*Short communications*

# Dissociation of the anorexic effects of fenfluramine and amphetamine following intrahypothalamic injection

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Injections of amphetamine and fenfluramine directly into the hypothalamus produced changes in food intake dependent upon the site of injection. No significant modulation occurred following injections into the ventromedial nucleus. In the lateral hypothalamus both drugs gave rise to an overall depression of feeding behaviour but the time-course of action for the drugs differed and there was a high negative correlation between the action of the two drugs within individual animals. These findings provide further evidence for the belief that fenfluramine and amphetamine exert their anorexic actions through the lateral hypothalamus rather than the ventromedial nucleus, but suggest that different chemical mechanisms are involved in the anorexia produced by each drug.

**Introduction.**—There is now considerable evidence indicating that amphetamine exerts its anorexic action by way of diencephalic mechanisms concerned with the control of food intake. Moreover, lesion and stimulation experiments seem to indicate that, within the diencephalon, amphetamine has a direct inhibitory action on the lateral hypothalamic area rather than the ventromedial nucleus (e.g. Grossman, 1967). These findings are consistent with the results of recent experiments showing that injections of amphetamine directly into the lateral hypothalamus exert a suppressant effect on food intake (Booth, 1968 ; Leibowitz, 1970).

In addition to this information about the site of action of amphetamine there is now evidence showing that the appetite suppressant effect of fenfluramine may also be mediated by the lateral hypothalamus. The anorexia produced by fenfluramine, like that of amphetamine, is not diminished by lesions of the ventromedial nucleus (Bernier, Sicot & Le Douarec, 1969), while on the other hand some electrophysiological recording studies have indicated that the most pronounced neurophysiological concomitant of fenfluramine injection is a slowing of activity in the lateral hypothalamus (Chhina, Kang, Singh & Anand, 1971). Moreover, the use of a hypothalamic model permitting a distinction to be made between the behavioural effects of drugs acting at the ventromedial nucleus or lateral hypothalamus has indicated that both fenfluramine and amphetamine exert an inhibitory effect on the lateral hypothalamus (Blundell, 1971).

The present experiment was designed to test the deductions arising from these experimental results by comparing the effects of amphetamine and fenfluramine injected directly into the lateral hypothalamus and ventromedial nucleus.

**Methods.**—Twelve male black-hooded rats (weight 300–340 g at the time of operation) were used. Stainless steel cannulae were implanted bilaterally into either the lateral hypothalamus (de Groot coordinates, A5·0, 1·5, 8·3) or the ventromedial nucleus (A5·8, 0·6, 8·5). In all implants the outer guide cannula was constructed from 23 gauge tubing and its tip was positioned 0·5 to 1·0 mm above the target hypothalamic area in order to avoid excessive tissue damage at the injection site. The fine inner trochar (28 gauge) protruded beyond the guide cannula to rest immediately above the target locus. Chemicals were administered in a volume of 1 $\mu$l and the injection procedure, together with the preparation of chemical solutions, was similar to that described previously (Blundell & Herberg, 1970).

Animals were kept on a 16-h food deprivation schedule with food pellets removed at 6 o'clock in the evening. Bilateral intrahypothalamic injections were given at 9.30 a.m. and measures of food intake were taken after 1 and 8 hours. At each feeding test a weighed amount of food in a metal tray was placed in the cage and during the feeding period spillage was collected on absorbent paper placed beneath wire grid floors. At the end of the feeding periods the remaining food together with spillage was weighed.

Three chemical treatments were administered: 20 $\mu$g of (±)-fenfluramine hydrochloride, 20 $\mu$g (+)-amphetamine sulphate, and 0·9% w/v NaCl solution (saline). Subjects served as their own controls and

TABLE 1. *Food intake (g) following bilateral chemical injections into the lateral hypothalamus*

| Time and duration of feeding test | (±)-Fenfluramine | (+)-Amphetamine | Saline |
|---|---|---|---|
| Injection day | | | |
| 1 h | 8·5±1·4 | 7·1±1·9* | 9·6±1·1 |
| 8 h | 20·3±2·9 | 21·5±2·0 | 22·9±2·1 |
| Post-injection day | | | |
| 1 h | 7·9±1·4 | 8·3±1·4 | 8·5±0·8 |
| 8 h | 21·5±2·8* | 22·3±4·4 | 25·1±1·8 |
| Total | 41·8±4·8* | 43·8±5·4 | 48·0±4·1 |

Values given are means±standard deviations.* Significantly different from saline score at $P<0·05$ (Wilcoxon T, 2 tailed test). This level of significance indicates that differences between treatments are all in the same direction.

the series of three drug treatments was administered twice to each subject. Animals therefore received six intrahypothalamic injections and the order of presentation was arranged so that each possible sequence of the three drugs appeared an equal number of times. Injections were given at 2 day intervals.

**Results.**—Measures of food intake were strongly influenced by the nature of the chemical injected and by the site of injection. Following drug injections at the ventromedial nucleus, a slight increase in food intake was observed, but none of the differences reached statistical significance. In contrast, at the lateral hypothalamus (Table 1) both drugs exerted a depressant action upon food intake which was apparent during the first hour after injection and was still in evidence on the day following drug administration. The most pronounced effect of amphetamine occurred immediately after injection while the maximal suppressant effect produced by fenfluramine was observed during subsequent feeding tests. Measures of total food intake showed a high negative correlation between the anorexic effect of amphetamine and fenfluramine (Spearman $rs=-0·72$).

Both drugs caused a substantial loss of weight following lateral hypothalamic injection. After 24 hours fenfluramine caused a loss of 9·2 g and amphetamine a loss of 7·7 g relative to controls; at 48 h the differences were 13·5 g and 7·8 g respectively.

**Discussion.**—The present study has shown that intrahypothalamic administration of the anorexic agents amphetamine and fenfluramine in food-deprived rats may influence feeding behaviour for at least 32 h after injection. The finding that lateral hypothalamic injections of amphetamine substantially depressed feeding while injections into the ventromedial nucleus gave rise to a mild enhancement of food intake confirms previous work (Leibowitz, 1970). In general the present experiment showed that fenfluramine injections produced a similar pattern of effects, but a detailed analysis of the results indicated certain differences in the action of the two drugs.

Statistically significant effects upon feeding activity were observed only after injections into the lateral hypothalamus. At this site of action each drug produced a depression of food consumption but with markedly different temporal characteristics. Amphetamine exerted a maximal anorexic action in the test 1 hour after injection during which period its appetite suppressant effect was superior to that of fenfluramine. However, the most pronounced effect of fenfluramine, relative to control injections, occurred during the final feeding test. Since measures of body weight loss also indicated an enduring action of fenfluramine compared with amphetamine, it therefore seems that the time-courses of action of the two drugs are quite different, a phenomenon which is also apparent after peripheral injections (Blundell & Leshem, unpublished).

In addition, correlation procedures revealed a further difference between the action of the drugs in the lateral hypothalamic area. Although treatment mean scores indicated that both drugs depressed feeding, within individual animals there was an inverse relationship between the efficacy of amphetamine and fenfluramine. For example, the food intake of one animal was depressed 13·4 g after fen-

fluramine but only 4·9 g after amphetamine, while another animal showed an opposite effect: 2·9 g reduction following fenfluramine and 5·3 g when amphetamine was injected. Thus, there appears to be no parity in the intensity of the anorexic effect of the two drugs when guided to identical loci in the lateral hypothalamic area through the same cannulae.

The differences observed between amphetamine and fenfluramine with respect to the time-course of the anorexic effect and to the intra-animal degree of anorexia suggest that, while both drugs may exert an appetite suppressant effect within the lateral hypothalamic area, they do so through different mechanisms. This suggestion is consistent with the belief that the anorexic effects of the drugs are mediated by differing chemical systems. Suppression of feeding by amphetamine seems to be mediated by an adrenergic system, for it has been shown that amphetamine anorexia in the rat is reduced by pretreatment with $\alpha$-methyl tyrosine, an inhibitor of noradrenaline synthesis (Holtzman & Jewett, 1971). However, the antagonism of fenfluramine depression of food intake by 5-hydroxytryptamine antagonists (Jesperson & Scheel-Krüger, 1970; Funderburk, Hazelwood, Ruckart & Ward, 1971) suggests that fenfluramine anorexia is mediated by a tryptaminergic, rather than an adrenergic, mechanism. Taken together, these findings suggest that the differences observed in the present experiment between the anorexic effects of amphetamine and fenfluramine may be due to the two drugs intervening in different portions of the hypothalamic chemical systems regulating food intake.

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