It appears that fenproporex and fenfluramine can interact with and inhibit the mechanism by which (+)-amphetamine but not tyramine releases noradrenaline. Our results lend support to the suggestion by Day (1967) that indirectly-acting sympathomimetic amines may produce their effects by at least two distinct mechanisms.

We are not aware of any previous reports of a dose-dependent reduction in blood pressure to ascending doses of (+)-amphetamine; this phenomenon occurs after pretreatment with either fenproporex or fenfluramine but the underlying mechanism has yet to be elucidated.

In further work it will be interesting to observe if fenproporex and fenfluramine antagonize the stimulant action of (+)-amphetamine on the central nervous system. Jespersen & Bonaccorsi (1969b) have shown fenfluramine to decrease the toxicity of (+)-amphetamine in grouped mice.

We are grateful to Bottu Laboratories of Paris for supplying us with a sample of fenproporex for pharmacological studies.

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Modification by a tricyclic series of compounds of the noradrenaline effect on the cat nictitating membrane

There is evidence that the noradrenaline-potentiating action of imipramine and amitriptyline and their desmethyl derivatives is due to their ability to prevent the uptake of noradrenaline by sympathetic nerve endings (Hertting, Axelrod & Whitby, 1961; Iversen, 1965). Another characteristic property of this class of antidepressants is their sympathetic α-receptor blocking action (Sigg, 1959). In an attempt to separate these two actions and determine the importance of the position of the methyl group, the six tricyclic compounds listed in Table 1 have been investigated for their ability to modify the response of the cat nictitating membrane to doses of noradrenaline (2–20 μg/cat).

Cats were anaesthetized with a mixture of chloralose and pentobarbitone. Blood pressure was recorded from the right carotid artery. Changes in the response of the left nictitating membrane to noradrenaline, injected into the left lingual artery retrogradely, by intravenous doses of the tricyclic compounds were measured. In some experiments, the nictitating membrane was chronically denervated by removal of the superior cervical ganglion 21 days previously, a procedure that eliminates uptake of injected noradrenaline into sympathetic fibres (Hertting, Axelrod & others, 1961).

All the compounds modified the noradrenaline action on the intact nictitating membrane; potentiation at low doses, possibly by reducing the uptake of noradrenaline into sympathetic nerve endings, was followed by inhibition at high doses which is indicative of the sympathetic α-receptor blockade. In all the denervated preparations, potentiation of the response was absent and only inhibition was found.

Table 1. *Maximum percentage increase of the cat nictitating membrane to intra-arterial noradrenaline (2–20 μg) produced by intravenous doses of the tricylic series of compounds.* Control responses are taken as 100%. Figures in brackets refer to the number of determinations.

Compound	Dose (mg/kg) base	Increase (% ± s.e.)
Imipramine	0·9	220 ± 46 (7)
Desipramine	0·09	260 ± 29 (7)
Trimipramine	0·02	160 ± 30 (6)
Desmethyltrimipramine ..	0·002	125 ± 7 (5)
Amitriptyline	0·2	160 ± 21 (4)
Nortriptyline	0·5	300 ± 37 (5)

Maximum potentiation for the iminodibenzyl compounds covered a ten-fold range in dosage between the desmethyl derivatives and the parent compounds, imipramine and trimipramine (Table 1). Furthermore, both the β-methyl substituted iminodibenzyl compounds (trimipramine and desmethyltrimipramine) were 45 times more potent than their respective unsubstituted compounds. On the other hand, doses of amitriptyline and nortriptyline producing the maximum potentiation were of a similar order although the degree of potentiation was different. In fact, the potentiation produced by nortriptyline was the highest found with the six tricyclic compounds, probably because it possesses only a weak sympathetic α-receptor blocking action. Besides uptake and blockade of the injected noradrenaline, there may be a local alteration by the tricyclic compounds in the blood flow to the nictitating membrane, although there was no significant alteration in the arterial blood pressure of the cat.

The present results show that the most potent of the tricyclic compounds that potentiated the noradrenaline effect was desmethyltrimipramine, in which the sole methyl group is substituted on the β-carbon atom.

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