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The effect of viloxazine on drug-induced inhibition of food intake in the rat

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In male Wistar rats trained to eat their normal daily dietary requirement in a restricted 2 h period, dose-dependent decreases in food consumption were produced by fenfluramine, tiflorex, mazindol and amphetamine. The antidepressant drug viloxazine (Vivalan) alone did not alter food intake significantly, nor did the drug prevent the inhibitory effects of either mazindol or amphetamine. However, complete prevention of the inhibitory effect of fenfluramine was achieved with 7·5 mg kg^{-1} viloxazine, while 40 mg kg^{-1} viloxazine similarly prevented the anorectic action of tiflorex. An interaction involving 5-hydroxytryptaminergic mechanisms is suggested, and since viloxazine given after fenfluramine or tiflorex produced no reversal of the inhibition of food intake, it is suggested that viloxazine prevents access of the anorectic agents to their site of action. The clinical significance of these interactions is discussed.

Anorexia nervosa, first described as a 'nervous consumption' by Richard Morton in 1694, is recognized as one of the most intractable psychiatric disorders, and one of the most resistant to pharmacological intervention.

The group of drugs most commonly cited in discussion of the treatment of anorexia are the tricyclic antidepressants, particularly amitriptyline (Mills 1976), but a wide variety of drugs, ranging from phenothiazines to 'appetite stimulants' such as cyproheptadine, have been tried (Halmi & Goldberg 1978), the diversity perhaps reflecting the fact that so far none has proved satisfactory.

The experiments reported here stemmed from clinical observations that the antidepressant viloxazine (Vivalan) had a beneficial effect in patients suffering from anorexia nervosa (H. Neubauer, personal communication). The reported clinical responses were remarkable but inevitably isolated, and for obvious reasons not readily confirmed by proper clinical trial. A search of the literature revealed no previous reports of increased food intake after viloxazine, either in man or in animals; on the contrary, the more common clinical finding is of nausea and decreased appetite. It was therefore decided to investigate the effects of viloxazine on appetite using an animal model. Clearly, no true behavioural model of anorexia nervosa exists in laboratory animals, and, because of the lack of understanding of the underlying causes of the disease, it is impossible to simulate the appropriate biochemical lesion. Our approach has therefore been to use drugs to decrease food intake, and the effects of viloxazine on this pharmacologically-induced anorexia are reported here.

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METHODS

Male Wistar rats (University of Bath strain), 120 g ± 2 g at the start of the experiments, were individually housed. Water was freely available but the animals were deprived of food for 22 h out of every 24 h. After an initial loss of weight, the animals quickly adapted to this restrictive regime and subsequently consumed their normal daily requirement of food in the 2 h feeding period between 14.00 h and 16.00 h. The animals were weighed daily, and no drugs were administered until a regular pattern of eating had been established, and the animals were gaining weight normally. This training period was generally between 12 and 14 days, after which time the amount of food consumed in the 2 h period had risen to between 15 and 20 g. A measured quantity, 30 g, of Oxoid 41B pellets was provided at the beginning of each feeding period, and at the end, the remainder, including any that had dropped through the grid-floor of the cage, was weighed. All drugs were given by i.p. injection, dissolved in 0·9% NaCl (saline); mazindol was first dissolved in M/30 HCl before dilution in saline. Viloxazine was injected 1 h before feeding began, all the others half-an-hour before. Statistical analysis was carried out using Student's *t*-test.

Drugs used: viloxazine HCl (Vivalan), ICI Ltd, fenfluramine HCl, Servier Laboratories Ltd, amphet-

amine HCl, Smith, Kline and French Laboratories Ltd, tifluorex HCl, Synthalabo Laboratories, mazindol, Sandoz Products Ltd. The gift of drugs from the Companies is gratefully acknowledged.

RESULTS

Viloxazine was administered alone in doses varying from 2·5 to 40 mg kg^{-1}. Although viloxazine-treated animals consistently ate more than control animals, this trend never reached the level of statistical significance. No other behavioural effects were observed after viloxazine in this dose range.

Fenfluramine, 2·5 to 10·0 mg kg^{-1}, caused a dose-dependent decrease in food intake. A control value of 17·8 ± 1·9 g was decreased to 13·9 ± 0·9 g, 10·8 ± 0·6 g, 6·7 ± 1·4 g and 6·7 ± 2·4 g by doses of 2·5, 5·0, 7·5 and 10 mg kg^{-1} respectively. The 81% decrease in food intake produced by 10 mg kg^{-1} fenfluramine was therefore chosen as the response against which to test viloxazine. Fig. 1 shows the dose-dependent inhibition of the fenfluramine response by previous administration of viloxazine. A dose of 7·5 mg kg^{-1} viloxazine was sufficient to abolish the fenfluramine-induced 'anorexia' completely.

A similar effect was observed with tiflorex, a close analogue of fenfluramine (Fig. 2). Again, complete inhibition of the anorectic effect was produced, although a higher dose of viloxazine, 40 mg kg^{-1}, was required. In contrast, the same dose of viloxazine failed to affect the inhibition of food intake produced by either amphetamine or mazindol (Figs 3 and 4).

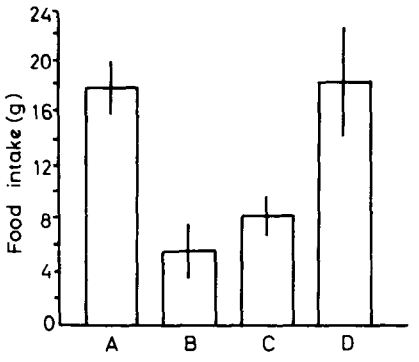

FIG. 1. Influence of viloxazine on fenfluramine-induced inhibition of food intake. In this and all subsequent figures, n = 6 unless otherwise indicated: means are shown ± s.e.m. A = control; B = fenfluramine, 10 mg kg^{-1}; C = fenfluramine, 10 mg kg^{-1} + viloxazine, 5 mg kg^{-1} (n = 5); D = fenfluramine, 10 mg kg^{-1} + viloxazine, 7·5 mg kg^{-1} (n = 5). Difference between B and C n.s.; difference between B and D = $P < 0{\cdot}01$. $t = 4{\cdot}0$.

DISCUSSION

The experiments reported here were carried out after clinical observations had suggested that viloxazine was able to stimulate appetite and to increase food intake in patients suffering from anorexia nervosa. Each of the four anorectic agents against which viloxazine has been tested are, or have been, successfully used to reduce food intake and to promote weight loss. The results of our experiments show a clear difference between the effect of viloxazine on fenfluramine and tiflorex on

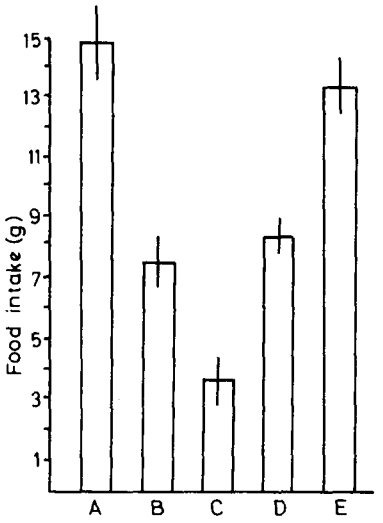

FIG. 2. Influence of viloxazine on tiflorex-induced inhibition of food intake. A = control; B = tiflorex, 5 mg kg^{-1}; C = tiflorex, 10 mg kg^{-1}; D = tiflorex, 10 mg kg^{-1} + viloxazine, 20 mg kg^{-1}; E = tiflorex, 10 mg kg^{-1} + viloxazine, 40 mg kg^{-1}. Statistical significance of differences. A–B $P < 0{\cdot}01$, $t = 3{\cdot}7$; A–C $P < 0{\cdot}001$, $t = 6{\cdot}2$; C–D $P < 0{\cdot}01$, $t = 3{\cdot}3$; C–E $P < 0{\cdot}001$, $t = 6{\cdot}9$.

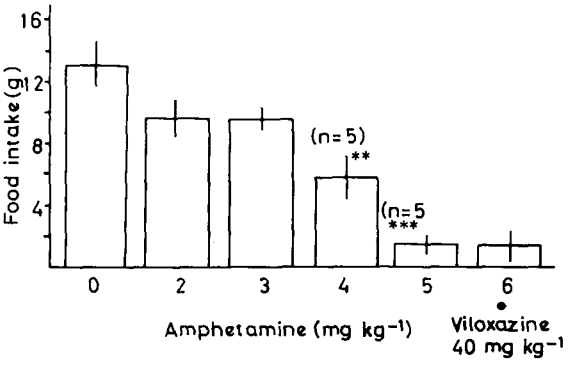

FIG. 3. Effect of amphetamine + viloxazine on food intake. Difference from control: ** = $P < 0{\cdot}01$; ***$P < 0{\cdot}001$.

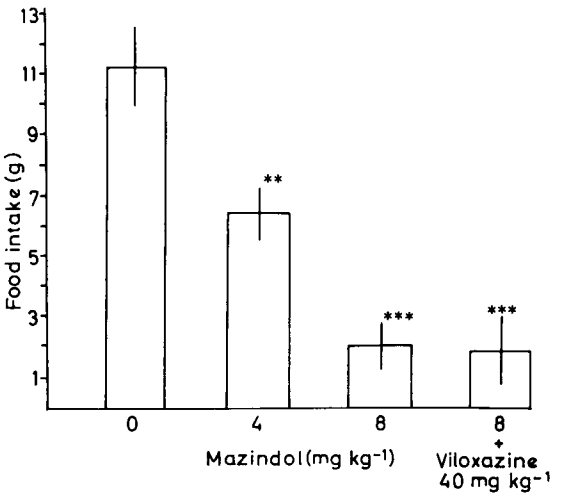

FIG. 4. Effect of mazindol + viloxazine on food intake. Difference from control: ** = $P < 0.01$, *** = $P < 0.001$.

the one hand and amphetamine and mazindol on the other. The most obvious correlate of this dichotomy is the established relationship between 5-hydroxytryptamine (5-HT) and the anorectic action of both fenfluramine and tiflorex (Costa et al 1971). Amphetamine and mazindol are not reported to have any significant effect on central 5-HT and it is generally assumed that the appetite-suppression produced by these agents is caused by interference with central catecholamines (Moore & Lariviere 1963). It has further been asserted that the action of fenfluramine on tryptaminergic mechanisms represents a stimulation of satiety, while amphetamine produces the same end response by decreasing hunger drive (Blundell & Lesham 1975).

It would appear, therefore, that any projected action of viloxazine on neuronal mechanisms controlling appetite and food intake is likely to be mediated through interference with tryptaminergic mechanisms. Viloxazine has been shown to be virtually devoid of uptake-inhibitory activity against 5-HT in synaptosomes (Blackburn et al 1978) and in platelets (Mallion et al 1972). In contrast, Von Voigtlander & Losey (1976) reported that viloxazine was capable of inhibiting *p*-chloromethylamphetamine-induced release of 5-HT in mouse brain, and it might be suggested that similar action against fenfluramine-induced depletion of 5-HT might account for the results of our experiments. However, the effects of viloxazine on 5-HT mechanisms are not invariably inhibitory. Thus Lippman & Pugsley (1976) showed a potentiation of 5-hydroxytryptophan (5-HTP)-induced hyperactivity as well as an increase in the facilitation of the extensor hindlimb reflex by 5-HTP in spinalized rats. A similar potentiation has been shown after microiontopheretic application of 5-HT to cortical neurons in the rat (Jones & Roberts 1977) and it has been suggested that these effects resulted from facilitated release of 5-HT from synaptosomes (Martin et al 1978). These apparently paradoxical and contradictory results also extend to the mechanism of food intake, since, in contrast to the results reported here, in experiments using obese animals given unlimited access to a varied diet, viloxazine decreased food intake and weight gain (Pleece et al 1978).

The most likely explanation for our results is that viloxazine has some ability to facilitate 5-HT release, an ability that may account for the 'anti-obesity' action of the drug. It may be further suggested that in promoting 5-HT release, viloxazine interferes with the access of drugs such as *p*-chloromethylamphetamine and fenfluramine, which themselves deplete intraneuronal stores of 5-HT. While prior administration of viloxazine prevented the fenfluramine-induced decrease in food intake, the action of fenfluramine was not modified by viloxazine when the order of drug administration was reversed.

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