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Biphasic action of a 5-hydroxytryptamine inhibitor on fenfluramine-induced anorexia

Injections of the anorexic drug fenfluramine have a potent effect on brain 5-hydroxytryptamine (5-HT) metabolism (e.g. Morgan, Cattabeni & Costa, 1972), and also give rise to behavioural changes similar to those produced by 5-hydroxytryptophan (Southgate, Mayer & others, 1971). In experiments which have included measures of feeding activity, it has been reported that 5-HT inhibitors such as methysergide (Jespersen & Scheel-Krüger, 1970) or methergoline (Funderburk, Hazelwood, & others, 1971) antagonize the suppression of feeding behaviour induced by fenfluramine. In keeping with traditional pharmacological procedures for evaluating anorexic action, these experiments used only brief measures of food intake: appetite was restored by 5-HT inhibitors in dogs 1 h after fenfluramine injection and in rats during a 2 h feeding test. However, it has recently been shown that observation of the time course of food intake modulation represents a crucial aspect of the analysis of the central action of anorexic drugs (Blundell & Leshem, 1973). Accordingly the present experiment was designed to investigate the temporal relation of the action of a 5-HT inhibitor (methysergide bimaleate) on fenfluramine-induced anorexia.

Male black hooded rats, 350 g, kept in single cages, were given sham injections daily for 1 week before the start of the experiment. In the first experiment feeding was measured either following a period of 48 h food deprivation, or when the animals were satiated. Monitoring of feeding began 30 min after drug injections and measurements of food intake (to the nearest 0·1 g) were taken at 1, 4, 8, and 24 h. Animals received subcutaneous injections (0·1 ml volume) of either 5·0 mg kg^{-1} methysergide bimaleate or 0·9% saline in conjunction with intraperitoneal injections (0·5 ml volume) of either 5·0 mg kg^{-1} (±)-fenfluramine hydrochloride or saline.

In the second experiment, food deprived animals received injections of fenfluramine plus methysergide or fenfluramine plus saline. Food intake was measured for a 1 h period and the interval between injection and the beginning of the feeding test was fixed at 0·5, 1·5, or 2·5 h.

The results of the first experiment showed that although methysergide alone produced no apparent effect on food intake, this drug exerted a biphasic action on fenfluramine-induced anorexia (Fig. 1). In the first hour of the feeding test, methysergide clearly antagonized the appetite suppressant action of fenfluramine (Fig. 1a) and animals which received injections of methysergide plus fenfluramine consumed significantly more food than animals injected with saline and fenfluramine (Mann Whitney

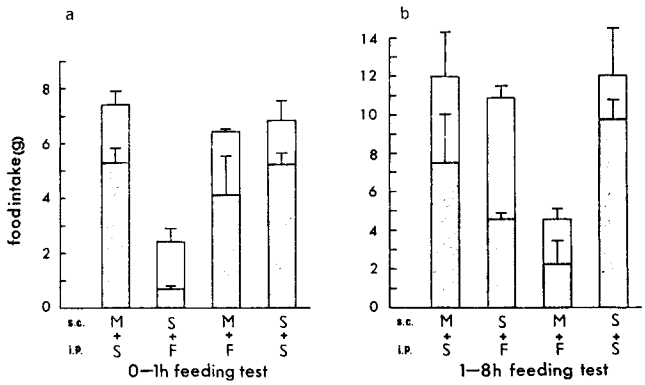

FIG. 1. Effect on food intake (mean and s.d.) of methysergide (M), Saline (S), and fenfluramine (F) administered subcutaneously (s.c.) or intraperitoneally (i.p.). Six animals for each condition (open columns = deprived; stippled columns = satiated). In the first hour of the feeding test methysergide injections antagonize fenfluramine anorexia but during the subsequent testing period a reversal of this effect occurs. In the 1–8 h test the methysergide-fenfluramine combination exerts a greater anorexic effect than fenfluramine alone.

U = 0, $P < 0{\cdot}01$). However, during the subsequent 7 h (Fig. 1b) the opposite effect was apparent: the combined administration of methysergide and fenfluramine exerted a greater anorexic action than fenfluramine alone ($P < 0{\cdot}01$). This progressive change in fenfluramine-induced anorexia from antagonism to augmentation brought about by methysergide was observed in both satiated and deprived animals showing that it was not simply a function of the feeding schedule. Measurement of food intake over the full 24 h period showed that animals receiving methysergide and fenfluramine ate significantly less than animals treated with fenfluramine and saline (mean food intake of 32·9 and 36·6 g respectively for deprived animals $P < 0{\cdot}02$). Thus, in this experiment a brief measure of food intake (0–1 h) would demonstrate that methysergide antagonized fenfluramine anorexia whereas a longer period of measurement (0–24 h) would indicate the opposite.

Intermediate measurements (not shown in figure) indicated that methysergide had begun to facilitate fenfluramine anorexia by the end of the 4 h test, and the

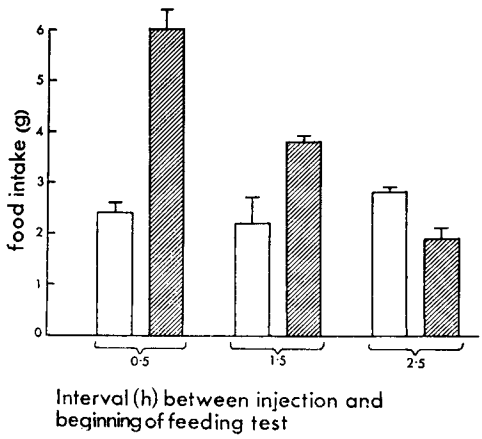

FIG. 2. Effect of combinations of fenfluramine plus saline (open columns) and fenfluramine plus methysergide (hatched columns) on food intake measured for a 1 h period. Six animals per condition. When the feeding tests begin 0·5 and 1·5 h after injection of the drugs, methysergide antagonizes fenfluramine anorexia. However, when the interval between injection and test is 2·5 h, methysergide facilitates the appetite suppressant effect of fenfluramine.

results of the second experiment showed that the reversal from antagonism to facilitation was taking place between 2·5 and 3·5 h after injection, (Fig. 2). Antagonism of fenfluramine anorexia by methysergide was in evidence for feeding tests ending 1·5 and 2·5 h after drug injection ($P<0·05$), but the methysergide and fenfluramine combination exerted a significantly greater anorexic effect than fenfluramine and saline ($P<0·05$) when the period between injection and end of feeding tests was 3·5 h. This finding not only throws light on the time course of the interaction between methysergide and fenfluramine but also indicates how the observed effect of methysergide upon fenfluramine-induced anorexia is dependent upon the interval between the injection and the feeding test. In similar experiments on amphetamine anorexia a study of the time course of action has revealed no interaction between methysergide and amphetamine with respect to food intake.

The investigation has confirmed the involvement of a tryptaminergic mechanism in fenfluramine anorexia but points to the importance of considering temporal parameters in the elucidation of this system. The results have shown how it would be possible to demonstrate that methysergide may antagonize, facilitate, or produce no apparent effect upon fenfluramine anorexia; the observed effect will depend upon the interval between drug injection and the onset of the feeding test (Fig. 2), and upon the duration of the feeding test itself (Fig. 1). This finding provides a tentative explanation for the recent report of the failure of methysergide to antagonize fenfluramine anorexia (Jespersen & Scheel-Krüger, 1973). The results of this study point to the unsuitability of traditional brief feeding tests for investigating appetite (e.g. Tedeschi, 1966) and suggest the need for continuous monitoring of food intake to provide a complete description of anorectic drug action.

We are grateful to Servier Laboratories who supported this work through a research grant.

We thank Sandoz Laboratories for supplying methysergide.

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January 31, 1973

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