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Dopamine D1 receptor antagonism impairs extinction of cocaine-cue memories

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Abstract

Increasingly, research suggests a role for dopamine D1 receptors in the consolidation of extinction of both appetitive and aversive memories. However, a role for D1 receptors in extinction of memories involving drug reward has yet to be established. Here we show that post-retrieval, but not delayed, systemic administration of the D1 receptor antagonist SCH23390 results in prolonged extinction of cocaine conditioned place preference (CPP), suggesting a critical role for D1 receptors in the consolidation of extinction of cocaine-cue memories.

Keywords

Dopamine; Extinction; Conditioned Place Preference; Addiction; Relapse; Rat

BRIEF COMMUNICATION

The relapse of addicts into drug seeking is often triggered by their exposure to drug-paired cues. Repeated pairing of a cue (person, place, paraphernalia, or emotional state) with administration of an addictive substance can lead to rapid and intense learning, and these drug-cue associations play a major role in maintaining habitual drug use. The strength of these learned associations is also observed during relapse. When previously drug-dependent individuals encounter these drug-paired cues, even following prolonged abstinence, they experience an intense conditioned physiological response accompanied by strong craving for the drug [1, 2]. Recent interest has focused on the possibility that these memories can be

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DISCLOSURE/CONFLICT OF INTEREST

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attenuated, potentially leading to novel treatments for addiction and other neuropsychiatric disorders.

The molecular mechanisms underlying drug-cue associations are being actively investigated [3–6]. Among the molecules under consideration, the protein kinase extracellular signal-regulated kinase (ERK) is known to have a crucial role. Psychostimulants and drug-paired cues both activate the ERK signaling cascade, inducing phosphorylation of ERK (pERK) in a number of brain regions including the nucleus accumbens core (AcbC) and the prefrontal cortex [7–10]. Dopamine (DA) D1 receptors are upstream mediators of psychostimulant- and cue-induced phosphorylation of ERK [11, 12]. ERK has long been implicated in learning and memory with roles in aspects of synaptic plasticity [13, 14] and learning-related processes [15–18]. Importantly, inhibition of pERK disrupts acquisition, expression, and reconsolidation of conditioned place preference (CPP) [8, 19, 20].

Increasingly, attention has focused on targeting extinction and reconsolidation mechanisms to disrupt drug-cue associations [21–23]. Furthermore, a growing body of literature suggests a role for DA D1 receptors in consolidation of extinction of aversive memories [24–26]. However, a role for DA D1 receptors in extinction of appetitive memories, such as CPP, has yet to be established. The experiment presented here was designed to directly examine the effects of D1 receptor antagonism on extinction of cocaine-CPP.

Male Sprague-Dawley rats were trained to associate one compartment of the CPP apparatus with cocaine administration. Conditioning took place in a three-chamber apparatus (Med Associates, St. Albans, VT) consisting of two larger compartments (28 × 21 cm) separated by a smaller compartment (12 × 21 cm). The two larger compartments were distinguished by different visual, olfactory, and tactile cues [27]. Animals were assessed for baseline preferences, then divided into four groups (to be given SCH23390 or saline) for which the initial preferences for each compartment did not differ significantly. Conditioning took place over the next 6 days. On each of the conditioning days animals received an injection of either cocaine-HCl (12 mg/kg, i.p.; Sigma-Aldrich, St. Louis, MO) or saline (1 ml/kg, i.p.) and were immediately confined to one compartment of the apparatus for 30 minutes. The drug treatment and compartment assignment were alternated during subsequent conditioning sessions (Figure 1). Forty-eight hours after the last training session, the animals were tested, in a drug-free state, for preference (Post-test 1). Any animal that did not display a preference of at least 90 seconds for the cocaine-paired compartment on Post-test 1 was eliminated from the study.

In the main experiment, the animals received an injection of one of three doses of the D1 antagonist SCH23390 (0.1, 0.4, or 1 mg/kg, i.p.; Sigma-Aldrich, St. Louis, MO) or saline vehicle (1 ml/kg, i.p.) immediately after Post-test 1, and were then returned to their home cage. Preference testing continued on subsequent days; post-test injections of SCH23390 or saline occurred each day until a “no-preference criterion” was reached. The no-preference criterion was defined as two consecutive days of testing during which the group’s mean preference score (time in the cocaine-paired compartment minus time in the saline-paired compartment) was less than 15% of the average preference of all groups at Post-test 1.

Post-test administration of SCH23390 was chosen in order to eliminate any potential effects of the D1 antagonist on performance, attention to the contexts, or other non-specific influences that might have occurred with pre-test administration. An additional control experiment was included to verify that the SCH23390 effects were specific to the time of memory retrieval. Animals were trained on cocaine-CPP as for the main experiment, but for the control experiment, either SCH23390 (1 mg/kg, i.p.) or vehicle was administered to animals in their home cages 6 h after the completion of each Post-test. This 6 h time-point

was chosen in order to ensure that the drug was given outside of the consolidation “window” (for review, see [28]).

Following CPP conditioning, all groups had developed a significant preference for the cocaine-paired compartment, as evidenced by a preference score that was significantly different from zero (One-sample t-test, vehicle: $t_{(7)} = 5.44$, $p < 0.001$; 0.1 mg/kg SCH23390: $t_{(9)} = 7.83$, $p < 0.0001$; 0.4 mg/kg SCH23390: $t_{(7)} = 6.26$, $p < 0.001$; 1 mg/kg SCH23390: $t_{(9)} = 7.81$, $p < 0.0001$). During subsequent daily, unreinforced preference testing (i.e., extinction training), the group that received post-test vehicle injections reached the no-preference criterion sooner than each of the three SCH23390 groups. Whereas the vehicle group reached the no-preference criterion on Post-test 5, post-test SCH23390 treatment dose-dependently prolonged the extinction relative to the vehicle treated group (Figure 2). The 0.1 mg/kg SCH23390 group reached the no-preference criterion on Post-test 6, and the 0.4 mg/kg and 1 mg/kg SCH23390 groups reached the criterion on Post-tests 9 and 10, respectively. Two-way ANOVA of Preference scores on Post-tests 1 through 5 revealed a significant overall effect of treatment, $F_{(3, 32)} = 3.15$, $p < 0.05$. Post-hoc analysis revealed significant differences between 0.4 mg/kg SCH23390 and vehicle (Student's t-test, $p < 0.05$), as well as 1 mg/kg SCH23390 and vehicle (Student's t-test, $p < 0.01$) across the first five Post-tests. Importantly, in the control experiment where animals received either SCH23390 (1 mg/kg, i.p.) or vehicle 6 h after each Post-test, no difference in extinction rate was seen between the groups (two-way ANOVA, $F_{(1, 15)} = 1.04$, $p > 0.05$).

In both the main experiment and the control experiment, SCH23390 administration resulted in increased locomotion, measured as total number of beam breaks within the CPP apparatus. Two-way ANOVA revealed a significant overall effect of treatment (main experiment: $F_{(3, 32)} = 4.78$, $p < 0.01$; control experiment: $F_{(1, 15)} = 34.15$, $p < 0.0001$). Interestingly, this effect was not dose-dependent, as post-hoc analysis revealed no significant differences between doses. This increased locomotion is not unexpected based on prior descriptions of behavioral effects resulting from repeated SCH23390 administration [29]. We do not believe this increased locomotion had a direct effect on rate of extinction since it was seen in both the main experiment where SCH23390 dose-dependently prolonged extinction, and in the control experiment where SCH23390 had no effect on rate of extinction.

Here we have shown that daily post-retrieval systemic administration of the D1 antagonist SCH23390 dose-dependently prolongs extinction of cocaine-CPP. The experimental literature suggests a precedent for the phenomenon of post-training SCH23390 administration prolonging extinction. Our finding is consistent with the ability of SCH23390 infusion into the infralimbic cortex (IL) to prolong extinction of auditory fear conditioning [25]. We postulate that the prolonged extinction demonstrated in our experiment results from impaired consolidation of extinction learning based on the known role of the medial prefrontal (mPFC, especially IL) cortex in mediating consolidation of extinction [30–32]. A potential role for mPFC dopaminergic neurotransmission in the consolidation of extinction is also supported by previous studies showing that 6-hydroxydopamine lesions of this region, which induce a DA depletion, result in impaired long-term extinction of fear conditioning [24, 26]. Our findings, along with those cited above, support a role for DA D1 receptors in extinction of both aversive and appetitive memories.

Considering potential mechanisms for these D1 receptor influences, the NMDA subtype of glutamate receptors in the mPFC is a known target of modulation by DA D1 receptors [33], and D1 receptors have been implicated in the occurrence of NMDA receptor-dependent synaptic plasticity in the mPFC [34]. Our present results do not provide direct evidence concerning the neural locus of the effects of D1 receptor antagonism on extinction of

cocaine-contextual memories. However, future studies investigating possible interactions of DA with other neurotransmitter systems, such as glutamate, in the mPFC are planned to further elucidate the role that DA plays in the processing of cocaine-cue memories.

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Research Highlights

- The role of dopamine D1 receptors in extinction of cocaine memories is unknown.
- Post-retrieval SCH23390 prolonged extinction of learned cocaine place preference.
- SCH23390 effects on extinction occurred dose-dependently.
- SCH23390's effects on extinction were unrelated to locomotor activity.
- D1 receptors are necessary for consolidating extinction of cocaine-cue memories.

Figure 1.

Schematic representation of the conditioned place preference procedure. On day 1, animals were tested for initial preference. Days 2–7 were conditioning days during which animals were given an injection of either cocaine or saline and confined to either one of the large outer chambers of the CPP apparatus. Although only one possible organization of days is shown here, the animals were counterbalanced such that there were equal numbers of animals who began conditioning on day 2 in each of the two environments (white vs. checkered). Because all four groups showed an initial non-significant preference for the checkered compartment, during conditioning cocaine injection was paired with confinement to the white compartment. At 48 hours after the last conditioning session, animals were tested again for preference in a manner identical to day 1, followed immediately by an injection of Vehicle or one of three doses of SCH23390. This procedure (test followed by injection) was repeated daily until each treatment group reached a pre-determined “no-preference” criterion.

Figure 2.

CPP expression indicated by time in the drug-paired compartment minus time in the drug-unpaired compartment ("Preference (sec)"). Dashed line indicates "no-preference" criterion, set at 15% of the average preference at Post-test 1. Final N's per group were as follows: vehicle and 0.4 mg/kg SCH23390 = 8 each, 0.1 mg/kg SCH23390 and 1 mg/kg SCH23390 = 10 each. (*) Indicates a significant effect of treatment (Post-test 1 through Post-test 5; two-way ANOVA, $p < 0.05$). Post-hoc analysis revealed significant differences between 0.4 mg/kg SCH23390 and vehicle (Student's t-test, $p < 0.05$), as well as 1 mg/kg SCH23390 and vehicle (Student's t-test, $p < 0.01$).

Table 1

Control experiment: CPP expression indicated by time in the drug-paired compartment minus time in the drug-unpaired compartment (Mean $\pm$ SEM). Final N's per group were as follows: delayed vehicle = 8, delayed SCH23390 = 9. Note that no difference in extinction rate was seen between the groups (two-way ANOVA, $F_{(1,15)} = 1.04$, $p > 0.05$).

Post-test	1	2	3	4	5
delayed SCH23390	253.98 $\pm$ 46.06	46.31 $\pm$ 47.26	92.56 $\pm$ 21.11	100.08 $\pm$ 53.79	93.98 $\pm$ 41.79
delayed Vehicle	255.11 $\pm$ 25.29	175.86 $\pm$ 71.72	186.03 $\pm$ 73.73	165.82 $\pm$ 84.17	126.51 $\pm$ 72.96

Post-test	6	7	8	9	10
delayed SCH23390	119.00 $\pm$ 49.38	40.91 $\pm$ 45.56	52.99 $\pm$ 37.97	37.41 $\pm$ 50.72	-69.98 $\pm$ 67.50
delayed Vehicle	135.36 $\pm$ 95.99	49.29 $\pm$ 65.90	112.11 $\pm$ 65.36	83.19 $\pm$ 70.80	61.80 $\pm$ 38.86