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ORIGINAL INVESTIGATION

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# Effects of intranucleus accumbens shell administration of dopamine agonists and antagonists on cocaine-taking and cocaine-seeking behaviors in the rat

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**Abstract** *Rationale:* Dopamine signaling in the nucleus accumbens (NAc) plays an important role in regulating drug-taking and drug-seeking behaviors, but the role of $D_1$- and $D_2$-like receptors in this regulation remains unclear. *Objectives:* Our objective was to study the role of NAc $D_1$- and $D_2$-like receptors in the reinstatement of cocaine-seeking behavior and the regulation of stabilized cocaine intake in rats. *Methods:* Using a within-session reinstatement procedure, whereby animals self-administer cocaine (90 min) and extinguish responding (150 min) in a single session, we assessed the ability of NAc microinfusions of the $D_1$ agonist SKF 81297 and the $D_2$ agonist 7-OH-DPAT to reinstate extinguished cocaine seeking. The effects of the $D_1$ antagonist SCH 23390 and the $D_2$ antagonist eticlopride pretreatment on agonist- and cocaine-primed reinstatement were also measured. Similar agonist and antagonist treatments were tested for their ability to modulate stabilized cocaine and sucrose self-administration. *Results:* Intra-NAc infusions of either SKF 81297 (0.3–3.0 μg) or 7-OH-DPAT (1.0–10.0 μg) dose-dependently reinstated cocaine seeking with greater efficacy in the medial core than in the shell subregion and at doses that also stimulated locomotor behavior. Intra-NAc shell infusions of SCH 23390 (1.0 μg) and eticlopride (3.0–10.0 μg) blocked cocaine-primed reinstatement (2.0 mg/kg, i.v.) and indiscriminately blocked reinstatement induced by either intra-NAc $D_1$ or $D_2$ agonists. Doses of agonists that triggered reinstatement failed to alter stabilized cocaine intake, whereas doses of antagonists that blocked reinstatement increased cocaine intake in the shell. *Conclusions:* Both $D_1$ and $D_2$ receptors in the NAc play a prominent, and perhaps cooperative, role in regulating cocaine-taking and cocaine-seeking behaviors.

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## Introduction

Dopamine $D_1$ and $D_2$ receptors mediate opposite effects on the reinstatement of cocaine-seeking behavior after extinction of cocaine self-administration. Thus, in rodent studies, selective stimulation of $D_2$ receptors is sufficient to strongly induce cocaine-seeking behavior, whereas selective stimulation of $D_1$ receptors is virtually without effect, even at equipotent locomotor-activating doses (Wise et al. 1990; Self et al. 1996; De Vries et al. 1999; Dias et al. 2004). Moreover, stimulation of $D_1$ receptors completely attenuates cocaine's ability to reinstate cocaine seeking, whereas stimulation of $D_2$ receptors facilitates cocaine-induced reinstatement (Self et al. 1996; Alleweireldt et al. 2002). This $D_1/D_2$ dichotomy also regulates cocaine seeking in nonhuman primates (Spealman et al. 1999; Khroyan et al. 2000) and may regulate craving responses in humans (Haney et al. 1998, 1999).

In the nucleus accumbens (NAc), $D_1$ and $D_2$ receptors are differentially expressed in distinct subpopulations of NAc neurons that project to different brain regions (Aubert et al. 2000; Lu et al. 1998; Steiner and Gerfen 1998), although there is evidence for colocalization in the same neurons (Aizman et al. 2000; Schwartz et al. 1998). $D_1$ and $D_2$ receptors also differ in their ability to couple stimulatory and inhibitory G-proteins that differentially regulate adenylyl cyclase activity (Lachowicz and Sibley 1997). These anatomical and functional differences suggest that $D_1$ and $D_2$ receptors in the NAc could contribute to the differential regulation of cocaine-seeking behavior found with systemic administration of $D_1$ and $D_2$ receptor agonists.

Previous studies have shown that dopamine receptors in the NAc have both necessary and sufficient roles in reinstating cocaine-seeking behavior in rats. Thus, intra-NAc microinfusions of dopamine reinstate cocaine seeking

(Cornish and Kalivas 2000), and NAc infusions of a $D_1$ antagonist block cocaine seeking induced by systemic priming injections of cocaine, but only when infused in the NAc shell, and not the core, subregion (Anderson et al. 2003). However, the relative ability of NAc $D_1$ and $D_2$ receptors to induce reinstatement is unknown.

Similarly, $D_1$ and $D_2$ dopamine receptors in the NAc may have an important role in regulating cocaine intake during self-administration when access to cocaine is relatively unrestricted (e.g., low fixed ratio reinforcement schedules). Thus, pretreatment with NAc infusions of either $D_1$ or $D_2$ receptor antagonists increases cocaine self-administration in a manner resembling reducing the injection dose in rats (Phillips et al. 1983; Maldonado et al. 1993; McGregor and Roberts 1993; Caine et al. 1995). Conversely, reverse dialysis of dopamine into the NAc, at concentrations similar to that achieved during cocaine self-administration, decreases cocaine intake (Hurd and Ponten 2000), but it is unclear whether local stimulation of either $D_1$ or $D_2$ receptors in the NAc is sufficient to produce a similar rate-decreasing effect.

We compared the ability of intra-NAc infusions of the $D_1$-selective agonist SKF 81297 (>500-fold $D_1/D_2$; Andersen and Jansen 1990) and the $D_2$-selective agonist 7-OH-DPAT (>1,000-fold $D_{2-3}/D_1$; Levesque et al. 1992; Gonzalez and Sibley 1995; Levant et al. 1996) to reinstate cocaine-seeking behavior. We utilized microinfusions in both the medial core and the shell subregion to determine whether local dopamine receptor activation would exhibit the same subregion specificity found with receptor blockade. We also compared the ability of the $D_1$-selective antagonist SCH 23390 (>1,000-fold $D_1/D_2$; Andersen 1988) and the $D_2$-selective antagonist eticlopride (>100,000-fold $D_2/D_1$; Hall et al. 1986) to block agonist- and cocaine-primed reinstatement of cocaine seeking when infused into the NAc shell. In addition, we determined whether doses of agonists and antagonists that were effective in modulating reinstatement would also modulate stabilized cocaine intake during self-administration when infused into the NAc shell.

## Materials and methods

### Animals and housing conditions

Male Sprague–Dawley rats initially weighing 275–325 g (Charles River Laboratories, Kingston, NY) were individually housed in wire cages with food and water available ad libitum, except during sucrose pellet self-administration. Experiments were conducted during the light cycle of a 12:12-h light:dark cycle (lights on at 0700 hours) in accordance with guidelines established by the National Institute of Health and the Institutional Animal Care and Use Committee at the University of Texas Southwestern Medical Center.

### Surgical procedures and apparatus

To facilitate the acquisition of operant behavior, all rats were initially food-restricted to prevent weight gain and were trained to lever-press for sucrose pellets on a fixed ratio 1 (FR1) reinforcement schedule until acquisition criteria had been achieved (100 sucrose pellets for three consecutive tests). After lever-press training, animals were fed ad libitum for at least 1 day and were surgically implanted with a chronic intrajugular catheter and 26-gauge bilateral intracerebral guide cannulae, as previously described (Self et al. 1998). Guide cannulae were aimed at the NAc core (±1.5 mm lateral) or shell (±0.8 mm lateral) subregions positioned 1.7 mm anterior to bregma and −5.7 mm ventral to dura with level skull (Paxinos and Watson 1998). Dummy cannulae (33 gauge), cut to extend 1 mm beyond the guide cannulae, were left in place throughout the experiment. Animals were allowed 5–7 days to recover before experimentation. Self-administration and reinstatement testing were performed in operant test chambers (Med-Associates, East Fairfield, VT) equipped with two response levers and an infusion pump system as described (Self et al. 1998).

### Microinfusion procedure

Prior to intracranial infusions, dummy cannulae were removed; infusions of 0.5 μl/side were administered through bilateral 33-gauge injection cannulae extending 1 mm beyond the tip of the guide over a 100-s period; and injection cannulae were left in place for 30 s to allow for diffusion into brain tissues before removal. Each intra-NAc treatment was separated by a minimum of 2 days of training to reestablish baseline performance. Animals received a maximum of 8–10 intracranial infusions to avoid excess tissue damage at the injection site.

### Cocaine self-administration procedure

Following recovery from surgery, lever-trained animals performed cocaine self-administration in daily 4-h sessions for 5–6 days/week. A single lever-press response (FR1) at the active lever produced a 0.5-mg/kg intravenous (i.v.) injection of cocaine delivered in 0.1 ml over 5 s, concurrent with illumination of a cue light located above the lever while house light was extinguished. Each injection was followed by an additional 10-s "time-out" (TO) period when the house light remained off; active lever-press responses during the injection–TO period (15 s) had no scheduled consequence. Responses on the inactive lever were recorded but also had no consequence.

After a minimum of 10 cocaine self-administration sessions, the sessions were reduced to 90 min and animals demonstrating stable self-administration baselines (injec-

tion totals varied by <10% from the mean of three consecutive sessions) were given intra-NAc infusions of $D_1$ or $D_2$ agonists and antagonists as pretreatments immediately prior to the test session. In these experiments, animals were assigned to various treatment groups such that the mean baseline self-administration rates in each group were similar. The $D_1$ agonist SKF 81297 (3.0 μg/side) and the $D_2$ agonist 7-OH-DPAT (10.0 μg/side) were tested at doses that were maximally effective in reinstatement testing. Similar effective doses of the $D_1$ antagonist SCH 23390 (3.0 μg/side) and the $D_2$ antagonist eticlopride (10.0 μg/side) were tested based on results from reinstatement tests. Since these antagonist doses produced positive effects on cocaine intake, lower doses of both SCH 23390 (0.5 and 1.0 μg/side) and eticlopride (1.0 and 3.0 μg/side) were used to determine dose thresholds.

### Reinstatement procedure

After a minimum of 10 cocaine self-administration sessions, animals were trained in a daily 4-h within-session reinstatement procedure. In this procedure, cocaine (0.5 mg/kg per injection) was available for the first 90 min of the session, followed by an extinction phase lasting 150 min when drug-paired lever responding produced only the injection cue light–TO sequence. Animals were trained in this procedure until responding during the final 60 min of the session had met extinction criteria (five responses or less at either lever for three consecutive daily sessions). The ability of intra-NAc infusions of phosphate-buffered saline (PBS), the $D_1$ agonist SKF 81297 (0.3 and 3.0 μg/side), or the $D_2$ agonist 7-OH-DPAT (1.0 and 10.0 μg/side) to reinstate drug-paired lever responding was measured in extinguished animals by removing them from the test chambers 5 min prior to the final hour of the test session, administering the intra-NAc infusion, and returning the animals to the test chambers, where the number of non-reinforced lever-press responses was recorded. In other experiments, the ability of intra-NAc infusions of the $D_1$ antagonist SCH 23390 (0.3 and 1.0 μg/side) or the $D_2$ antagonist eticlopride (1.0, 3.0, and 10.0 μg/side) to block cocaine-induced reinstatement was tested by infusing the antagonist immediately prior to a priming injection of 2.0 mg/kg of cocaine administered intravenously in 0.4 ml over 20 s. In addition, the ability of $D_1$ (SCH 23390, 1.0 μg/side) or $D_2$ (eticlopride, 10.0 μg/side) antagonists to block $D_1$ (SKF 81297, 3.0 μg/side) or $D_2$ (7-OH-DPAT, 10.0 μg/side) agonist-induced reinstatement was tested by sequential intra-NAc administration of antagonists and agonist infusions (combined volume 1.0 μl). Most animals in both self-administration and reinstatement experiments were tested with at least two different agonist or antagonist treatment regimens, counterbalanced for dose order (within treatment) and test drug (between treatments) across animals such that no two experiments were composed of the same animals.

### Locomotor activity procedure

Locomotor activity was conducted in eight cocaine-trained animals 1 week after their last reinstatement test. Locomotor activity was assessed in a circular corridor (a 12-cm-wide runway) equipped with four photocell detectors located equidistantly at 90° intervals around the 1.95-m circumference. Each 6-h locomotor activity test session was divided into three 120-min phases (habituation, vehicle infusion, and dopamine agonist infusion). Following the habituation phase, animals were removed from the test chambers, given intra-NAc infusions of PBS, and returned to the chambers. Locomotor activity was then recorded for 120 min. After 2 h, animals were removed again, given intra-NAc infusions of either the $D_1$ (SKF 81297, 3.0 μg/side) or $D_2$ (7-OH-DPAT, 10.0 μg/side) agonist at a dose that was determined to be maximally effective in reinstatement tests, and returned to the chambers for the final 120 min of testing. Each animal was given both the $D_1$ and $D_2$ agonists on consecutive days in a counterbalanced order.

### Sucrose self-administration procedure

Animals were surgically implanted with only the intra-NAc guide cannulae as described above and subsequently maintained on a restricted diet (fed after each daily test session) to prevent weight gain over the course of testing. Following acquisition of lever-press behavior (FR1) as described above, animals self-administered 50 sucrose pellets in daily sessions and were tested with intra-NAc infusions after response rates had stabilized (the time to self-administer 50 pellets varied by <20% of the mean of three consecutive tests). On the test day, animals were given bilateral intra-NAc infusions of SKF 81297 (3.0 μg/side), 7-OH-DPAT (10.0 μg/side), SCH 23390 (0.5, 1.0, and 3.0 μg/side), or eticlopride (1.0, 3.0, and 10.0 μg/side), corresponding to doses tested in cocaine self-administration experiments. Doses and test drugs were counterbalanced across animals as described above.

### Histological verification

Nucleus accumbens infusion sites were determined in chloral-hydrate-anesthetized (400 mg/kg, i.p.) animals by infusing 0.5 μl of cresyl violet dye through bilateral injection cannulae as described above. Animals were immediately decapitated, brains were removed, and 0.8-mm-thick coronal slices were collected throughout the forebrain and analyzed under a dissecting microscope for the location of infusion sites according to the stereotaxic coordinates of Paxinos and Watson (1998). Micrographs for core and shell infusion sites were taken from cresyl-violet-stained brain sections (40 um) in animals that received nine NAc infusions of PBS, SKF 81297 (2×0.3 and 3.0 μg/side),

and 7-OH-DPAT (2×1.0 and 10.0 μg/side), at least 2 days apart, prior to perfusion with formalin.

### Data analysis

Self-administration and reinstatement data were analyzed with between-subject statistical analyses, since some animals exhibited catheter failure or failed to recover baseline response rates before completing all test doses within a treatment condition. Reinstatement data for each agonist in the core and shell subregions were analyzed using a three-factor region × dose × lever analysis of variance (ANOVA) with repeated measures on lever (drug-paired vs inactive). Subsequent reinstatement experiments in the NAc shell used a two-factor dose/drug × lever ANOVA with repeated measures on lever. Cocaine and sucrose self-administration data were analyzed with a two-factor dose/drug × treatment ANOVA with repeated measures on treatment (baseline vs treatment). Locomotor time course data following PBS and agonist infusions were pooled into 1-h bins (expressed as a percentage of baseline activity; photocell counts in the 1-h period preceding each infusion) and analyzed by two-factor region × time bin ANOVA with repeated measures on time bin. Interactive effects were followed by simple main effects analyses and post hoc tests with Dunnett's test (compared to PBS or the lowest inactive dose), Fisher's least significant difference (LSD) test (when multiple control groups were present), or Student's paired *t* tests, corrected for multiple comparisons (drug-paired vs inactive lever or baseline vs test day) where appropriate. Statistical significance was preset at $p<0.05$.

### Drugs

SKF 81297 [(±)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide], 7-OH-DPAT [(+)-7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin], SCH 23390 [*R*-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine], and eticlopride [*S*(−)-3-chloro-5-ethyl-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-6-hydroxy-2-methoxybenzamide hydrochloride] were purchased from Sigma (St. Louis, MO). All drugs were dissolved in PBS (pH 5.5) vehicle. Cocaine hydrochloride was obtained from the National Institute on Drug Abuse (Research Triangle Park, NC) and was dissolved in sterile-filtered physiological saline.

## Results

### NAc infusions of $D_1$ or $D_2$ receptor agonists reinstate cocaine-seeking behavior

Table 1 shows that cocaine self-administration baselines in the first 90 min of the within-session reinstatement procedure were similar across treatment conditions for experiments shown in Figs. 1, 3, and 4. Figure 1 shows that intra-NAc infusions of the $D_1$ agonist SKF 81297 dose-dependently and selectively reinstated drug-paired lever responding (dose × lever, $F_{2,80}=10.365$, $p<0.001$), with greater effects in the core than in the shell subregion (region × lever, $F_{1,80}=12.247$, $p=0.001$; effect of region, $F_{1,80}=10.184$, $p<0.01$). A subsequent analysis of interactive effects found that both 0.3- and 3.0-μg/side doses of SKF 81297 increased drug-paired lever responding in the shell ($F_{2,44}=7.53$, $p<0.01$) and in the core ($F_{2,36}=5.67$, $p<0.01$) when compared to PBS-infused controls. NAc infusions of the $D_2$ agonist 7-OH-DPAT also induced selective drug-paired lever responding in a dose-dependent manner (dose × lever, $F_{2,65}=7.858$, $p=0.001$), again with greater effects in the core than in the shell subregion (region × lever, $F_{1,65}=13.518$, $p<0.05$; effect of region, $F_{1,65}=6.611$,

**Table 1** Mean number of cocaine self-injections during the 90-min self-administration phase of the within-session reinstatement procedure

| Dopamine agonist reinstatement | Previous day mean (±SEM) | Treatment day mean (±SEM) |
|---|---|---|
| Shell | | |
| PBS vehicle | 27.0 (1.45) | 27.6 (1.73) |
| 0.3 μg of SKF 81297 | 28.64 (1.4) | 31.5 (3.34) |
| 3.0 μg of SKF 81297 | 25.87 (1.7) | 26.87 (1.5) |
| PBS vehicle | 27.4 (1.49) | 27.6 (1.73) |
| 1.0 μg of 7-OH-DPAT | 27.56 (1.64) | 29.46 (1.55) |
| 10.0 μg of 7-OH-DPAT | 30.71 (2.1) | 30.67 (2.38) |
| Core | | |
| PBS vehicle | 32.2 (2.48) | 35.73 (3.19) |
| 0.3 μg of SKF 81297 | 33.9 (2.87) | 34.91 (3.15) |
| 3.0 μg of SKF 81297 | 37.11 (5.42) | 35.39 (4.16) |
| PBS vehicle | 33.2 (2.49) | 34.73 (3.19) |
| 1.0 μg of 7-OH-DPAT | 38.0 (4.6) | 37.0 (3.16) |
| 10.0 μg of 7-OH-DPAT | 32.2 (3.95) | 35.42 (4.6) |
| **Dopamine antagonist–cocaine reinstatement** | **Saline mean (±SEM)** | **Cocaine mean (±SEM)** |
| PBS vehicle | ND | 32.33 (1.90) |
| 0.3 μg of SCH 23390 | 33.62 (1.21) | 33.30 (1.64) |
| 1.0 μg of SCH 23390 | 30.5 (1.78) | 30.0 (1.93) |
| 1.0 μg of eticlopride | 30.7 (1.66) | 31.8 (2.19) |
| 3.0 μg of eticlopride | 31.88 (2.85) | 31.69 (2.02) |
| 10.0 μg of eticlopride | 30.67 (3.06) | 32.36 (1.08) |
| **Dopamine antagonist–agonist reinstatement** | **3.0 SKF 81297 mean (± SEM)** | **10.0 7-OH-DPAT mean (± SEM)** |
| PBS vehicle | 35.33 (2.21) | 38.83 (3.38) |
| 3.0 μg of SCH 23390 | 37.0 (3.54) | 34.73 (2.39) |
| 10.0 μg of eticlopride | 40.33 (1.56) | 40.78 (2.91) |

Values represent mean cocaine self-injections (±SEM) prior to the reinstatement test and on the previous day of baseline testing (agonist alone)
*ND* Not determined

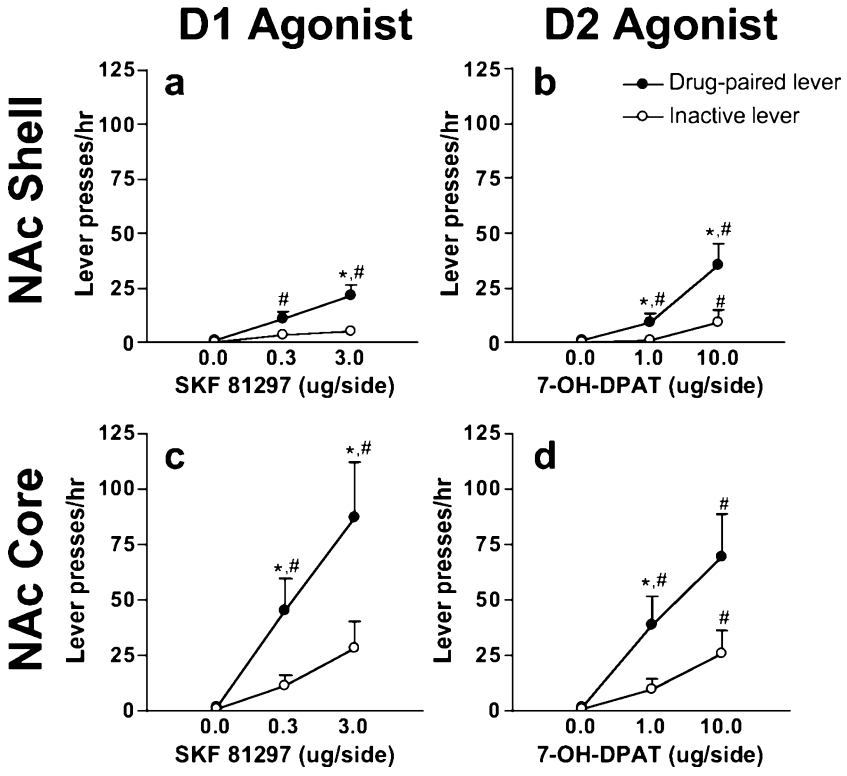


**Fig. 1** Intra-NAc infusions of the $D_1$ receptor agonist SKF 81297 and the $D_2$ receptor agonist 7-OH-DPAT dose-dependently increase drug-paired lever responding in both the shell (**a**, **b**) and the core (**c**, **d**) subregions in a within-session reinstatement procedure. Data represent the mean±SEM for $n$=11–20 animals/treatment for SKF 81297 and $n$=10–13 for 7-OH-DPAT. *$p$<0.05 compared to inactive lever responses (paired $t$ test); $^{\#}p$<0.05 compared to PBS-infused controls (Dunnett's test)

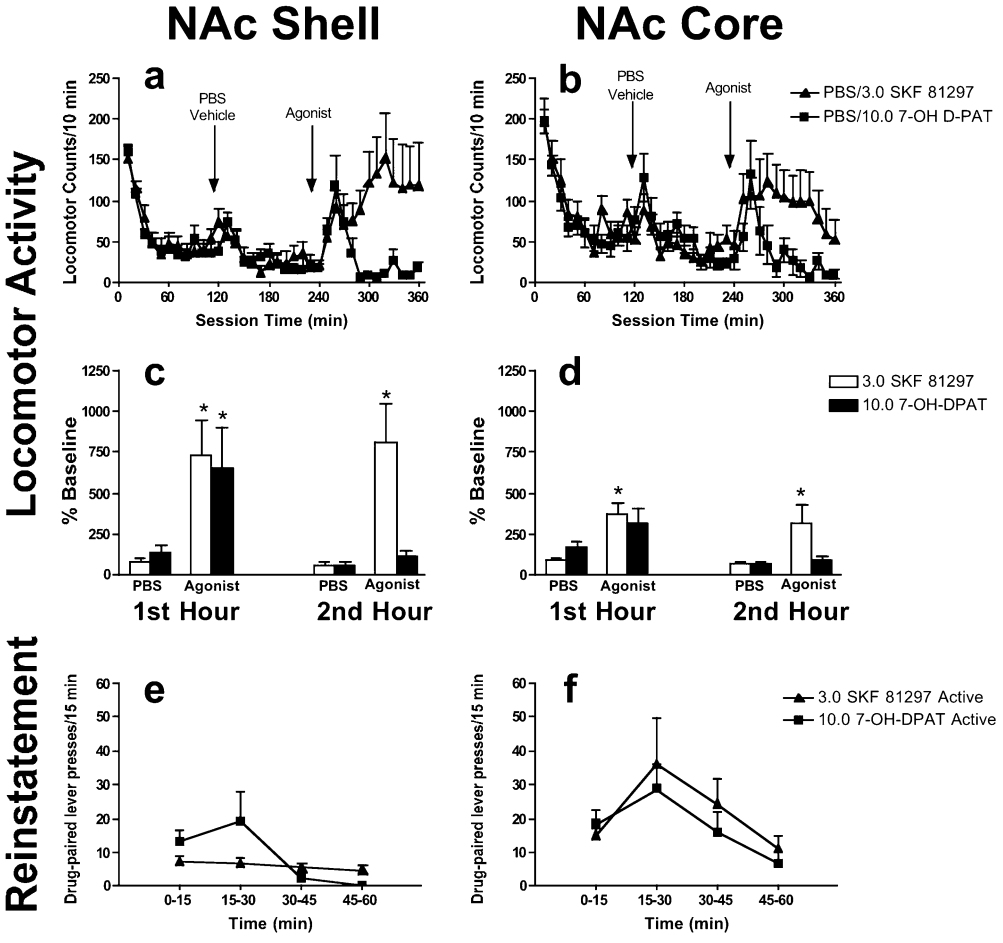


**Fig. 2** **a**, **b** Time course of locomotor activation shows that the $D_1$ agonist SKF 81297 (3.0 μg/side) produces enduring locomotor activation compared to transient increases following the $D_2$ agonist 7-OH-DPAT (10.0 μg/side) when infused in both the shell and the core subregions. **c**, **d** Pooled hourly data from **a** and **b** expressed as percent baseline locomotor activity in the 1 h preceding each infusion. Data represent the mean±SEM for $n$=8 animals in each treatment condition. *$p$<0.05 compared to PBS infusions (Fisher's LSD test). **e**, **f** Temporal differences in locomotor activation are paralleled by transient (7-OH-DPAT) and sustained (SKF 81297) reinstatement of cocaine seeking with NAc shell infusions, but only transient reinstatement is found with core infusions (data from Fig. 1 are shown in 15-min time bins)

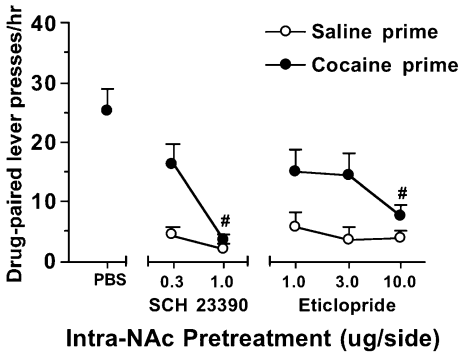


**Fig. 3** NAc shell infusions of the $D_1$ receptor antagonist SCH 23390 and the $D_2$ receptor antagonist eticlopride dose-dependently block cocaine-primed reinstatement of cocaine seeking (2.0 mg/kg, i.v.). Data represent the mean±SEM for $n$=20 animals for PBS/cocaine and $n$=8–14 for antagonist pretreatments. $^{\#}p<0.05$ compared to PBS-infused cocaine-primed controls (Dunnett's test)

$p<0.05$). Both 1.0- and 10.0-μg/side doses of 7-OH-DPAT infusions increased drug-paired lever responding in the shell ($F_{2,32}$=9.67, $p$=0.001) and in the core ($F_{2,33}$=6.49, $p<0.01$).

The highest dose of 7-OH-DPAT increased inactive lever responding above PBS control levels in the shell ($F_{2,32}$=3.32, $p<0.05$) and in the core ($F_{2,33}$=3.65, $p<0.05$). However, drug-paired lever responding exceeded inactive lever responding at both doses of 1.0 μg/side ($t_{12}$=2.79, $p<0.05$) and 10.0 μg/side ($t_9$=4.79, $p<0.01$) in the shell and at the lower 1.0-μg/side dose in the core ($t_{11}$=3.23, $p<0.05$). In contrast, SKF 81297 did not increase inactive lever responding above PBS-infused controls, and drug-paired lever responding exceeded inactive lever responding at the higher 3.0-μg/side dose in the shell ($t_{19}$=3.88, $p<0.01$) and at both doses of 0.3 μg/side ($t_{12}$=2.92, $p<0.05$) and 3.0 μg/side ($t_{13}$=3.86, $p<0.01$) in the core.

The reinstating effects of intra-NAc $D_1$ and $D_2$ agonists were compared with their ability to stimulate unconditioned locomotor activity in cocaine-trained animals tested in environmentally distinct locomotor test chambers. Figure 2 shows that the maximally effective doses of SKF 81297 (3.0 μg/side) and 7-OH-DPAT (10.0 μg/side) in reinstatement also stimulated locomotor activity, but with substantially different temporal profiles. NAc infusions of the $D_2$ agonist 7-OH-DPAT increased locomotor activity when infused into both the core and the shell (effect of treatment, $F_{3,42}$=7.995, $p<0.001$), but with no difference between brain regions. 7-OH-DPAT-induced locomotion was transient in the shell ($F_{3,21}$=4.87, $p<0.01$) and in the core ($F_{3,21}$=4.632, $p<0.05$), since effects dissipated to PBS control levels by the second hour after infusion. The $D_1$ agonist SKF 81297 also induced similar locomotor activity in both the core and the shell (effect of treatment, $F_{3,42}$=10.439, $p<0.001$). However, in contrast to 7-OH-DPAT, SKF-81297-induced locomotor activity endured for at least 2 h after infusion into either the shell ($F_{3,21}$=6.54, $p<0.01$) or the core ($F_{3,21}$=6.06, $p<0.01$). Although the absolute locomotor response to both agonists did not differ between subregions (Fig. 1a and b), the relative increase in locomotion appeared greater in the shell due to a somewhat lower baseline activity (1 h preceding infusion) in shell-cannulated animals (Fig. 2c and d).

The temporal profile of reinstatement produced by the $D_1$ and $D_2$ agonists in the NAc shell paralleled the profile of locomotor stimulation (Fig. 2e). Thus, infusions of SKF 81297 (3.0 μg/side) produced a low but sustained drug-paired lever responding throughout the 1-h reinstatement test session, whereas 7-OH-DPAT (10.0 μg/side) produced a transient but more robust drug-paired lever responding that peaked 15–30 min postinfusion. In the core, infusion of SKF 81297 induced transient increases in reinstatement that peaked after 15–30 min while locomotor stimulation endured, whereas 7-OH-DPAT transiently increased both reinstatement and locomotor activity (Fig. 2f).

## NAc shell infusions of $D_1$ or $D_2$ receptor antagonists block cocaine-induced reinstatement

Figure 3 shows that pretreatments with NAc shell infusions of either the $D_1$ antagonist SCH 23390 or the $D_2$ antagonist eticlopride dose-dependently attenuated cocaine-seeking induced by an i.v. priming injection of cocaine, producing a significant pretreatment × lever interaction ($F_{9,121}$=5.15, $p<0.001$) and main effects of pretreatment ($F_{9,121}$=6.08, $p<0.001$) and lever ($F_{1,121}$=64.42, $p<0.001$). Pretreatment with $D_1$ and $D_2$ antagonists reduced drug-paired lever responding ($F_{9,121}$=8.05, $p<0.001$) but had no significant effect on low inactive lever response rates (not shown). Neither SCH 23390 nor eticlopride reinstated responding when infused into the NAc prior to i.v. injections of saline.

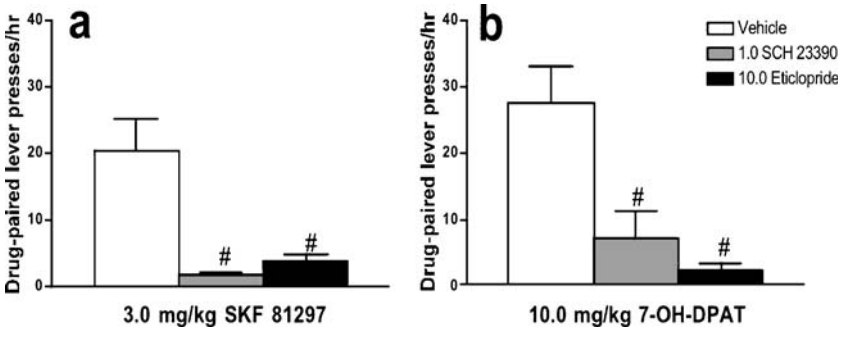


**Fig. 4** Coinfusion of SCH 23390 or eticlopride in the NAc shell block **a** SKF-81297-induced and **b** 7-OH-DPAT-induced reinstatement of cocaine seeking. Data represent the mean±SEM for $n$=9–14 animals/treatment condition. $^{\#}p<0.05$ compared to PBS/agonist coinfused controls (Dunnett's test)

### Crossblockade of $D_1$- and $D_2$-agonist-induced reinstatement by coinfusion with either $D_1$ or $D_2$ antagonists in the NAc shell

Using doses of SCH 23390 and eticlopride that attenuated cocaine-primed reinstatement, we tested the ability of both $D_1$ and $D_2$ antagonists to attenuate the reinstating effects of either $D_1$ or $D_2$ agonist when coinfused into the NAc shell. Figure 4a shows that NAc shell infusions of either SCH 23390 or eticlopride blocked the reinstatement of cocaine seeking induced by the $D_1$ agonist SKF 81297, resulting in a significant treatment × lever interaction ($F_{2,30}$=6.36, $p$<0.01) and a main effect of treatment ($F_{2,30}$=5.34, $p$=0.01). Both $D_1$ and $D_2$ antagonists attenuated drug-paired lever responding induced by SKF 81297 when compared to PBS/agonist coinfused controls ($F_{2,30}$=8.52, $p$=0.001), but had no significant effect on low inactive lever response rates (not shown). Similarly, Fig. 4b shows that coinfusion with either SCH 23390 or eticlopride blocked the reinstating effects of intra-NAc shell 7-OH-DPAT, producing a significant treatment × lever interaction ($F_{2,31}$=10.86, $p$<0.001) and a main effect of treatment ($F_{2,31}$=6.97, $p$<0.01). Both antagonists attenuated drug-paired lever responding induced by the $D_2$ agonist 7-OH-DPAT ($F_{2,31}$=9.66, $p$<0.001) without affecting inactive lever responses.

### NAc shell infusions of $D_1$ or $D_2$ receptor agonists fail to alter stabilized cocaine self-administration

Intra-NAc shell infusions of SKF 81297 (3.0 μg/side) and 7-OH-DPAT (10.0 μg/side) had no effect on the rate of cocaine intake over 90 min of self-administration when compared to stabilized baseline self-administration rates (FR1), despite the fact that both treatments reinstated cocaine seeking and produced a substantial locomotor behavior. Moreover, no transient alterations were revealed when self-administration data were divided into 30-min post-infusion bins across the 90-min test session (exemplary response records for individual animals are shown in Fig. 5a). However, in the absence of cocaine, intra-NAc shell infusions of the $D_2$ agonist 7-OH-DPAT (10.0 μg/side) reduced the rate of sucrose pellet self-administration, resulting in a sevenfold increase in the latency to self-administer 50 sucrose pellets compared to baseline responding ($t_5$=8.00, $p$<0.001) (Fig. 5b). In contrast, similar infusions of the $D_1$ agonist SKF 81297 (3.0 μg/side) failed to alter the rate of sucrose pellet self-administration.

### NAc shell infusions of $D_1$ or $D_2$ receptor antagonists increase cocaine self-administration

Figure 6 shows that pretreatment with NAc shell infusions of the $D_1$ antagonist SCH 23390 or the $D_2$ antagonist eticlopride increased cocaine self-administration rates at doses equivalent to and above those that significantly blocked cocaine-induced reinstatement (shown in Fig. 3).

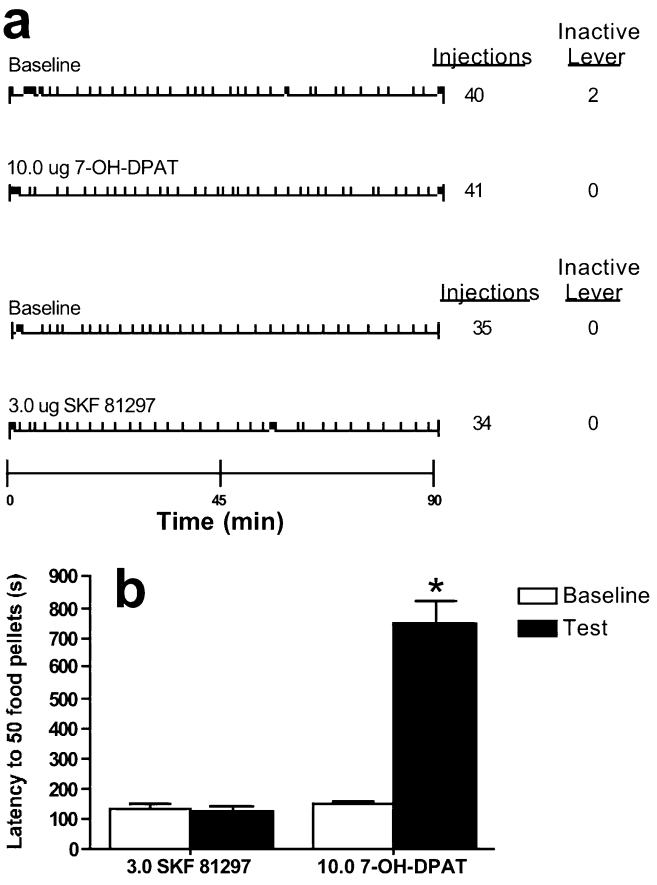


**Fig. 5** Intra-NAc shell infusions of the $D_1$ and $D_2$ agonists SKF 81297 and 7-OH-DPAT fail to reduce stabilized cocaine self-administration. **a** Representative self-administration records for individual animals during baseline cocaine self-administration (day prior to treatment) and following intra-NAc agonist treatment (from $n$=8–9 animals/treatment). Upward hatchmarks denote the time of each self-injection. **b** Similar intra-NAc infusions of 7-OH-DPAT (10.0 μg/side), but not SKF 81297 (3.0 μg/side), prolong the latency to self-administer 50 sucrose pellets. Data represent the mean± SEM for $n$=6 animals/treatment condition. *$p$<0.05 compared to baseline self-administration (paired $t$ test)

SCH 23390 produced a significant pretreatment × dose interaction ($F_{2,20}$=4.34, $p$<0.05) and a main effect of pretreatment vs baseline self-administration rates ($F_{1,20}$= 22.60, $p$<0.001). SCH 23390 pretreatments increased cocaine intake at doses of 1.0 μg/side ($t_7$=4.78, $p$<0.01) and 3.0 μg/side ($t_6$=2.92, $p$<0.01), but not at 0.5 μg/side, compared to baseline self-administration. NAc infusions of SCH 23390 dose-dependently increased cocaine self-administration rates throughout the 90-min test session, without disrupting the regularity of self-administration patterns (Fig. 6a and e). In contrast, pretreatment with these doses of SCH 23390 failed to alter the rate of sucrose pellet self-administration ($n$=5–6 animals/dose; data not shown).

NAc infusions of the $D_2$ antagonist eticlopride also produced a significant pretreatment × dose interaction ($F_{2,19}$= 6.57, $p$<0.01) and a main effect when compared to self-administration baselines ($F_{1,19}$=11.88, $p$<0.01). Eticlopride pretreatments increased cocaine intake at the 10.0-μg/side dose ($t_6$=2.86, $p$<0.01), but not at 1.0- or 3.0-μg/side dose,

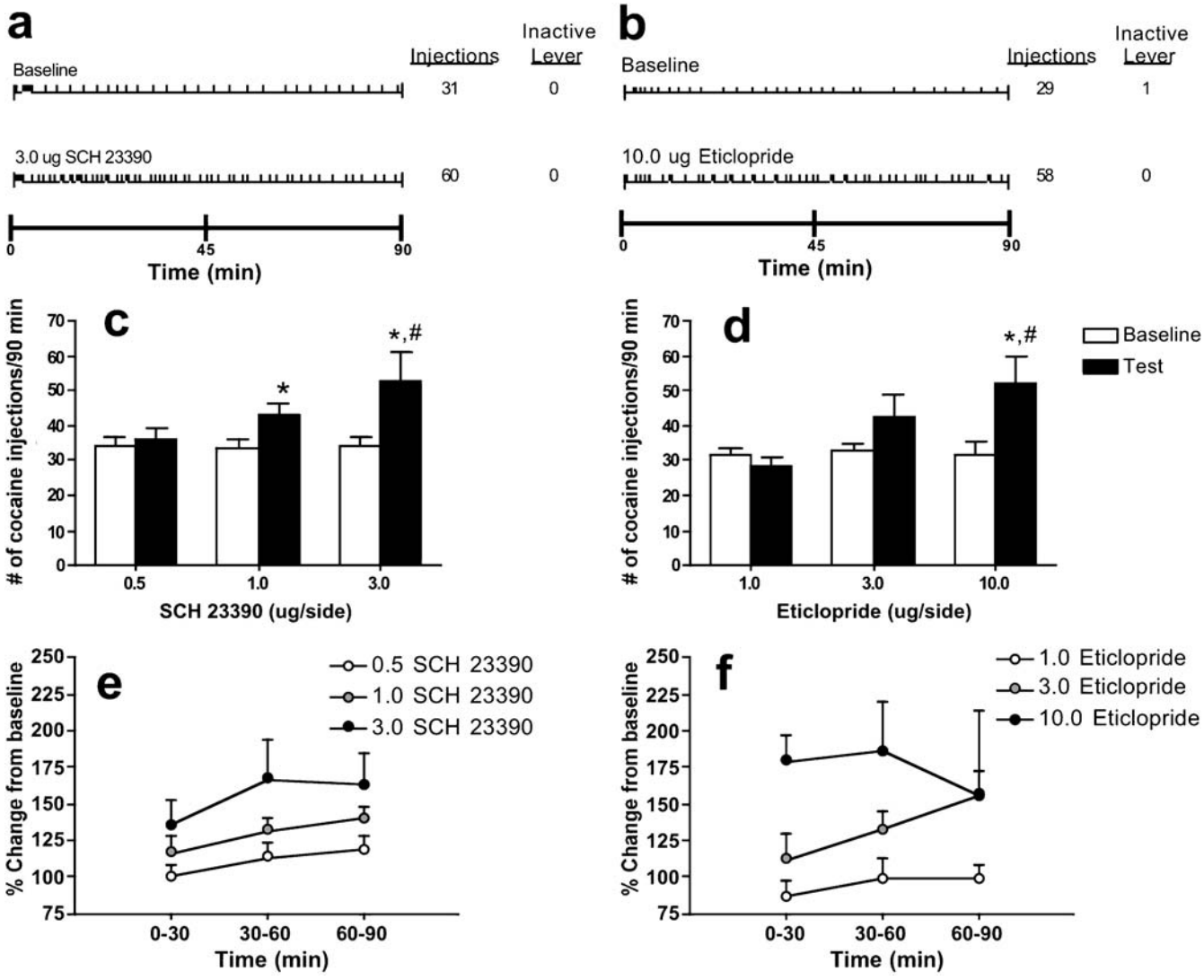


**Fig. 6** Intra-NAc shell infusions of the $D_1$ and $D_2$ antagonists SCH 23390 and eticlopride increase stabilized cocaine self-administration. **a**, **b** Representative self-administration records for individual animals during baseline and following intra-NAc antagonist treatment. **c**, **d** SCH 23390 and eticlopride dose-dependently increase cocaine intake compared to baseline self-administration totals and **e**, **f** throughout the 90-min test session when expressed as a percentage of baseline in 30-min time bins. Data represent the mean± SEM for $n$=6–8 animals/treatment condition. *$p$<0.05 compared to baseline self-administration (paired $t$ test) or $^{\#}p$<0.05 compared to the lowest ineffective dose of antagonist (Dunnett's test)

consistent with the dose threshold for the blockade of reinstatement. Eticlopride dose-dependently increased cocaine self-administration throughout the 90-min test session without disrupting the regularity of self-administration patterns (Fig. 6b and f). These doses of eticlopride produced no effect on sucrose pellet self-administration rates ($n$=6 animals/dose; data not shown).

### Histological verification of infusion sites

Figure 7 shows the NAc infusion sites for animals receiving shell and core administration of $D_1$ and $D_2$ agonists and antagonists. NAc shell sites were clustered in the ventral medial shell region, whereas core sites were clustered in the medial core. Only animals with both left and right infusion sites confined to either core (16 of 17) or shell (46 of 49) were included in the analysis. Micrographs of typical shell and core infusions sites show no evidence of widespread cell loss.

## Discussion

### The role of NAc dopamine receptors in cocaine seeking

Intra-NAc infusions of either $D_1$- or $D_2$-selective agonists dose-dependently reinstated cocaine-seeking behavior. The ability of the $D_2$ agonist 7-OH-DPAT to reinstate cocaine seeking is consistent with the effects of systemic administration, whereas reinstatement induced by the $D_1$ agonist

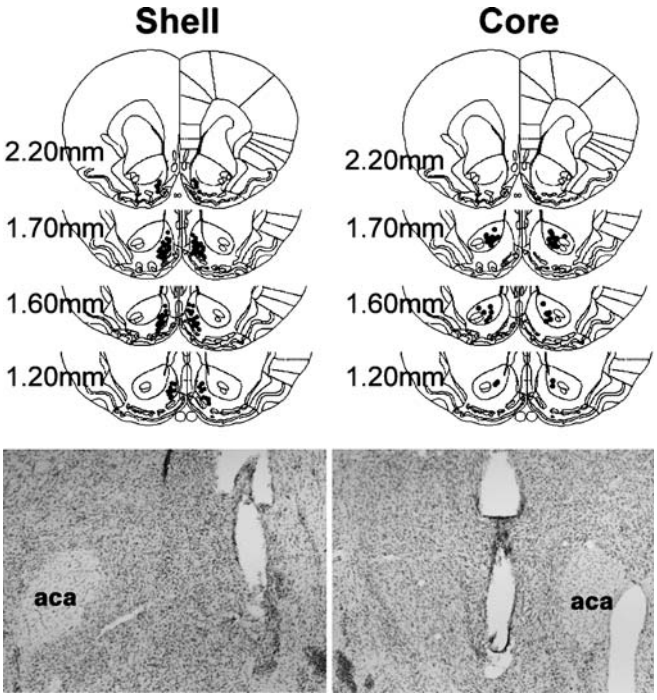


**Fig. 7** Localization of intra-NAc infusions sites (*filled circle*) in the medial NAc shell and core. Lower panels show photomicrographs of representative animals receiving nine microinfusions of PBS and experimental doses of the $D_1$ and $D_2$ agonists into the NAc shell (*left*) and NAc core (*right*)

SKF 81297 is opposite to the effects of systemic administration (Alleweireldt et al. 2002; Self et al. 1996). These differences are not attributable to differential psychomotor activation with systemic and intra-NAc infusions, since both routes of administration modulate cocaine-seeking behavior at doses that also stimulate locomotor activity. Instead, these results indicate that selective activation of either $D_1$ or $D_2$ receptors in the NAc is sufficient to trigger a cocaine-seeking response. Therefore, while $D_2$ receptors in the NAc could contribute to reinstatement induced by systemic $D_2$ agonist administration, it seems unlikely that NAc $D_1$ receptors would contribute to the attenuation of cocaine seeking by systemic $D_1$ agonist administration (but see discussion below).

Given that systemic cocaine injections preferentially increase dopamine levels in the NAc shell of rats (Hedou et al. 1999; Pontieri et al. 1995), and that blockade of $D_1$ receptors in the shell, but not the core, has been shown to block cocaine-primed reinstatement of cocaine seeking (Anderson et al. 2003), we compared the ability of $D_1$ and $D_2$ receptor antagonists to block cocaine-induced reinstatement in the NAc shell. We found that blockade of either $D_1$ or $D_2$ receptors in the NAc shell attenuates cocaine seeking elicited by i.v. injections of cocaine. These results are similar to the effects of systemic $D_1$ or $D_2$ antagonist administration in rats (Alleweireldt et al. 2002; Weissenborn et al. 1996) and monkeys (Khroyan et al. 2000), indicating that $D_1$ and $D_2$ receptors in the NAc shell each have a critical role in cocaine-induced reinstatement of cocaine seeking. Interestingly, both $D_1$- and $D_2$-selective antagonists completely and indiscriminately attenuated reinstatement induced by either the $D_1$- or $D_2$-selective agonist when agonist/antagonist combinations were coinfused into the NAc shell. These results suggest that some degree of endogenous dopamine tone at both $D_1$ and $D_2$ receptors is required to enable either receptor to mediate the reinstatement of cocaine-seeking behavior. This notion is supported by well-established cooperative interactions between $D_1$ and $D_2$ receptors in the NAc on neuronal firing (Hopf et al. 2003; White 1987), locomotor activity (Dreher and Jackson 1989; Essman et al. 1993; Koshikawa et al. 1996), and reinforcement mechanisms (Ikemoto et al. 1997), and is consistent with the effects of systemic administration of $D_1$ and $D_2$ receptor ligands (Waddington and Daly 1993).

## Differential regulation of cocaine intake by intra-NAc agonist and antagonist infusions

In contrast to their effects in reinstatement, neither the $D_1$ nor the $D_2$ agonist altered stabilized cocaine self-administration when infused into the NAc shell and thus failed to recapitulate the rate-decreasing or additive-like interaction with cocaine (prolonging the postinjection pause) typically found with systemic administration in rats (Caine et al. 1999; Hubner and Koob 1990; Pulvirenti and Koob 1994; Self et al. 1996, 2000). In contrast, both the $D_1$ antagonist SCH 23390 and the $D_2$ antagonist eticlopride increased stabilized cocaine intake when infused into the NAc shell, similar to the effect of systemic administration (e.g., Britton et al. 1991; Corrigall and Coen, 1991). These findings suggest that $D_1$ and $D_2$ receptors in the NAc shell are saturated with dopamine during cocaine self-administration, and receptor blockade reveals their inhibitory regulation of cocaine intake by shortening the pause between successive self-injections. However, given that reverse dialysis of dopamine into the NAc reduces cocaine intake (Hurd and Ponten 2000), coactivation of both $D_1$ and $D_2$ receptors within the NAc may be required for such localized effects. Alternatively, agonist-mediated inhibition of cocaine intake could require a more widespread activation of dopamine receptors within the NAc, or a concurrent activation of dopamine receptors in other brain regions. In this regard, dopamine antagonists increase cocaine intake when infused into several other brain regions, including the ventral tegmental area, prefrontal cortex, amygdala, and bed nucleus of the stria terminalis (Caine et al. 1995; Epping-Jordan et al. 1998; Hurd et al. 1997; McGregor and Roberts 1993, 1995; Ranaldi and Wise 2001; Sun and Rebec 2005).

The behavioral effects of $D_1$ and $D_2$ agonists and antagonists are not attributable to generalized effects on response rates, since they differentially altered lever-press responding during cocaine and sucrose self-administration and in reinstatement experiments. Thus, both $D_1$ and $D_2$ agonists increased responding in reinstatement and had no effect on cocaine self-administration; the $D_2$ agonist decreased, rather than increased, responding for sucrose

pellets, similar to the effect of systemic administration (Franklin and Tang 1995; Hoffman et al. 1990; McQuade et al. 2003). Conversely, the $D_1$ and $D_2$ antagonists decreased cocaine-induced responding in reinstatement, but increased cocaine self-administration while having no effect on sucrose self-administration. Therefore, changes in lever-press rates in self-administration and reinstatement experiments are likely due to motivational, rather than performance-related, influences.

## Dopaminergic involvement of both core and shell in cocaine seeking

The $D_1$ and $D_2$ receptor agonists reinstated cocaine-seeking behavior when infused into either the core or the shell subregion, although more robust effects were found with core infusions. The ability of core infusions to induce greater cocaine seeking cannot be attributed to greater psychomotor activation, since absolute locomotor activities were similar following core and shell infusions. These results suggest that dopamine receptor activation in both subregions is sufficient to trigger cocaine-seeking behavior, whereas receptor activation in the shell, but not the core, is necessary for cocaine-induced reinstatement (Anderson et al. 2003). While this latter finding agrees with the ability of cocaine to increase dopamine levels selectively in the shell, exposure to unanticipated cocaine-associated cues increases dopamine selectively in the core (Ito et al. 2000). Thus, it is possible that dopaminergic neurotransmission in the shell and core differentially mediates cocaine- and cue-elicited relapse to cocaine seeking, respectively.

It is important to note that we obtained positive effects with dopamine agonist infusions in the medial core, whereas Anderson et al. (2003) obtained negative effects with antagonist infusions in the lateral core. Although we cannot rule out the potential for diffusion between subregions, the fact that agonist-induced locomotor activation had similar time courses in both the core and the shell suggests that the behavioral effects were mediated by receptors in the vicinity of the infusion site. In addition, the transient reinstatement produced by intra-NAc infusion of the $D_2$ agonist is consistent with local receptor activity in either the core or the shell.

The shell subregion receives limbic innervation that may be more pertinent to the reinforcing actions of cocaine, while the core is thought to represent a major component of the motor circuit, but the distribution of $D_1$ and $D_2$ dopamine receptors does not differ substantially between subregions (Heimer et al. 1991). The role of each subregion in the reinstatement of cocaine-seeking behavior is less clear, since dopamine antagonists block cocaine-induced reinstatement in the shell, but $\gamma$-aminobutyric acid-receptor-mediated inhibition of the core also attenuates reinstatement (McFarland and Kalivas 2001). Our results suggest that dopaminergic input to both the core and shell is important. The fact that 7-OH-DPAT produced greater cocaine-seeking responses in the core is preliminary evidence that the $D_2$ subtype of the $D_2$ receptor family mediates this effect, since $D_3$ receptors are not expressed in the core and $D_4$ receptors are expressed at low levels in the NAc (Bouthenet et al. 1991; Van Tol et al. 1991; Seeman and Van Tol 1994; Diaz et al. 1995). Similarly, the $D_1$—rather than the $D_5$—subtype of the $D_1$ receptor family could mediate the effects of SKF 81297, since D5 receptor messenger ribonucleic acid is absent in the rat NAc (Tiberi et al. 1991). However, conclusive evidence will require further work with subtype-selective ligands, and these data do not rule out the possible actions of $D_3$, $D_4$, or $D_5$ receptors in other brain regions on the reinstatement of cocaine-seeking behavior.

## Opposite effects of systemic and intra-NAc $D_1$ agonist administration on reinstatement

One of the most intriguing findings is that intra-NAc infusions of the $D_1$ agonist induce cocaine-seeking behavior, whereas systemic administration inhibits cocaine seeking. The most straightforward explanation for this difference is that $D_1$ receptors in other brain regions mediate the inhibitory effects of systemic $D_1$ agonist administration on reinstatement. However, we found that intra-ventral-tegmental-area infusions of SKF 81297 also reinstate cocaine seeking in rats (K. -H. Choi and D. W. Self, unpublished observations), an effect possibly mediated by releasing glutamate from afferent fibers onto dopamine neurons (Adell and Artigas 2004). In the dorsal medial (but not prelimbic) prefrontal cortex and amygdala, dopamine receptor antagonists have been shown to block cocaine seeking induced by systemic cocaine injections or cocaine cues (Capriles et al. 2003; McFarland and Kalivas 2001; Park et al. 2002; See et al. 2001; Sun and Rebec 2005; Weiss et al. 2000), indicating that dopamine receptors in these regions also play a necessary role in the reinstatement of cocaine-seeking behavior. Given that infusions of $D_1$ receptor antagonists into these brain regions also increase cocaine self-administration, $D_1$ receptors in multiple regions could contribute to inhibitory regulation, or satiation, of cocaine seeking during self-administration.

Thus, it is possible that the satiating effects of systemic $D_1$ agonist administration require a simultaneous stimulation of $D_1$ receptors in multiple brain regions. It is also possible that $D_1$ receptors on NAc neurons have different neuromodulatory effects when $D_1$ agonists are focally applied than when active throughout the brain. For example, $D_1$-receptor-mediated activation of prefrontal cortical afferents to NAc neurons alters the response to local $D_1$ receptor activation, which produces opposing effects depending on whether NAc neurons are in “up” or “down” states (O’Donnell 2003). If so, then such highly localized $D_1$ receptor activation would not recapitulate the neuromodulatory effects of systemic $D_1$ agonist administration or mesolimbic dopamine activity throughout the brain. Another caveat is that benzazepine-based $D_1$ receptor agonists are reported to cause an amphetamine-like elevation in dopamine levels when microinjected into striatal brain

regions (Tomiyama et al. 1995). This dopamine-releasing action is not found with systemic $D_1$ agonist administration (Zetterstrom et al. 1986) and is not mediated by $D_1$ receptors, but could underlie the prolonged locomotor activation found with intra-NAc infusions of SKF 81297 relative to 7-OH-DPAT. Reinstatement induced by such an amphetamine-like action in the NAc would be sensitive to blockade by either $D_1$ or $D_2$ receptor antagonists, since both antagonists blocked cocaine-induced reinstatement.

## Conclusions

In summary, we found that microinfusion of either $D_1$ or $D_2$ receptor agonists into the medial core and shell of the NAc triggers cocaine-seeking behavior, and these effects are codependent on both $D_1$ and $D_2$ receptor activity. These results firmly establish a role for NAc $D_2$ receptors in the induction of cocaine-seeking behavior and suggest that NAc $D_1$ receptors may cooperate with $D_2$ receptors in mediating cocaine seeking, while the inhibitory effect of systemic $D_1$ agonist administration may involve $D_1$ receptors in different or multiple brain regions. In contrast, stabilized cocaine self-administration is sensitive to either $D_1$ or $D_2$ receptor blockade in the NAc, but not $D_1$ or $D_2$ receptor stimulation, suggesting that NAc dopamine receptors are saturated during cocaine self-administration. These findings suggest that $D_1$ and $D_2$ receptors in the NAc play a major role in regulating both drug-taking and drug-seeking behaviors.

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