Interactive effect of (±)-fenfluramine and (+)-amphetamine on feeding in rats

Fenfluramine has been found to antagonize a number of behavioural and physiological effects brought about by amphetamine including compulsive gnawing (Berger, Brown & Krantz, 1973), the toxicity phenomenon in grouped mice (Bizzi, Bonaccorsi & others, 1970), pressor response (Berry, Poyser & Robertson, 1971), constriction of isolated tail arteries (Jesperson & Bonaccorsi, 1969a) and the reduction in pentobarbitone sleeping time (Berger & others, 1973). In addition, fenfluramine produces an initial counteractive effect on amphetamine induced hyperthermia (Jesperson & Bonaccorsi, 1969b) and hyperactivity (Berger & others, 1973), which is followed by a prolongation of the amphetamine response (Jonsson & Gunne, 1972).

In all these instances fenfluramine administered alone produces little effect or gives rise to a response opposite to that of amphetamine. In fact the only action which amphetamine and fenfluramine have in common is anorexia, though the effect of concurrent administration of amphetamine and fenfluramine on food intake has never been reported. However, since it has been suggested that, because of chemical similarities, amphetamine and fenfluramine may compete for the same receptors (Jesperson & Bonaccorsi, 1969b), observation of the effect on feeding of simultaneous administration of these two drugs may throw light upon the mode of action of the drugs. This possibility was investigated in the following experiment.

Male hooded rats (mean weight 347 g) were housed individually and kept on a 12 h light–dark cycle. Water was freely available and the rats were fed powdered food presented in specially prepared containers which trapped spillage. During the experimental periods animals were deprived of food at 18·00 each evening and food tests were given on the following day at 10·00. Because of the importance of time course effects of anorexic drugs noted previously (Blundell, Latham & Leshem, 1973), food intake was measured (to the nearest 0·1 g) at 1, 4, 6 and 24 h. Drug injections were given 30 min before food presentation and animals were habituated to the intraperitoneal injection procedure and to the deprivation schedule for 10 days before the start of the experiment proper. Over the course of the experiment six drug treatments were administered: (+)-amphetamine sulphate (1·0 and 2·0 mg kg^{-1}), (±)-fenfluramine hydrochloride (5·0 and 10·0 mg kg^{-1}), 0·9% saline, and concurrent injection of fenfluramine (5·0 mg kg^{-1}) and amphetamine (1·0 mg kg^{-1}).

The results are summarized in Table 1 and show that amphetamine and fenfluramine, when injected alone, give rise to a dose-dependent reduction in food intake. However, the most profound effect on feeding was observed after the administration of the smallest doses of amphetamine and fenfluramine in combination. This injection produced a marked and lasting reduction of food intake, and feeding was depressed below the level of all other drug scores at the 4, 6, and 24 h tests (Wilcoxon, maximum $T = 5$, $N = 12$, $P < 0{\cdot}01$ two-tailed test). This finding shows clearly that fenfluramine does not antagonize the anorexic action of amphetamine, nor is there competitive inhibition between the anorexic effects of the two drugs. On the contrary, the anorexic effects of amphetamine and fenfluramine appear to summate, a finding consistent with the belief that the drugs exert selective effects on different components of the brain amine systems involved in the regulation of feeding: amphetamine anorexia depending on a noradrenergic system (Ahlskog & Hoebel, 1973) and fenfluramine anorexia mediated by a serotonergic mechanism (Samanin, Ghezzi & others, 1972). Moreover, the overall anorexic effect could be attributed to a combination of the brief action of amphetamine together with the more enduring effect of fenfluramine (Le Douarec, Schmitt & Laubie, 1966).

Table 1. *Effect of amphetamine and fenfluramine on feeding measured periodically over 24 h.*

Drug	Dose (mg kg^{-1})	Feeding period (h) 0–1	0–4	0–6	0–24
Amphetamine	1·0	3·0 ± 1·5†	12·7 ± 5·4*	18·0 ± 4·1	35·7 ± 7·2
	2·0	0·1 ± 0·2†	9·5 ± 2·5†	14·6 ± 2·7*	33·3 ± 4·0*
Fenfluramine	5·0	6·1 ± 4·0†	10·4 ± 3·6†	13·4 ± 4·0**	34·7 ± 8·5
	10·0	4·9 ± 3·1†	8·3 ± 2·5†	11·0 ± 5·1	33·5 ± 7·6*
Fenfluramine and amphetamine	5·0 + 1·0	1·0 ± 1·4†	2·6 ± 3·4†	6·5 ± 5·2†	27·8 ± 6·8†
Saline control	—	9·2 ± 2·9	14·0 ± 2·2	18·4 ± 2·9	38·1 ± 4·8

Figures show mean food intake (g) ± standard deviations and each score is the mean reading from 12 animals. Symbols indicate significance levels for comparisons between drug scores and saline control values; * $P<0{\cdot}025$, ** $P<0{\cdot}01$, † $P<0{\cdot}005$. (Wilcoxon matched pairs, one tailed test).

However, an alternative interpretation arises from the observation that amphetamine and fenfluramine injected in combination produce more than a simple additive effect of the two drugs injected separately. Table 1 shows that for the 4, 6 and 24 h tests the effect of the combined injection is significantly greater than the sum of the individual reductions in food intake (maximum T = 9, N = 12, $P < 0{\cdot}02$). Thus, fenfluramine seems to produce a prolongation of the initial potent anorexic response of amphetamine, a phenomenon which is similar to the potentiating effect of fenfluramine on amphetamine induced hyperactivity and hyperthermia noted previously. A possible explanation for this constellation of observations may be provided by the report that fenfluramine administration gives rise to a prolonged elevation of brain and plasma levels of amphetamine lasting for at least 12 h after injection (Jonsson & Gunne, 1972).

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