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7-OH-DPAT Injected Into the Accumbens Reduces Locomotion and Sucrose Ingestion: D_3 Autoreceptor-Mediated Effects?

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GILBERT, D. B. AND S. J. COOPER. *7-OH-DPAT injected into the accumbens reduces locomotion and sucrose ingestion: D_3 autoreceptor-mediated effects?* PHARMACOL BIOCHEM BEHAV **52**(2) 275–280, 1995.—7-hydroxy-*N,N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT) injected bilaterally in the nucleus accumbens (NAC) resulted in profound, noncatatonic, dose-dependent (0.3–3 mg total dose) hypolocomotion but without inducing yawning. It also decreased intake of a highly preferred 3% sucrose solution (1 μg total dose). Systemic injection of 7-OH-DPAT (0.1–3.0 mg/kg, IP) similarly induced hypolocomotion while failing to induce yawning. In none of these studies did rats show any signs of hyperlocomotion or any stereotyped responses normally associated with D_2 or mixed D_1/D_2 receptor stimulation. These data suggest that hypolocomotion elicited by 7-OH-DPAT in the NAC may be mediated at the D_3 receptor as distinct from the D_2 dopamine receptor. We discuss the possibility that the behavioural effects we observed are mediated at D_3 autoreceptors.

7-OH-DPAT D_3 and D_2 autoreceptors Ingestion Locomotion Nucleus accumbens

RECENT work with receptor cloning experiments supports the hypothesis that five forms of DA receptor may currently exist (11). Two of the five have been described as D_1-like (D_1 and D_5), and the other three as D_2-like. Considerable interest has focussed recently on one of the D_2-like types, the D_3 receptor, which has been cloned by Sokoloff and co-workers (27). Mapping studies have shown that the D_3 receptor is distributed to areas including limbic forebrain, nucleus accumbens (NAC), and the islets of Calleja in rat (15,16,27) and human (14) brains. Agonists with a high affinity for the D_3 receptor include quinpirole (27–29), quinelorane (18), and 7-hydroxy-*N,N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT) (8,16,26). There is some suggestion that the compounds (+)-AJ76 and (+)-UH232 may be D_3-preferring antagonists (27); recently, these compounds have been used in this role in behavioural studies (12,35,36).

To date there have been relatively few studies on the behavioural pharmacology of D_3 receptor stimulation, although some attention has been focussed on the behavioural effects of 7-OH-DPAT.

It has been shown that, given systemically, 7-OH-DPAT will induce hypolocomotion (1,7,31,37), but some hyperlocomotion was seen at a high 10-mg/kg dose (1). In complete contrast, one study reported that 7-OH-DPAT produced apomorphine-style hyperlocomotion at low doses (17). Interestingly, this one anomalous study was the only locomotion study cited in a recent article suggesting that 7-OH-DPAT may not preferentially stimulate D_3 receptors (10). One early study reported mainly hypolocomotion with 7-OH-DPAT introduced into the NAC (24). These authors, however, referred to the drug as DP-7-ATN and did not consider their findings in terms of D_3-receptor stimulation (although this was probably because there was little or no evidence to suggest that D_3 receptors existed at that time). Some, but not all of these

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studies reported 7-OH-DPAT-induced yawning at low doses (1,8). Significantly, Caine and Koob showed that nonreinforcing doses of 7-OH-DPAT potently decrease cocaine self-administration in rats, suggesting that 7-OH-DPAT may reduce cocaine-induced reward (2). They suggested that 7-OH-DPAT may be acting at presynaptic D_3 receptors. However, as they pointed out, lack of a D_3-specific antagonist makes this a difficult pharmacologic question to answer. A more recent study has shown that 7-OH-DPAT inhibits prepulse-inhibition in rats (an animal model relevant to schizophrenia) (33).

There is still, however, a question as to whether 7-OH-DPAT is a D_3-specific agent and, if so, whether its behavioural effects are mediated at D_3 autoreceptors (18), at postsynaptic D_3 receptors (31,37), or indeed, at both (8,27). Therefore, the current study attempted to investigate this problem by looking at the effect of 7-OH-DPAT on two indices of DA function in the behaving rat. Thus, injection of 7-OH-DPAT over a wide dose range systemically and directly into the NAC might determine, on behavioural grounds, the extent to which the compound stimulates receptors other than D_3 receptors (i.e., D_2 or mixed D_1/D_2 receptors). Any hyperlocomotion (and/or behavioral stereotypic responses, such as sniffing, vacuous chewing, or grooming) would suggest that 7-OH-DPAT acted at postsynaptic D_1/D_2 receptors (34), whereas hypolocomotion alone would probably indicate that the drug had acted elsewhere, possibly at D_3 autoreceptors (18).

Therefore, in the present experiments, we considered the effects of either systemic or intraaccumbens administration of 7-OH-DPAT on locomotor activity and also investigated the effect of intraaccumbens administration of 7-OH-DPAT on 3% sucrose intake in nondeprived rats.

METHOD

Subjects

A total of 22 adult male hooded rats (general strain, bred in the Psychology Laboratory at Birmingham) served as subjects. Between testing they were housed in large, clear plastic home cages with free access to standard laboratory rat food and water. They were kept at 21°C on a 12 L : 12 D regime (lights on at 0700 h) and were always tested during the morning light period. They were regularly handled and weighed every day. They weighed 300–400 g at testing.

Drugs

7-OH-DPAT was dissolved in isotonic saline and administered either centrally (0.3–3.0 μg) or IP (0.1–3.0 mg/kg) according to the procedure.

d-Amphetamine sulphate was also dissolved in 0.9% saline and given IP at a dose of 3 mg/kg as a positive control. IP injections were given in a volume of 1 ml/kg body wt.

Apparatus

Five simple, circular open-field corridors, constructed at the University of Birmingham, were used to measure coarse ambulation. Each box consisted a large outer cylinder, 25 cm high, with a diameter of 40 cm, made of black plastic. A clear plastic cylinder also 25 cm high but only 20 cm in diameter was fixed centrally in the larger black circus. Thus, an outer corridor, or annulus, 10 cm wide was formed. A light source was suspended in the centre of the clear plastic circle and three photosensitive cells were fixed 120° apart, 3 cm above the floor, to the outer circle. Each time the rat walked past a cell, the light was interrupted and the movement was recorded. The light interruptions were electronically recorded for each box.

Test procedures

Intracerebral injection of 7-OH-DPAT: Effect on locomotion.

Surgery. At least a week before testing, 12 of the animals were deeply anaesthetized with 60 mg/kg IP Sagatal (barbiturate), their scalps were shaved, and then they were mounted on a stereotaxic apparatus. An incision was made along the midline, and the scalp and connective tissue were gently blunt-dissected away to either side. Two small holes were drilled in the skull suface at the appropriate location and two stainless-steel guide cannulae (21 ga, cut to 16 mm; Cooper's Needle Works Ltd., Birmingham, UK) were aimed bilaterally to the central NAC using the following coordinates: Bregma +1.7 mm; lateral 1.3 mm to midline and ventrally 5 mm below dura 19. Three small stainless-steel anchor screws were positioned on the skull surface, and dental cement was used to secure the guide cannulae in place. A suture was placed to the front and rear of the wound and, to prevent blockage, modified injection cannulae (26 ga, cut to 20 mm) were placed as stylets in the guide cannulae. Following surgery, the rats were returned to their home cages and allowed at least 3 days to recover (most animals had 7 days, but the last two to receive implants had only 3; they showed absolutely no adverse reaction to handling).

Test. Before drug testing, the rats were allowed 3 days of 30 min/day acclimatisation to the apparatus. Then, four solutions of 7-OH-DPAT were prepared (vehicle, 0.3, 1.0, or 3.0 mg/ml, respectively) and were coded A–D. Each rat received each solution in a blind and randomised, balanced order. Two injection cannulae (26 ga, cut to 20 mm) were fixed into fine plastic tubing so that they were left just sufficient length to protrude 1–1.5 mm beyond a guide cannula. The plastic tubing was cut to 1 m in length (to allow movement) and the other ends were each attached to a 10-μl Hamilton microsyringe. The microsyringes were then placed in a Sage Instruments infusion pump, set to deliver 1 μl/min. The rats were sufficiently tamed to allow relatively easy introduction of the injection cannulae, and each hemisphere was injected with 0.5 μl over 30 s. After the infusion, the injection cannulae were left in place for 20–30 s to allow diffusion of the drug. The injection cannulae were removed and quickly replaced by stylets.

Each rat was then placed immediately into the apparatus. The rats were under continuous observation during the procedure, and any stereotyped behaviour or yawns were noted. The number of beam crossings was recorded every 5 min for 30 min. The rat was then returned to its home cage. Testing took place on Mondays, Wednesdays, and Fridays. On completion of the fourth test day, the code was broken and the data were analysed according to dose.

Intracerebral injection of 7-OH-DPAT: Effect on sucrose intake. The same 12 rats that were subjects in Experiment 1 served as subjects in this study. They were housed between testing and treated exactly as before. Following the locomotor experiment, the rats were adapted daily to drinking 3% sucrose for 40 min/day. During the morning light period, they were transferred to small stainless-steel test cages, where they were offered the sucrose in plastic inverted, graduated cylinders. Intake was recorded every 5 min for 20 min, then at two

further 10-min intervals, to make a total test of 40 min, by which time drinking had effectively ceased (see Fig. 2). When intake baselines had stabilised after 5 days, the rats were tested with 7-OH-DPAT. 7-OH-DPAT (1 mg/ml) and saline vehicle were blind coded "A" and "B" and injected centrally to the NAC exactly as before: half of the rats received A and half got B. Immediately following the drug infusion, the animals were allowed access to the sucrose. The animals drank without drug administration the next day (as a baseline check) and received the second injection on the third day.

Histology. At the end of Experiment 2, the rats were killed by halothane overdose and a small amount of india ink was injected in place of 7-OH-DPAT. They were decapitated and their heads were placed in formalin. At least 10 days later, the brains were removed and the injection sites verified with coarse sectioning by comparison with the stereotaxic atlas (19). The spread of the india ink infusion was easy to see; it never exceeded the NAC.

Systemic administration of 7-OH-DPAT: Effect on locomotion. The remaining 10 rats were then used. Before and between testing they were housed in small groups, but otherwise treated exactly the same as the rats that took part in the intracerebral administration studies. Solutions of 0.1, 0.3, 1.0, and 3.0 mg/ml 7-OH-DPAT were blind coded A–E (including vehicle), and all the rats received all doses. The same open-field apparatus as before was used. Rats were allowed 3 days' preexposure to the apparatus of 30 min/day. On Mondays, Wednesdays, and Fridays, the rats were injected IP and placed immediately into the apparatus, where the light beam interruptions were recorded every 5 min for 30 min. As before, the rats were observed by DBG for any signs of hyperlocomotion, stereotypic responses, or drug-induced yawning. At the end of testing with 7-OH-DPAT the code was broken. Finally, the rats received 3 mg/kg *d*-amphetamine IP as a positive control.

Data Analysis

The data were analysed using analysis of variance (ANOVA), followed by Dunnett's *t*-test, comparing a given dose with vehicle at a given time, where appropriate.

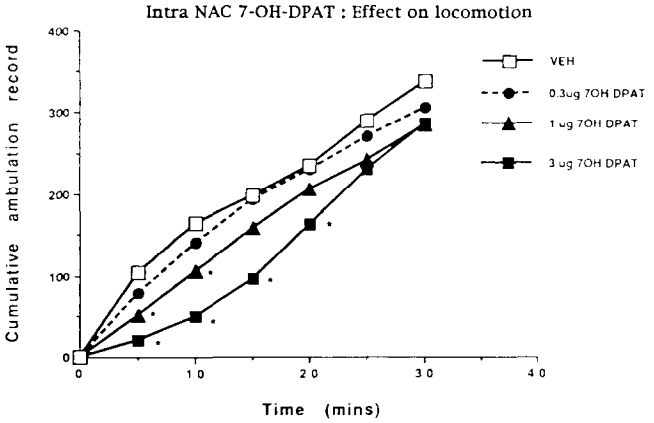

FIG. 1. 7-OH-DPAT (0.3–3.0 μg total dose) injected into the NAC induces profound, but short-lasting hypolocomotion in a dose-dependent way. *$p < 0.05$ compared to vehicle administration. (SEs were 10–20 counts per data point but are not shown for the sake of clarity). $n = 12$.

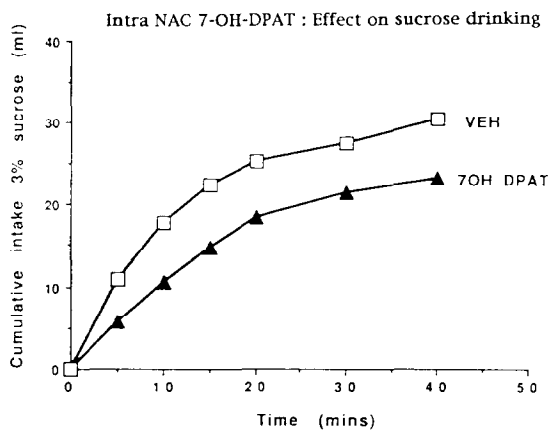

FIG. 2. 7-OH-DPAT (1.0 mg total dose) injected into the NAC reduces intake of palatable, 3% sucrose solution in 12 nondeprived rats. ANOVA revealed that at each time point in the drug condition, animals drank significantly less than in the vehicle condition ($p < 0.05$). (SEs were 1–3 ml, but are not shown for the sake of clarity).

RESULTS

Effect of Intra-Accumbens 7-OH-DPAT on Locomotion

Following vehicle administration, the rats interrupted the light beams about 100 times in the first 5 min, and thereafter at a steady rate of about 50 crossings/5 min (Fig. 1). Intra-accumbens 7-OH-DPAT significantly reduced this locomotion in a dose-dependent way (Fig. 1). The effect was greatest at 10 min and had completely disappeared by 25 min. After 10 min, the 7-OH-DPAT-induced reduction in ambulation was 43 and 70% after doses of 1 and 3 μg, respectively. The rats were not catatonic. They were not stiff-limbed and they could move if gently prodded. No rat showed signs of hyperlocomotion or obvious stereotyped responses at any time or any dose; neither did any rat exhibit drug-induced yawning.

Effect of Intra-Accumbens 7-OH-DPAT on Sucrose Ingestion

Figure 2 shows that following 1 μg 7-OH-DPAT (total dose; i.e., 0.5 μg/hemisphere), the rats drank significantly less sucrose than did vehicle-injected rats. The effect was greatest at 10 and 15 min post-drug administration. After this point, the rats drank at the same rate in the 7-OH-DPAT and vehicle conditions.

Effect of IP 7-OH-DPAT on Locomotion

Intraperitoneal 7-OH-DPAT (0.1–3.0 mg/kg) induced significant hypolocomotion (Fig. 3). There was no sign whatsoever of hyperlocomotion. No animal exhibited behavioural stereotypy after any dose of 7-OH-DPAT, nor did any rat yawn. Following amphetamine (3.0 mg/kg, IP), the rats showed profound hyperlocomotion (Table 1) and all of the signs of behavioural stereotypy normally associated with a moderate dose of that drug (e.g., exessive sniffing and some rearing), although these were not formally recorded.

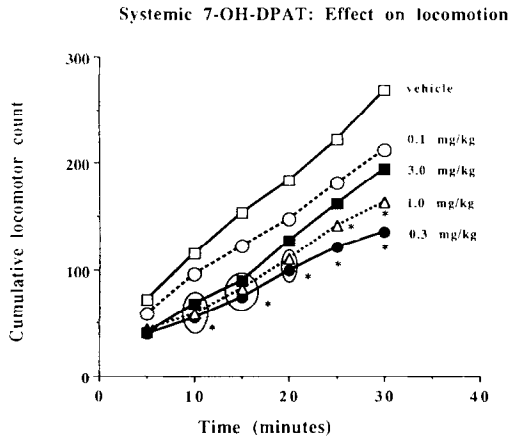

FIG. 3. 7-OH-DPAT (0.1–3.0 mg/kg, IP) given immediately before testing induces only hypolocomotion. The test was as before (n = 10). *$p < 0.05$ compared to vehicle. (SEs were 15–20 counts per data point but are not shown for the sake of clarity). There was no sign of hyperlocomotion or any stereotyped responding. In the same animals, *d*-amphetamine (3.0 mg/kg, IP) induced profound hyperlocomotion two to three times the vehicle count, as well as stereotyped rearing and sniffing (see Table 1).

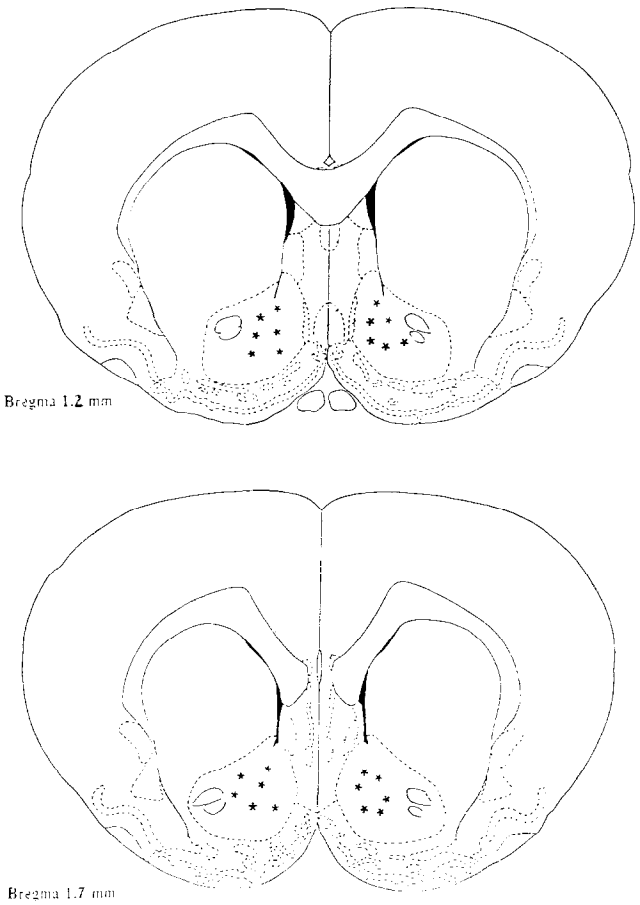

FIG. 4. In every case the tip of the injection cannula was in the NAC. The distribution of the cannulae tips was restricted and within 1 mm^3 of the target site, just lateral to the anterior commissure. [Figure adapted from Paxinos and Watson (19).]

Cannula Placement Verification

Figure 4 shows that all of the injection sites were within the NAC; all were within 1 mm^3 of the target, just lateral to the anterior commissure.

DISCUSSION

7-OH-DPAT (0.3–3.0 μg) introduced intracerebrally to the NAC induced a profound but short lasting hypolocomotion (Fig. 1). It failed to induce hyperlocomotion at any dose tested (but the possibility exists that a subtle, late, but long-lasting hyperlocomotion may have been missed by our 30-min test). This observation is in agreement with an earlier study, where 7-OH-DPAT was introduced into the NAC (24), although in that early report, the authors did not consider D_3 activity for 7-OH-DPAT which, to further confuse the matter, was at that time referred to as DP-7-ATN. Previous work has shown that injecting DA and more general DA agonists into the NAC induces increased locomotion (3,6,20,32) and stereotyped responses (23). These stimulant effects of DA and *d*-amphetamine were blocked by DA antagonists that commonly blocked D_2 receptors (4,5,21–23). Second, it has been reported that a low dose of apomorphine injected into the NAC results in reduced locomotion (32), and apomorphine has been reported to have equal affinity for the D_2 and D_3 receptor (28,29). Third, a recent review concluded that hyperlocomotion and stereotypic behaviour occurs as a result of D_2 (or mixed D_1/D_2) receptor stimulation (34). Therefore, these three lines of evidence support the idea that the hypolocomotion seen after intraaccumbens 7-OH-DPAT is mediated at D_3 and not at D_2 receptors.

The hypolocomotion seen after IP administration of 7-OH-

TABLE 1

EFFECT OF 3 mg/kg *d*-AMPHETAMINE (IP) ON LOCOMOTION

Time (min)	5	10	15	20	25	30
Vehicle	72 ± 9.8	43 ± 7	39 ± 4.6	31 ± 4.4	37 ± 5.5	47 ± 5.6
d-AMPH	114 ± 8.3*	77 ± 6.4†	119 ± 11.4*	176 ± 24*	166 ± 26*	171 ± 32*

d-Amphetamine (3.0 mg/kg IP) given immediately before rats were placed in the apparatus induces characteristic marked hyperlocomotion. Scores are the mean number of light beam crossings per 5 min (n = 10) ± SE.

*$p < 0.01$, †$p < 0.05$, compared to vehicle.

DPAT (Fig. 3) concurred with the results from the central administration study and confirm previous findings with D_3 receptor stimulation (1,7,31,37). Again, at no time following any dose of 7-OH-DPAT did the the rats show stereotyped movement or hyperlocomotion, again suggesting that this agent has no appreciable effect at D_2 or D_1 with D_2 receptors. It is hard to reconcile the current data with the one report that 7-OH-DPAT is like apomorphine in that it induces hyperlocomotion (17). It is possible that strain differences can account for the difference, although our rats responded perfectly as expected when challenged with *d*-amphetamine (Table 1). As well as confirming the majority of studies that reported 7-OH-DPAT-induced hypolocomotion (1,7,31,37), the present study may indicate that reduced activity seen after systemic 7-OH-DPAT is mediated by D_3 receptors in the NAC.

Following an infusion of 1 μg 7-OH-DPAT to the NAC, the rats drank significantly less of a preferred 3% sucrose (Fig. 3). This is the first example of the effects of D_3 receptor stimulation on an ingestive response. A previous paper reported that a low dose of apomorphine injected into the NAC reduced feeding (32); this effect was suggested to be mediated at DA autoreceptors. There has been previous discussion on how apomorphine also stimulates D_3 receptors (29). It has previously been suggested that 7-OH-DPAT may reduce cocaine-induced reward (2), and the current observations indicate that 7-OH-DPAT may act to reduce the hedonic properties of ingesting 3% sucrose solution. Clearly, however, our current observations do not exclude the possibility of a general behavioural effect of 7-OH-DPAT, as distinct from a specific effect to reduce the reward value of significant stimuli.

Taken together, the current data are consistent with the idea that this D_3 agonist acts specifically at DA autoreceptors, and therefore, that not all autoreceptors are of the D_2 subtype. The data do not entirely rule out the possibility that the hypolocomotion seen following 7-OH-DPAT administration is mediated via a population of postsynaptic D_3 receptors (31,37); however, the postsynaptic hypothesis seems to us to be a less plausible notion. Work with lesions of the presynaptic dopaminergic innervation of the NAC (which should abolish the DA-reducing effect of 7-OH-DPAT) may resolve this issue.

In a parallel study, we have shown voltammetrically that 7-OH-DPAT acts quickly to reduce an electrically stimulated DA-generated voltammetric signal (Gilbert, Millar, and Cooper, in press). Briefly, in our parallel study we adopted an in vivo procedure and showed reduced NAC DA in response to electrical stimulation of the ventral tegmental area following systemic 7-OH-DPAT; this effect was not affected by the D_2-specific DA antagonist, sulpiride. Moreover, a recent study with microdialysis supports our voltammetric findings; that report found that (+)7-OH-DPAT had a high affinity for D_3, but not D_2 receptors (25). Thus, taken together, the evidence suggests to us that the present results indicate that 7-OH-DPAT stimulates autoreceptors, which may be D_3 receptors, without stimulating postsynaptic D_2 receptors. However, the current results cannot rule out the possibility that presynaptic D_2 receptors may at least in part mediate the effects of 7-OH-DPAT, although this possibility seems unlikely to us.

We found no evidence of drug-induced yawning in any of these studies, confirming two previous reports where no D_3 receptor-mediated yawning was noted (7,31). In contrast, there are at least two studies in which some doses of 7-OH-DPAT were found to induce yawning (1,8). It appears that with respect to yawning, 7-OH-DPAT is effective only at a narrow dose range around 0.1 mg/kg systemically. With quinpirole-induced yawning, it has also been suggested that dopamine agonist-induced yawning is a D_3-mediated event (13). Where there is uncertainty about which receptors are involved in DA agonist-induced yawning [e.g., (9,13,30] and whether D_3 receptors are presynaptic (18,25), postsynaptic (31,37), or both (8,27), it may be that comparative yawning studies with the latest D_2 and D_3 agents will provide fruitful insight into these questions.

In summary, we suggest that 7-OH-DPAT reduces locomotion and sucrose ingestion by acting at a population of DA autoreceptors; the evidence is mounting that they are probably of the D_3 subtype. These autoreceptors are found in the NAC, but further work is required to determine whether there are other specific locations for them. They may prove significant in the study of drug-induced reward and of reward in general.

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