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RELATIONSHIP BETWEEN TYRAMINE POTENTIATION AND SELECTIVE INHIBITION OF MONOAMINE OXIDASE TYPES A AND B IN THE RAT VAS DEFERENS

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1 The degree of selective monoamine oxidase (MAO) inhibition produced by (−)-deprenyl, clorgyline, LY51641 and tranylcypromine was examined in relation to modification of tyramine and noradrenaline contractile responses of the rat isolated vas deferens.

2 All inhibitors possessed reversible α-adrenoceptor blocking activity, determined against noradrenaline on the denervated vas deferens. For LY51641 and tranylcypromine, antagonism was competitive, with pA_2 values of 6.17 and 5.26.

3 Clorgyline, LY51641 and (−)-deprenyl (10^{-5}M) inhibited the tyramine response while present in the organ bath: LY51641, which was the most potent as an α-adrenoceptor blocker, produced this effect at 10^{-6}M. Responses to tyramine and noradrenaline were potentiated on washing out the inhibitors, but noradrenaline potentiation was seen only when tyramine had been present in the system.

4 Tranylcypromine (10^{-6}M) potentiated responses to noradrenaline and tyramine while present in the organ bath.

5 Potentiation of tyramine responses by clorgyline and LY51641 occurred at 91% and 64% inhibition of MAO type A respectively, although full potentiation of the tyramine response was elicited only when substantial inhibition of both enzyme types occurred. Selective inhibition of MAO type B by 67% (with deprenyl) was not associated with tyramine potentiation.

Introduction

Potentiation of the pressor effect of tyramine and other indirectly acting sympathomimetic amines is one of the most troublesome side effects of monoamine oxidase (MAO) inhibitors (Blackwell, 1963). The demonstration that MAO exists in multiple forms (Youdim, Collins & Sandler, 1969; Squires, 1972) led to the possibility of developing selective inhibitors, which may inhibit brain MAO without markedly affecting peripheral deamination of tyramine (Youdim, Collins & Sandler, 1971). The MAO type which shows greatest affinity for noradrenaline and 5-hydroxytryptamine (5-HT) is selectively inhibited by clorgyline and referred to as MAO-A (Johnston, 1968), while a second enzyme type (MAO-B) shows greatest affinity for amines such as benzylamine and β-phenylethylamine (PEA), and is selectively inhibited by (−)-deprenyl (Knoll & Magyar, 1972). Tyramine is a substrate for both forms of the enzyme (Johnston, 1968). Human brain MAO consists mainly of MAO-B (Squires, 1972; Riederer, Youdim, Rausch, Birkmayer, Jellinger & Seemann, 1978), whereas peripheral sympathetic neurones contain mainly MAO-A (Jarrot & Iversen, 1971; Neff & Goridis, 1972).

The pressor effect of orally-administered tyramine is not enhanced in human subjects receiving (−)-deprenyl (Elsworth, Glover, Reynolds, Sandler, Lees, Phuapradit, Shaw, Stern & Kumar, 1978) whereas administration of clorgyline is accompanied by tyramine potentiation (Lader, Sakalis & Tansella, 1970). Knoll (1978) showed that (−)-deprenyl inhibited the effects of tyramine on isolated smooth muscle preparations. Recently, we reported that another selective MAO-B inhibitor, AGN 1135, did not potentiate tyramine pressor effects, and also inhibited tyramine contractile effects on the rat isolated vas deferens in higher concentrations *in vitro* (Finberg, Tenne & Youdim, 1981). High concentrations of (−)-deprenyl and AGN 1135, however, inhibit MAO-A and MAO-B, and subsequent potentiation of the tyramine response was seen on washing out the inhibitors. In order to relate tyramine potentiation to selective MAO-A or MAO-B inhibition, the degree of selective MAO inactivation produced by several irreversible inhibitors has now been measured in the conditions of the organ-bath experiments, and correlated with modification of contractile responses to tyramine and noradrenaline.

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Methods

Organ bath experiments

Sprague-Dawley rats (200 to 300 g) were killed by a blow on the head, the vasa deferentia removed and suspended in 15 ml organ baths containing Krebs solution gassed with 5% CO_2 in O_2 and maintained at 37°C. Isometric contractions were measured with Statham UL5 transducers coupled to Brush-Gould or Beckman physiological recorders. Tyramine (2.9 to 29 μM) and noradrenaline (0.16 to 1.6 μM) were added alternately to the bath and allowed to act for 1 min before washing out. A period of 4 min was maintained between washing and addition of the next drug. Doses of tyramine and noradrenaline were chosen which caused a 600 mg increase in tension of the preparation. Preliminary experiments had shown that this was about 30% of the maximum tension developed by the tissue in response to either agonist. Control responses to tyramine and noradrenaline were obtained and then one of the inhibitor drugs was added to the bath, and responses determined in the presence of the inhibitor. A total of 4 additions of inhibitor were made, the drug being added immediately after a change of bath fluid. Subsequently, responses to tyramine and noradrenaline were determined after washing out the inhibitor. Modification of tyramine and noradrenaline responses was expressed as:

$$\text{(a)}\ \frac{\text{response in presence of inhibitor} \times 100}{\text{response before addition of inhibitor}}$$

and

$$\text{(b)}\ \frac{\text{response following washout of inhibitor} \times 100}{\text{response before addition of inhibitor}}$$

Tyramine and noradrenaline results in the presence of inhibitor were the mean of two responses, whereas following washout of inhibitor, responses gradually increased to a high level and the mean of 2 to 3 elevated responses was used.

This type of experimental design was employed since full dose-response curves could not be determined in these conditions. Four or more vas deferens were used for each concentration of inhibitor. Results in drug-treated tissues were compared with response ratios measured in tissues not exposed to MAO inhibitors.

Following determination of contractile responses, tissues were homogenized in 0.32 M sucrose with a Ystral tissue disperser, the homogenates frozen at − 20°C, and MAO activity determined the next day.

Determination of monoamine oxidase activity

Tissue homogenates were incubated in 0.05 M phosphate buffer (pH 7.4) with [^{14}C]-5-HT (1 mM), [^{14}C]-tyramine (1 mM) or [^{14}C]-β-phenylethylamine (0.02 mM) at 37°C for 20 min. Deaminated metabolites were subsequently separated from the parent amines by passing the incubate over a small Amberlite CG 50 column as described by Tipton & Youdim (1976). The amount of ^{14}C-labelled metabolite in the eluate was determined by liquid scintillation counting in a Packard Model 524 counter. Proteins were determined by the method of Lowry, Rosebrough, Farr & Randall (1951) and enzyme activity calculated as nmol product formed mg^{-1} protein h^{-1}. Activity of MAO inhibitor-treated tissues was expressed as a percentage of the activity in control tissues. In a separate experiment, the inhibitory activity of each inhibitor added directly to a homogenate of control vas deferens was also determined.

Determination of α-adrenoceptor blocking activity

Rat vasa deferentia were surgically denervated under ether anaesthesia as described by Birmingham (1970). Seven days later, the vasa deferentia were

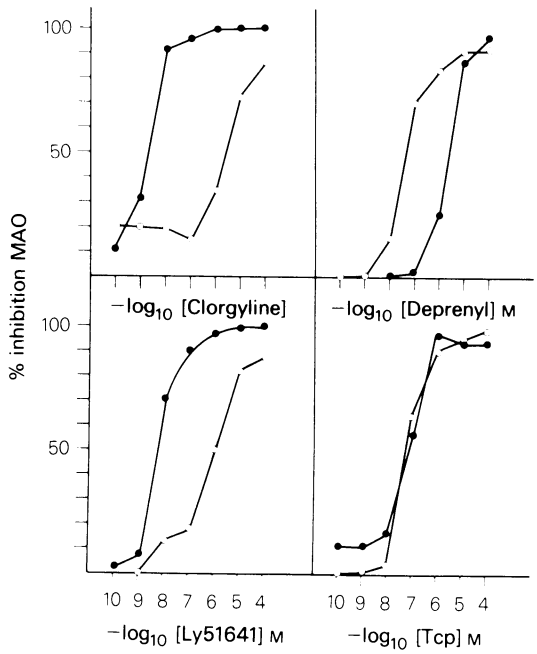

Figure 1 Inhibition of monoamine oxidase (MAO) in vas deferens homogenate *in vitro* by clorgyline, (−)-deprenyl, LY51641 and tranylcypromine (Tcp). The inhibitors were added to the incubation mixture containing homogenate of control vas deferens and ^{14}C-labelled substrates to attain the final concentrations shown. Substrates: (●) 5-HT (1.0 mM); (○) β-phenylethylamine (0.02 mM).

prepared for recording contractile responses as described above. Cumulative dose-response curves to noradrenaline were determined in the absence or presence of several concentrations of the various inhibitors as described by Van Rossum (1963) and pA_2 values calculated as described by Tallarida, Cowan & Adler (1979). Efficiency of the denervation procedure was assessed by: (a) increase in sensitivity of the tissue to noradrenaline by a factor of 15 together with an increase in the maximum response; (b) absence of response to tyramine, and (c) absence of response to electrical field stimulation (60 V, 1 ms pulses between two parallel electrodes 10 mm apart on either side of the tissue).

Drugs and solutions

Tyramine hydrochloride and (−)-noradrenaline bitartrate were obtained from Sigma. Clorgyline hydrochloride was obtained from May & Baker, N[2 - (2 - chlorophenoxy) - ethyl] cyclopropylamine HCl (LY 51641) from Eli Lilly, tranylcypromine sulphate from Smith, Kline & French, (±)-amphetamine sulphate from Teva (Israel) and (−)-deprenyl was a gift from Professor J. Knoll, Semmelweis University of Medicine, Budapest, Hungary. The Krebs solution had the following composition (mM): NaCl 118, KCl 4.7, $CaCl_2$ 2.5, $MgCl_2$ 1.2, NaH_2PO_4 1.2, $NaHCO_3$ 25 and glucose 11.

Results

Responses to noradrenaline and tyramine

Clorgyline When added directly to vas deferens homogenates, clorgyline inhibited 5-HT oxidation by 90% at a concentration of 10^{-8}M (Figure 1) with little or no change in PEA oxidation; selectivity of inhibition for MAO-A was maintained up to a concentration of 10^{-6}M clorgyline. In organ bath experiments (Figure 2), the inhibitory effect of clorgyline, as with all other inhibitors, was weaker, and 90% inhibition of MAO-A was achieved only at 10^{-6}M. However, selectivity of action against MAO-A was still apparent at this concentration. Tyramine responses were significantly potentiated by clorgyline at concentrations of 10^{-6}M and above, with no significant change in noradrenaline responses. At a clorgyline concentration of 10^{-5}M, tyramine responses were significantly depressed in presence of the inhibitor and potentiated following wash out. Noradrenaline responses were not significantly altered in the presence of the inhibitor, but were significantly enhanced following wash out. However, this enhancement of the noradrenaline response was not maintained and noradrenaline responses generally returned towards control levels by the fourth or fifth response following wash out of the inhibitor, whereas tyramine responses remained elevated. Potentiation of the noradrenaline response was dependent on the serial administration of noradrenaline and tyramine. When noradrenaline was given alone, responses were reduced in the presence of clorgyline (10^{-1}M) and returned to normal on wash out (Figure 3).

LY51641

This inhibitor was less selective, and less potent than clorgyline in its action against 5-HT oxidation. When added directly to tissue homogenates, 90% inhibition of 5-HT oxidation was seen at 10^{-7}M (Figure 1); in the whole tissue; however, this concentration of LY51641 produced only 65% inhibition of MAO-A (Figure 4). Responses to tyramine, however, were potentiated following wash out of LY51641 at this concentration. Increase in LY51641 concentration to 10^{-6}M in organ bath experiments produced 85% inhibition of 5-HT oxidation. Tyramine and noradrenaline responses were significantly inhibited when this concentration of LY51641 was present in the bath, but were potentiated following wash out of the inhibitor. Further increase in concentration of LY51641 to 10^{-5}M produced marked blockade of responses both to tyramine and noradrenaline in the presence of the inhibitor, and potentiation of effects of both sympathomimetic amines following its wash out (Figure 4).

(−)-Deprenyl

(−)-Deprenyl produced selective inhibition of PEA oxidation in tissue homogenate and whole organ experiments. At a concentration of 10^{-6}M added to a tissue homogenate, PEA oxidation was inhibited by 85% (Figure 1), but only by 65% when the same concentration was used in the organ bath (Figure 5). No significant alteration in tyramine or noradrenaline response was seen at this concentration of (−)-deprenyl. When the bath concentration of (−)-deprenyl was increased to 10^{-5}M, 5-HT oxidation was inhibited by 92% together with 77% inhibition of MAO-B. Both tyramine and noradrenaline responses were inhibited in presence of (−)-deprenyl at 10^{-5}M, but responses to both amines were potentiated following wash out of the inhibitor. In the absence of tyramine, noradrenaline responses were insignificantly potentiated (Figure 3). These effects were accentuated when the (−)-deprenyl concentration was increased to 10^{-4}M. As with clorgyline and LY51641, responses to noradrenaline subsequently returned towards control levels after the phase of potentiation, although tyramine responses remained potentiated. Attempts were made to increase the

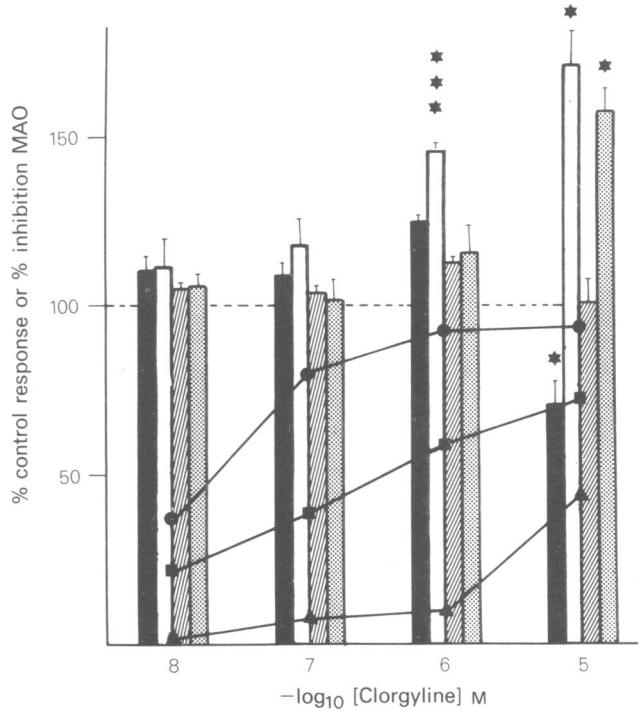

Figure 2 Modification of tyramine- and noradrenaline-induced (submaximal) contractions of rat isolated vas deferens by clorgyline, shown as % control response (before addition of inhibitor); vertical lines show s.e.mean. Solid columns: response to tyramine in presence of inhibitor; open columns: response to tyramine following wash-out of inhibitor; hatched columns: response to noradrenaline in presence of inhibitor; stippled columns: response to noradrenaline following wash-out of inhibitor. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ for difference between inhibitor-treated and control experiments (Student's t test). On same scale is shown % inhibition of MAO in the tissue using as substrate: (●) 5-HT (1.0 mM); (■) tyramine (1.0 nM), (▲) β-phenylethylamine (0.02 mM). Statistical variability has been omitted from MAO results for sake of clarity.

degree and selectivity of MAO-B inhibition by prolonging incubation time with the inhibitor. When a (−)-deprenyl concentration of 10^{-6}M was maintained in the organ bath for 30 min, a slightly greater degree of inhibition of MAO-A and MAO-B (57% and 73% respectively) was seen than when this concentration was maintained for 20 min but responses to tyramine and noradrenaline were not significantly modified. When a concentration of 2×10^{-7}M (−)-deprenyl was maintained in the bath for 45 min, PEA oxidation was selectively inhibited (67%) with no inhibition of 5-HT oxidation and without change in response to the sympathomimetic amines (responses to tyramine and noradrenaline $102.4 \pm 2\%$ and $100 \pm 1\%$ control values respectively, $n = 4$).

Tranylcypromine

The effect of tranylcypromine on responses to tyramine and noradrenaline was essentially different from that of the other inhibitors investigated. At 10^{-6}M, tranylcypromine caused a powerful potentiation of the contractile effects of both sympathomimetic amines while present in the bath fluid (Figure 6). On washing out the inhibitor, noradrenaline responses returned to control levels, while tyramine responses remained potentiated. This concentration of tranylcypromine caused 76% inhibition of MAO type A. On increasing the tranylcypromine concentration to 10^{-5}M, tyramine responses were completely suppressed in the presence of the inhibitor, but greatly potentiated following wash out. The greatest degree of tyramine potentiation (+180%) of all inhibitors used was seen with this concentration of tranylcypromine. As with the lower concentration of tranylcypromine, noradrenaline responses were potentiated in presence of the inhibitor, and returned to normal on washing out. When tissue MAO activity was determined following organ bath experiments, tranylcypromine showed slight selectivity for MAO type A, although no selectivity was seen when the

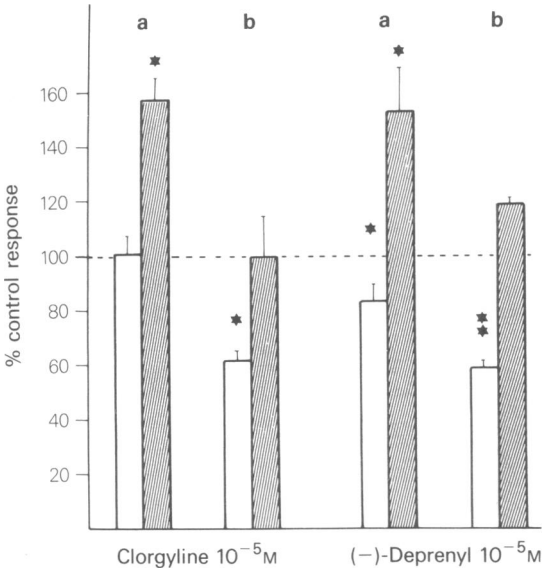

Figure 3 Modification of noradrenaline-induced contractions of rat isolated vas deferens by clorgyline (10^{-5}M) and (−)-deprenyl (10^{-5}M): (a) when tyramine had been present in the organ bath; (b) when tyramine was absent from the system. Open columns: responses in presence of inhibitor; hatched columns: responses following wash-out of inhibitor shown as % control response (before addition of inhibitor); vertical lines indicate s.e.mean. $*P<0.05$; $**P<0.01$ for differences from similar, control experiments, without an MAO inhibitor.

inhibitor was added to a tissue homogenate (Figures 1, 6).

Modification of contractile responses by tranylcypromine was compared with that produced by (±)-amphetamine. The latter amine (10^{-5}M) caused a reversible enhancement of both tyramine and noradrenaline responses (Figure 6).

α-Adrenoceptor blocking effects in denervated vas deferens

All MAO inhibitors used showed reversible α-adrenoceptor blocking properties in the denervated vas deferens (Figure 7). No enhancement of noradrenaline response was seen at any concentration of inhibitor on the denervated organ. Parallel shifts of the noradrenaline dose-response curve were produced by increasing concentrations of all inhibitors. Clorgyline also reduced the maximum response to noradrenaline at the highest concentration used (3×10^{-5}M). Slopes of the Schild plots (Arunlakshana & Schild, 1959) for LY51641 and tranylcypromine were 1.03 and 0.82, indicative of competitive antagonism, with pA_2 values of 6.17 and 5.26. For deprenyl and clorgyline, Schild plot slopes were 0.75 and 0.66, indicating a non-competitive component in the α-adrenoceptor antagonism. None of the compounds inhibited the contractile response to 39 mM KCl at concentrations above those which markedly suppressed the noradrenaline response.

Discussion

The net effect of an MAO inhibitor on the tyramine response is the resultant of MAO inhibition together with other actions, including α-adrenoceptor blockade, inhibition of amine uptake, and intrinsic sympathomimetic effect of the inhibitor. For the inhibitors used here, only inhibition of MAO is an irreversible phenomenon, whereas the other effects are reversible.

In the clinical setting, modification of the effect of orally administered tyramine is the major concern. In the whole animal, the effects of tyramine may be enhanced by reduction of intestinal and hepatic metabolism following MAO inhibition, leading to increased blood levels of the amine. Irrespective of increased blood levels, however, the peripheral effects of tyramine may be enhanced if neuronal MAO is inhibited, since both intraneuronal tyramine metabolism, as well as metabolism of released noradrenaline, will be reduced. Tyramine releases noradrenaline into a cytoplasmic pool, rather than by exocytosis, since dopamine β-hydroxylase (a marker of vesicles) is not released together with the neurotransmitter (Chubb, De Potter & De Schaepdryver, 1972). Since free cytoplasmic noradrenaline is normally kept at a low level by neuronal MAO (Trendelenburg, 1972), the size of this cytoplasmic pool would be considerably increased by inhibition of neuronal MAO (mainly type A, see above) thus leading to potentiation of the effects of indirectly-acting amines. The demonstration that clorgyline potentiates the effects of intravenously injected tyramine in the pig without inhibiting hepatic metabolism of this amine (Sandler, Glover, Ashford & Esmail, 1980), as well as the observation that the pressor effect of amphetamine (itself not a substrate for MAO) is potentiated by clorgyline but not deprenyl (Simpson, 1978), provide evidence that a neuronal mechanism is involved in potentiation of the effects of indirectly acting amines, as well as inhibition of metabolism of the amine itself. Other effects of deprenyl, including inhibition of amine uptake and reduction of noradrenaline release, were invoked by Knoll (1978) and Knoll & Magyar (1972) to explain the lack of tyramine potentiation by deprenyl. However, these effects are seen only in higher concentrations than are required to inhibit selectively MAO type B.

The present results provide further evidence that

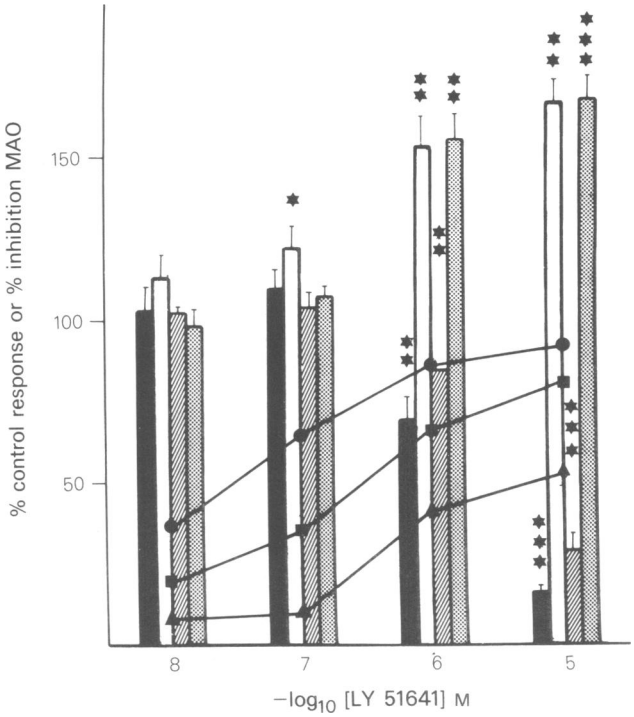

Figure 4 Modification of tyramine- and noradrenaline-induced contractions of rat isolated vas deferens and inhibition of monoamine oxidase (MAO) in the tissue by LY51641. For description, see legend to Figure 2.

selective inhibition of MAO type A is associated with potentiation of the effects of tyramine. Selective inhibition of most of the B-type enzyme, was not achieved under the conditions of these experiments, and so the converse (i.e. lack of tyramine potentiation in the presence of selective MAO type B inhibition) could not be conclusively demonstrated. The extent of MAO type A inhibition necessary to cause significant tyramine potentiation was different for clorgyline and LY51641, and the maximal degree of potentiation obtained also varied with all the inhibitors studied. Thus not only MAO inhibition, but also other intrinsic properties of the inhibitors such as catecholamine release, presumably play a part in the net result obtained. The present experiments demonstrate the importance of measuring whole tissue MAO activity, which was less susceptible to inhibition by the various drugs used than was the enzyme activity of a tissue homogenate. It should be pointed out, however, that some of the MAO activity of the whole tissue may have been contributed by inner layers of tissue, which may be less accessible to agonists added to the organ bath than the outer layers of tissue.

Of the four inhibitors investigated, clorgyline, deprenyl and LY51641 showed similar characteristics in that they inhibited tyramine and noradrenaline responses when present in the bath, and potentiated their effects on wash out. The reversible enhancement of the noradrenaline response in presence of a low concentration (10^{-6}M) of tranylcypromine suggests an amphetamine-like property. In agreement with these findings, tranylcypromine has been previously shown to reduce neuronal amine uptake (Hendley & Snyder, 1968) and to possess intrinsic sympathomimetic properties (Zirkle & Kaiser, 1964).

Depression of the tyramine response is most clearly correlated with α-adrenoceptor blocking activity of the inhibitors, since the most active in both respects was LY51641. Together with potentiation of tyramine responses, however, was seen potentiation of the noradrenaline response in experiments where both amines were administered. This potentiation of the noradrenaline response is indicative of inhibition of neuronal amine uptake by the combination of MAO inhibition together with tyramine treatment. Inhibition of MAO was shown to reduce neuronal amine uptake in the isolated heart (Trendelenburg, Graefe & Henseling, 1976), and the addition of tyramine may potentiate this effect by competition with noradrenaline for uptake (Burgen & Iversen,

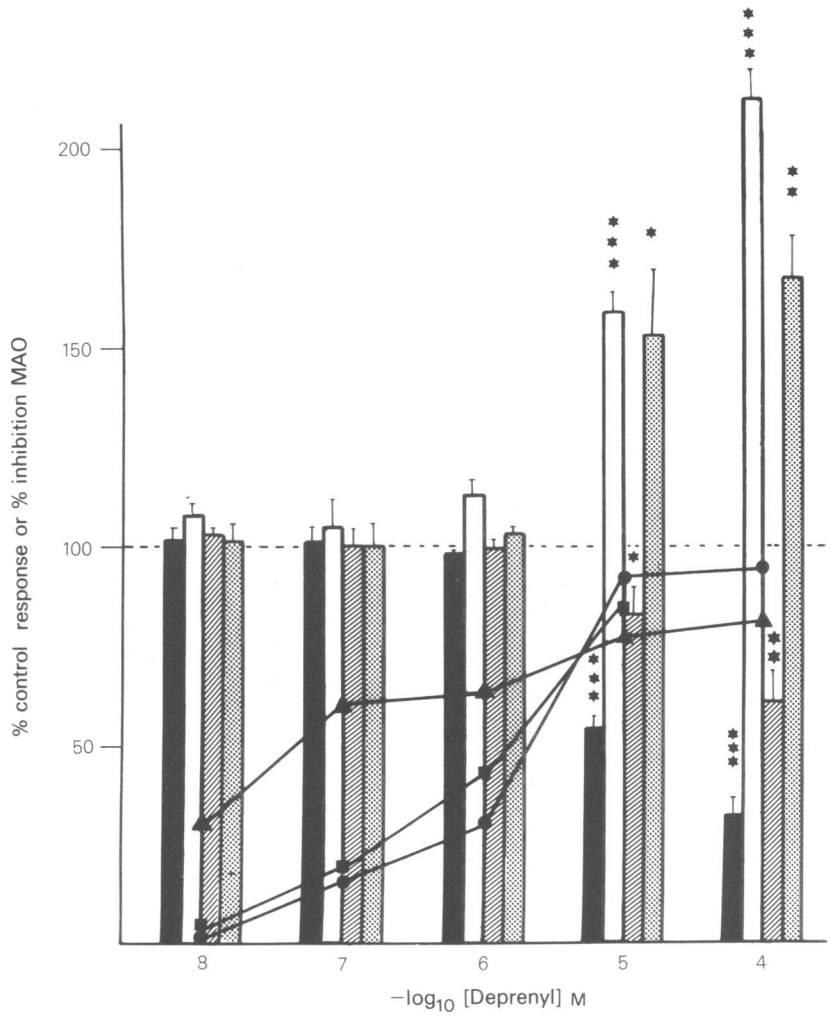

Figure 5 Modification of tyramine- and noradrenaline-induced contractions of rat isolated vas deferens, and inhibition of monoamine oxidase (MAO) in the tissue by (−)-deprenyl. For description, see legend to Figure 2.

1965) or enlargement of the cytoplasmic noradrenaline pool.

These considerations show that the final effect of an MAO inhibitor on tyramine responses will depend on the balance between its effects on neuronal uptake, α-adrenoceptors and noradrenaline release. The presence of strong postsynaptic α-adrenoceptor blocking potency, as in LY51641, may influence the effectiveness of the drug as an antidepressant. Therapeutic properties of MAO inhibitors may also be related to their effects on inhibition of amine uptake, which *in vivo* may be enhanced by the presence of endogenous tyramine, or other indirectly acting amines (e.g. β-phenylethylamine). Such a mechanism may explain the shared antidepressant properties of MAO inhibitors and tricyclic uptake blockers.

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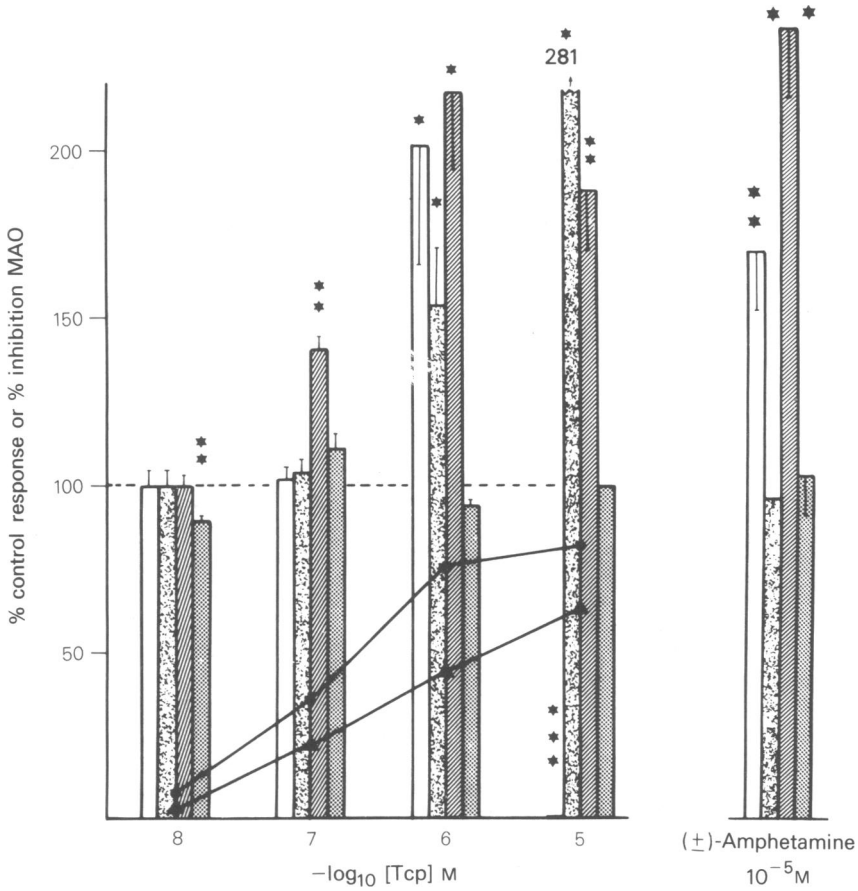

Figure 6 Modification of tyramine- and noradrenaline-induced contractions of rat isolated vas deferens, and inhibition of monoamine oxidase (MAO) in the tissue by tranylcypromine (Tcp). Also shown modification of tyramine and noradrenaline responses by (±)-amphetamine (10^{-5}M). For description, see legend to Figure 2.

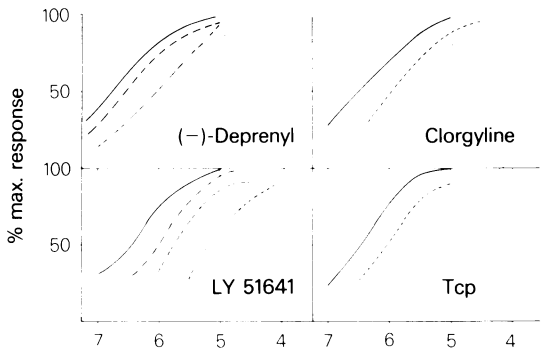

Figure 7 Modification of noradrenaline-induced contractions of denervated rat vas deferens by monoamine oxidase (MAO) inhibitors. Tcp = tranylcypromine Final bath concentration of (−)-noradrenaline (-$\log_{10}$M) shown on abscissae. For concentrations of MAO inhibitors: —— control response; —— · —— 10^{-6}M; — — · — — 3×10^{-6}M; — — — 10^{-5}M; · · · · 3×10^{-5}M.

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