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Sucrose Sham-Feeding in the Rat After Administration of the Selective Dopamine D_2 Receptor Agonist N-0437, *d*-Amphetamine or Cocaine

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COOPER, S. J., I. N. RUSK AND D. J. BARBER. *Sucrose sham-feeding in the rat after administration of the selective dopamine D_2 receptor agonist N-0437, d-amphetamine or cocaine.* PHARMACOL BIOCHEM BEHAV 32(2) 447–452, 1989.—Drugs which act as agonists at dopamine receptors, or which increase dopamine release (e.g., *d*-amphetamine, cocaine) are known to reduce food intake. The present experiments investigated, for the first time, the effects of a highly selective dopamine D_2 receptor agonist, N-0437 (0.3–3.0 mg/kg, IP), on 5% sucrose sham-feeding in gastric fistulated rats, and compared these results with those of *d*-amphetamine (0.1–3.0 mg/kg, IP) and cocaine (3.0–10.0 mg/kg, IP). The results showed that sucrose sham-feeding was resistant to the effects of N-0437, even though the D_2 agonist dose-relatedly reduced sucrose real-feeding in intact animals. The two psychomotor stimulants, *d*-amphetamine and cocaine, produced some reductions in sham-feeding, although in the case of the highest dose of *d*-amphetamine, the pronounced reduction in the consumption of sucrose was probably secondary to induced behavioral stereotypy. The results suggest that D_2 receptor stimulation may interact with satiety cues to reduce ingestion of sucrose, but that in the absence of potent satiety stimuli D_2 receptor stimulation is ineffective. Furthermore, N-0437 appeared not to be equivalent to either *d*-amphetamine or cocaine in their effects to reduce sucrose sham-feeding.

Dopamine D_2 receptors Cocaine *d*-Amphetamine N-0437 Sham-feeding Sucrose

d-AMPHETAMINE increases dopamine release in the brain (13, 21, 30, 41, 43). Cocaine also increases dopamine release, and inhibits dopamine reuptake presynaptically (7, 11, 36, 38). Both drugs reduce the consumption of food (2, 5, 6), and it is probable that their effect on food intake is linked to increased central dopaminergic activity, [e.g., (14, 28, 29)]. In agreement with this, drugs which are dopamine receptor agonists are effective in reducing food intake (1, 3, 18–20). Since the peripherally-active dopamine antagonist, domperidone, does not block the anorectic effect of dopamine agonists (10), it can be assumed that the reduction in feeding depends upon central dopaminergic mechanisms (9). Thus, an increase in central dopamine release should stimulate dopamine receptors and reduce feeding behavior.

An important distinction has been drawn between D_1 and D_2 dopamine receptor subtypes, and selective agonists and antagonists for each subtype are now available (23,44). N-0437, 2-(N-propyl-N-2-thienylethylamino)-5-hydroxytetralin, is a potent and highly selective D_2 agonist, with little affinity for D_1 sites (4, 22, 46–49). We have recently demonstrated that it dose-relatedly reduced food consumption in rats and mice (40). Its suppressant effect on feeding was reversed by the highly selective D_2 antagonist, YM-09151-2 (32,44). Hence, stimulation of postsynaptic D_2 receptors is sufficient to reduce food consumption. In further support of this view, we have subsequently shown that (−)N-0437, which has greater affinity for D_2 sites than the (+) enantiomer (49), is the more potent in suppressing palatable food consumption (Timmerman *et al.*, submitted for publication). It is interesting to note that direct injections of dopamine or *d*-amphetamine into the perifornical region of the lateral hypothalamus have anorectic effects (27–29). Dopamine receptors in this region are exclusively of the D_2 subtype (37). Although the relationship between stimulation of postsynaptic D_2 receptors and feeding behavior seems clear, nevertheless, the behavioral and/or physiological mechanisms which mediate the reduction in food ingestion have still to be characterized fully.

Increasing use has been made of the gastric sham-feeding rat to study the effects of drugs, neurotransmitters and neuropeptides on food intake. Cholecystokinin, insulin, dopamine antagonists, benzodiazepine inverse agonists, naloxone and *d*-fenfluramine not only suppress real-feeding, but also produce marked reductions in sham-feeding (12, 16, 17, 25, 26, 33, 35, 39, 42). However, effects of treatments on sham-feeding do not always correspond to effects on real-feeding. For example, the peripheral cholinergic antagonist, atropine methyl nitrate, has been shown to reduce sucrose sham-feeding but not real-feeding (31, 34, 50). Conversely, glucagon inhibits real-feeding but not sham-feeding (15). It is clearly of interest, therefore, to determine if enhanced dopaminergic activity and stimulation of D_2 receptors is suf-

ficient to reduce sham-feeding behavior, in the same way that real-feeding is suppressed. An answer to this question should help to define dopaminergic involvement in feeding processes in greater detail.

Hence, the general aim of the present experiments was to evaluate *d*-amphetamine, cocaine and the selective D_2 agonist, N-0437, for possible effects on sucrose sham-feeding. The results carry important implications for understanding the relationships between central dopamine neurotransmission and the control of ingestional responses.

METHOD

Animals

The subjects were twenty-two adult male hooded rats (General strain, bred in this laboratory), and weighed 250–350 g. They were housed individually in stainless steel cages, and were maintained under a 12 hr light:12 hr dark cycle (lights on at 0700 hr). Except for periods of pretest deprivation and testing, the rats had ab lib access to standard food pellets (Diet 41B, Heygate and Sons, U.K.) and water. Room temperature was kept constant at 21°C.

Drugs

N-0437 hydrochloride (22) was generously supplied by Nelson Research, Irvine, CA. It was dissolved in distilled water and administered intraperitoneally 20 min prior to the feeding tests. It was injected in doses from 0.3–3.0 mg/kg, on the basis of previous experiments (40). *d*-Amphetamine sulphate (provided by Smith Kline and French Laboratories, Welwyn Garden City, U.K.) and cocaine hydrochloride (provided by May & Baker Ltd., Dagenham, Essex, U.K.) were dissolved in isotonic saline, and injected 20 min prior to sham-feeding tests. *d*-Amphetamine was administered in doses 0.1–3.0 mg/kg (40), and cocaine was injected in doses 3.0–10.0 mg/kg [on the basis of previous data (2, 5, 45)]. Doses are expressed in terms of salt form.

Procedure

Ten rats were trained to drink a 5% sucrose solution (w/v) in test cages which were identical to their home cages, except that the normal food and water supply were removed. The sucrose solution was presented in a 50 ml graduated cylinder, the metal spout of which protruded into the test cage. The rats then underwent surgery to implant a chronic gastric cannula. Each cannula was made from a Perspex tube (i.d. 6 mm; o.d. 8 mm; length 14 mm), which was flanged at each end. A collar of Marlex mesh (Bards Implants, Billerica, MA), 25 mm diameter, was fitted around the cannula shaft and held in place with dental acrylic. Surgery details are described in (25). After surgery, the rats were given a one-week period of recovery with ad lib access to food pellets and water. They were then familiarised with the sham-feeding procedure in the experimental cages, drinking 5% sucrose with the gastric cannula open, as described previously (25).

Each animal was injected with each dose of N-0437 (0.3, 1.0 and 3.0 mg/kg) and a vehicle injection according to a randomised sequence, with at least 48 hr between successive treatments. Food was removed from the home cage 4 hr before the sham-feeding test. Injections were given 20 min before the sham-feeding tests, stomachs were rinsed out with repeated washes of tepid water to remove all traces of food, and tests began at 1400 hr. During the tests, sucrose solution intake was measured at 5 min intervals for 60 min, and then at 10 min intervals for a second 60 min period. At the completion of testing, stomachs were again rinsed, cannulas closed and the rats returned to their home cages. Drainage was collected in trays placed beneath the test cages, and these were weighed before and after testing to ensure that amounts collected were not less than those consumed.

Following completion of the N-0437 study, sham-feeding rats were tested in turn with *d*-amphetamine (0.1, 0.3, 1.0, 3.0 mg/kg IP) and cocaine (3.0, 5.6, 10.0 mg/kg IP), according to the procedures described above. At least one week intervened between experiments with the three compounds.

Twelve intact rats were tested in 120 min tests of 5% sucrose consumption utilizing a procedure identical to that which was used in the sham-feeding study. They were injected IP with either N-0437 (0.3, 1.0 and 3.0), or vehicle, 20 min before the sucrose test in the test cages. After an interval of one week, ten of the rats were tested following *d*-amphetamine (0.1–3.0 mg/kg IP).

The sucrose consumption data were analysed by analysis of variance, and Dunnett's *t*-test (52).

TABLE 1

EFFECTS OF N-0437, A SELECTIVE DOPAMINE D_2 RECEPTOR AGONIST, ON CUMULATIVE 5% SUCROSE INTAKE IN SHAM-FEEDING AND REAL-FEEDING RATS

	N-0437 (mg/kg)			
	0	0.3	1.0	3.0
Sham-feeding (n=10)				
15 min	24.3 ±1.8	21.4 ±1.5	20.3 ±2.4	17.9 ±2.6
30 min	41.2 ±4.7	36.3 ±4.4	38.1 ±3.6	31.1 ±5.2
60 min	53.0 ±4.9	55.6 ±8.0	57.8 ±6.2	46.7 ±9.5
120 min	71.7 ±11.3	73.8 ±10.7	74.2 ±7.9	64.6 ±13.3
Real-feeding (n=12)				
15 min	19.4 ±1.4	14.2* ±1.5	12.5‡ ±1.3	8.5‡ ±1.3
30 min	21.3 ±1.2	14.8‡ ±1.5	12.6‡ ±1.4	9.4‡ ±
60 min	24.3 ±1.5	19.6* ±2.1	16.5‡ ±1.8	11.4‡ ±1.4
120 min	33.5 ±2.5	29.0 ±2.4	24.5‡ ±0.8	19.9‡ ±2.4

The results are shown in terms of mean ± S.E.M. sucrose intake (ml). Levels of significance in comparison with vehicle condition: *$p<0.05$; †$p<0.01$; ‡$p<0.005$ (Dunnett's *t*-test).

RESULTS

N-0437

The cumulative intake of 5% sucrose solution following the administration of N-0437 (0.3–3.0 mg/kg) to sham-feeding rats is shown in Table 1. After 15 min, despite the small reduction in intake at 3.0 mg/kg, there was no overall significant effect of N-0437 on sucrose ingestion, $F(3,27)=1.63$, N.S. At each subsequent time interval, sucrose sham-feeding was not significantly affected by N-0437: 30 min, $F(3,27)=1.17$; 60 min, $F(3,27)=0.59$; 120 min, $F(3,27)=0.17$.

TABLE 2

EFFECTS OF *d*-AMPHETAMINE ON CUMULATIVE 5% SUCROSE INTAKE IN SHAM-FEEDING AND REAL-FEEDING RATS

	d-Amphetamine (mg/kg)				
	0	0.1	0.3	1.0	3.0
Sham-feeding (n=10)					
15 min	24.5	21.0	22.9	12.7‡	2.8‡
	±1.3	±1.6	±1.9	±2.5	±1.9
30 min	44.3	39.8	41.4	23.9‡	4.1‡
	±3.7	±2.9	±4.1	±4.8	±3.1
60 min	71.0	60.2	68.2	40.6‡	4.5‡
	±7.6	±6.8	±8.3	±8.7	±3.6
120 min	86.8	75.6	85.4	70.0	7.1‡
	±9.9	±9.9	±10.8	±12.7	±3.7
Real-feeding (n=10)					
15 min	16.0	18.7	19.7	15.9	3.6‡
	±1.4	±0.9	±1.8	±1.0	±1.4
30 min	24.8	24.6	22.0	20.3	4.5‡
	±1.6	±1.7	±1.7	±2.0	±1.9
60 min	28.9	28.4	27.1	26.0	10.0‡
	±1.5	±2.4	±1.9	±2.3	±2.7
120 min	43.8	42.9	41.4	39.9	21.3‡
	±2.4	±3.0	±3.0	±2.3	±4.6

The results are shown in terms of mean ± S.E.M. sucrose intake (ml). Levels of significance (see Table 1).

In contrast, consumption of 5% sucrose solution by nonfistulated rats was dose-dependently reduced by N-0437. There was a significant effect of N-0437 on sucrose intake within the first 15 min of the test period, $F(3,33)=10.56$, $p<0.001$ (Table 1). Sucrose intake was significantly reduced by 27% at 0.3 mg/kg, 36% at 1.0 mg/kg, and 56% at 3.0 mg/kg. The suppressant effect of N-0437 on cummulative intake remained at each subsequent time interval: 30 min, $F(3,33)=18.0$, $p<0.001$; 60 min, $F(3,33)=15.1$, $p<0.001$; 120 min, $F(3,33)=10.7$, $p<0.001$. There was little or no evidence of any recovery from the initial 15 min effect of N-0437 over the rest of the 2 hr test period.

Hence, N-0437 (0.3–3.0 mg/kg) dose-dependently reduced 5% sucrose solution ingestion in nonfistulated rats, but did not have any significant effect on sucrose sham-feeding.

d-*Amphetamine*

The results for the effects of *d*-amphetamine (0.1–3.0 mg/kg) on sucrose sham-feeding are shown in Table 2. During the first 15 min period of the test, *d*-amphetamine significantly reduced sucrose ingestion, $F(4,36)=28.3$, $p<0.001$. There was no effect of *d*-amphetamine at the two smaller doses, 0.1 and 0.3 mg/kg. However, after 1.0 mg/kg of *d*-amphetamine, sucrose sham-feeding was significantly reduced by 48%, and by 89% after 3.0 mg/kg. The suppressant effect of 1.0 mg/kg of *d*-amphetamine, sucrose sham-feeding was significantly reduced by 48%, and by 89% after 3.0 mg/kg. The suppressant effect of 1.0 mg/kg of *d*-amphetamine remained for the first hour of the sham-feeding test, but recovery from it became apparent during the second hour. In contrast, the marked effect of 3.0 mg/kg of *d*-amphetamine remained throughout the 2 hr period of testing, and there was virtually no recovery. In nonfistulated animals consuming the 5% sucrose solution, ingestion was suppressed throughout the 2 hr test period after 3.0 mg/kg of *d*-amphetamine, but there was little effect on ingestion at smaller doses, 0.1–1.0 mg/kg (Table 2). Informal observations indicated that *d*-amphetamine induced intense stereotyped responses (head-weaving in a fixed location) after the 3.0 mg/kg dose.

Cocaine

The results for the effects of cocaine (3.0–10.0 mg/kg) on sucrose sham-feeding are shown in Table 3. During the first 15 min period of the test, cocaine significantly reduced sucrose ingestion, $F(3,24)=6.8$, $p<0.01$. Cocaine was effective at 5.6 mg/kg and produced a 35% reduction in intake. At 10.0 mg/kg, it produced a 45% reduction in sucrose sham-feeding. A suppressant effect of cocaine on cumulative sucrose intake was still in evidence at the 30 min interval, $F(3,24)=4.85$, $p<0.01$, although there was only a 30–31% reduction at doses of 5.6 mg/kg and 10.0 mg/kg. The effect of cocaine was relatively short-lived, and for the remaining 90 min of the test, there was clear evidence of recovery so that cumulative sham-feeding was no longer significantly reduced by the drug.

DISCUSSION

N-0437

An important result was that the highly selective dopamine D_2-receptor agonist, N-0437 (0.3–3.0 mg/kg) did not significantly affect sucrose sham-feeding. Nevertheless, over the same dose-range, N-0437 reduces palatable food consumption in nondeprived rats, intake of powdered chow

TABLE 3

EFFECTS OF COCAINE ON CUMULATIVE 5% SUCROSE INTAKE IN SHAM-FEEDING RATS

	Cocaine (mg/kg)			
	0	3.0	5.6	10.0
15 min	26.6 ±2.0	23.6 ±2.8	17.4† ±3.8	14.7‡ ±2.3
30 min	39.3 ±2.9	38.6 ±5.8	27.2† ±5.8	27.6† ±4.9
60 min	51.4 ±4.8	60.8 ±7.3	42.0 ±10.4	44.7 ±6.4
120 min	69.1 ±8.2	78.7 ±7.3	54.2 ±12.7	68.1 ±9.9

The results are shown in terms of mean ± S.E.M. sucrose intake (ml) N=9 per group. Levels of significance (see Table 1).

in food-deprived rats (40), and real-feeding of a 5% sucrose solution (present experiments). Hence, the effects of N-0437 on sucrose real-feeding are dissociated from any effect on sham-feeding. As noted in the introduction, many drugs and neuropeptides suppress both real- and sham-feeding of sucrose solutions. The present results with N-0437 are analogous to findings with glucagon (15), since both have an asymmetric effect which is opposite to that of atropine methyl nitrate, which reduces sucrose sham-feeding but not real-feeding (31, 34, 50). We have also recently found that the β_2-adrenergic agonist, salbutamol, did not affect sucrose sham-feeding (Cooper and Barber, unpublished data), even though it reduced sucrose consumption in intact animals (8). It appears that real- and sham-feeding of sucrose are regulated, to some degree at least, by separable neurochemical mechanisms.

Gastric sham-feeding rats exhibit a satiety deficit (53), and their sucrose consumption appears to be maintained by the palatability of oropharyngeal stimulation (51). If this is the case, then the present data argue strongly that N-0437 does not suppress the palatability of sucrose sham-feeding. If the result with N-0437 can be generalised, then it seems unlikely that the anorectic effects of dopamine agonists, particularly those acting at D_2 receptors, depends on inhibition of palatability factors which maintain ingestional behavior. If this hypothesis is confirmed, it follows that stimulation of D_2 receptors in the perifornical region of the hypothalamus would not be expected to suppress sucrose sham-feeding either. Further research bearing on this important issue would be worthwhile.

At present, we are not able to specify in detail the behavioral and physiological mechanisms which underlie suppression of sucrose real-feeding by N-0437. The compound's lack of effect on sham-feeding indicates that a nonspecific motor interference is unlikely to be responsible. Stimulation of D_2 receptors may interact with satiety cues which operate during sucrose real-feeding, and together bring about a reduction in intake. In the absence of relevant satiety cues in sucrose sham-feeding, therefore, D_2 receptor stimulation remains ineffective.

d-*Amphetamine and Cocaine*

Both psychomotor stimulants reduce food intake, and also cause substantial increases in brain dopamine release. Both drugs reduced sucrose sham-feeding (Tables 2 and 3). In the case of *d*-amphetamine, significant reductions occurred at doses of 1.0 and 3.0 mg/kg. At the same doses, *d*-amphetamine reduced palatable food consumption and operant responding for food under a FR8 schedule of reinforcement (40). In all these cases, responses were markedly suppressed at 3.0 mg/kg, coinciding with the induction of intense stereotyped behavior. There is no reason, therefore, to assume that *d*-amphetamine, at least in higher doses, reduces sucrose sham-feeding through any direct effect on food palatability. At 1.0 mg/kg, the reduction in sucrose sham-feeding was less pronounced, and further work is needed to establish if this effect represents a direct effect on ingestional responses. Cocaine's effects, at 5.6 and 10.0 mg/kg, were relatively transient, [c.f., (2)]. In a 30 min test of palatable food consumption, cocaine reduced feeding over the same dose-range (45), and similiar mechanisms may underlie its effects on sham-feeding and real-feeding. Observational studies are in progress in our laboratory to determine if cocaine's effects on feeding responses are nonspecific secondary to behavioral stimulation, or include a component of direct effect on appetite or satiety.

The data for *d*-amphetamine and cocaine indicate that increased dopamine release is not equivalent in behavioral terms to direct stimulation of D_2 receptors. N-0437, at doses which reduce palatable food intake in intact animals, did not reduce sucrose sham-feeding. This result indicates that N-0437 does not act in the same manner as classical psychomotor stimulants, and therefore we can be more confident that its effects on feeding responses are not merely secondary to general behavioral stimulation. At a biochemical level, drugs which release dopamine would be expected to produce effects mediated at both D_1 and D_2 receptors (24). Hence, psychomotor stimulant effects may require concurrent stimulation of D_1 and D_2 receptors, as distinct from exclusive stimulation of one or other receptor subtype. It is worth bearing in mind that, to date, there have been no reports on sucrose sham-feeding after selective D_1 receptor-stimulation. Hence, at present, we cannot rule out a role for dopamine D_1 receptor stimulation in relation to sucrose sham-feeding.

D_2 *Receptor Agonists and Antagonists*

An important issue raised by the present results with N-0437 is the question of the relationship between agonist and antagonist activity at D_2 receptors in the case of sucrose sham-feeding.

Selective D_2 receptor antagonists reduce sham-feeding, and from these data it has been suggested that dopamine activity at D_2 receptors is necessary for the reward effect of sucrose during sham-feeding (16,42). From this point of view, it might be predicted that D_2 agonist activity would increase sucrose sham-feeding. Our present results failed to confirm such an effect. At first sight, the agonist and antagonist data appear to be discrepant, but it is quite possible that dopamine D_2 receptors may be involved in at least two distinct aspects of feeding. Predictions about agonist and antagonist effects may therefore be somewhat complex.

The rewarding effect of sucrose consumption could be blocked by D_2 antagonists (16,42). In addition, dopamine may also contribute to meal termination through enhancement of satiety cues. This second mechanism would explain why D_2 receptor stimulation decreases meal size (Clifton, Rusk and Cooper, submitted). It would also explain the ability of N-0437

to reduce sucrose ingestion in intact rats, in the present study, together with its lack of effect on sucrose sham-feeding. D_2 receptor stimulation, in association with satiety signals, may be sufficient to reduce food consumption.

Discovering the relationships between aspects of dopamine neurotransmission and the control of feeding responses remains a challenging task. The present results indicate that stimulation of dopamine D_2 receptors using the highly selective agonist, N-0437, had little effect on sucrose sham-feeding. In contrast, real-feeding was dose-dependently reduced by N-0437, indicating a possible interaction between D_2 agonist activity and within-meal satiety cues.

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