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BRIEF REPORT

# Cocaine seeking and taking: role of hippocampal dopamine D1-like receptors

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**Abstract**

Despite the well-documented involvement of dopamine D1-like receptor stimulation in cocaine-induced goal-directed behaviours, little is known about the specific contribution of D1-like receptor populations in the dorsal hippocampus (DH) to drug context-induced cocaine-seeking or drug-reinforced instrumental behaviours. To investigate this question, rats were trained to lever press for un-signalled cocaine infusions in a distinct context followed by extinction training in a different context. Cocaine-seeking behaviour (non-reinforced lever responding) was then assessed in the previously cocaine-paired and extinction contexts. SCH23390-induced D1-like receptor antagonism in the DH, but not the overlying trunk region of the somatosensory cortex, dose-dependently inhibited drug context-induced cocaine-seeking behaviour, without altering cocaine-reinforced instrumental responding, cocaine intake, food-reinforced instrumental responding, or general motor activity, relative to vehicle treatment. These findings suggest that D1-like receptor stimulation in the DH is critical for the incentive motivational effects and/or memory of cocaine-paired contextual stimuli that contribute to drug-seeking behaviour.

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**Key words:** Cocaine, context, dopamine D1-like receptor, hippocampus, reinstatement.

## Introduction

The dorsal hippocampus (DH) has been implicated in cocaine cue-induced incentive motivation and goal-directed behaviours. Consistent with this, DH neural activation correlates with self-reports of cue-induced craving in cocaine users (Kilts et al., 2001; Wexler et al., 2001; Volkow et al., 2004). Furthermore, DH neuronal inactivation disrupts the ability of a cocaine-paired context to reinstate extinguished cocaine-seeking behaviour in laboratory animals (Fuchs et al., 2005).

The DH exhibits dense dopamine D1-like receptor (D1R) expression (Khan et al., 2000; Gangarossa et al., 2012), and D1R stimulation in the DH plays a critical role in drug-reinforced instrumental and drug context-induced conditioned behaviours. Rats self-administer methamphetamine directly into the DH, and this phenomenon is dependent on D1R stimulation in the DH (Ricoy and Martinez, 2009). Similarly, D1R stimulation in the DH is required for the expression of morphine- and methamphetamine-conditioned place preference (CPP; Rezayof et al., 2003; Ricoy and Martinez, 2009). However, it is unclear whether D1Rs in the DH play a role in goal-directed behaviours induced by cocaine-associated environmental stimuli or cocaine *per se*.

To investigate this question, we evaluated the dose-dependent effects of SCH23390, a D1R antagonist, in the DH or the trunk region of the somatosensory cortex (SStr; adjacent anatomical control region), on cocaine-reinforced instrumental behaviour and drug context-induced reinstatement of cocaine-seeking behaviour. In addition, we evaluated the possible rate-altering effects of intra-DH SCH23390 administration on food-reinforced instrumental responding and general locomotor activity.

## Materials and method

### *Animals*

Male Sprague-Dawley rats (Charles-River, $n$=38; 250–275 g) were individually housed in a temperature- and humidity-controlled vivarium on a reversed light/dark cycle. Rats were maintained on 20–25 g of rat chow per day and *ad libitum* water. Protocols for housing and treatment of the rats followed the 'Guide for the Care and Use of Laboratory Rats' (Institute of Laboratory Animal Resources, Commission on Life Sciences 2011) and were

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approved by the Institutional Animal Care and Use Committee.

### Food training and surgery

To expedite cocaine self-administration training, rats were first trained to lever press under a fixed-ratio 1 (FR-1) schedule of food reinforcement (45 mg pellets; Noyes, USA) overnight. Forty-eight hours later, they were surgically implanted with an intravenous jugular catheter and 26-Ga stainless steel guide cannula (Plastics One, USA) aimed bilaterally at the DH (angled laterally by 15°; AP −3.4, ML±3.1, DV −2.15 mm, relative to bregma) or SStr (angled laterally by 15°; AP −3.4, ML±3.1, −0.65 mm, relative to bregma). The food training, surgery and post-operative care procedures have been described previously (Fuchs et al., 2007, 2008; Xie et al., 2010).

### Cocaine self-administration and extinction training

Schematics illustrating the experimental timeline are shown in Fig. 1*a*. After surgical recovery, daily 2 h sessions were conducted in operant conditioning chambers configured to one of two distinct contexts (Contexts 1 and 2, see Supplementary Materials and Methods). Presses on one lever (active) resulted in cocaine reinforcement [cocaine hydrochloride; 0.15 mg/0.05 ml/infusion, ~0.5 mg/kg/infusion i.v., (NIDA, USA)] under a FR-1/20 s time-out schedule, as described previously (Fuchs et al., 2007, 2008; Xie et al., 2010). Responses on a second (inactive) lever were recorded but had no scheduled consequences. Training continued until rats reached an acquisition criterion (i.e. 10 sessions with $\geqslant$10 cocaine infusions/session). Rats then received a minimum of seven daily two-hour extinction-training sessions in the alternate context (Context 1 or 2). During extinction training, responses on both levers were recorded but had no scheduled consequences. Before the fourth extinction-training session, rats were adapted to the intracranial micro-infusion procedure, as described previously (Fuchs et al., 2007). Training continued until rats reached an extinction criterion ($\leqslant$25 active lever responses/session on 2 consecutive days) that permits detection of statistically significant extinction learning and reinstatement of drug-seeking behaviour at test.

### Experiment 1

#### Reinstatement testing

Rats (DH-cannulated, $n$=23; SStr-cannulated, $n$=7) received two one-hour test sessions in the previously cocaine-paired context and two one-hour test sessions in the extinction context, as described previously (Xie et al., 2010). Micro-infusions were administered over 2 min immediately before testing. The injectors extended 1 mm ventral past the guide cannula and were left in place for 1 min before and after the infusion. Testing order in the two contexts (cocaine-paired or extinction context first), treatment order (antagonist or vehicle first), and SCH23390 treatment dose (vehicle and 0.1 or 1.0 $\mu$g/0.5 $\mu$l/hemisphere) were counterbalanced based on cocaine intake, when appropriate. Between tests, rats received daily extinction training sessions until they re-obtained the extinction criterion. During testing, responses on both levers were recorded, but had no programmed consequences.

#### Locomotor activity and food-reinforced instrumental behaviour

Pharmacological manipulations may produce motor effects that alter the expression of motivated behaviour. Hence, at least 72 h after the last reinstatement test session, we examined the effects of intra-DH SCH23390 administration on general locomotor activity and food-reinforced lever responses in a subset of DH-cannulised rats ($n$=12), as described in Supplementary Materials and Methods.

### Experiment 2

#### Cocaine-reinforced instrumental behaviour

After reaching the acquisition criterion for cocaine self-administration training, the second subset of DH-cannulised rats ($n$=8) received eight two-hours cocaine self-administration test sessions. During testing, active lever presses resulted in cocaine reinforcement under a (FR-1) 20 s time-out schedule. Immediately before testing, the rats received intra-DH micro-infusions of SCH23390 (0.1 or 1.0 $\mu$g/0.5 $\mu$l/hemisphere) or the $GABA_B$/$GABA_A$ agonist cocktail, baclofen/muscimol (B/M; 106.8/5.7 ng/0.5 $\mu$l/hemisphere) in order to temporarily inhibit DH neural activity. This B/M dose in the DH inhibits context-induced cocaine-seeking behaviour (Fuchs et al., 2007). Treatment order (vehicle, 0.1 $\mu$g SCH23390 1.0 $\mu$g SCH23390, B/M) and the order of cocaine doses (0.075 or 0.15 mg/0.05 ml/infusion) at test were counterbalanced based on cocaine intake during cocaine self-administration training.

#### Histology

Rats were overdosed using ketamine hydrochloride and xylazine (66.6 and 1.3 mg/kg intravenous or 199.8 and 3.9 mg/kg i.p., respectively, depending on catheter patency). The brains were dissected out, post-fixed, sectioned, and stained with cresyl violet (Kodak, Rochester, NY). The most ventral point of each cannula track was mapped onto schematics from the rat brain atlas (Paxinos and Watson, 1997).

### Data analysis

Data were analysed using mixed-factorial or repeated measures analyses of variance (ANOVAs) and Tukey *post-hoc* tests, when appropriate. Alpha was set at 0.05.

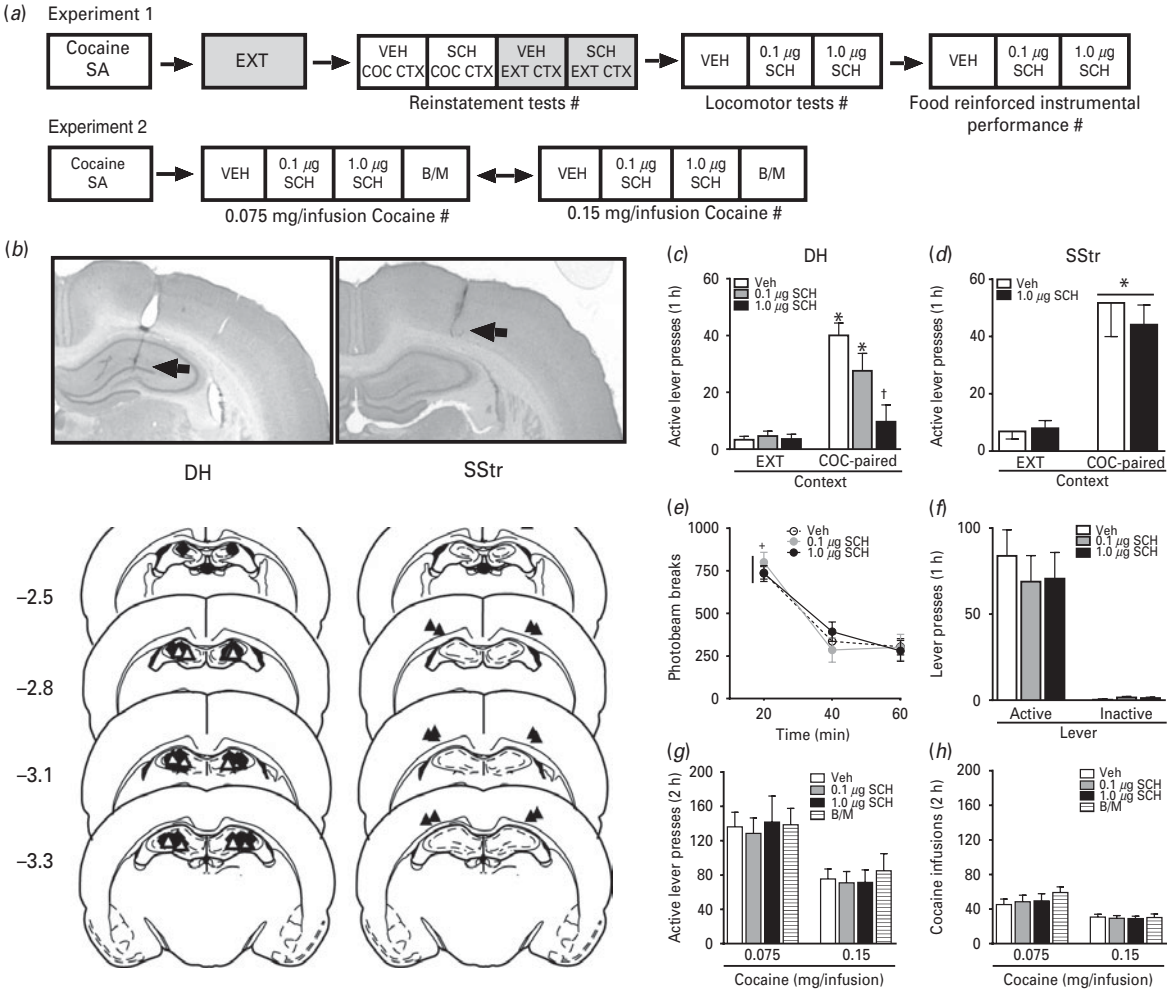


**Fig. 1.** Schematic illustrates the experimental timeline (*a*). *Hash symbols* and *bi-directional arrow* represent counterbalanced testing orders. Photomicrographs of representative cresyl violet-stained sections and schematics adapted from the rat brain atlas of Paxinos and Watson (1997) show injection cannula placements within the DH and SStr (*b*). In Panel B, *arrows* identify the most ventral point of the infusion cannula tracts. Numbers indicate the distance from bregma in mm. *Filled diamonds* (0.1 μg SCH23390), *filled circles* (1.0 μg SCH23390), and *filled triangles* (1.0 μg SCH23390) represent the most ventral point of cannula tracts for rats in Experiment 1, and *open triangles* represent the most ventral point of cannula tracts for rats in Experiment 2. In Experiment 1, SCH23390 or vehicle was infused bilaterally into the DH (*c: n*=11–23/dose) or SStr (*d: n*=7/dose) immediately prior to tests of non-reinforced active lever responses (mean/1 h±S.E.M) in the extinction (EXT) and previously cocaine-paired contexts (COC-paired). After reinstatement testing, the effects of intra-DH SCH23390 were assessed on locomotor activity (*e*: mean photo beam breaks/1 h±S.E.M) and food-reinforced instrumental behaviour (*f*: mean active and inactive lever presses/1 h±S.E.M) in a subset of rats. In Experiment 2, SCH23390, B/M (106.8/5.7 ng/0.5 μl/hemisphere), or vehicle was administered bilaterally into the DH immediately prior to the assessment of cocaine-reinforced lever responding (*g: n*=10/dose) and cocaine intake (*h: n*=10/dose). *Asterisks* represent significant difference relative to responding in the extinction context (*c*: ANOVA context simple main effect, Tukey test, $p<0.05$; *d*: ANOVA context main effect, $p<0.05$). *Daggers* represent significant difference relative to vehicle treatment (*c*: ANOVA treatment simple main effect, Tukey test, $p<0.05$). *Plus sign* represents significant difference relative to all other time points (*e*: ANOVA time simple main effect, Tukey test, $p<0.05$).

## Results

Cannula placement was verified in the target brain regions bilaterally in all rats (Fig. 1*b*). All DH-cannulised ($N$=31) and SStr-cannulised ($n$=7) rats exhibited stable responding on the active lever during the last three self-administration training days with a within-subject variability of <10% in daily cocaine intake. The mean number of active lever responses was 68.64±6.50, and the mean daily cocaine intake (±S.E.M) was ~12.75±0.56 mg/kg per session (25.50±1.13 infusions). There was no pre-existing difference between the DH- and SStr-cannulised groups or between the subsequent treatment groups (0.1 or 1.0 μg/0.5 μl/hemisphere of SCH23390 in Experiment 1) in active or inactive lever responding during the last three days of cocaine self-administration training (all group main and interaction effects, $F_{(1–2,21–72)}$=0.34–2.74, $p$=0.08–0.71).

Upon removal of cocaine reinforcement, active and inactive lever responding gradually declined in the DH-cannulised and SStr-cannulised groups (all time main effects, $F_{(6,126–168)}$=18.90–21.72, $p$=0.0001) in Experiment 1. There was no pre-existing difference between the DH- and SStr-cannulised groups or the subsequent SCH23390 dose treatment groups in active or inactive lever responding during the last seven days of extinction training (all group main and interaction effects, $F_{(1–6,21–168)}$=0.60–3.96, $p$=0.06–0.74) or in the mean number of daily sessions (±S.E.M; 7.47±0.13) needed to reach the extinction criterion. Collapsed across groups, the average active and inactive lever responding (±S.E.M) decreased from 77.16±13.16 and 20.37±5.53 on the first day of extinction training to 8.00±1.55 and 1.20±0.34 on the last day of extinction training, respectively.

During reinstatement tests, following vehicle administration into the DH, active and inactive lever responding was independent of order effects with respect to testing context, treatment order (vehicle or SCH23390 first) and treatment received on the other test day (SCH23390 dose). Therefore, data were collapsed across these variables to form a single vehicle condition. Inactive lever responding at test was low in all experiments and unaltered by the pharmacological manipulations (all treatment main and interaction effects, $F$s<3.48, $p$>0.07; Supplementary Figure S1).

In Experiment 1, SCH23390 administration into the DH ($n$=11–12/dose) attenuated active lever responding as a function of testing dose and context (Fig. 1*c*; treatment main, context main, and interaction effects, $F_{(1–2,43)}$=7.16–53.34, $p$=0.0001–0.002). Following vehicle pre-treatment administered into the DH, exposure to the cocaine-paired context increased active lever responding relative to the extinction context (Tukey test, $p$<0.05). The 1.0 $\mu$g dose – but not the 0.1 $\mu$g dose – of SCH23390 decreased active lever responding in the cocaine-paired context (Tukey test, $p$<0.05). Furthermore, neither dose altered responding in the extinction context, relative to vehicle.

Following vehicle pre-treatment administered into the SStr (anatomical control region; $n$=7), exposure to the cocaine-paired context increased active lever responding relative to the extinction context (context main effect, $F_{(1,6)}$=24.64, $p$=0.003). However, administration of the behaviourally effective, 1.0 $\mu$g, dose of SCH23390 into the SStr failed to alter active lever responding in either context, relative to vehicle (Fig. 1*d*; treatment main and interaction effects, $F_{(1,6)}$=0.25–0.51, $p$=0.50–0.63).

During the subsequent locomotor activity test session, in a subset of DH-cannulised rats ($n$=12), the number of photo beam breaks gradually decreased (time main effect, $F_{(2,22)}$=87.33, $p$=0.0001; 20-min interval 1>2–3, Tukey test, $p$<0.05). Furthermore, the 0.1 or 1.0 $\mu$g dose of SCH23390 did not alter the number of photo beam breaks, relative to vehicle (treatment main and interaction effects, $F_{(2–4,22–44)}$=0.64–1.30, $p$=0.29–0.63; Fig. 1*e*). In the same group of rats, food reinforcement elicited greater responding on the active lever than on the inactive lever (lever main effect, $F_{(1,11)}$=38.11, $p$=0.001). Furthermore, the 0.1 or 1.0 $\mu$g dose of SCH23390 did not alter food-reinforced active or inactive lever responding, relative to vehicle (all treatment main and interaction effects, $F_{(2,22)}$=0.29–0.36, $p$=0.70–0.75; Fig. 1*f*).

In Experiment 2, rats ($n$=8) exhibited decreased cocaine-reinforced lever responding and cocaine intake when reinforced with the 0.15 mg infusion dose of cocaine, relative to 0.075 mg infusion dose (dose main effects, $F_{(1,7)}$=15.18–25.83, $p$=0.001–0.006), a pattern expected on the descending end of the inverted U-shaped cocaine dose-effect curve (Sizemore et al., 1997; Piazza et al., 2000). Independent of cocaine dose, SCH23390 treatment (0.1 or 1.0 $\mu$g dose) in, or B/M-induced neural inactivation of, the DH failed to alter cocaine-reinforced lever responding (Fig. 1*g*) or cocaine intake (Fig. 1*h*), relative to vehicle (all main treatment and treatment by cocaine dose interaction effects, $F_{(3,21)}$=0.44–2.23, $p$=0.11–0.73).

## Discussion

The present study evaluated the role of D1Rs in the DH in cocaine-reinforced instrumental responding and drug context-induced reinstatement of extinguished cocaine seeking. The findings suggest that the DH plays a differential role in these behaviours.

D1R antagonism in the DH, but not the SStr, dose-dependently inhibited drug context-induced reinstatement of cocaine-seeking behaviour. These effects did not reflect an SCH23390-induced performance deficit since our manipulations did not alter food- or cocaine-reinforced instrumental responding, or general motor activity, relative to vehicle. The present study did not intend to dissect the role of D1Rs subpopulations within specific sub regions of the DH in drug context-induced reinstatement of cocaine seeking. However, the micro-infusion sites were primarily located in the CA1-CA3 subregions of the DH where D1R stimulation is required for hippocampal-dependent learning and memory (O'Carroll et al., 2006; Bethus et al., 2010). Therefore, adding to this literature and to a recent report implicating DH $\beta$-adrenoceptors in CPP memory retrieval (Otis et al., 2014), we conclude that D1Rs in the DH play a critical role in the incentive motivational effects and/or memory of cocaine-paired contextual stimuli that contribute to instrumental drug-seeking behaviour.

Interestingly, D1R antagonism in the DH failed to alter cocaine self-administration, independent of cocaine dose, and these effects were recapitulated using B/M-induced general neuronal inactivation of the DH. Multiple infusion and order effects were not apparent but cannot be ruled out given that a within-subject testing design was used. Nevertheless, this outcome was unexpected because D1R stimulation in the DH is required for

instrumental responding reinforced by intra-DH methamphetamine administration paired with conditioned stimulus (CS) presentation (Ricoy and Martinez, 2009). It is unlikely that D1R antagonism in the past study attenuated methamphetamine self-administration by inhibiting the conditioned reinforcing effects of, or memory for, the metamphetamine-paired CS, since tetrodotoxin-induced neural inactivation of the DH fails to alter CS-induced reinstatement of cocaine-seeking behaviour (Fuchs et al., 2005). Instead, the reinforcing effects of methamphetamine in the DH are elicited by enhanced dopaminergic neurotransmission and D1R stimulation in the DH. However, the reinforcing effects of systemic cocaine administration can be fully maintained by extra-DH neuronal substrates.

Remarkably, context-induced cocaine-seeking behaviour may be a result of *reciprocal* interaction between the DH and midbrain dopamine cell body regions, primarily in the ventral tegmental area (VTA). Ascending information sharing may involve dopamine release from terminals of the VTA or substantia nigra (Swanson, 1982; Gasbarri et al., 1994, 1997) and, according to a recent report, co-release of dopamine from noradrenergic terminals of the locus coeruleus (Smith and Greene, 2012). However, the critical source of dopamine has yet to be dissected. Furthermore, conclusions regarding the involvement of dopamine have to be made with the caveat that, while SCH23390 is considered the prototypical D1-like antagonist (Alleweireldt et al., 2002; Sun and Rebec, 2005; Berglind et al., 2006; Bossert et al., 2007, 2009; Chaudhri et al., 2009), it has a 46-fold lower, yet moderate, affinity for the serotonin 5-HT2c receptor as an agonist [*in vitro* $K_i$=9.3 nM (Rupniak et al., 1986; Kalkman et al., 1998)]. Systemic 5-HT2c receptor stimulation attenuates explicit cue- and context-induced cocaine-seeking behaviours (Zavala et al., 2007; Fletcher et al., 2008). Therefore, SCH23390-induced 5-HT2c receptor stimulation in the DH may have contributed to the effects on context-induced cocaine-seeking behaviours.

Descending information sharing between the DH CA3 subregion and the VTA occurs through a multi-synaptic neural circuit, with the dorsal-lateral septum (LS) serving as a relay structure (Luo et al., 2011). Excitatory output from the DH CA3 subregion ultimately triggers the disinhibition of VTA dopamine neurons and dopamine release, and the functional integrity of this circuit is also necessary for drug context-induced cocaine-seeking behaviour (Luo et al., 2011). Other studies have demonstrated that dopamine D1R stimulation in the DH can enhance DH pyramidal neuron excitability (Edelmann and Lessmann, 2013). Thus, the ascending circuit in the DH may form a positive feedback loop with the DH–dLS–VTA circuit to promote drug context-induced cocaine seeking.

Plasticity in D1R-mediated signalling pathway within the DH may enhance drug-related learning and memory and it may contribute to the development of compulsive cocaine-seeking behaviours. Consistent with this, enhanced D1R mRNA levels in the dentate gyrus of the DH are associated with the development of cocaine-conditioned place preference (Tanaka et al., 2011), and D1R stimulation in the CA1 sub region of the DH is required for cocaine-induced enhancement in long-term potentiation (Stramiello and Wagner, 2010). Therefore, understanding putative, drug-induced or experience-based neuroplasticity in D1R function within the DH may aid in the development of effective treatments for drug relapse prevention.

## Supplementary material

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S1461145714000340.

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## Statement of Interest

None.

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