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Effect of Dexfenfluramine on Saccharin Drinking: Behavioural and Pharmacological Studies

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HIGGINS, G. A., D. M. TOMKINS, C. X. POULOS AND E. M. SELLERS. *Effect of dexfenfluramine on saccharin drinking: Behavioural and pharmacological studies.* PHARMACOL BIOCHEM BEHAV 47(2) 307-315, 1994.—We have previously reported that the 5-hydroxytryptamine (5-HT) releaser/reuptake blocker dexfenfluramine suppresses voluntary ethanol intake. To further analyse the generality of these findings, in the present study we examined the effect of equivalent doses of dexfenfluramine (0.5-2.5 mg/kg) on the intake of another preferred fluid, saccharin. Saccharin was made available for 2 h daily across a wide concentration range chosen to promote varying degrees of intake. Following stable levels of intake, the behaviour of vehicle-pretreated rats was assessed immediately prior to (anticipatory/preparatory phase) and during (consumatory phase) saccharin access. These behaviours were compared and contrasted with those produced following dexfenfluramine pretreatment at the optimally preferred saccharin concentration (0.2%). In a preliminary study the effects of various 5-HT antagonists were also examined against the dexfenfluramine response. The present results suggest that dexfenfluramine produced a dose-related suppression of saccharin intake at doses similar to those which reduced ethanol intake. However, the magnitude of this suppression was similar across each saccharin concentration. Behavioural analysis indicated that the profile of the dexfenfluramine (0.5- and 1-mg/kg doses only) suppression of the 0.2% solution was similar to that observed in vehicle-pretreated rats presented with saccharin solutions of lesser palatability to this concentration. Pharmacological studies indicated a 5-HT_1 (non-5-HT_{1C}) receptor involvement in the dexfenfluramine response. These studies imply that at certain doses dexfenfluramine may produce a subtle alteration in the motivation to consume a preferred fluid.

Dexfenfluramine Saccharin Behavioral satiety sequence 5-HT Rat Palatability Anticipatory behaviour Metergoline

DRUGS which elevate 5-HT function—notably, 5-HT releasers (e.g., *dl*- or *d*-fenfluramine [dexfenfluramine]) and 5-HT reuptake inhibitors (e.g., fluoxetine)—reduce food and palatable fluid intake (3,8). Precisely how these effects are mediated has been the subject of considerable research. It seems that at least one mechanism may involve an enhancement of satiety. Thus, following ingestion of a meal, rats normally display a characteristic behavioural pattern of activity followed by grooming and terminated by resting behaviour (1). This behavioural sequence is taken as an index of satiety (i.e., the postprandial satiety sequence). It seems that both fenfluramine and fluoxetine produce an early termination of eating behaviour without affecting initiation of feeding, resulting in less food eaten followed by an earlier onset of the complete satiety sequence [(3,6,7); but see (25)]. Although these results are consistent with a satiety hypothesis, recent studies suggest that other factors may also be involved in the suppressant effects of 5-HT drugs on consummatory behaviour.

Rats chronically implanted with an open gastric fistula (i.e., sham feeding rats) will ingest copious amounts of a palatable fluid. Such animals are considered to show a pronounced satiety deficit, and instead, the feeding response appears to be under predominantly oropharyngeal control (34). However, both fluoxetine and dexfenfluramine potently suppresses sucrose sham feeding in the gastric-fistulated rat (29). Further studies also support the contention that 5-HT agonists (direct and indirect) may suppress feeding where palatability serves as the primary impetus for this behaviour. Thus, in nondeprived rats dexfenfluramine and fluoxetine have been

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reported to reduce sucrose and saccharin consumption, respectively (5,19), and peripheral injections of 5-HT suppress intakes of both fluids (24). Also, dexfenfluramine has been shown to potently suppress intake of palatable chow in nondeprived rats (14,25,30).

The aim of the present study was to examine the effect of dexfenfluramine on saccharin consumption. The animals were non-food-deprived and saccharin was made available at a range of concentrations chosen to promote varying degrees of intake, thus providing an operational index of palatability (12,19). An advantage of this procedure is that as with drug (e.g., cocaine, heroin) reinforcement, increasing the saccharin concentration results in an inverted-U concentration–effect function (see 12,19). Examination of the dexfenfluramine effect across saccharin concentrations may enable some assessment as to the nature of any suppressant effect. For example, pretreatment with opioid antagonists such as naloxone appears to produce a rightward shift to a heroin dose–effect curve, which suggests that this treatment has specifically diminished the reinforcing value of heroin (17). Alternatively, Fletcher et al. (12) found that the 5-HT_{1A} receptor agonist 8-OH-DPAT produced a leftward shift in a saccharin concentration–effect function. This finding can be seen as an indication of an enhancement of the incentive value of saccharin. An issue in the present study, therefore, is whether dexfenfluramine will produce a shift as well as a reduction in the saccharin dose–effect curve.

As another part of the present study, in addition to studying fluid intake, a behavioural analysis was also made in control pretreated animals prior to, and during, saccharin access. Therefore comparisons could be made between the behavioural effects seen following dexfenfluramine treatment at the optimally preferred saccharin concentration. This novel approach to studying the effects of dexfenfluramine was deemed appropriate because it enabled an assessment of drug effects on preparatory/anticipatory as well as consummatory behaviours associated with feeding (2). The doses of dexfenfluramine were derived from a previous study as showing marked suppressions in the intake of another preferred solution, 5% ethanol (14). Finally, the effect of various selective 5-HT receptor antagonists were also examined against the dexfenfluramine response in an attempt to provisionally identify the receptor subtype underlying this effect.

METHODS

Animals and Housing

The test subjects were 40 male Wistar rats (Charles River, Quebec, Canada) which were individually housed in hanging wire mesh cages (18 × 30 × 18 cm, W × L × H) for the duration of the experiment. Food and water was available ad lib except for 1 h prior to and during the 2 h of access to the test solution. A 12-h light/dark cycle (lights on 0600–1800) was used and the experimental room was regulated for constant temperature (22–24°C) and humidity (30–60%).

Drugs and Injections

The test compounds and their sources were as follows: dexfenfluramine hydrochloride (Servier, Nevilly-Sur-Seine, France), metergoline (Farmitalia, Milan, Italy), ritanserin (Janssen Pharmaceutica, Beerse, Belgium), ondansetron hydrochloride (Glaxo, Ware, Herts, UK), and xylamidine tosylate (Burroughs Wellcome, Research Triangle Park, NC). All drugs were freshly prepared on the day of testing in saline, and all doses refer to that of the free base, except for dexfenfluramine, whose dose is expressed as the salt. This was to enable comparisons with other studies (14). Metergoline was first dissolved in 1 M ascorbic acid before being made up to final volume with saline; ritanserin was initially mixed with a small quantity of 0.01 M tartaric acid before addition of saline. The final pH of these solutions was then adjusted to 5–6 with 1 N sodium hydroxide solution. Controls received the appropriate vehicle. All other drugs were dissolved in saline following gentle warming.

5-HT antagonists were administered SC either 30 min (metergoline, ondansetron), 60 min (ritanserin), or 2.5 h (xylamidine) before dexfenfluramine, which was administered IP 30 min before access to test solutions.

Procedure

Effects of dexfenfluramine on saccharin intake: Study 1. Forty rats were randomly allocated to one of five groups (n = 8 per group), each of which was assigned a different concentration of saccharin to drink. The concentrations (w/v) of sodium saccharin (Sigma Chemical Co., St. Louis) were 0.04%, 0.1%, 0.2%, 1%, and 0% (water). These solutions were presented in a richter tube attached to the front of the rats' home cage. Availability of solutions was for 2 h daily between 1300 and 1500. The amount of fluid consumed at the end of the 2-h period was recorded to the nearest 0.1 ml. All rats received an IP injection of saline daily (2 ml/kg dose volume) 30 min before saccharin access. This was to 1) familiarize rats to the injection procedure and 2) serve as a cue to signal forthcoming saccharin availability.

Thirty days of saccharin access were required before intakes stabilized, and at that time over the course of two consecutive days each animal was behaviourally assessed for 15 min prior to and for the initial 45 min of saccharin access. For this part of the study, each animal was observed at 15-s intervals and behaviour was recorded into one of four mutually exclusive categories: drinking (access period) or "time in front" (preaccess period), active, grooming, and resting. The "time in front" measure included active behaviour directed at the cage front, including nose poking in the area where the richter tubes were due to be placed. The "active" category included sniffing, rearing, locomotion, and scanning.

On day 37 drug testing began. According to a randomized block design each rat received each treatment (saline vehicle; dexfenfluramine 0.5, 1, 2.5 mg/kg) 30 min prior to saccharin presentation. Drug days were spaced every third day; on intervening days the animals received an IP injection of saline as usual. Following each drug injection, fluid intakes were recorded at 30 min, 1 h, and 2 h.

At the completion of this study (i.e., day 47) all rats were switched to the 0.2% saccharin solution for the remainder of the experiment. Following a further period of 9 days, 12 rats were selected (previous groups: 8 × 0.2%, 3 × 1%, 1 × water) on the basis of showing stable and comparatively high levels of 0.2% saccharin intakes. Each rat again received either saline or dexfenfluramine (0.5, 1, 2.5 mg/kg IP) 30 min prior to 0.2% saccharin presentation. The rats received each treatment according to a randomized design on every third day. In addition to saccharin intakes being recorded at 45 and 120 min, the rats were behaviourally assessed according to the methods described previously.

Effects of 5-HT receptor antagonists against dexfenflura-

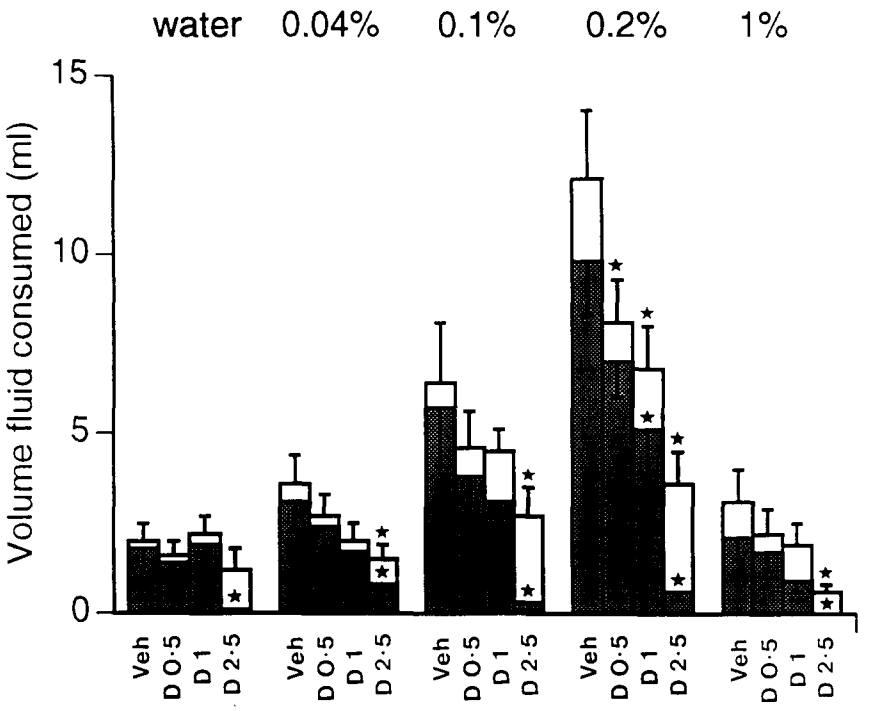

FIG. 1. The effects of dexfenfluramine on the intake of saccharin solutions of varying concentration measured at 30 min (solid) and 2 h (clear) postaccess. $n = 8$ animals per saccharin concentration. *$p < 0.05$ vs. vehicle pretreatment (Duncan's multiple range test).

mine-induced suppression of 0.2% saccharin drinking: Study 2. By the end of study 1 (i.e., day 67), of the original 40 rats which entered the experiment 20 rats were discarded on the basis of showing low (i.e., less than 6 ml daily) or inconsistent intake of 0.2% saccharin. Of the remaining 20 rats (original groups: 8 × 0.2%, 2 × water, 1 × 0.04%, 3 × 0.1%, 6 × 1%), each was allocated into two groups of 10 rats. Each group contained rats of comparable drug/saccharin history and mean saccharin intakes. After a further period of 4 days baseline, the effects of the 5-HT antagonists metergoline, ritanserin, ondansetron, and xylamidine against the suppressant effects of dexfenfluramine (1 mg/kg) were studied. Antagonist doses and pretreatment times were selected from the literature as blocking 5-$HT_{1/2}$, 5-$HT_{1C/2}$, 5-HT_3, and peripheral 5-HT receptors in vivo respectively (see Discussion). Each antagonist was studied at one dose (except ondansetron at two doses), so four treatment groups per antagonist were required (except ondansetron with six): 1) antagonist vehicle/saline, 2) antagonist vehicle/dexfenfluramine, 3) antagonist/saline, and 4) antagonist/dexfenfluramine. Each rat received all treatments every third day in a counterbalanced design and saccharin intakes were recorded at 30 min and 120 min. Two antagonists were studied per group: Group A received metergoline and ondansetron; group B received ritanserin and xylamidine.

Statistics

All data were analyzed by either one- or two-way analysis of variance (ANOVA). Post hoc comparisons between means were made using either Duncan's test or Dunnett's test. The accepted level of significance was $p < 0.05$.

RESULTS

Effect of Varying Saccharin Concentration on Subsequent Intake and Behaviour

In accordance with other studies, across the saccharin concentration range studied (0–1%) there were marked differences in intake. This may clearly be seen in the fluid intakes of vehicle-pretreated rats shown in Fig. 1, $F(4, 35) = 9.9$, $p < 0.01$. The optimal concentration selected was 0.2%, although the intake of the 0.1% saccharin solution was also significantly greater than water. At the 0.04% and 1% concentrations, intakes were similar to water, and therefore the saccharin concentration–response curve was an inverted-U shape. Under conditions of saline pretreatment most of the drinking was confined to the initial 30-min access period.

In terms of the rats' behaviour during the 15-min preaccess period, despite marked differences in subsequent intakes there were only modest changes. Thus, "active" behaviour was increased, $F(4, 35) = 3.0$, $p < 0.05$, and correspondingly resting decreased, $F(4, 35) = 3.0$, $p < 0.05$, at the 0.1%, 0.2%, and 1% saccharin concentrations relative to water and 0.04% saccharin concentration (Fig. 2). Grooming, $F(4, 35) = 1.7$, NS, showed a modest increase, whilst tube-directed behaviour was consistently low and indistinguishable across groups, $F(4, 35) = 3.0$, $p < 0.7$, NS.

Behaviour during the first 45 min of fluid access was essentially similar across all types, with drinking followed by activity/grooming and terminating in resting behaviour (Fig. 2). Subtle changes were seen by a significant Solution × Time interaction for drinking, $F(32, 280) = 15.2$, $p < 0.01$; active,

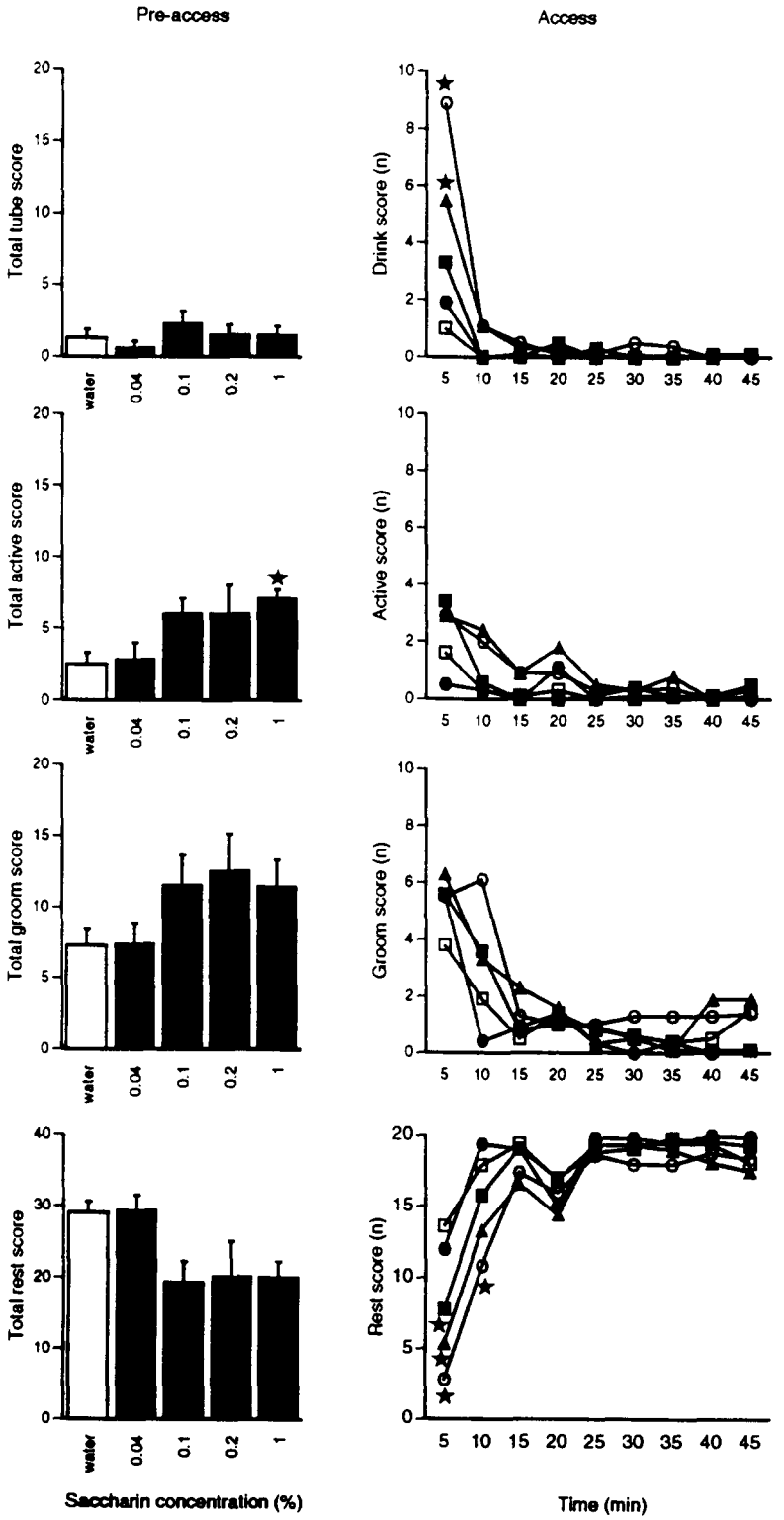

FIG. 2. Temporal sequence of consummatory and other behaviours during access to saccharin solutions of varying concentration. Also shown is the total behavioural score for these animals during the 15-min period prior to saccharin access. □ = water, ● = 0.04%, ▲ = 0.1%, ○ = 0.2%, ■ = 1%. *$p < 0.05$ vs. water group (Dunnett's t test).

$F(32, 280) = 1.9$, $p < 0.01$; and resting behaviour, $F(32, 280) = 15.2$, $p < 0.01$. Post hoc testing showed that drinking behaviour was significantly prolonged and, conversely, the onset of resting behaviour was delayed (Fig. 2) at the 0.1% and 0.2% saccharin concentrations. In each case, however, drinking had largely subsided from 10 min of access, and resting predominated beyond the 15-min period.

Effect of Dexfenfluramine on Saccharin Drinking: Intake Studies

The effect of dexfenfluramine pretreatment on saccharin intake is shown in Fig. 1. One-hour intakes were omitted for clarity. At 30 min, a significant main effect of dose, $F(3, 105) = 26.4$, $p < 0.01$, and a significant Dose × Saccharin Concentration interaction, $F(12, 105 = 3.2$, $p < 0.01$, were found. Post hoc testing revealed drinking suppressions of all fluids following dexfenfluramine pretreatment (2.5 mg/kg). However, despite showing clear trends towards suppression, only at the 0.2% saccharin concentration was a significant effect seen at a lower (1 mg/kg) dexfenfluramine dose. In percentage terms, the magnitudes of decrease across each saccharin concentration were 22–33% (0.5 mg/kg) and 45–57% (1 mg/kg). Water intake was unaffected by these lower dexfenfluramine doses.

At 2 h, a significant main effect of dose, $F(3, 105) = 12.6$, $p < 0.01$, and a significant Dose × Saccharin Concentration interaction, $F(12, 105) = 1.9$, $p < 0.05$, were recorded. The pattern of results were similar to the 30-min measurements, except that water intake was not affected by dexfenfluramine and, conversely, 0.2% saccharin intake was significantly reduced at each dose (see Fig. 1). In percentage terms, the magnitudes of decrease following dexfenfluramine pretreatment across each saccharin concentration were 25–33% (0.5 mg/kg) and 30–44% (1 mg/kg).

Effects of Dexfenfluramine on 0.2% Saccharin Intake: Behavioural Studies

In accordance with the previous study, dexfenfluramine (0.5–2.5 mg/kg) produced a marked suppression of 0.2% saccharin drinking at both the 45-min, $F(3, 33) = 33.9$, $p < 0.01$, and the 2-h time point, $F(3, 33) = 32.4$, $p < 0.01$. Post hoc testing showed that this suppression was significant for all doses (see Table 1).

At all doses, dexfenfluramine failed to modify rat behaviour during the 15-min saccharin preaccess period. However, as expected, dexfenfluramine markedly affected behaviour during the subsequent access period (Fig. 3). Both drinking, $F(3, 33) = 11.3$, $p < 0.01$, and resting behaviour, $F(3, 33) = 7.4$, $p < 0.01$, were decreased, and active behaviour increased, $F(3, 33) = 13.6$, $p < 0.01$. Grooming was essentially unaffected, $F(3, 33) = 1.3$, NS. Post hoc tests indicated that drinking behaviour was significantly reduced by comparison to controls at all doses, suggesting that rate of drinking was relatively unaffected by dexfenfluramine. The significant effect on active and resting behaviour relative to controls was confined to the 2.5-mg/kg dexfenfluramine dose.

Effect of 5-HT Antagonists Against the Dexfenfluramine-Induced Suppression of 0.2% Saccharin Intake

In each antagonist-interaction study, dexfenfluramine significantly reduced 0.2% saccharin intake (Fig. 4). This suppression was antagonised by metergoline (1 mg/kg), but not by ritanserin (1 mg/kg), xylamidine (3 mg/kg), or ondansetron (0.1 and 1 mg/kg) pretreatment. At the doses studied, no 5-HT antagonist alone had any effect on saccharin intake, except for metergoline, which significantly increased this measure at 30 min (vehicle/vehicle 9.7 ± 1.0 ml; metergoline/vehicle 13.9 ± 1.3 ml; $p < 0.01$, Dunnetts t test) and at 120 min (Fig. 4).

DISCUSSION

In the first part of the present study we examined the behaviour of rats prior to and during access to saccharin solutions of varying concentration. Because intakes varied by as much as fivefold across this range, clearly each solution held differing incentive properties. As the rats were not food-deprived prior to fluid access and saccharin provides no nutritional value, these properties were presumably related to the taste, or palatability, of the saccharin solution. It was of interest to note that despite the varied levels of consumption, preaccess behaviour differed only to a mild degree across the groups. Thus, "active" and grooming behaviour was increased slightly across the 0.1–1% saccharin concentrations; however, there was no difference between each of these concentrations despite large differences in subsequent intake. It may be that the conditioned stimuli (food removal, saline injection) used to signal forthcoming saccharin availability, and thus elicit anticipatory behaviour, was of insufficient proximity or salience in the present experiment. Alternatively, saccharin itself, despite inducing significant drinking behaviour upon presentation, is unable to serve as a sufficient motivational stimulus to elicit marked anticipatory behaviour prior to presentation. Further studies are required to test these alternatives. Following subsequent access, each saccharin solution produced essentially the same sequence of behaviours, the

TABLE 1

EFFECT OF DEXFENFLURAMINE ON THE CONSUMPTION OF A 0.2% SACCHARIN SOLUTION AT 45 MIN AND 2 H POSTACCESS

		45 min	120 min
Vehicle		9.1 ± 0.9 ml	12.0 ± 1.2 ml
Dexfenfluramine	0.5 mg/kg	6.8 ± 0.5 ml*	8.2 ± 0.8 ml*
	1 mg/kg	5.3 ± 0.8 ml*	6.6 ± 0.8 ml*
	2.5 mg/kg	2.1 ± 0.3 ml*†	4.0 ± 0.5 ml*†

Animals received vehicle or dexfenfluramine IP 30 min before saccharin access. $n = 12$ rats. *$p < 0.01$ vs. vehicle pretreatment. †$p < 0.01$ vs. all other treatments (Duncan's multiple range test).

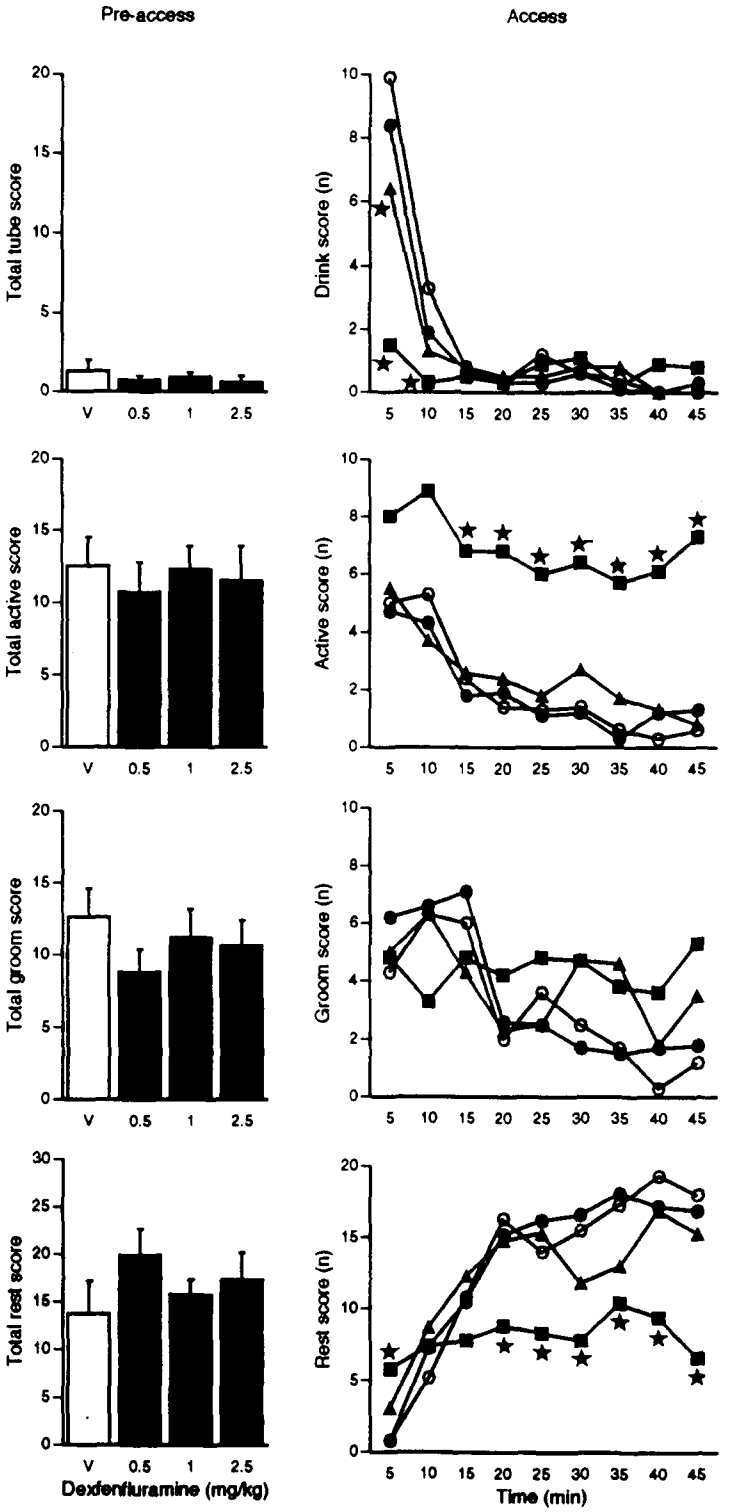

FIG. 3. Effect of dexfenfluramine on the temporal sequence of consummatory and other behaviours during access to 0.2% saccharin solutions. Also shown is the total behavioural score for these animals during the 15-min period prior to saccharin access. ○ = vehicle, ● = 0.5 mg/kg, ▲ = 1 mg/kg, ■ = 2.5 mg/kg. *$p < 0.05$ vs. vehicle pretreatment (Dunnett's t test).

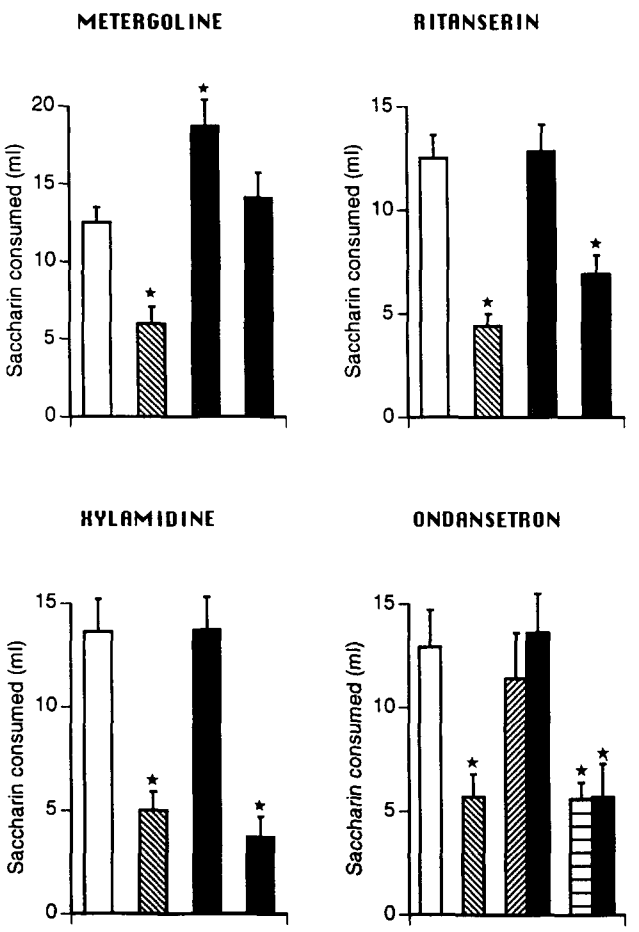

FIG. 4. Effect of metergoline (1 mg/kg), ritanserin (1 mg/kg), ondansetron (0.1, 1 mg/kg), and xylamidine (3 mg/kg) against dexfenfluramine-induced suppression of 0.2% saccharin drinking. □ = vehicle/vehicle, ▨ = vehicle/dexfenfluramine 1 mg/kg, ▩ = antagonist/vehicle, ■ = antagonist/dexfenfluramine 1 mg/kg, except for the ondansetron study where ▨ = ondansetron 0.1 mg/kg/vehicle, ▩ = ondansetron 1 mg/kg/vehicle, ▤ = ondansetron 0.1 mg/kg/dexfenfluramine 1 mg/kg, ■ = ondansetron 1 mg/kg/dexfenfluramine 1 mg/kg. *$p < 0.01$ vs. vehicle/vehicle group (Dunnett's t test).

only difference being in their temporal relationship. Drinking was followed briefly by active/grooming behaviour, which in turn was followed by resting. This behavioural sequence is similar to that described by various workers as representing the normal behavioural response of rats when they feed to satiety (1,4,25). However, previous studies have clearly shown that food-deprived rats presented with saccharin as their sole food source do not display this satiety sequence (18). The most parsimonious explanation for these discrepant results probably relates to definitions of satiety and the motivational impetus for saccharin drinking between the two studies. Thus, in food-deprived rats (18) satiety is initiated by a cessation of hunger, which saccharin, due to its lack of calorific content, is unable to attain. However, in nonhungry rats saccharin drinking is initiated by taste and is under oropharyngeal control (26,27). Under these circumstances, once the rat has sampled a sufficient quantity of saccharin this alone is sufficient to terminate intake and promote behaviours reflective of satiety.

An important feature of the present investigation was to examine the effect of dexfenfluramine on the relative intake of saccharin solutions of varying palatability (i.e., the effect on the saccharin concentration-effect function). As indicated in the introduction, a rightward shift of this concentration-effect curve could indicate a reduction in reinforcement efficacy of the target substance, whereas a leftward shift might indicate enhancement [see (12,17)]. Dexfenfluramine at doses which did not influence water consumption clearly reduced saccharin intake. However, there was no detectable shift in the concentration-effect function of saccharin; instead, the magnitude of this decrease was essentially proportional across the varying concentrations of saccharin. This suggests that dexfenfluramine does not affect the relative incentive value of various saccharin concentrations to the animal. Furthermore, because dexfenfluramine reduced intake across all saccharin concentrations of perhaps differing taste quality (sweet-bitter), it seems unlikely that this treatment specifically affected certain orosensory aspects of this stimulus.

Leander (19), using a similar paradigm, reported that fluoxetine reduced saccharin consumption across each saccharin concentration without shifting the concentration that produced relative peak intake. The present study, which as far as we are aware is the first report of a 5-HT releaser in this model, is entirely consistent with these findings.

In a subsequent experiment designed to further examine the nature of this suppression, rats were retested with dexfenfluramine at the optimally preferred saccharin concentration (0.2%) and behaviour was concomitantly measured. These studies indicated that at the 0.5- and 1-mg/kg doses (both of which significantly reduced intake and left the behavioural sequence intact) the termination of drinking and onset of resting seemed enhanced by dexfenfluramine. This profile was similar to that seen in control rats presented with saccharin solutions of lesser palatability to 0.2% (compare Figs. 2 and 3) and may be consistent with an enhancement of satiety following dexfenfluramine pretreatment. In any case, these data probably exclude a motoric deficit explanation for this effect because the behavioural sequence remained intact [cf. (4)]. Also, rats pretreated with 0.5–1 mg/kg dexfenfluramine have been reported to maintain appropriate responses in other behavioural schedules, including operant responding for food reinforcement [e.g., see (15)]. At the 2.5-mg/kg dose, however, dexfenfluramine produced a complete disruption of the behavioural sequence. Thus, "active" behaviour was increased throughout the observation period in a manner analogous to that reported by Montgomery and Willner (25). Precisely what process underlies this behavioural change is presently unclear, although recent studies showing differential tolerance to the anorectic and behavioural satiety sequence effects of fenfluramine (23) may suggest separate mechanisms underlie each response. With regards to the issue of tolerance in the present study, we clearly failed to see such an effect with dexfenfluramine. Indeed, some animals received as many as 10 injections of dexfenfluramine, although the suppressant effects on saccharin drinking remained consistent in magnitude throughout.

In a preliminary study at dose levels and injection schedules previously shown to produce blockade of their respective 5-HT receptor subtypes in vivo (13,14,16,32), the 5-$HT_{2/1C}$ antagonist ritanserin, the 5-HT_3 antagonist ondansetron, and the peripheral 5-HT antagonist xylamidine all failed to modify the suppressant effects of dexfenfluramine on 0.2% saccharin intake. However, the 5-$HT_{1/2}$ receptor antagonist metergoline

completely blocked this effect, implying a 5-HT_1 receptor involvement. Indeed, this finding is consistent with many studies showing that metergoline, but not ritanserin or xylamidine, may block the anorectic effect of dexfenfluramine in deprivation-induced or palatability-induced feeding paradigms [(5,28,32); but see (14,30) with respect to ritanserin]. Perhaps the most interesting result from this part of the study was that metergoline pretreatment alone actually increased saccharin drinking relative to controls. Elevations of feeding in satiated rats (9,11), enhancement of runway performance for food reinforcement (28), and increased amphetamine self-administration (21) have all been reported following metergoline pretreatment. This suggests that central 5-HT systems may, under particular experimental conditions, exert a subtle inhibitory control over consummatory or reinforced behaviour in general, and that this may be increased in amplitude by exogenously applied direct and indirect 5-HT agonists. In this context of endogenous 5-HT systems regulating behaviour it is noteworthy that increased responding for reinforcers as diverse as sucrose (35), cocaine (20), and ethanol [see (33)] has been reported in rats following central 5,7 DHT lesions.

In the present study, therefore, dexfenfluramine suppressed the intake of a range of saccharin solutions at doses with little or no effect on water intake. Considered alongside the findings that at similar doses dexfenfluramine also reduces ethanol drinking (14,22) and, more recently, intravenous heroin self-administration (15), this may be seen to support the accumulating evidence that 5-HT systems have a general role in regulating consummatory behaviour. Whether manipulations to this system produce any degree of selectivity for substances of differing motivational value to the animal [cf. (14,33)] was not supported by the present study, at least using dexfenfluramine. Thus, saccharin intake was reduced to a similar degree across various concentrations by dexfenfluramine pretreatment; there was no shift of the saccharin concentration–effect curve. Similarly, Fletcher (10) reported that dexfenfluramine pretreatment did not affect saccharin preference at doses which reduced overall fluid intake. Also, Neill and Cooper (31) failed to observe a selective effect of dexfenfluramine on the intake of a preferred isotonic saline solution. Nevertheless, in the present study, although dexfenfluramine reduced saccharin consumption, at low doses it appeared to preserve the normal behavioural satiety sequence following saccharin ingestion, arguing against a simple disruptive effect on motoric behaviour [see also (4,15)]. Clearly, it remains to be established precisely how indirect 5-HT agonists such as dexfenfluramine regulate consummatory/reinforced behaviour.

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