (Figures 1 and 5). However, in combination, 10 μM (−)-deprenyl abolished the facilitating action of 10 μM (+)-deprenyl and, together, the two stereoisomers had no significant action on tyramine-induced release of [^{3}H]-NA compared with tyramine alone (Figure 5).

Effect of monoamine oxidase inhibitors on cortical MAO activity

Figures 6 and 7 show the effects of different doses of clorgyline, (+)-deprenyl and (−)-deprenyl on PEA and 5-HT oxidation in rat cortical tissue slices. (−)-Deprenyl and (+)-deprenyl, in low concentrations (1 and 10 μM), selectively inhibited PEA oxidation (Figure 7) but did not affect 5-HT oxidation (Figure 6). However, at higher concentrations, (−)-deprenyl (20 and 50 μM) significantly inhibited both forms of the enzyme (95–99% inhibition of PEA oxidation, $P<0.001$; 86–92% inhibition of 5-HT oxidation, $P<0.001$).

(−)-Deprenyl was a somewhat more potent inhibitor of both forms than (+)-deprenyl. Clorgyline, at both 1 and 10 μM, substantially inhibited both forms of the enzyme (>90% inhibition for both substrates, $P<0.001$). The effects of a combination of 1 μM (−)-deprenyl plus 1 μM clorgyline were similar to those of 1 μM clorgyline alone, inhibiting PEA oxidation by 97.5% and that of 5-HT by 95%: 10 μM (−)-deprenyl plus 10 μM (+)-deprenyl was somewhat less potent than 10 μM (−)-deprenyl alone, inhibiting PEA oxidation by 60%, with no effect on 5-HT oxidation.

Discussion

The results show clearly that the different effects of

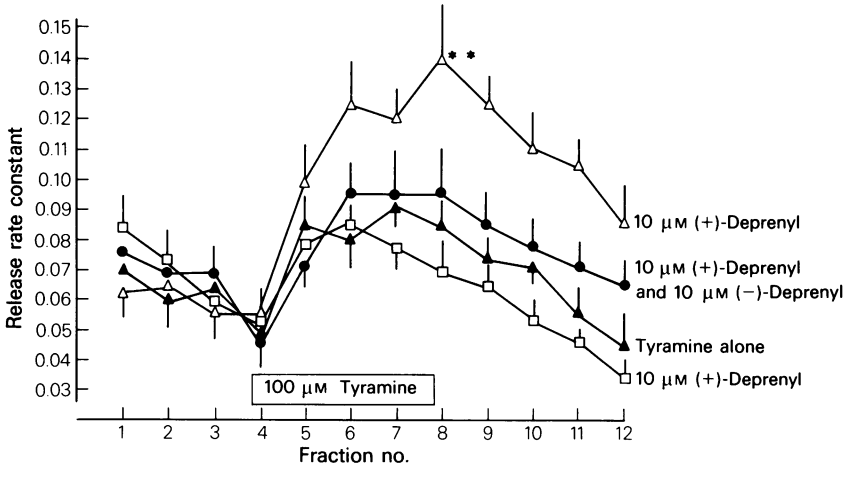

Figure 5 Combinations of 10 μM (+)-deprenyl in perfusing buffer on tyramine (100 μM)-induced release of radioactivity from superfused slices of rat cerebral cortex prelabelled *in vitro* with 10^{-8} M [^{3}H]-noradrenaline. For experimental details and expression of results see legend to Figure 1. Each point is the mean of 4–8 observations: vertical bars indicate 1 s.e.mean. Tyramine alone (▲); 10 μM (+)-deprenyl (△); 10 μM (−)-deprenyl (□); 10 μM (+)-deprenyl in combination with 10 μM (−)-deprenyl (●). Statistical significance from tyramine(alone)-induced release indicated by $P<0.02$ less than control activity (Student's t test).

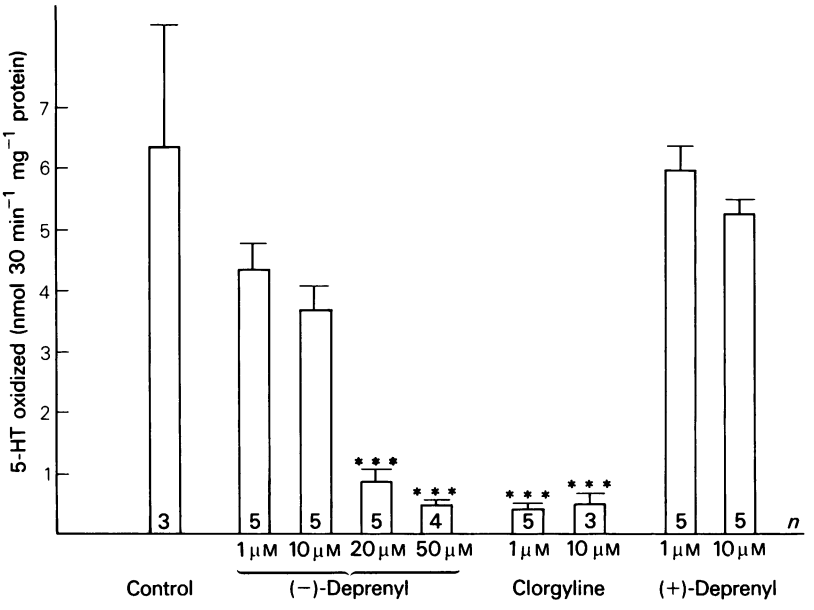

Figure 6 Effect of (−)-deprenyl (1–50 μM), (+)-deprenyl (1 and 10 μM) and clorgyline (1 and 10 μM) on [^{14}C]-5-hydroxytryptamine (5-HT) oxidation in rat cerebral cortex slices. Tissue slices (~5–10 mg) were perfused for 40 min with Krebs-Ringer buffer containing concentrations of MAO inhibitors as indicated above. Results are expressed as nmol 5-HT oxidized 30 min^{-1} mg^{-1} protein. Each column is the mean of n observations as indicated: vertical bars indicate 1 s.e.mean. Statistical comparisons of the MAO activity are with control values using the Student's t test: $^{**}P<0.01$; $^{***}P<0.001$.

these three MAO-inhibitor drugs on tyramine-induced release of NA from cortical slices cannot be explained solely in terms of their irreversible inhibitory action on MAO. (+)-Deprenyl (10 μM), a concentration of inhibitor that significantly inhibited MAO-B but not MAO-A, caused a significant poten-

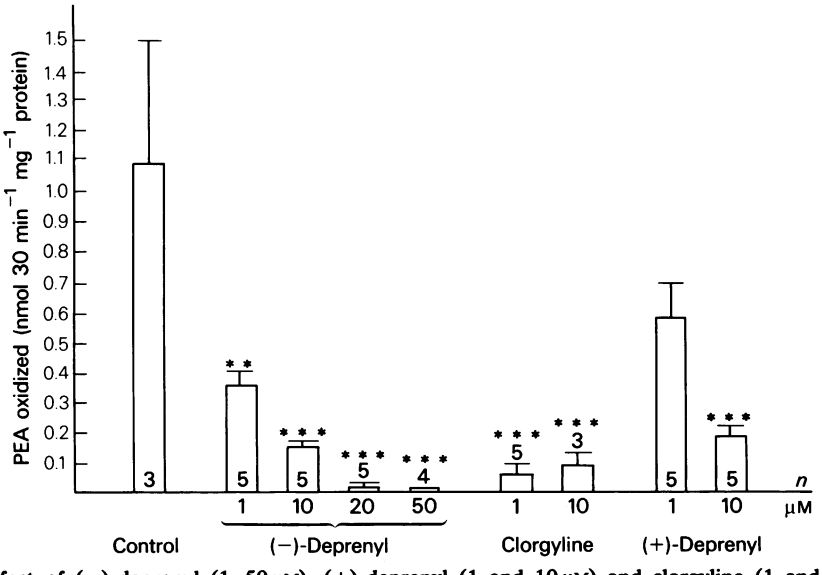

Figure 7 Effect of (−)-deprenyl (1–50 μM), (+)-deprenyl (1 and 10 μM) and clorgyline (1 and 10 μM) on [^{14}C]-phenylethylamine (PEA) oxidation on the same tissue slices as Figure 6. Results are expressed as nmol PEA oxidized 30 min^{-1} mg^{-1} protein. ***less than control values, $P<0.001$

tiation of NA release. Conversely, (−)-deprenyl (10 μM), while inhibiting both forms of the enzyme rather more potently than the (+)-isomer, caused a decrease of NA release. At a higher concentration, (−)-deprenyl (50 μM) potently inhibited both forms of the enzyme (>90% inhibition) and caused a significant decrease in NA release. Clorgyline (1 and 10 μM) also substantially inhibited both forms of MAO (>92% inhibition) but caused a significant potentiation of tyramine-induced release of NA.

These effects of clorgyline are compatible with its acting either by inhibiting the breakdown of tyramine or increasing intraneuronal NA levels. The mechanism of action of (+)-deprenyl in potentiating the release is less clear. At 10 μM, it did not significantly inhibit MAO-A, although it did inhibit MAO-B. As MAO-A predominates in rat brain, it appears to be exerting its releasing action without substantially inhibiting tyramine or NA oxidation. It may be that it is acting directly to potentiate the effect of tyramine, either at uptake or release sites. However, it must be remembered that we have only measured irreversible MAO inhibition here and that (+)-deprenyl may have caused competitive inhibition of MAO-A by virtue of its degradation to (+)-amphetamine (Reynolds, Elsworth, Blau, Sandler, Lees & Stern, 1978), a potent and reversible MAO-A inhibitor (Green & El Hait, 1980; Miller, Shore & Clarke, 1980) as well as a releaser of cerebral NA. Indeed, apart from potentiating tyramine-induced release of NA, (+)-deprenyl appears to have an amphetamine-like NA releasing action in its own right, enhancing spontaneous efflux from cortical slices (Figure 2). Thus, (+)-deprenyl may have exerted its effects by some type of facilitated release action or by an indirect reversible inhibition of the oxidation of the intraneuronal NA.

The effects of (−)-deprenyl were, perhaps, the most interesting. At 50 μM, it significantly decreased the release of NA, but even in lower concentrations, it was able to counteract the potentiating effects of (+)-deprenyl or clorgyline. Thus 10 μM (−)-deprenyl negated the effect of 10 μM (+)-deprenyl (Figure 5) and 1 μM (−)-deprenyl that of 1 μM clorgyline (Figure 4). Thus, (−)-deprenyl may not only lack the 'cheese effect' itself (Elsworth *et al.*, 1978) but, if we may project to the whole organism, may also have the ability to block such an effect arising from other drugs.

Knoll (1978) has previously shown with various isolated contractile systems that (−)-deprenyl, in concentrations of 5 μg ml^{-1} (approximately 25 μM), can block the tyramine-potentiating effects of other MAO inhibitors such as U-1424 or J-508. He attributed the effect to (−)-deprenyl blocking the uptake of tyramine. However, Finberg, Tenne & Youdim (1981) have shown that monoamine uptake blocking effects at this concentration are unlikely to be sufficiently great to provide a full explanation. They suggest that (−)-deprenyl is more likely to act by blocking the active efflux of NA from the cytoplasm. Clearly the effects of (−)-deprenyl are crucially dependent on the dose used and many of its actions are only apparent at higher concentrations. At 10 mg kg^{-1} (approximately 50 μM), Simpson (1978) has demonstrated sympathomimetic effects on the rat cardiovascular system. At a concentration of 30 μM, Finberg *et al.* (1981) observed a depression in response of the isolated vas deferens of the rat to tyramine but a potentiation on washout of the drug. They also noted direct potentiation of NA effects with 10 μM (−)-deprenyl. However, in man at 10 mg doses (approximately 1 μM distributed in the body mass), (−)-deprenyl is a remarkably safe drug and largely free from any side effects.

Although it may be of some benefit in bipolar or non-endogenous depression (Mann, Frences, Kaplan, Kocsis, Peselow & Gershon, 1982) at low doses, (−)-deprenyl does not seem to be as effective an antidepressant (Mendis, Pare, Sandler, Glover & Stern, 1981) as clorgyline (Lipper, Murphy, Slater & Buchsbaum, 1979; Murphy, Lipper, Pickar, Jimerson, Cohen, Garrick, Alterman & Campbell, 1981) and the non-selective MAO inhibitors e.g. phenelzine (Youdim & Paykel, 1981). This may well be because MAO-A inhibition is necessary for any antidepressant efficacy of MAO inhibitors (Pickar, Cohen, Jimerson, Lake & Murphy, 1981); however, it is also a possibility that facilitated release of NA by tyramine, a central counterpart of the 'cheese effect', is responsible for any therapeutic benefit achieved with these drugs (Sandler, 1981), rather than mere enzyme inhibition as such. Should MAO-A inhibition eventually prove essential, however, it remains to be determined whether the combination of a selective MAO-A or non-selective MAO inhibitor, together with a low dose of (−)-deprenyl, will provide a safe and effective antidepressant.

Reprint requests and correspondence to M.S., please.

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