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Evidence for Serotonergic Involvement in Saccharin Preference in a Two-Choice Test in Rehydrating Rats

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COOPER, S. J. AND D. J. BARBER. *Evidence for serotonergic involvement in saccharin preference in a two-choice test in rehydrating rats.* PHARMACOL BIOCHEM BEHAV 47(3) 541-546, 1994.—Adult male rats were adapted to a 20-h water-deprivation schedule and trained to drink a 0.1% sodium saccharin and water in a two-choice test (30 min). Several direct acting serotonergic receptor agonists (putatively agonists at the 5-HT_{2C} receptor), MK212, *m*CPP, and TFMPP, respectively, blocked the saccharin taste preference normally exhibited in this test. Water intake was unaffected. Taken with earlier evidence that these drugs reduce salt taste preference in rehydrating rats, it appears that they may inhibit taste preferences more generally, and that this effect may be closely related to their well-documented anorectic effect. At 3.0 mg/kg, *d*-fenfluramine almost completely blocked the saccharin taste preference, although *l*-fenfluramine (0.3 and 1.0 mg/kg) exhibited only hyperdipsic effects. 5-HT creatinine sulphate (0.3-3.0 mg/kg) also produced hyperdipsic effects, but showed no sign of blocking sweet taste preference. As a positive control, it was also shown that the opioid receptor antagonist, naloxone, reduced saccharin taste preference.

d- and *l*-Fenfluramine 5-HT *m*CPP TFMPP MK212 Naloxone Taste preference Saccharin Rats

THERE is abundant evidence that central serotonergic mechanisms play an important role in the control of feeding responses (1,2,10,16). One important line of evidence is that selective 5-hydroxytryptamine (5-HT) receptor agonists suppress food consumption. For example, anorectic effects have been described for MK212 [2-chloro-6-(piperazin-1-yl)pyrazine], *m*CPP [1-(*m*-chlorophenyl)piperazine], and TFMPP {1-[3-(trifluoromethyl)phenyl]piperazine} (5,6,23,26,33,35). Pharmacological characteristics of the action of these drugs, particularly in relation to the 5-HT receptor subtype(s) that mediate their anorectic effects, are discussed elsewhere (10,16), although there is a certain amount of evidence that points to an important role for 5-HT_{1C}/5-HT_2 receptors (see Reference Note). Such drugs may affect the motivation to feed by terminating a meal sooner and advancing the appearance of behavioral indices of satiety (26).

A question that has emerged in studies of anorectic drugs, in general, is the possible relationship between the effects they have on food consumption, on the one hand, and on taste preferences, on the other. Thus, opioid receptor antagonists not only reduce food intake (14), but also affect sweet and salt taste preferences (15,21,28,37). Benzodiazepine receptor inverse agonists also reduce food consumption (8,9) and attenuate saccharin preference (9,12). It may be relevant to consider, therefore, serotonergic influences on taste preferences, because any such effect may have a bearing on the anorectic effects of serotonergic agonists.

Previously, we have investigated the effects of several serotonergic agonists on preference for a dilute (0.9%) salt solution in rehydrating rats. In these experiments, we found that MK212, *m*CPP, and TFMPP shared an effect to block the preference for salt taste (11,13). Given these results, it was important to establish whether the effects of these drugs are restricted to salt taste preference, or extend to saccharin preference too. There has already been a certain amount of interest in serotonergic mechanisms and sweetness, although the evidence has not been conclusive. Borsini and colleagues (3) reported that the indirectly acting 5-HT agonist, *d*-fenflura-

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mine, reduced sucrose intake in free-feeding rats, and Neill and Cooper (31,32) observed that several serotonergic anorectic drugs were effective in dose-dependently reducing sucrose sham feeding. In the case of the noncaloric sweetener, sodium saccharin, Leander (27) showed that fluoxetine, a 5-HT uptake inhibitor, suppressed consumption of 0.001–0.1 M solutions. He suggested that fluoxetine's effect on sweetness-induced ingestion may be related to its anorectic effect. More conclusive evidence, however, may come from two-choice preference tests. In the present experiments, therefore, serotonergic agonists were administered to thirsty rats given the choice between a preferred 0.1% sodium saccharin solution and water.

The direct acting serotonergic agonists that we investigated were MK212, *m*CPP, and TFMPP. An important aim was to compare their effects in a sweet taste preference test with the data previously obtained in salt taste preference tests (11,13). In addition, we investigated effects of both *d*- and *l*-fenfluramine on sweet taste preference. Earlier, Fletcher had failed to find any effect of *d*-fenfluramine on sodium saccharin preference in water-deprived rats (18).

A further drug to be investigated was 5-hydroxytryptamine (5-HT) itself, which acts peripherally to produce an anorectic effect (17,19,20,36) but also has a hyperdipsic effect (24,25, 29). These effects are pharmacologically distinguishable (30). Previously, Montgomery and Burton reported that 5-HT reduced 0.1% sodium saccharin consumption in both single-bottle acceptance tests and two-bottle preference tests (29). On the basis of these results, they suggested that "5-HT may reduce the incentive value of food-related stimuli" (p. 265). Within the present series of experiments dealing with serotonergic agonists and saccharin intake in a choice test, we thought it important to reevaluate this possibility.

Finally, naloxone was tested as a positive control, because opioid receptor antagonists have previously been shown to reduce sweet taste preferences reliably in rats (7,28,37).

METHOD

Animals

The animals were adult, male blackhooded rats that were bred in our laboratory. They were housed individually in stainless steel cages with ad lib access to food pellets (modified Diet 41B, Heygate & Sons). They were maintained under a 12 L : 12 D cycle (lights on at 0700) and the room temperature was maintained at 21–22°C. The animals were accustomed to being handled and weighed 250–400 g.

Drugs

d- and *l*-Fenfluramine hydrochloride were kindly supplied by Institut de Recherches Internationales Servier (Neuilly sur-Seine, France); MK-212 [2-chloro-6-(piperazin-1-yl)pyrazine] was obtained from Merck Sharp & Dohme (Harlow, UK); naloxone hydrochloride was supplied by Du Pont de Nemours (Glenolden, PA); *m*CPP [1-(*m*-chlorophenyl)piperazine] dihyrochoride and TFMPP {1-[3-(trifluoromethyl)phenyl]-piperazine} hydrochloride were purchased from RBI (Semat Technical Ltd., St. Albans, Herts, UK). 5-HT creatinine sulphate was purchased from Sigma Chemical Co. All drugs were dissolved in isotonic saline and injected IP, with the exception of naloxone HCl, which was injected SC. All were given in a volume of 1 ml/kg, 20 min before the start of the drinking tests. Doses refer to the salts, and were chosen on the basis of previous work (7,11,13,31–33).

Procedure

Over a 7-day period, the animals were adapted to a 20-h water-deprivation schedule, with water available in the home cages for 4 h each day. They were then trained in a two-choice test, and had access to a 0.1% sodium saccharin solution and water provided in two 50-ml calibrated tubes. They were tested daily for 30 min immediately after the period of water deprivation. After each test, the home cage water supply was restored for a further 3.5 h. During this adaption period, animals also received injections of the drug vehicle (isotonic saline) on several occasions to familiarise them with the injection procedure.

The saccharin taste preference tests were conducted as described previously, including a procedure to avoid side preferences and perservative responses (12). At the start of the test, animals were given 30-s access to the left-hand drinking tube alone (which on 50% of occasions contained the 0.1% saccharin solution) and then 30-s access to the right-hand tube alone (this contained water when the left-hand tube contained the saccharin solution, and vice versa). This ensured that each rat sampled both the saccharin solution and the water at the start of each test. For the remaining 29 min of the test session, both drinking tubes were available, and all the collected data refer to this choice period. The volumes of saccharin solution and water consumed were recorded to the nearest 0.5 ml Familiarisation with the preference test was achieved over 6 days, during which the position of the saccharin spout was switched between right and left sides as a further precaution against the development of position habits.

Groups of animals (N = 10–20) were tested with each drug. Each animal received each dose of the drug under test, as well as the vehicle injection. The sequence of injections was counterbalanced across subjects within each group. At least 48 h separated successive injections of the same drug. During the intervals between drug testing, the water-deprivation schedule was maintained and animals continued to receive daily 30-min test sessions. One week was allowed between successive drug treatments, and each animal was tested with no more than 3 drugs.

The data were analysed using analysis of variance (ANOVA) and Dunnett's t-test. Intake scores (ml) for each fluid were analysed separately, or total fluid intake in the choice test was analysed. Where mentioned, "saccharin preference" refers to the ratio of saccharin solution intake to total intake, and is expressed as a percentage.

RESULTS

As Figure 1 indicates, the rats expressed a strong preference (75%) for the 0.1% sodium saccharin solution over water. MK212 (0.3–3.0 mg/kg, IP) had no effect on water consumption ($F < 1.0$), but dose-dependently reduced saccharin intake, $F(3, 42) = 12.1$, $p < 0.0001$. At 1.0 mg/kg, MK212 reduced saccharin intake by 25%, and at 3.0 mg/kg, reduced it by 68%. As a result, the sweet taste preference was completely abolished at 3.0 mg/kg.

Figure 2 shows that *m*CPP (0.3–3.0 mg/kg, IP) also had no effect on water consumption ($F < 1.0$), but dose-dependently reduced saccharin intake, $F(3, 27) = p < 0.005$. At 1.0 mg/kg *m*CPP, saccharin intake was reduced by 33%, and by 51% at 3.0 mg/kg. A similar set of results were obtained with TFMPP (Fig. 3). There was no effect on water intake ($F < 1.0$), but saccharin intake was significantly reduced, $F(3, 36) = 8.2$, $p < 0.0001$. At 3.0 mg/kg TFMPP, the preference for saccharin was completely blocked.

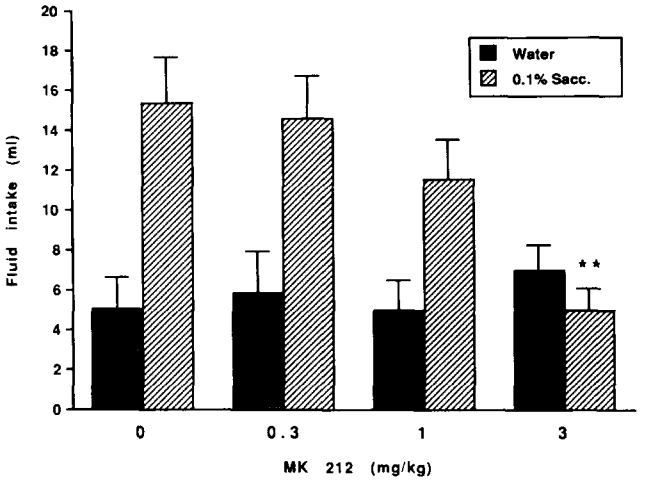

FIG. 1. Effects of MK212 (0.3-3.0 mg/kg) on 0.1% sodium saccharin preference in a two-choice test. Rats were 20 h water deprived prior to the 30-min choice test. Data are shown as mean intake (ml) + SEM $N = 15$ per group. Levels of significance for comparisons between individual group means and the vehicle control: $*p < 0.05$; $**p < 0.01$ (Dunnett's t-test).

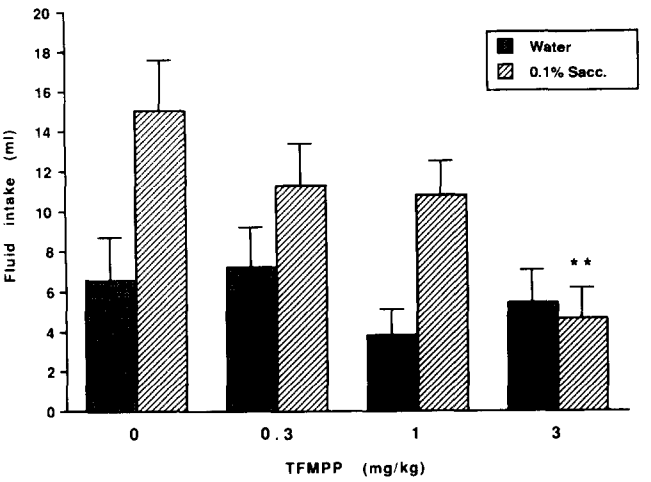

FIG. 3. Effects of TFMPP (0.3-3.0 mg/kg) on sodium saccharin preference in water-deprived rats. $N = 15$ per group. Other details are as described in Fig. 1 legend.

d-Fenfluramine (0.3-3.0 mg/kg) significantly affected total fluid intake in the two-choice test, $F(3, 42) = 9.39$, $p < 0.0001$, but its effects were biphasic. There was a significant increase at 0.3 mg/kg from a control level of 16.7 ± 1.0 ml to 19.5 ± 1.0 ml (16.8% increase, $p < 0.05$), and a significant decrease at 3.0 mg/kg to 12.4 ± 1.1 ml (25.7% decrease, $p < 0.05$). Its effects on saccharin and water intake are shown in Fig. 4. It had no overall effect on water consumption ($F < 1.0$), but significantly affected saccharin intake, $F(3,42) = 7.26$, $p < 0.0005$. At 0.3 mg/kg, there was a slight increase in saccharin intake, no apparent effect at 1.0 mg/kg, and abolition of the saccharin preference at 3.0 mg/kg.

l-Fenfluramine (0.3-3.0 mg/kg) also significantly affected total fluid intake, $F(3, 43) = 10.06$, $p < 0.0001$ (Table 1). The effect was nonmonotonically related to dose, because there were increases at 0.3 and 1.0 mg/kg, respectively, but no effect at 3.0 mg/kg. It had no overall effect on water consumption, but significantly affected saccharin intake, $F(3, 42) = 3.56$, $p < 0.02$. As Table 1 indicates, at 0.3 and 1.0 mg/kg l-fenfluramine stimulated saccharin consumption, increasing intake by 53% at 0.3 mg/kg.

Administration of 5-HT (0.3-3.0 mg/kg) also stimulated overall fluid intake significantly, $F(3, 54) = 4.51$, $p < 0.007$ (Table 2). It stimulated water intake, $F(3, 54) = 3.55$, $p < 0.02$, with an 80% increase in consumption occurring at 3.0 mg/kg. It also significantly increased saccharin consumption, $F(3, 54) = 3.02$, $p < 0.04$, with some increases in evidence at 0.3 and 1.0 mg/kg, respectively (Table 2).

As expected, naloxone (0.3-3.0 mg/kg, SC) reduced 0.1% sodium saccharin solution intake in the two-choice test, $F(3,$

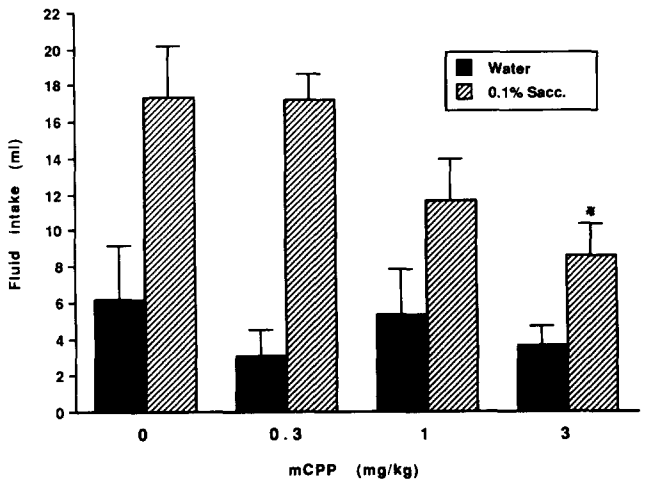

FIG. 2. Effects of mCPP (0.3-3.0 mg/kg) on sodium saccharin preference. $N = 10$ per group. Other details are as described in Fig. 1 legend.

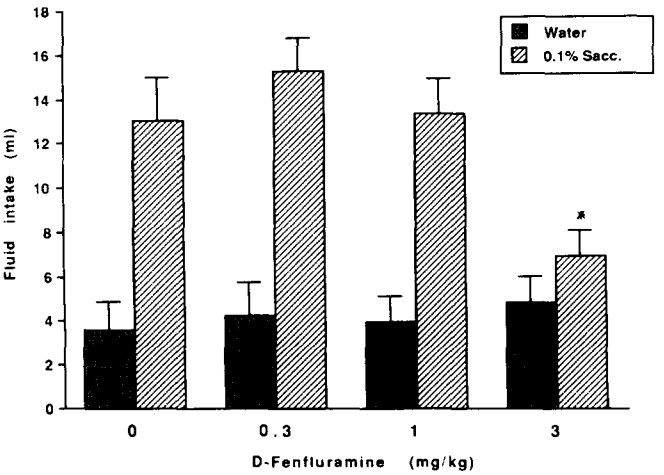

FIG. 4. d-Fenfluramine, at 3.0 mg/kg, reduced sweet taste preference in water-deprived rats. $N = 15$ per group. Other details are as described in Fig. 1 legend.

TABLE 1

EFFECT OF L-FENFLURAMINE ON 0.1% SODIUM SACCHARIN SOLUTION AND WATER CONSUMPTION, RESPECTIVELY, IN A TWO-CHOICE TEST

	Dose (mg/kg)			
	0	0.3	1.0	3.0
Saccharin intake (ml)	8.9 ± 1.8	13.6 ± 1.6*	12.5 ± 1.9	8.5 ± 1.5
Water intake (ml)	6.0 ± 1.7	4.7 ± 1.8	6.1 ± 1.7	5.4 ± 1.4
Total intake (ml)	14.9 ± 1.4	18.3 ± 1.1*	18.6 ± 1.1*	13.9 ± 1.3

Results are shown as mean intake (ml) ± SEM. $N = 15$ per group.

Level of significance for individual comparisons with the vehicle control condition: $*p < 0.05$ (Dunnett's t-test).

5) = 8.38, $p < 0.001$, without affecting water intake ($F < 1.0$) (Fig. 5). This result is in agreement with earlier studies.

DISCUSSION

We have shown previously that MK-212, *m*CPP, and TFMPP, each of which has been previously described as a 5-HT_{1C} or 5-$HT_{1B/1C}$ receptor agonist (but see Reference Note), block the preference for a 0.9% sodium chloride solution in a two-choice test (11,13). The present results indicate that these drugs, given in a dose of 3 mg/kg, IP, attenuated or blocked the preference for a 0.1% sodium saccharin solution in water-deprived rats. These data indicate, therefore, that this group of serotonergic agonists acts to suppress taste preferences more generally. Because each drug is effective as an anorectic agent (5,6,23,26,33,35), it seems possible that a serotonergic inhibition of orally initiated palatability may be one factor, at least, in contributing to their appetite-suppressant effects. These serotonergic agonists are not a unique example, of course, and it has been demonstrated that opioid antagonists, like naloxone, not only reduce food consumption but also block sweet and salt taste preferences (15). At this behavioral level, therefore, there is an equivalence between the effects of these serotonergic agonists and opioid antagonists, suggesting that opioid peptides act in functional opposition to a serotonergic inhibitory influence over food ingestion and taste preferences.

Unlike MK-212, *m*CPP, and TFMPP, peripherally acting 5-HT did not block saccharin preference. Both anorectic (17,19,20,30,32,34,36) and hyperdipsic (19,24,25,29) effects of 5-HT are well documented, and are mediated by distinctly different mechanisms. In the present series of experiments, 5-HT creatinine sulphate (1.0 and 3.0 mg/kg) significantly increased total fluid intake, reflecting its hyperdipsic effect. At 1.0 mg/kg, saccharin consumption was increased, whereas at 3.0 mg/kg, water intake was enhanced (Table 2). Presumably, not too much significance can be attached to these particular changes, although it could be pointed out that there was a 73% preference for the saccharin solution under the vehicle condition and this reduced to a 56% preference at 3.0 mg/kg 5-HT, due to the increased water intake at this dose. However, this is quite unlike the effects of the serotonergic agonists, described above, that uniformly reduced saccharin intake without significantly affecting concurrent water intake.

The present results for 5-HT are not in agreement with those previously described by Montgomery and Burton (29). They found that 2.0 mg/kg 5-HT reduced 0.1% saccharin intake in both a single-bottle acceptance test and in a two-bottle choice test. They suggested that 5-HT reduces consumption of "food-like" substances (i.e., its anorectic effect), and that the saccharin solution was treated by rats as if it were a food. In contrast, we found no evidence of a decrease in saccharin consumption produced by 5-HT, and therefore could provide no confirmation that the saccharin solution was "food-like" in our procedure. In the earlier study (29), the rats were not water deprived before the test, and the duration of the intake measurement period was 2 h. The present work used water-deprived rats, and the test period was shorter (30 min). Because the rats were thirsty, it seems implausible that they would treat a dilute saccharin solution as "food-like," and the present data did reveal a hyperdipsic effect.

The 5-HT data provide an important comparison when considering the results for *d*- and *l*-fenfluramine. Both isomers are anorectic drugs, although the *d*-isomer is the more potent

TABLE 2

EFFECT OF 5-HT CREATININE SULPHATE ON 0.1% SODIUM SACCHARIN SOLUTION AND WATER CONSUMPTION, RESPECTIVELY, IN A TWO-CHOICE TEST

	Dose (mg/kg)			
	0	0.3	1.0	3.0
Saccharin intake (ml)	12.7 ± 1.6	14.3 ± 1.3	16.1 ± 1.1*	11.7 ± 1.8
Water intake (ml)	4.8 ± 1.1	4.0 ± 1.1	4.1 ± 1.1	8.6 ± 1.5*
Total intake (ml)	17.4 ± 1.1	18.3 ± 0.8	20.4 ± 0.9*	20.8 ± 1.0*

Results are shown as mean intake (ml) ± SEM. $N = 20$ per group.

Level of significance for individual comparisons with the vehicle control condition: $*p < 0.05$ (Dunnett's t-test).

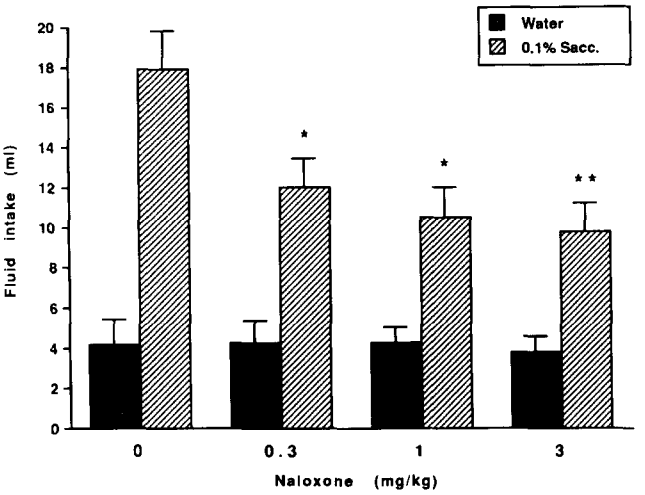

FIG. 5. The opioid receptor antagonist, naloxone (0.3–3.0 mg/kg, SC), significantly reduced sodium saccharin intake in a two-choice test. $N = 10$ per group. Other details are as described in Fig. 1 legend.

in reducing food intake. At a small dose of 0.3 mg/kg, *d*-fenfluramine produced a slight elevation in saccharin intake (Fig. 4). Earlier, we noted an analogous effect occurring at this dose in a salt preference experiment; *d*-fenfluramine significantly increased the consumption of a 0.9% NaCl solution (11). Quite unexpectedly, the present experiments showed that, at 0.3 and 1.0 mg/kg, *l*-fenfluramine had a hyperdipsic effect that reflected increases in sodium saccharin consumption (Table 1). Taken together, these results suggest that, in small doses at least, *d*- and *l*-fenfluramine have slight hyperdipsic effects, and furthermore, that the two isomers may be more or less equipotent in this regard. It seems parsimonious, at the present time, to suggest a link between the hyperdipsic effect of the fenfluramine isomers and peripheral 5-HT's effect on drinking responses.

Only *d*-fenfluramine, at the highest dose tested (3.0 mg/kg), blocked saccharin intake selectively (Fig. 4), and this effect may be more closely akin to the central effects of MK-212, *m*CPP, and TFMPP. It is interesting that Fletcher failed to detect any effect of *d*-fenfluramine on percentage saccharin preference scores in 23-h water-deprived rats (18). He did find, however, that *d*-fenfluramine (0.63–2.5 mg/kg) significantly and dose-dependently reduced consumption of either 0.05% or 0.2% sodium saccharin solutions; nevertheless, slight reductions in concurrent water intake (which were not significant) were sufficient to offset the effect on saccharin intake so that saccharin preference scores were unaltered. If the fluid intakes are considered separately, therefore, his data are not inconsistent with our results for 3.0 mg/kg *d*-fenfluramine. However, preference scores in his experiments remained unaltered (about 90% for 0.2% saccharin, and about 65% for 0.05% saccharin) following *d*-fenfluramine treatments, whereas in our study the preference score for the 0.1% solution dropped from a baseline level of about 80% to about 55% after 3.0 mg/kg *d*-fenfluramine.

Fletcher (18) attributed *d*-fenfluramine's effects on saccharin and water intake to "a subtle motor deficit," but this was by default, because no direct evidence for such an impairment was provided. However, we wish to reject this notion, because we have been quite unable to find any reduction in the rates at which rats lick for saccharin solution or water following the administration of *d*-fenfluramine (Morris and Cooper, in preparation). Instead, it may be instructive to consider further the separate intake data from his and our experiments. In Fletcher's 0.2% saccharin intake experiment, 2.5 mg/kg *d*-fenfluramine reduced the saccharin intake by about 11 g; it reduced water intake by 1 g or less. Essentially, this result is equivalent to a demonstration that *d*-fenfluramine reduced saccharin acceptance, because the saccharin intake was near-maximal. The data for the 0.05% saccharin choice are more critical to the issue. It is noteworthy that his 0.05% saccharin intake values over the dose range of 0.63–2.5 mg/kg *d*-fenfluramine [(18) Fig. 2, p. 688] are very close to our values for 0.3–3.0 mg/kg *d*-fenfluramine (Fig. 4). The difference between the two sets of results lies in the concurrent water intake data. In his experiment, the largest proportion of the drop in water intake occurred at the smallest dose of 0.63 mg/kg; intake dropped by about 2 g. Thereafter, increasing the dose of *d*-fenfluramine to 2.5 mg/kg decreased intake by only about an additional 1 g. In contrast, in the present and earlier study (11), small doses of *d*-fenfluramine failed to reduce fluid intake. An important distinction between Fletcher's work (18) and the present experiments is that his data were collected for independent groups of animals, and ours were collected using animals as their own controls. If, by chance, water intake was slightly high in his saline control group, then an apparent drop in intake would occur even at a dose as small as 0.63 mg/kg *d*-fenfluramine. In the present study, using animals as their own controls, we found no evidence for any reduction in concurrent water intake at any dose tested. On balance, therefore, it seems unwarranted to assert unequivocally that *d*-fenfluramine has no effect on preference for sodium saccharin solution in water-deprived rats. Clearly, *d*-fenfluramine significantly reduces saccharin drinking, but evidence that it may attenuate or block the preferred choice of saccharin remains limited to the present data (Fig. 4).

In summary, therefore, a number of 5-HT receptor agonists, MK-212, *m*CPP, and TFMPP (which should now be classed as 5-HT_{2C} receptor agonists; see Reference Note) reduced the consumption of 0.2% sodium saccharin solution without significantly affecting concurrent water consumption. The opioid receptor antagonist, naloxone, served as a positive control and reduced saccharin intake selectively. Peripherally acting 5-HT exhibited hyperdipsic effects in the same test. *d*- and *l*-Fenfluramine also affected fluid intake, although their effects were less straightforward. Unexpectedly, *l*-fenfluramine showed hyperdipsic effects, and *d*-fenfluramine appeared to block the preferred intake of saccharin, but only at a dose of 3.0 mg/kg.

Reference Note

5-HT receptor nomenclature has been in a state of flux. For several years, the accepted classification has been that proposed by Bradley and colleagues (4), which distinguished three main groups of 5-HT receptor, 5-HT_1, 5-HT_2, and 5-HT_3. In a new classification scheme that has been agreed by the Serotonin Club Receptor Nomenclature Committee, at a meeting held in Houston, TX, September 1992 (22), a fourth 5-HT receptor group has been added (5-HT_4), and, significant for the present data and other work on 5-HT and ingestional responses, the 5-HT_{1C} receptor has been reclassified as the 5-HT_{2C} receptor. It is recommended that the 5-HT_{1C} appellation is no longer used (22). Drugs that include MK-212, *m*CPP, and TFMPP, previously referred to as 5-HT_{1C} receptor agonists, should therefore, in the future, be described as

5-HT_{2C} receptor agonists. The 5-HT_{2C} receptor is not a new receptor, but is a previously recognised receptor that has regrouped with other 5-HT_2 receptor subtypes, all of which are linked positively to phospholipase C.

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