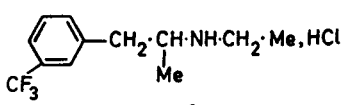
REFERENCES

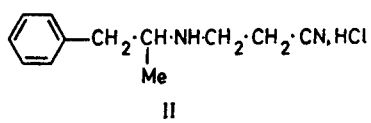
ADRIAN, E. D. (1941). *J. Physiol., Lond.*, **100**, 159–191.
AMMASSIAN, V. E. (1952). *Res. Publs Ass. Res. nerv. ment. Dis.*, **30**, 371–402.
BHARGAVA, V. K. (1969). Ph.D. Thesis Council for National Academic Awards, London.
BHARGAVA, V. K. & MELDRUM, B. S. (1969). *Br. J. Pharmac.*, **37**, 112–122.
BRADBURY, M. W. B. & DAVSON, H. (1964). *J. Physiol., Lond.*, **170**, 195–211.
COLLIER, B. & MITCHELL, J. F. (1966). *Ibid.*, **185**, 22–23*P*.
COLLIER, B. & MITCHELL, J. F. (1967). *Ibid.*, **188**, 83–98.
MARSHALL, W. H. (1941). *J. Neurophysiol.*, **4**, 25–43.

Inhibition by appetite suppressants of the pressor response to (+)-amphetamine in anaesthetized cats

Recently Jespersen & Bonaccorsi (1969a) reported an anti-amphetamine activity of fenfluramine (I) in the isolated tail artery of the rat. These authors observed that the constrictor response to tetrabenazine in the presence of amphetamine was inhibited by fenfluramine in this preparation. At the time of publication we were investigating the effects of another appetite suppressant, fenproporex (II), on the cardiovascular system of the anaesthetized cat where we found that after intravenous administration of fenproporex, (+)-amphetamine failed to produce a substantial pressor response. As a result of this observation we made further experiments which included studies of the effects of both fenproporex and fenfluramine on the pressor responses to tyramine as well as (+)-amphetamine. Cats anaesthetized with sodium pentobarbitone were used and all agents were injected intravenously.



I



II

Fenproporex was shown to have no pressor activity and relatively large doses (3–10 mg/kg) caused marked but transient reductions in blood pressure. When (+)-amphetamine, 0·01–0·1 mg/kg, was administered after a 10 mg/kg dose of fenproporex little or no rise in blood pressure resulted. These doses of (+)-amphetamine produced pressor responses in cats that received no fenproporex, or when given before fenproporex (Fig. 1A). Increasing the dose of (+)-amphetamine did not overcome the inhibitory effect of fenproporex, in fact larger doses (1–10 mg/kg) in the presence of fenproporex caused dose-dependent reductions in blood pressure (see also Fig. 1A). In further experiments, a dose of (+)-amphetamine to produce a marked pressor response (usually 0·03–0·1 mg/kg) was administered before and after various doses of fenproporex. We observed that whereas a 1 mg/kg dose of fenproporex caused only a slight reduction of the (+)-amphetamine pressor response, a 3 mg/kg dose usually caused complete inhibition. At this stage, larger doses of (+)-amphetamine again produced depressor responses.

When the above experiments were repeated using tyramine instead of (+)-amphetamine, no inhibition by fenproporex of the pressor responses to tyramine was observed (Fig. 1B) and in some instances the tyramine response was potentiated. Subsequent doses of (+)-amphetamine (0·1–5 mg/kg) failed to elicit pressor responses, the blood pressure being either unaffected or reduced according to the dose.

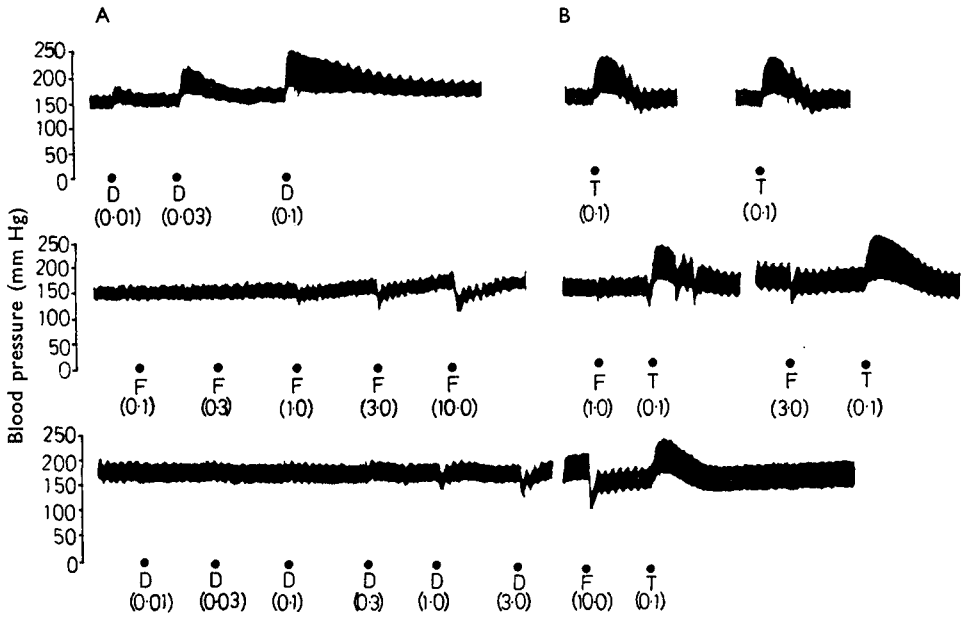


FIG. 1.A. Blood pressure responses to (+)-amphetamine (D) in an anaesthetized cat before (top trace) and after (bottom trace) repeated administration of fenproporex (F, middle trace). Both drugs were administered intravenously. Doses in mg/kg.

B. Blood pressure responses to tyramine (T) in an anaesthetized cat before (top trace) and after (middle and bottom traces) increasing doses of fenproporex (F). Both drugs were administered intravenously. Doses in mg/kg.

Unlike fenproporex, fenfluramine had some pressor activity and doses of 0·3–3·0 mg/kg caused marked elevations in blood pressure after an initial short-lasting fall. Pressor responses to (+)-amphetamine (0·01–0·3 mg/kg) were reduced by fenfluramine; subsequently, higher doses of (+)-amphetamine (1, 2, 3 and 5 mg/kg) produced a prolonged and dose-related fall in blood pressure. Conversely, the pressor response to fenfluramine was reduced by previous administration of (+)-amphetamine. The tyramine response was unaltered or potentiated by fenfluramine.

Both fenproporex and fenfluramine had little effect on the pressor response to noradrenaline at times when the pressor response to (+)-amphetamine had been modified.

Tachyphylaxis to the pressor effects of certain indirectly-acting sympathomimetic amines such as mephentermine or phenylethylamine follows the repeated administration of these agents (Day, 1967); concomitantly, the pressor responses to (+)-amphetamine but not those to tyramine are reduced. Day (1967) suggested that indirectly-acting sympathomimetic amines could be divided into two classes depending on whether their administration reduced the responses to (+)-amphetamine or tyramine.

Fenfluramine is a pressor amine and tachyphylaxis to its pressor response has been reported (Franko, Honkomp & Ward, 1965). However, in the present studies tachyphylaxis to fenfluramine was not a prerequisite to the observation of reduced responses to (+)-amphetamine. Under similar conditions, the pressor response to tyramine was unaltered or potentiated.

The results with fenproporex are interesting as this drug does not raise the blood pressure and yet is very effective in its selective inhibition of the (+)-amphetamine pressor response.

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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REFERENCES

DAY, M. D. (1967). *Br. J. Pharmac. Chemother.*, **30**, 631–643.
FRANKO, B. V., HONKOMP, L. J. & WARD, J. W. (1965). *J. Pharm. Pharmac.*, **17**, 222–226.
JESPERSEN, J. & BONACCORSI, A. (1969a). *Ibid.*, **21**, 776–777.
JESPERSEN, J. & BONACCORSI, A. (1969b). *Europ. J. Pharmac.*, **8**, 364–368.

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).