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Effects of the 5-HT Uptake Inhibitors, Femoxetine and Paroxetine, and a 5-$HT_{1A/B}$ Agonist, Eltoprazine, on the Behavioural Satiety Sequence

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McGUIRK, J., R. MUSCAT AND P. WILLNER. *Effects of the 5-HT uptake inhibitors, femoxetine and paroxetine, and a 5-$HT_{1A/B}$ agonist, eltoprazine, on the behavioural satiety sequence.* PHARMACOL BIOCHEM BEHAV **41**(4) 801–805, 1992. – In rats allowed access to a 35% sucrose solution, following a 4-h period of food and water deprivation, an initial period of sucrose consumption was followed by a short period of grooming and exploratory behaviour, later superseded by resting. This "behavioural satiety sequence" was advanced in time by the 5-HT uptake inhibitors femoxetine and paroxetine and by the 5-$HT_{1A/B}$ agonist eltoprazine at anorectic and subanorectic doses. These effects, which are similar to those previously observed with another 5-HT uptake inhibitor, fluoxetine, are compatible with an increase in postprandial satiety.

5-HT uptake inhibitors 5-HT_1 receptors Femoxetine Paroxetine Eltoprazine
Behavioural satiety sequence Rat

WHEN hungry animals feed to satiety, they exhibit a characteristic sequence of postprandial behaviours, known as the behavioural satiety sequence: In the rat, the offset of eating is followed by a short period of active behaviours such as locomotion, sniffing, and grooming, followed in turn by a longer period of resting (1,21). The behavioural satiety sequence was first described in animals consuming food pellets (16) or a balanced liquid diet (1,21), and has subsequently been observed following consumption of a variety of other solid and liquid diets, including concentrated sucrose solutions (12,23). However, the satiety sequence is normally seen only in animals that have consumed a calorie-rich diet; resting is not usually seen, for example, following the consumption of saccharin or weak sucrose solutions or following sham feeding (1,10,12). The satiety sequence therefore seems to be a reliable behavioural correlate of a state of postingestive satiety.

Numerous studies have demonstrated that energy intake can be decreased by drugs that enhance the activity of endogenous serotonin (5-HT), such as 5-HT precursors, releasers, or uptake inhibitors. These drugs reliably decrease the consumption of calorie-rich solid or liquid diets, with some studies suggesting a preferential suppression of carbohydrate intake [see (2,7) for reviews]. However, whether these action result from the enhancement of physiological processes associated with the onset of satiety is uncertain. The behavioural satiety sequence is one technique that has been used to address this issue.

Previous studies have reported that the 5-HT uptake inhibitor fluoxetine advanced the onset of the behavioural satiety sequence: In addition to bringing consummatory behaviour to a premature termination, fluoxetine also advanced the onset of resting (4,23). These effects have been observed following a meal of lab chow (4) or a 35% sucrose solution (23). However, the prototypical "serotonergic" anorectic drug, fenfluramine (14), did not have this effect. Instead of potentiating postprandial resting, fenfluramine reliably and potently suppressed resting, following a meal of wet mash (powdered chow plus water) (12) or 35% sucrose (12,23). This effect was present even at subanorectic doses and was seen with *d*-fenfluramine, the active isomer (8), as well as with racemic *dl*-fenfluramine (12,23). It is at present unclear how this difference in the behavioural actions of fluoxetine and fenfluramine is to be explained.

By way of an initial approach to this problem, we sought in the present study to establish which pattern of activity is more typical of other serotonergic anorectic drugs. Two of

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the drugs examined, paroxetine and femoxetine, are specific 5-HT uptake inhibitors (3,21) that, like other 5-HT uptake inhibitors, reduce food intake on acute administration to rats (15). The hypophagic actions of fenfluramine (13,19) and of the 5-HT uptake inhibitor sertraline (11) are known to be mediated by 5-HT_1 receptors, and food intake is reliably decreased by directly acting 5-HT_1 agonists, such as *m*-chlorophenylpiperazine (*m*-CPP), trifluoromethylphenylpiperazine (TFMPP), quipazine, and RU24969 (6,9,19). We therefore also examined the effects on satiety behaviour of a 5-HT_1 agonist, eltoprazine (20). Drug effects were examined in rats consuming a "meal" of 35% sucrose, following 4-h food and water deprivation, so that data would be directly comparable with those obtained in our earlier study of fluoxetine and fenfluramine (23), which used the same procedure.

METHOD

Subjects

Male Lister hooded rats (National Institute for Medical Research, Mill Hill, U.K.) weighing approximately 300 g were maintained on a 12 L: 12 D cycle (lights on at 0800 h). Animals were housed singly and, except as described below, lab chow (Lillico, Herts.) and water were freely available. The three experiments were conducted in parallel during spring 1989.

Procedure

Other than the drugs administered, the procedures followed in the present experiments were identical to those used previously (23); these conditions were adopted because they give rise to stable levels of sucrose consumption and a reliable behavioural satiety sequence in untreated or vehicle-treated animals.

Testing was carried out between 1600 and 1800 h, following deprivation of food and water for 4 h. The test consisted of the presentation of a preweighed bottle containing a 35% sucrose solution, which was available for 40 min. Animals were observed for the duration of the test, and every 15 s behaviour was scored, using a BBC microcomputer, in one of five mutually exclusive categories: drinking, active, grooming, standing motionless, or lying down, each behaviour represented by a separate keystroke. For the purposes of analysis and presentation, the two latter categories were considered together as "resting behaviour"; instances of "standing" were infrequent, and excluding them from the "resting" category did not alter the pattern of results obtained. The category "active," which includes sniffing, rearing, and locomotion, was used when none of the other categories were applicable; thus, the use of this category does not in itself carry any implication of a stimulant effect. All observations were made by the same rater, who was blind as to drug treatment.

Drug treatment commenced after sucrose intakes had stabilized, which required six twice-weekly sessions. Three groups of animals (n = 12) were tested following acute treatment with paroxetine (0, 1, 2, or 4mg/kg), femoxetine (0, 2.5, 5, or 10mg/kg), or eltoprazine (0, 0.5, 1, or 2mg/kg), respectively. Each animal received all doses of one drug only. Doses were chosen on the basis of pilot studies. The four doses of each drug were administered in a counterbalanced order such that, on any trial, three animals received each drug dose, with a minimum of 2 drug-free days between tests.

Drugs

Paroxetine HCl and femoxetine HCl (Ferrosan, Seborg, Denmark) and eltoprazine HCl (Duphar, Weesp, The Netherlands) were dissolved in physiological saline; doses were calculated as salts. Drugs were injected IP 45 min prior to testing in a volume of 1 ml/kg; physiological saline was used for control injections.

Analysis

Data were analyzed by analysis of variance (ANOVA), supplemented by tests of simple main effects and planned comparisons (24). Separate analyses were performed for each drug and for each behavioural observation category.

RESULTS

All three drugs significantly reduced sucrose intake [paroxetine: $F(3,33) = 3.73$, $p = 0.02$; femoxetine: $F(3,33) =$

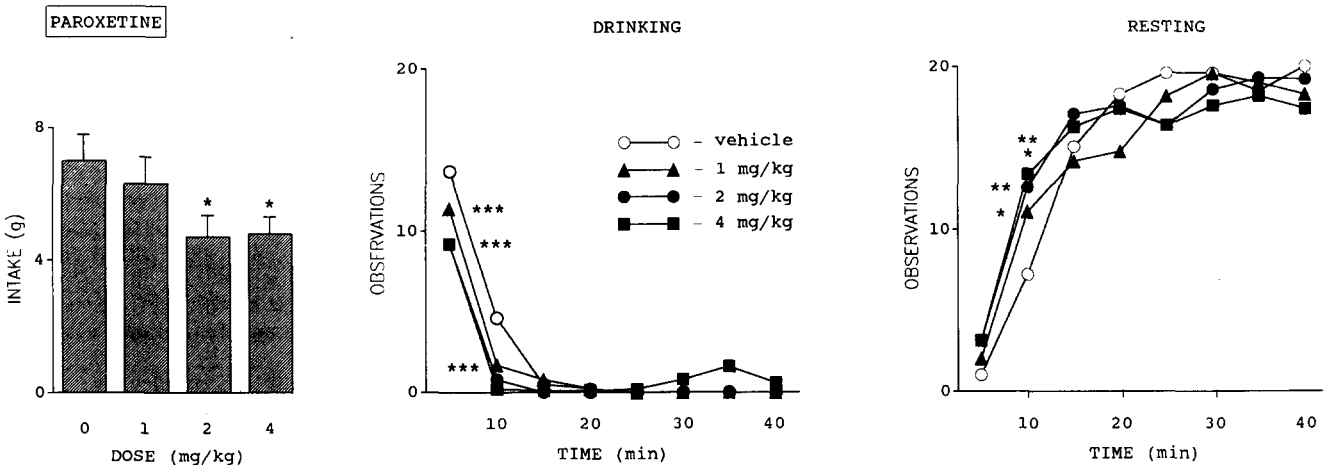

FIG. 1. Effects of paroxetine on sucrose intake (left) and on drinking (centre) and resting (right) behaviours. Values for drinking and resting are the mean frequency of each type of observation in each 5-min period (max = 20). The frequencies of other behaviours are summarized in Table 1. Asterisks represent significant changes from vehicle pretreatment: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

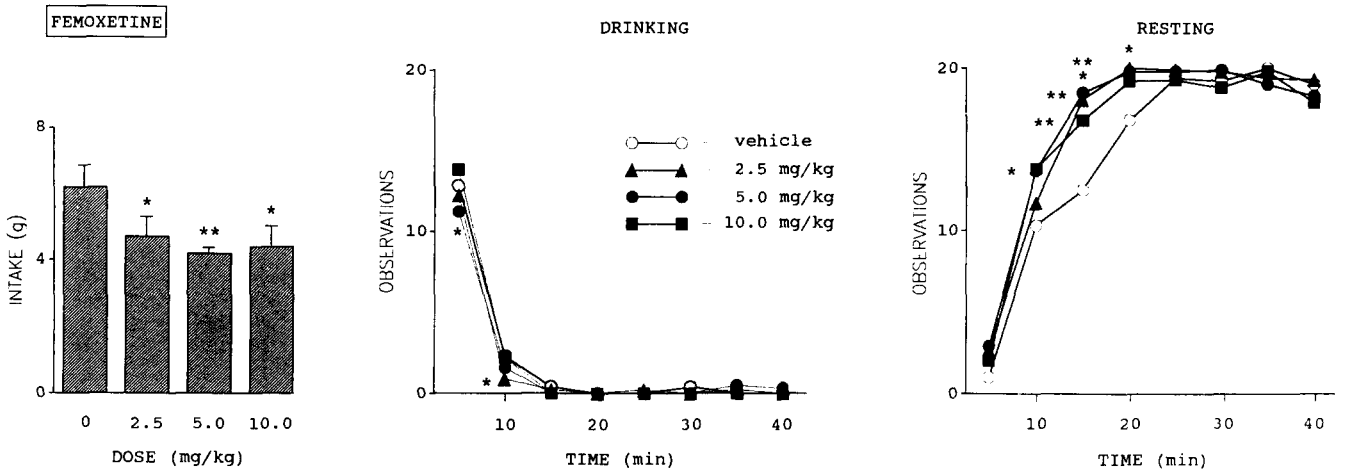

FIG. 2. Effects of femoxetine on sucrose intake (left) and on drinking (centre) and resting (right) behaviours. Values for drinking and resting are the mean frequency of each type of observation in each 5-min period (max = 20). The frequencies of other behaviours are summarized in Table 1. Asterisks represent significant changes from vehicle pretreatment: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

3.35, $p < 0.05$; eltoprazine: $F(3,33) = 12.48$, $p < 0.001$]. The effects of femoxetine and paroxetine were slightly greater at the intermediate than at the highest dose, although in neither case were the differences between effective doses significant (Figs. 1 and 2, left panels).

Drug effects on the behavioural satiety sequence are shown in Table 1 and Figs. 1-3, (middle and right panels). Under vehicle conditions, drinking was the predominant behaviour in the early part of the session (Figs. 1-3, middle panels), superseded by a period of active behaviours and grooming (not shown), followed in turn by resting, which was the predominant behaviour later in the session (Figs. 1-3, right panels).

Paroxetine dose dependently reduced drinking time, $F(3,33) = 3.04$, $p < 0.05$, leading to an early termination of drinking [dose × time interaction, $F(21,231) = 4.37$, $p < 0.001$]; these effects were significant at the lowest dose tested, which did not significantly reduce intake. Paroxetine did not significantly alter activity or grooming, $F(3,33) = 1.51$, 1.38, NS. The main effect of paroxetine on resting was also nonsignificant, $F(3,33) = 0.4$, NS, but there was a significant dose × time interaction, $F(21,231) = 2.4$, $p < 0.001$, with a significant simple main effect ($p < 0.001$) in the second 5-min time period; the effect at this time was significant at all doses of paroxetine (Fig. 1).

Femoxetine also tended to reduce drinking early in the session (Fig. 2); in this case, the overall effect of the drug was nonsignificant, $F(3,33) = 1.3$, NS, but there was a significant simple main effect of drug in the first 5-min time period, $F(3,264) = 5.36$, $p < 0.05$. Femoxetine reduced activity, $F(3,33) = 4.53$, $p < 0.01$, and advanced the offset of grooming [dose × time interaction: $F(21,231) = 1.69$, $p < 0.05$; results not shown]. However, the most striking effect was an increase in resting behaviour, $F(3,33) = 3.97$, $p = 0.02$,

TABLE 1

BEHAVIOURAL EFFECTS OF PAROXETINE, FEMOXETINE, AND ELTOPRAZINE*

Drug	Dose (mg/kg)	Drinking	Activity	Grooming	Resting
Paroxetine	0	19.1	9.0	12.8	119.2
	1	14.0	7.8	21.2	116.8
	2	10.2†	10.8	12.6	124.0
	4	12.6*	12.0	16.0	120.0
Femoxetine	0	16.0	9.5	16.2	118.4
	2.5	13.6	6.0*	10.5	131.2†
	5	13.4	4.6†	9.5*	132.0†
	10	16.0	6.7*	10.7	124.2*
Eltoprazine	0	14.1	10.6	18.4	117.2
	0.5	8.5*	12.6	9.1*	130.4
	1	5.1†	16.0	5.0†	133.9*
	2	5.7†	26.6‡	5.7*	121.4

*Values are the mean number of observations of each type of behaviour (max = 160). $*p < 0.05$, $†p < 0.01$, $‡p < 0.001$, relative to vehicle.

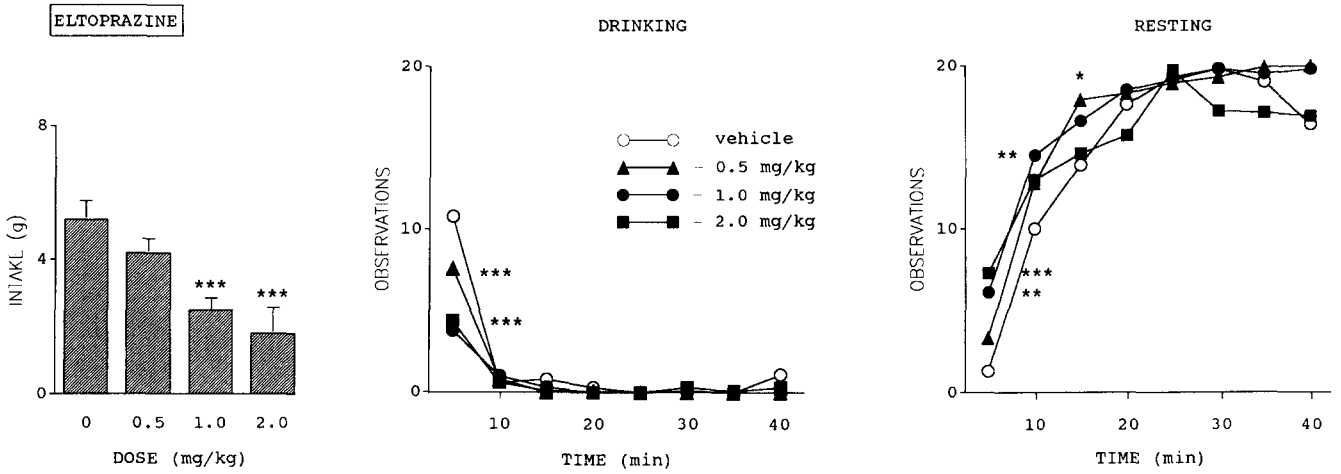

FIG. 3. Effects of eltoprazine on sucrose intake (left) and on drinking (centre) and resting (right) behaviours. Values for drinking and resting are the mean frequency of each type of observation in each 5-min period (max = 20). The frequencies of other behaviours are summarized in Table 1. Asterisks represent significant changes from vehicle pretreatment: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. Asterisks above 10 min refer to the adjacent 5-min values; they are displaced for clarity.

with significant simple main effects in the second ($p < 0.05$), third ($p < 0.001$), and fourth ($p < 0.05$) 5-min time periods (Fig. 2).

Eltoprazine, like paroxetine, caused a dose-dependent reduction in drinking, $F(3,33) = 7.95$, $p < 0.001$, which was significant at all doses, including the lowest, which did not significantly reduce intake (Fig. 3). The highest dose of eltoprazine significantly increased activity, $F(3,33) = 5.25$, $p < 0.01$, at the expense of grooming, $F(3,33) = 5.29$, $p < 0.01$; from informal observations, it was clear that the highest dose of eltoprazine caused a marked stimulation of locomotor behaviour. As with paroxetine, the main effect of eltoprazine on resting was nonsignificant, $F(3,33) = 2.54$, NS, but there was a significant dose × time interaction, $F(21,231) = 2.11$, $p < 0.01$: All doses increased resting early in the session, with significant simple main effects in the first ($p < 0.001$), second ($p < 0.05$), and third ($p < 0.05$) time periods (Fig. 3).

DISCUSSION

Although the effects vary slightly between drugs, the actions of all three agents in suppressing consumption time and advancing the onset of resting are compatible with an enhancement of postprandial satiety (1,21). In the case of paroxetine and eltoprazine, the behavioural changes were present at doses that did not significantly reduce the quantity of sucrose consumed. A very similar pattern of effects has previously been reported for the 5-HT uptake inhibitor fluoxetine both in our own earlier study, using the identical procedure (23), and in chow-fed nondeprived animals (4). The effects of femoxetine in particular, which significantly advanced grooming as well as resting, were very similar to those previously reported for fluoxetine. By contrast, fenfluramine has been reported to disrupt the behavioural satiety sequence (12,23). While the present results provide no further insight into this anomalous effect of fenfluramine, they demonstrate that fenfluramine is atypical: Three 5-HT uptake inhibitors, as well as the 5-HT_1 agonist eltoprazine, have now been shown to potentiate the behavioural satiety sequence on acute administration, with fenfluramine as the exception.

It has previously been reported that the anorectic effect of fenfluramine was antagonized by nonspecific 5-HT antagonists, or by a 5-$HT_{1A/1B}$ antagonist, but not by selective 5-HT_2 or 5-HT_3 antagonists, leading to the conclusion that the effects were most likely mediated by 5-HT_1 receptors (13,18). The same conclusion was reached in a similar study of the 5-HT uptake inhibitor sertraline (12). However, the subtype of 5-HT_1 receptor responsible for the hypophagic action of endogenous 5-HT has not yet been determined. Most of the directly acting 5-HT_1 agonists known to reduce food intake, such as *m*-CPP, TFMPP, quipazine, and RU24969 (6,8,9, 17,19), are active, to varying degrees, at 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C} receptors. However, their 5-HT_{1A} activity cannot be responsible for the hypophagic effect since specific 5-HT_{1A} agonists reduce food intake only at high doses, which cause gross behavioural abnormalities; at lower doses, thought to act preferentially at presynaptic 5-HT_{1A} autoreceptors, specific 5-HT_{1A} agonists increase food intake (5,17). These findings implicate 5-HT_{1B} and 5-HT_{1C} receptors in 5-HT-mediated hypophagia (8,17).

The present observation that eltoprazine enhanced satiety behaviour is of considerable interest in this context. In contrast to other 5-HT_1 agonists, eltoprazine is an agonist at 5-HT_{1A} and 5-HT_{1B} receptors, but a 5-HT_{1C} antagonist (20). This implies that a selective stimulation of 5-HT_{1B} receptors may be sufficient to elicit the behavioural satiety sequence. A further implication is that 5-HT_{1B} receptors, possibly localized within the paraventricular nucleus of the hypothalamus (8), may be primarily responsible for mediating the hypophagic effects of 5-HT uptake inhibitors.

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