Does fenfluramine act via norfenfluramine?

Goudie, Taylor & Wheeler (1974) recently demonstrated that behavioural and appetite depressant effects of norfenfluramine were strikingly similar to those of fenfluramine. In several species fenfluramine is de-alkylated to norfenfluramine (Bruce & Maynard, 1968; Beckett & Brookes, 1967; Morgan, Cattabeni & Costa, 1972). These findings suggest that the anorectic properties of fenfluramine could be due to its metabolite norfenfluramine.

Samanin, Ghezzi & others (1972) and Clineschmidt (1973) demonstrated that lesions which specifically affect the serotonergic systems in the brain antagonized the anorectic properties of fenfluramine. We have investigated the possible central action of fenfluramine and its metabolite norfenfluramine by injections of small amounts directly into the brain of rats.

For the local injections, the area of the nucleus interstitialis of the stria terminalis was chosen because its involvement in the regulation of food intake is indicated by experiments on the elicitation of feeding behaviour by α-adrenoceptor stimulating drugs (Booth, 1967; Davis & Keesey, 1971; Broekkamp & van Rossum, 1972), and the neostriatum was chosen because it contains the highest synthesizing capacity for 5-hydroxytryptamine and therefore seems to be highly innervated by serotonergic nerves (Mandell, Knapp & Hsu, 1974).

Bilateral implantation of two cannulae was made stereotaxically in male Wistar rats of 200-250 g. In two groups the cannulae were aimed at the nucleus interstitialis of the stria terminalis and in two groups the cannulae were placed into the neostriatum.

Post mortem examination of the brains confirmed that the injection sites were in the area A 7·3 ± 0·35, L 2·4 ± 0·7 and D 0·9 ± 0·4 within the neostriatum and A 6·65 ± 0·4, L 0·9 ± 0·4 and D −1·0 ± 0·5 within the nucleus interstitialis of the stria terminalis with reference to the atlas of König & Klippel (1963).

The drugs were dissolved in saline and injected in a volume of 0·5 μl into each hemisphere.

The anorectic effect was measured on the intake of cold cooked white rice in a 30 min period. The injections were made 15 min before the test period began. The animals were housed and tested individually and had laboratory chow and tap water freely available. The rats were made accustomed to the diet and the injection procedure in the week preceding the injections. Injections were made every other day in ascending dosage until an anorectic effect was evident or the dose became unreasonably high. The sequence of doses was concluded with a second saline injection.

Table 1. *Amount of rice eaten in a half hour period following injections of saline, norfenfluramine and fenfluramine.*

Treatment (μg)	Neostriatum		Nucleus interstitialis of the stria terminalis	
	Fenflur. n=7	Norfenflur. n=6	Fenflur. n=6	Norfenflur. n=6
saline	4·7±1	5·1±1·3	5·5±0·8	5·7±1
2 × 2·5	4·6±0·9	6·9±1·2	5·1±1·2	5·6±0·6
2 × 5	4·2±0·8	7·3±1·6	5·9±0·6	5·8±1·3
2 × 10	3·2±0·3	0·7±0·3*	6·2±0·9	2·1±0·9*
2 × 20	3·6±0·4		5·9±0·7	
2 × 40	4·3±0·9		4·9±1·3	
saline	5·0±0·7	4·9±1·3	6·1±1·2	5·1±0·6

The amounts eaten are given in grams ± the standard error of the mean; * = $P<0·05$; Two-tailed Mann-Whitney U-Test. Drugs were: (±)-fenfluramine HCl and norfenfluramine HCl.

As shown in Table 1, even high dosages of fenfluramine are inactive when administered via the intracerebral route. Under identical conditions norfenfluramine is active in moderate doses. There was a significant difference in the amount of rice eaten by the rats with nucleus interstitialis cannulae and those with neostriatal cannulae after norfenfluramine administration (Mann-Whitney U-test; two-tailed; $P<0{\cdot}05$).

It is unlikely that fenfluramine is inactive because of a more rapid removal from the brain since Morgan & others (1972) have shown that both fenfluramine and norfenfluramine persist in the brain for up to 24 h after a systemic injection. Our results are comparable to the results of Kramer, Rubicek & Turner (1973) who demonstrated that after topical application only norfenfluramine is effective in inducing mydriasis whereas after systemic injections both drugs are active. Together these findings add substance to the suggestion that the central anorectic properties of fenfluramine are mediated mainly by norfenfluramine.

A further screening of other brain sites with norfenfluramine is necessary before it can be concluded that the neostriatum is the main site of action after systemic administration.

The authors thank Dr. R. Vroom and The Servier Company for the generous gift of fenfluramine HCl and norfenfluramine HCl.

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August 28, 1974

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