Psychopharmacology (1985) 86:197–204

Psychopharmacology

Low doses of the putative serotonin agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) elicit feeding in the rat

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Abstract. The effects of the putative serotonin agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) on food intake in non-deprived male rats were investigated. Low doses of 8-OH-DPAT (15–60 μg/kg) significantly increased food intake, without affecting drinking, grooming, rearing or locomotion. Microstructural analysis of the elicited feeding behaviour revealed that the rate of eating after 8-OH-DPAT treatment was very similar to that previously reported following 16 h food deprivation. Higher drug doses (250–4,000 μg/kg) also elicited feeding and caused locomotor stimulation and serotonin-related stereotyped behaviour (i.e. forepaw padding, headweaving, wet dog shakes, flat body posture). When feeding and stereotypy were observed concurrently, response competition was evident and feeding behaviour was fragmented into numerous short eating bouts. As drug-induced stereotypy declined with time, this fragmented pattern of eating was succeeded by long bouts of eating which were similar to those observed at doses of 15–60 μg/kg 8-OH-DPAT. The induction of feeding by a serotonin agonist appears paradoxical, since drugs which enhance brain serotonergic activity usually inhibit feeding.

Key words: 8-OH-DPAT – Feeding – Locomotion – Stereotypy – Serotonin – Rat

Considerable experimental evidence suggests relationships between serotonin metabolism and control of food intake. Alterations in either the availability or the composition of food can affect brain serotonin metabolism (reviewed, Curzon 1985) while pharmacological manipulation of serotonin metabolism can affect food intake (reviewed, Blundell and Latham 1982). In general, drugs which increase serotonergic activity decrease food intake (Blundell 1977). For example, the serotonin precursor 5-hydroxytryptophan (5-HTP) reduces food intake in food-deprived rats (Joyce and Mrosovsky 1964; Blundell and Leshem 1975). Fenfluramine, a potent anorectic drug, releases serotonin, and its anorectic action can be blocked by serotonin antagonists, or depleters (Garattini and Samanin 1976). In addition, there is evidence that hypothalamic serotonin receptors are involved in the inhibition of feeding. Thus, Leibowitz and Papadakos (1978) have reported that 1–10 μg serotonin applied to the medial paraventricular nucleus of the hypothalamus produces a dose-dependent suppression of feeding in hungry rats.

Although there is strong evidence that enhanced brain serotonergic activity inhibits feeding, treatments which decrease serotonergic activity have not always produced increases in food intake. Peripheral injection of the serotonin depleting agent parachlorophenylalanine (PCPA) has been reported to suppress feeding, whereas intraventricular treatment produced a transient hyperphagia (Blundell 1977; Hoebel et al. 1978). Similarly, there is disagreement regarding the ability of the serotonin neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) to increase feeding (Saller and Stricker 1976; Coscina 1978; Hoebel et al. 1978). However, the serotonin antagonists methysergide and cyproheptadine have been reported to increase food intake (Baxter et al. 1970; Blundell and Leshem 1974).

Most of the above studies involved measurement of gross food intake in severely food-deprived animals, an approach which has been subject to much criticism (reviewed, Blundell and Latham 1982). In particular, as the feeding behaviour of rodents consists of a sequence of eating bouts which are interspersed with episodes of other activity (e.g. drinking, grooming, exploration, sleep) (Wiepkema 1971), detailed "microstructural analysis" of eating behaviour in free-feeding animals has proved more valuable in the characterization of the effects of pharmacological manipulations on food intake (Blundell and Latham 1982). This form of analysis was therefore adopted in the present study of the effect of the novel serotonin agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) on feeding in rats.

8-OH-DPAT, an ergot congener synthesised by Arvidsson and colleagues (1981), has been claimed to possess potent and selective activity at central serotonin receptors. Thus, it decreased brain serotonin but not catecholamine synthesis in rats (Hjorth et al. 1982) and produced a behavioural syndrome (forepaw padding, headweaving, flat body posture) which is characteristic of postsynaptic serotonin receptor activation (Hjorth et al. 1982). In addition, 8-OH-DPAT stimulated male rat sexual behaviour, reducing the number of intromissions preceding ejaculation (Ahlenius et al. 1981). This was an entirely unexpected finding, since other drugs which produce increased post synaptic serotonin receptor activation, i.e. 5-HTP or serotonin uptake inhibitors, decrease sexual behaviour, whereas it is increased by the serotonin synthesis inhibitor PCPA (Gessa and Tagliamonte 1975; Ahlenius et al. 1980).

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The present study demonstrates that 8-OH-DPAT has a similarly paradoxical effect on feeding behaviour as, despite evidence that it activated post-synaptic serotonin receptors, it increased food intake.

Materials and methods

Animals. Ninety-six male Sprague-Dawley rats (350 ± 50 g, Charles River UK) were used. The animals were housed in individual plastic cages in a room with a 12 h dark/light cycle (lights on 6 a.m.). Food pellets (22 F diet, Labsure, Poole, Dorset) and tap water were freely available and testing was conducted during the light phase of the cycle (10.30 a.m.–4.30 p.m.). Temperature in the test room and holding room was maintained at 20 ± 1° C.

Apparatus and procedure. Testing was conducted in individual Perspex cages (dimensions 25 × 25 × 21 cm) with grid floors, in a room adjacent to the holding room. The rooms were maintained at a similar ambient temperature and level of illumination. The animals were habituated to the test cages overnight before testing. Food pellets and wood blocks were placed on the cage floor and water was available from a graduated tube. Immediately prior to testing, the rats were removed from the test cages and placed in holding cages while the test cages were cleaned and prepared for the test. A weighed amount of food (three pellets) and three wood blocks (which were approximately the same size as food pellets and were used to test for non-specific drug-induced gnawing) were placed in each test cage. The rats were injected with drug or 0.9% NaCl and immediately placed in the test cages. During the next 2 h, two observers, one of whom was unaware of drug treatment (inter rater reliability $r = 0.9$ or better), recorded the behaviour of the animals from an adjacent room via closed circuit television. Various parameters of ingestive behaviour (Table 1) and components of motor activity (Table 2) were recorded using hand-held counters and stopwatches. Scores were totalled over eight 15-min intervals during the 2-h test. At the end of the test the remaining food, together with any spillage, was weighed and food intake calculated.

Drugs. 8-Hydroxy-2-(di-*n*-propylamino) tetralin hydrobromide (8-OH-DPAT) (Research Biochemicals Inc. Wayland, MA, USA), was dissolved by gentle warming in 0.9% NaCl and injected SC in the flank in a volume of 1 ml/kg. Controls received an equivalent volume of 0.9% NaCl by the same route. Each animal was tested once only.

Design and statistical analysis. The 96 subjects were randomly allocated to one of 12 treatment groups given 0, 3.75, 7.5, 15, 30, 60, 125, 250, 500, 1,000, 2,000 or 4,000 μg/kg 8-OH-DPAT ($n = 8$ rats per group). The dose groups were tested in a random sequence. The data collected on each behavioural parameter were analysed by Kruskal-Wallis one-way analysis of variance (ANOVA) (Siegel 1956). Where ANOVA yielded a significant result, groups were compared using the Mann-Whitney *U*-test (2-tailed). A probability level of $P < 0.05$ was considered as significant.

Table 1. Parameters used in the microstructural analysis of feeding behaviour.

Feeding parameter	Description
Total food intake (g)	Food eaten during 2 h
Feeding bout frequency (*n*)	Number of episodes of eating food pellets. A feeding episode (or bout) consisted of the time spent holding a food pellet with the paws and chewing it (eating) or holding a food pellet against the cage floor while eating. Recording ceased when the animal ceased chewing and swallowed the food
Feeding bout duration (min)	Time spent eating food during each bout
Gnawing bout frequency (*n*)	Number of episodes of chewing wood blocks
Gnawing bout duration (min)	Time spent chewing wood during each bout
Drinking bout frequency (*n*)	Number of drinking episodes
Drinking bout duration (min)	Time spent drinking during each episode
Latency to feed (min)	Time to onset of first feeding bout
Local feeding rate (g/min)	Weight of food consumed divided by time spent eating

A bout of any activity (e.g. feeding, drinking) was defined as an episode of activity which was separated temporally by 15 s or more from any other episode of activity

Table 2. Elements of spontaneous motor activity recorded in the analysis of the behavioural effects of 8-OH-DPAT

Behavioural element	Description
Locomotion (*n*)	Frequency of cage crossing
Rearing (*n*)	Frequency of standing on hindlimbs
Forepaw padding (*n*)	Frequency of episodes of clonic forepaw movements
Wet dog shakes (*n*)	Frequency of head and body shakes
Headweaving (*n*)	Frequency of repetitive up and down or side to side head movements
Grooming (*n*)	Frequency of epidodes of body washing and cleaning
Hindlimb stretching (*n*)	Frequency of episodes of tonic extension of a hindlimb
Resting (min)	Duration of time spent asleep or inactive

Results

1. 8-OH-DPAT-induced feeding. Rats, being nocturnal, consume most of their food at night. Thus, in the present study, which was conducted during the daytime, only one of eight control animals ate any food. In contrast, 8-OH-DPAT markedly increased feeding with a maximum effect at 500 μg/kg (see Fig. 1). The decline of feeding at higher 8-OH-DPAT doses probably resulted from the disruptive effect of drug-induced stereotyped behaviour (see below). ANOVA confirmed that 8-OH-DPAT had a significant effect on feeding ($H = 35.6$, 11 *df*, $P < 0.001$) and individual comparisons revealed that 15–4,000 μg/kg of the drug significantly increased food intake. Figure 2 shows that feeding elicited by low doses of 8-OH-DPAT (15–125 μg/kg) had a long latency to onset (40–55 min) but as dosage in-

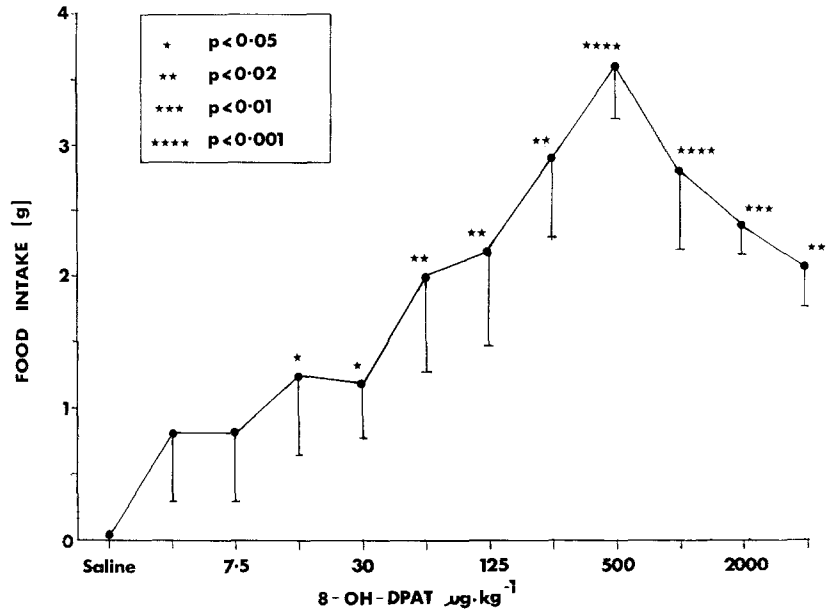

Fig. 1. Effects of 8-OH-DPAT on food intake in the rat. Values on the abscissa refer to geometrically increasing drug doses. Each point represents the mean (±SE) intake for eight rats during a 2-h test. Significant differences between groups are marked by *asterisks* and were determined by 2-tailed Mann-Whitney *U*-test following a significant ANOVA result

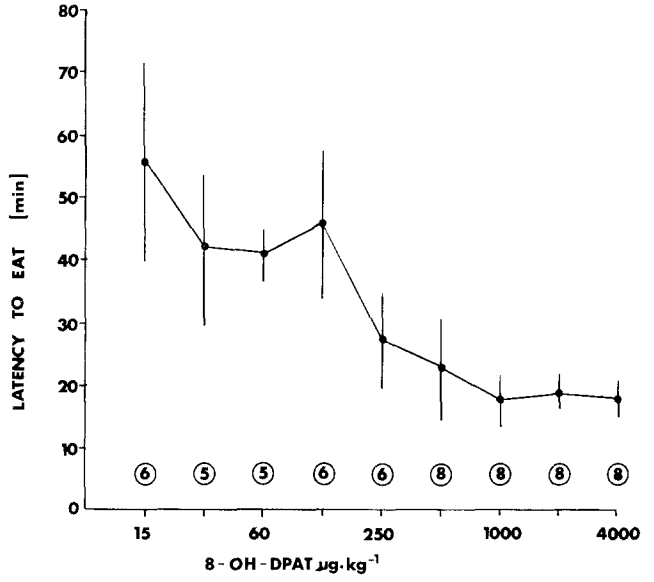

Fig. 2. Latency to onset of 8-OH-DPAT-induced feeding in the rat. The number of rats showing a feeding response in each group of eight rats is *circled*. Values for rats given saline, 3.75 and 7.5 µg/kg 8-OH-DPAT are omitted, since most animals in these groups did not show a feeding response. Details are as described in Fig. 1

creased to 1,000 µg/kg the latency decreased to about 20 min.

8-OH-DPAT produced a dose-dependent increase in the duration of feeding ($H=58.29$, 11 *df*, $P<0.001$), and between group comparisons revealed that doses of 15, 125, 250, 500, 1,000, 2,000 and 4,000 µg/kg 8-OH-DPAT elicited significant increases in time spent feeding (see Fig. 3). The temporal distribution of time spent feeding was dependent on the dose of 8-OH-DPAT administered. Thus, feeding induced by low doses of 8-OH-DPAT generally occurred 40–75 min after injection, whereas that elicited by high doses of the drug was apparent from 15–30 min until 105–120 min after injection.

8-OH-DPAT produced a dose-dependent increase in the number of feeding bouts ($H=63.8$, 11 *df*, $P<0.001$), with significant effects being evident at doses of 125–4,000 µg/kg of the drug (see Fig. 3). It is important to note that 8-OH-DPAT-induced increases in food intake did not appear to be due to stereotyped gnawing produced by the drug. Thus, rats given a choice of eating food pellets or gnawing wood blocks consistently chose to eat food pellets after 8-OH-DPAT treatment (see Fig. 3).

Table 3 shows the effects of 8-OH-DPAT on eating rate. At high doses of 8-OH-DPAT there was a decline in eating rate associated with the appearance of drug-induced stereotypy (see below). A similar pattern is evident in the data for duration of eating bouts (Table 3) and it can be seen that 8-OH-DPAT at doses of 15–60 µg/kg produced the longest bouts of eating.

Figure 4 shows that 8-OH-DPAT had less pronounced and more variable effects on drinking than on feeding. However, ANOVA revealed a significant effect on drinking ($H=26.6$, 11 *df*, $P<0.01$). Between group comparisons indicated that only 500 µg/kg 8-OH-DPAT (the drug dose which produced a maximal increase in food intake) significantly increased drinking. 8-OH-DPAT-induced drinking appeared to be prandial in nature, i.e. drinking was generally associated with feeding.

8-OH-DPAT treatment had no significant effects on rearing and grooming (data not shown).

2. 8-OH-DPAT-induced locomotor stimulation and stereotypy. Figure 5 shows that 8-OH-DPAT had a biphasic effect on locomotion (cage crossing) with a peak stimulant effect evident at 1,000 µg/kg. The less marked effects at 2,000 and 4,000 µg/kg 8-OH-DPAT were associated with the appearance of intense stereotypy. ANOVA revealed that the drug significantly increased locomotion ($H=69.8$, 11 *df*, $P<0.001$). Further analysis showed that 125–4,000 µg/kg 8-OH-DPAT significantly increased cage crossing, whereas lower doses of the drug had no effect on locomotion. The effects of 8-OH-DPAT on duration of time spent resting were generally opposite to those on locomotion. The drug produced a dose-dependent decrease in time spent resting ($H=66.8$, 11 *df*, $P<0.001$), with significant effects being evident at 250–4,000 µg/kg 8-OH-DPAT. The effects of the drug on serotonin-related stereotyped behaviour generally paralleled those on locomotion with significant effects being

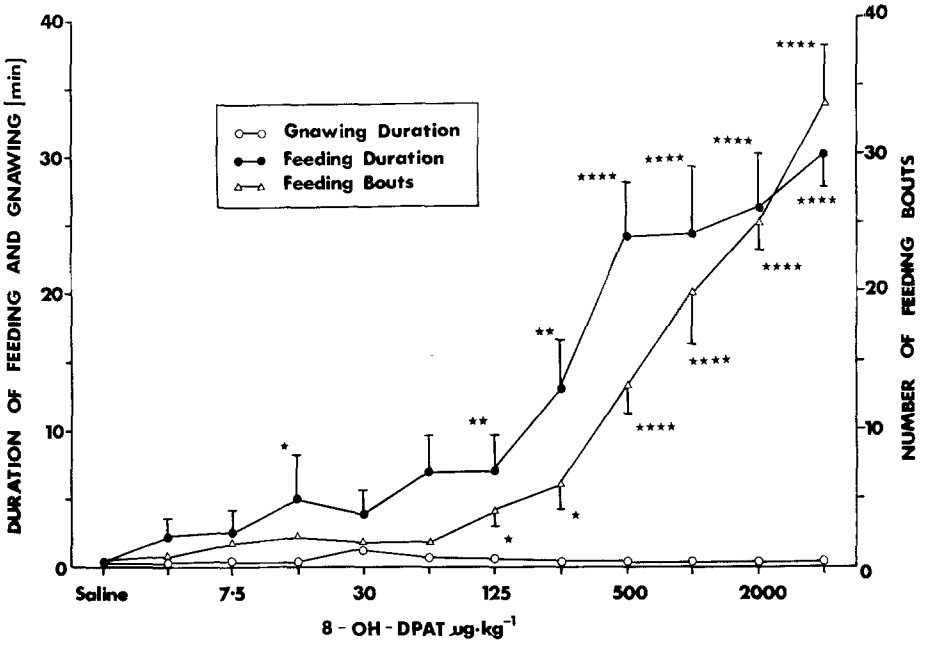

Fig. 3. Effects of 8-OH-DPAT on number of feeding bouts, duration of time spent feeding and duration of time spent gnawing during a 2-h test. Details are as described in Fig. 1

Table 3. Effects of 8-OH-DPAT on local eating rate and duration of eating bouts

8-OH-DPAT μg/kg	Local rate of eating (g/min)	Duration of eating bouts (min)	No. rats eating
Saline	–	–	1/8
3.75	0.35	2.5	3/8
7.5	0.32	1.3	3/8
15	0.23	2.4	6/8
30	0.31	2.2	5/8
60	0.27	4.1	5/8
125	0.30	1.75	6/8
250	0.22	2.06	6/8
500	0.15	1.8	8/8
1,000	0.12	1.2	8/8
2,000	0.09	1.0	8/8
4,000	0.07	0.9	8/8

Parameters for saline treatment are omitted as only one of eight rats showed a feeding response

evident at high doses (see Fig. 5). 8-OH-DPAT (125–4,000 μg/kg) produced dose-dependent increases in forepaw padding ($H=82.5$, 11 *df*, $P<0.001$) and headweaving ($H=69.0$, 11 *df*, $P<0.001$). In addition, (at doses of 250 μg/kg and above) it produced a novel behaviour, the tonic extension of a single hindlimb (hindlimb stretching). Episodes of hindlimb stretching had durations of 1–30 s, although most episodes were of the order of a few seconds in length. It was temporally associated with either forepaw padding or headweaving (or both) and was generally evident only during the 1st h after injection. Hindlimb stretching was clearly distinct from hindlimb abduction in which both hindlimbs are splayed, and which is commonly associated with serotonergic stimulation (see Jacobs 1976). In the present study, 8-OH-DPAT was never observed to induce hindlimb abduction.

8-OH-DPAT significantly increased the incidence of wet dog shakes ($H=30.5$, 11 *df*, $P<0.01$). There was considerable within group variation and thus, only doses of 250, 500 and 4,000 μg/kg of the drug produced a significant effect (see Fig. 5). It also produced a flat body posture associated with stereotyped behaviour although this response was not assessed quantitatively.

3. Relation between 8-OH-DPAT-induced feeding and stereotypy. Feeding behaviour elicited by 8-OH-DPAT treatment could be differentiated into two distinct forms: (1) eating elicited by low doses (15–125 μg/kg) which consisted of one or two long eating bouts of several minutes in length; (2) eating elicited by high drug doses (2,000–4,000 μg/kg) which consisted of numerous short eating bouts of less than 1 min in length, interspersed with stereotyped behaviour (hence the slow eating rate of animals given high doses of 8-OH-DPAT, see Table 3). Animals given 250–1,000 μg/kg 8-OH-DPAT initially displayed fragmented eating associated with the competing response of drug-induced stereotypy, which was succeeded by longer eating bouts as stereotypy dissipated. Thus, an examination of the temporal distribution of eating bouts elicited by 125–4,000 μg/kg 8-OH-DPAT revealed a dose-related increase in bouts which peaked 15–60 min after injection and declined thereafter (see Fig. 6A). Stereotypy induced by 125–4,000 μg/kg 8-OH-DPAT was maximal in the first 15 min after injection and then declined (see Fig. 6B). (N.B. stereotypy in this case refers to forepaw padding, which is used as a representative example as it had a similar time course to other 8-OH-DPAT-induced stereotyped behaviour.) At doses of 125–1,000 μg/kg of the drug, stereotypy dissipated within 60 min of injection, whereas at 2,000 and 4,000 μg/kg it was evident throughout the 2-h test. A comparison of the temporal distribution of feeding bouts and the time course of stereotypy (compare Fig. 6A and B) indicates that feeding responses did not occur during the first 15 min after injection when stereotypy was maximal. As stereotypy dissipated, numerous short bouts of feeding were evident which were succeeded (at doses of 125–1,000 μg/kg) by a few long feeding bouts after recovery from stereotypy. At the highest doses (2,000 and 4,000 μg/kg 8-OH-DPAT), the rats exhibited stereotypy and fragmented bouts of eating throughout the test.

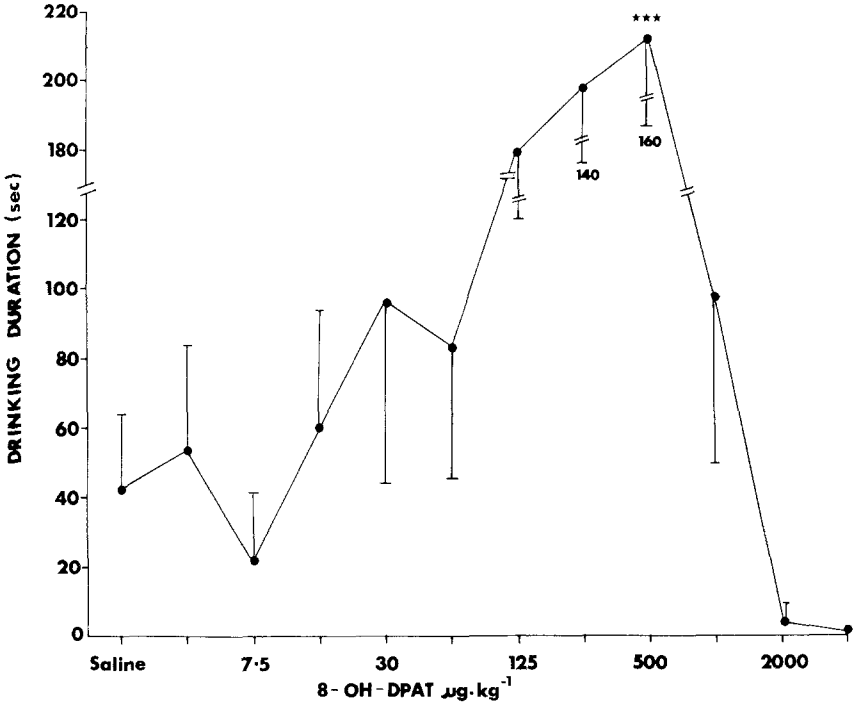

Fig. 4. Effects of 8-OH-DPAT on duration of time spent drinking during a 2-h test. Details are as described in Fig. 1

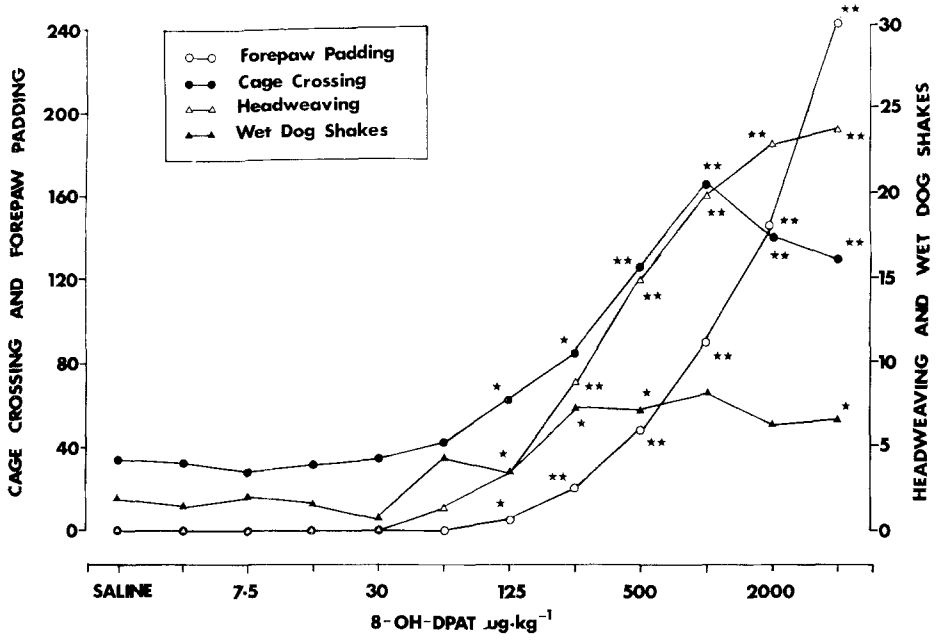

Fig. 5. Effects of 8-OH-DPAT on cage crossing, forepaw padding, headweaving and wet dog shakes and during a 2-h test. Standard errors are omitted for clarity. * $P<0.05$, ** $P<0.01$. Other details are as described in Fig. 1

Discussion

The present study demonstrates that the putative serotonin receptor agonist 8-OH-DPAT given in small doses (15–60 μg/kg) specifically increases the food intake of rats without producing concomitant changes in drinking or motor activity (see Table 4). Examination of the microstructure of the elicited feeding revealed that the local rate of eating produced by low doses of 8-OH-DPAT was comparable with that previously reported to occur after 16-h food deprivation (Blundell and Latham 1978). Larger doses of 8-OH-DPAT (125–4,000 μg/kg) also elicited feeding and produced locomotor stimulation and serotonin-dependent stereotyped behaviour. There was clear evidence of response competition between 8-OH-DPAT-induced feeding and stereotypy. Thus, when the two responses occurred concurrently, feeding behaviour was inhibited or fragmented into numerous short eating bouts during which relatively little food was ingested. When drug-induced stereotypy had dissipated, however, rats treated with 125–1,000 μg/kg 8-OH-DPAT engaged in prolonged feeding bouts which were similar to those elicited by 15–60 μg/kg of the drug.

Despite the concurrence of feeding and serotonergic stereotypy, when higher doses of 8-OH-DPAT were given,

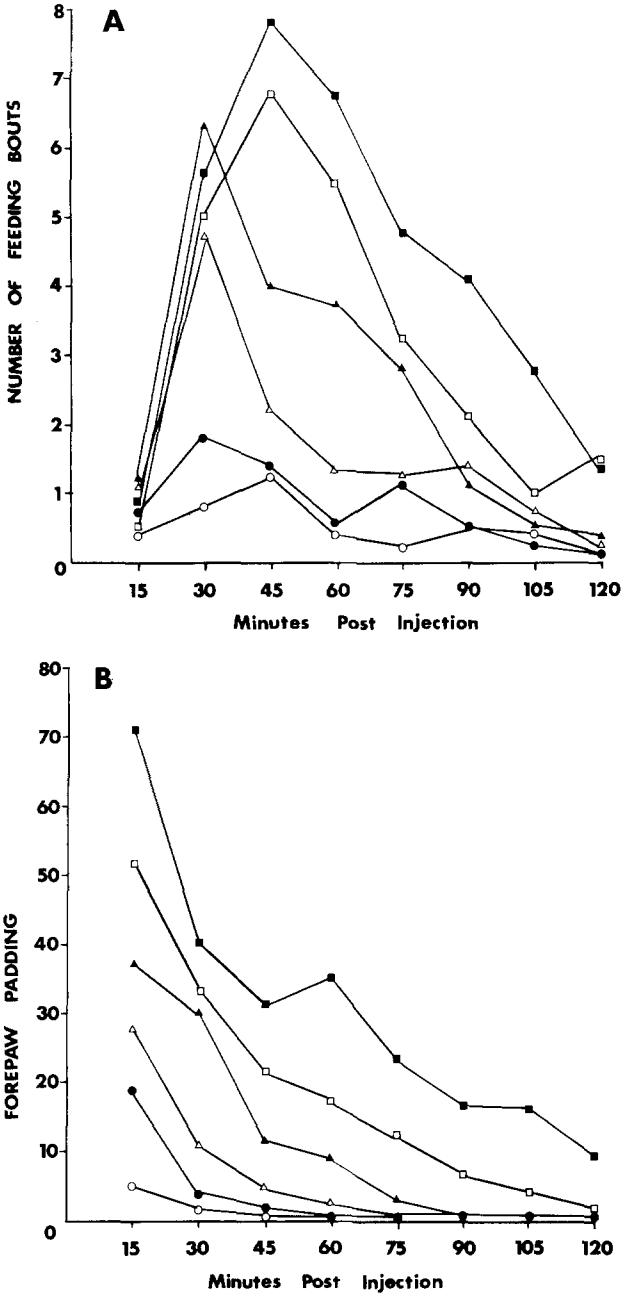

Fig. 6A. Temporal distribution of feeding bouts elicited by high doses (125–4,000 μg/kg) of 8-OH-DPAT. o–o 125 μg/kg 8-OH-DPAT, ●–● 250 μg/kg 8-OH-DPAT, Δ–Δ 500 μg/kg 8-OH-DPAT, ▲–▲ 1,000 μg/kg 8-OH-DPAT, □–□ 2,000 μg/kg 8-OH-DPAT, ■–■ 4,000 μg/kg 8-OH-DPAT. Symbols show the number of feeding bouts in the preceding 15 min. **B** Time course of stereotypy induced by high doses of 8-OH-DPAT (forepaw padding is used as a representative example). Details are as described in Fig. 6A

there was no evidence that the feeding was stereotyped in nature. Previous studies have shown that large doses of drugs such as the dopamine agonist apomorphine elicit non-specific stereotyped gnawing of wood or cage bars, (Ernst 1967; Costall and Naylor 1973). However, in the present study when animals were given a choice between chewing food pellets and wood blocks they clearly preferred the food pellets.

The observation of feeding induced by a putative serotonin receptor agonist was paradoxical, since drugs which enhance serotonergic neurotransmission generally reduce

Table 4. 8-OH-DPAT treatment produces a specific increase in feeding in rats

	Saline	8-OH-DPAT 15 μg/kg	8-OH-DPAT 60 μg/kg
Food intake (g)	0.02	1.25[a]	2.0[a]
Locomotion (*n*)	33.1	31.1	42.2
Rearing (*n*)	43.0	35.6	38.2
Grooming (*n*)	18.6	18.1	25.6
Resting (min)	85.0	84.1	75.7
Drinking (s)	42.4	60.4	83.5

[a] Significant difference from saline treatment

food intake (see Introduction). However, our findings are somewhat analogous to the report by Ahlenius and colleagues (1981) that 8-OH-DPAT stimulates male rat sexual behaviour. This was also paradoxical as many drug experiments indicate that serotonin inhibits rat sexual behaviour (Meyerson and Malmnas 1978). Therefore, it has been proposed that 8-OH-DPAT, as well as being a post-synaptic serotonin agonist, may also be an agonist at presynaptic serotonin autoreceptors or even a serotonin antagonist in certain brain regions (Ahlenius et al. 1981; Ahlenius and Larsson 1984). Evidence from radiolabelled ligand binding studies appears to support the autoreceptor hypothesis (Gozlan et al. 1983). Thus [^{3}H] 8-OH-DPAT binding sites in the striatum were located presynaptically and exhibited pharmacological properties expected of presynaptic serotonin autoreceptors (Gozlan et al. 1983). In addition, it has been claimed that 8-OH-DPAT reduces the potassium-evoked release of [^{3}H] serotonin in cortical and striatal slices in vitro (Hamon et al. 1984). Moreover, 8-OH-DPAT given intravenously inhibits the firing of serotonergic neurones located in the dorsal raphe (T.H. Svensson, unpublished data cited in Ahlenius et al. 1981). Therefore, the action of 8-OH-DPAT on putative serotonin autoreceptors might reduce the release of serotonin and thus increase feeding. This interpretation could explain the present data and is consistent with current theories concerning the role of serotonin in the control of food intake (Blundell 1977; Blundell and Latham 1982). However, Middlemiss (1984) and Galzin (personal communication) have failed to replicate the finding of Hamon et al. (1984) that 8-OH-DPAT inhibits the release of [^{3}H] serotonin in vitro and claim that the drug is devoid of activity at the serotonin autoreceptor. An alternative explanation of our data is that 8-OH-DPAT may be a serotonin antagonist at a particular population of receptors. In this regard, it is noteworthy that the serotonin antagonists methysergide and cyproheptadine are reported to increase food intake in rats and humans (Baxter et al. 1970; Noble 1969; Blundell and Leshem 1974). It has also been proposed that 8-OH-DPAT may be an agonist at one or more putative postsynaptic serotonin receptor subtypes ($5HT_{1A}$, $5HT_{1B}$) (Middlemiss and Fozard 1983; Tricklebank et al. 1984; Hall et al. 1985). Clearly, further studies are necessary to clarify the relationship between 8-OH-DPAT-induced feeding and central serotonergic mechanisms.

It is conceivable that 8-OH-DPAT may act on catecholaminergic mechanisms. The structurally similar aminotetralins 5-OH-DPAT and 2-amino-6,7-dihydroxy-1,2,3,4, tetrahydronaphthalene (ADTN) are dopamine receptor agonists (McDermed et al. 1978; Poat et al. 1980) and interestingly, ADTN injected into the hypothalamus, nucleus accumbens

or lateral ventricle of the rat was reported to induce feeding (Poat et al. 1980). The feeding was abolished by phentolamine but unaffected by haloperidol or propranolol, indicating that the response may be mediated by α-adrenoceptors. Furthermore, central application of dopamine or noradrenaline can stimulate or suppress feeding depending on the site of injection (reviewed, Leibowitz 1980).

Systemic injection of the dopamine agonist apomorphine has been reported to increase food intake in satiated rats and decrease food intake in food deprived rats (Eichler and Antelman 1977). Similarly, preliminary data from our laboratory suggests that 8-OH-DPAT decreases food intake in food-deprived rats. However, this may simply be due to the disruptive effect of drug-induced stereotypy on feeding. Although the presently available biochemical evidence does not support a direct catecholamine involvement in the mediation of 8-OH-DPAT-induced behaviour (Hjorth et al. 1982), it is clear that further studies are required to examine the possibility that the drug may be an adrenergic or dopaminergic agonist.

Although 8-OH-DPAT-induced feeding is in part consistent with 8-OH-DPAT-induced sexual arousal (Ahlenius et al. 1981; Ahlenius and Larsson 1984; Morali and Larsson 1984), these effects may be mediated by different neurochemical mechanisms. Thus, 8-OH-DPAT-induced feeding is evident at doses ten times lower than the minimal dose reported to stimulate male rat sexual behaviour (see Ahlenius et al. 1981). Further, a maximal effect on male rat sexual behaviour occurred at 4,000 μg/kg 8-OH-DPAT, which is eight times higher than that required for a maximal effect on feeding. In the present study, we observed that after injection of 4,000 μg/kg 8-OH-DPAT, intense stereotypy is produced which initially suppresses feeding and subsequently causes fragmented bouts of eating. Feeding induced by low doses of 8-OH-DPAT had a long latency to onset (40–55 min), which could indicate mediation by a metabolite rather than by the drug itself.

The present data largely confirm previous reports that high doses of 8-OH-DPAT produce locomotor stimulation and various stereotyped components (flat body posture, forepaw padding, headweaving) of the so-called serotonin syndrome (Hjorth et al. 1982; Arvidsson et al. 1981). In addition, we observed that 8-OH-DPAT (250–4,000 μg/kg) produced intermittent hindlimb lifting and flicking (hindlimb stretching) as described by Tricklebank et al. (1984).

In conclusion, the principal finding of this study is that, although activation of postsynaptic serotonin receptors by classical serotonin agonists or releasers decreases food intake, the putative serotonin receptor agonist 8-OH-DPAT strikingly increases the food intake of non-deprived rats. This could be due to an agonist action of the drug at serotonin autoreceptors or a serotonin antagonist action in certain brain regions. Alternatively, the response may be due to an agonist action at a postsynaptic serotonin receptor subtype or an effect on catecholamine mechanisms.

Acknowledgements. We thank Miss S. Mootoo for technical assistance and the MRC for financial support.

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Received October 23, 1984; Final version January 30, 1985