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Double dissociation between actions of dopamine D1 and D2 receptors of the ventral and dorsolateral striatum to produce reinstatement of cocaine seeking behavior

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HIGHLIGHTS

- Stimulation of D1R, but not D2R, of the NAcc induces reinstatement of cocaine-seeking.
- Stimulation of D2R, but not D1R, of the DLS induces reinstatement of cocaine-seeking.
- Blockade of D1R or D2R of the NAcc impedes reinstatement by systemic D2R agonist.
- Blockade of D1R and D2R of the DLS impedes reinstatement by systemic D2R agonist.

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ABSTRACT

One of the hallmarks of addiction is the enduring vulnerability to relapse. Following repeated use, cocaine (COC) induces neuroadaptations within the dopamine (DA) system, arguably underlying several aspects of COC-seeking behavior. Peripheral stimulation of D2, but not D1, receptors induces relapse. However, where in the brain these effects occur is still matter of debate. The D1 and D2 receptors (D1R; D2R) are highly expressed in the nucleus accumbens (NAcc) and the dorsolateral striatum (DLS), but their specific involvement in the reinstatement of COC-seeking remains elusive. We assessed the reinstating effects of intracerebral infusions of agonists of D1R (SKF82958) or D2R (quinelorane) within the NAcc or DLS of rats after extinction of COC self-administration (COC SA). To assess whether we could block peripheral D2 agonist (quinelorane) induced reinstatement, we simultaneously infused either a D1R (SCH23390) or a D2R (raclopride) antagonist within the NAcc or DLS. When infused into the NAcc, but not into the DLS, SKF82958 induced reinstatement of COC-seeking; conversely, quinelorane had no effect when injected into the NAcc, but induced reinstatement when infused into the DLS while the D1R agonist has no effect. While administration of raclopride into the NAcc or DLS impedes the reinstating effect of a systemic quinelorane injection, the infusion of SCH23390 into the NAcc or DLS surprisingly, blocks the reinstatement induced by the peripheral D2R stimulation. Our results point to a double dissociation between D1R and D2R of the NAcc and DLS, highlighting their complex interactions within both structures, in the reinstatement of COC-seeking behavior.

1. Introduction

Although the factors responsible for the resumption of COC taking in human are not completely understood, acute re-exposure to the drug has been identified as a major determinant of relapse. In an animal model of relapse, an acute "priming" injection of COC results in a robust reinstatement of a formerly acquired and then extinguished drug self-administration (SA) behavior (for reviews, see Shaham et al., 2003; Stewart, 2000). Cocaine increases synaptic DA in the mesocorticolimbic system (Di Chiara, 1999; Torregrossa and Kalivas, 2008), which under

Abbreviations: Nucleus Accumbens, (NAcc); Dorsolateral Striatum, (DLS); D1 receptor, (D1R); D2 receptor, (D2R)

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normal conditions is responsible for regulating motivation and reward (Wise, 2004). Repeated exposures to COC lead to changes at both molecular and cellular levels in this pathway and this process has been proposed to underlie the transition to addiction and the vulnerability to relapse (Robinson and Berridge, 1993).

The ventral (nucleus accumbens; NAcc) and dorsal divides of the striatum are major targets of the DAergic pathway, being both highly influenced by DAergic inputs arising from the midbrain ventral tegmental area (VTA) and Substantia Nigra (SN), respectively (Voorn et al., 2004). In this sense, it is hypothesized that COC-induced plasticity in these circuits underlies several aspects of drug seeking behavior (Pierce and Vanderschuren, 2010) through the recruitment of the ascending spiraling circuitry arising from VTA projections to the NAcc, eventually reaching the SN and dorsal portions of the striatum (Everitt, 2014; Haber and Behrens, 2014).

Dopamine signaling in the NAcc drives different kinds of responses to rewarding (both natural and pharmacological) and aversive stimuli (Floresco, 2015) and the role of NAcc DAergic innervation in reinstatement has been demonstrated both in humans and rodents (for reviews, see Baler and Volkow, 2006; Bossert et al., 2005; Venniro et al., 2016). For instance, injection of DA or DA releasing agents such as amphetamine in the NAcc induces reinstatement of COC-seeking in rats with an history of COC SA (Cornish and Kalivas, 2000; Park et al., 2002). Chronic COC or amphetamine consumption has been shown to recruit progressively the dorsal part of the striatum (Letchworth et al., 2001; Porrino et al., 2004). Indeed, the dorsal striatum and more specifically its dorsolateral part (DLS) is proposed to play a key role in the transition to compulsive drug use (Everitt et al., 2008), being responsible for the habitual aspects of drug-seeking after prolonged drug SA (Belin and Everitt, 2008; Zapata et al., 2010).

Regarding reinstatement or relapse, an increased DA release in the dorsal striatum has been shown when both rats and human addicts are reexposed to COC cues (Ito et al., 2002; Volkow et al., 2006). In accord, the reversible inactivation of the DLS or the DA blockade within this region have been shown to attenuate context and cue-induced reinstatement of COC-seeking; similar results have been observed after inactivation of the SN, the primary DA input to the DLS (Fuchs et al., 2006; See et al., 2007).

Whether in the NAcc or DLS, DA acts on five subtypes of metabotropic membrane receptors. These receptors belong to either the D1-like (D1 and D5) or D2-like (D2, D3, and D4) family based on their structural and pharmacological properties (for review, see Beaulieu and Gainetdinov, 2011). Both D1R and D2R play an essential but differential role in the reinstatement of COC-seeking behavior. Whereas the systemic administration of D2R antagonists reduce priming-induced reinstating effects of peripherally administered COC (Schenk and Gittings, 2003; Spealman et al., 1999; Weissenborn et al., 1996), systemic D2R agonists are able to strongly reinstate COC-seeking behavior (Dias et al., 2004; Self et al., 1996; Weissenborn et al., 1996). On the other hand, D1R agonists injected systemically do not induce reinstatement by themselves (De Vries et al., 2002, 1999; Dias et al., 2004; Self et al., 1996; Spealman et al., 1999). They rather reduce the reinstating effect of a peripheral COC priming, which is evidenced as well by the administration of D1R antagonists (Alleweireldt et al., 2003; Self et al., 1996; Spealman et al., 1999). These differential responses to D1R and D2R agents raise the question of the central implications of D1 and D2 receptors. Within the NAcc, although many studies suggest a rewarding/reinforcing role for the D1R and an aversive/punishing role for the D2R (Hikida et al., 2013; Kravitz et al., 2012; Lobo et al., 2010; Volman et al., 2013), some results do not support this dichotomy (Soares-Cunha et al., 2016; Steinberg et al., 2014; Trifilieff et al., 2013).

Together, these data convey that both D1R and D2R play differential roles within both striatal subregions, and show that they are crucial for the reinstatement of COC-seeking and relapse. Yet the mechanisms and the specific regions where these receptors act to induce the reinstatement of COC-seeking remain elusive. Given their importance, we sought to tease apart the reinstating effects of both DA receptor subtypes within the two striatal regions (i.e. NAcc and DLS) as well as their participation on the systemic D2R agonist-induced reinstatement of COC-seeking (Dias et al., 2004).

2. Material and methods

2.1. Subjects

Male Wistar rats (Charles River Laboratories, France) weighing 225–275 g were used. Rats were housed in cages in groups of two in a temperature (22 °C) and humidity (60%) controlled environment, subjected to a reversed 12 h light/dark cycle (lights on from 20:00 to 08:00 h). Food and water were available *ad libitum*. All experiments were conducted during the dark phase of the light/dark cycle (activity phase in rats) and performed in accordance with the European directive (86/609/EEC), with approval of the *Centre National de la Recherche Scientifique* (CNRS), concerning the use of laboratory animals and under the French Ministry of Research and Innovation authorization # 50120123-A.

2.2. Surgery

2.2.1. Intravenous catheter implantation

Animals were deeply anesthetized with isoflurane (4–5% induction, 1–2% maintenance) and an indwelling catheter (SILASTIC tubing; Dow Corning, Midland, MI) was surgically implanted into the right jugular vein. The proximal end of the catheter was secured to the vein with surgical silk sutures and passed subcutaneously to the top of the back, where it exited into a connector (modified 22-gauge cannula). The distal end of the catheter was connected to stainless steel tubing encased in dental cement anchored with a square of mesh (Small Parts Inc., USA).

2.2.2. Intracerebral surgeries

Bilateral implantation of stainless-steel guide cannulae was carried out immediately after the implantation of the catheter into the jugular vein for SA experiments. The rats were positioned in a stereotaxic apparatus and implanted with bilateral 26-gauge guide cannulas targeting the NAcc or DLS using the following coordinates relative to bregma: NAcc – anteroposterior (AP) + 1.5 mm; mediolateral (ML) ± 1.3 mm; dorsoventral (DV) - 4.0 mm; DLS – AP + 0.8 mm; ML ± 3.4 mm; DV -3.8 mm (Paxinos and Watson, 2007). The guide cannulae were aimed at either 1.5 mm (for DLS) or 2.5 mm (for NAcc) above the target region. For the fixation of the guiding cannula to the skull, dental cement was used, with the addition of four screws.

Animals were monitored and weighed daily after the two surgeries and were allowed to recover for at least 10 days prior to any behavioral training. During this period, they were flushed daily with 0.2 ml of an ampicillin solution (0.1 g/ml Totapen; ConvaTec, Paris, France) containing heparin (300 IU/ml) to maintain catheter patency.

2.3. Behavioral apparatus

Operant conditioning for COC reinforcement was conducted in twelve standard operant conditioning chambers (30 cm height × 40 cm length × 36 cm depth, Imetronic, Pessac, France). The experimental chambers were located in an experimental room equipped with white noise generators and each of them was individually housed in a wooden sound-attenuating box fitted with ventilation fans. Each experimental chamber had two clear Plexiglass walls on the front and back sides and two opaque panels on the left and right sides and the floor consisted of 6 mm diameter steel bars spaced 15 mm apart, center-to-center. Two retractable levers (4.5 cm wide) were located on each extremity of the left panel (7 cm above the floor) and were counterbalanced as “active” lever (AL) and “inactive” lever (IL). Illumination of a soft house-light

bulb (2 W) signaled the start of the sessions. During SA sessions, animals were connected through a Silastic tube protected by a metal spring with a swivel to a 10 ml syringe fitted into an external pump. Presses on the AL activated the external pump and delivered intravenous saline (SAL) or COC infusions. Each infusion was paired with a 3 s presentation of a cue light located above the AL and followed by a 20 s time out period.

2.4. Cocaine self-administration and reinstatement tests

The behavioral procedures have been described previously (Dias et al., 2004; Keiflin et al., 2008).

2.4.1. Acquisition and extinction phases

After recovery from surgery, rats were placed in the operant chambers and trained to lever press on a FR1 schedule for SAL or COC (250 μg/infusion) SA in daily 2 h sessions. Each session started with a free non-contingent infusion. Depression of the AL resulted in the delivery of 100 μl drug solution over a period of 3s accompanied by the illumination of a cue light above the AL, while the house light was switched off. Each injection was followed by a 20s time out period during which lever responding was without consequences. Depression of the IL was recorded but had no programmed consequence. After 15 training sessions on average [ranging from 13 to 18 sessions], COC SA rats achieved stable responding; for which the criterion was to reach less than 10% variation over the last three SA sessions (see Supplemental Fig. S1 for acquisition data of each experiment). Subsequently, all animals underwent 15 days on average of extinction sessions during which each AL press resulted in the presentation of the cue light and an infusion of saline for both groups. At the end of the extinction period, the number of lever presses stabilized at a low level of responding (see Supplemental Fig. S2 for extinction data of each experiment).

2.4.2. Reinstatement phase

Reinstatement was characterized by the renewal of lever pressing on the previously AL in extinction conditions. Responding on levers was recorded during the 2 h reinstatement sessions. As during the extinction phase, AL responding elicited the illumination of the cue light and an infusion of saline; IL responses were recorded but had no consequences. First, on two consecutive days, rats were submitted to either a saline or a COC (15 mg/kg; i.p.) challenge immediately before being placed in the apparatus to verify that a COC priming induced reinstatement in all animals.

Next, the ability of intracerebral administrations of different doses of a DA D1R or DA D2R agonists to reinstate COC-seeking behavior was assessed in different test sessions conducted every 3 days interspersed by two extinction sessions. Two injection needles (30-gauge, Small Parts inc., USA) were lowered bilaterally through the implanted brain cannula to reach the targetted brain structures (NAcc or DLS). Using a micro-infusion syringe pump connected via tubing (PE10, silastic tubing, Down Corning) to the injection needles, the DA receptor agonists or antagonists at different doses or phosphate-buffered saline (PBS) were bilaterally infused over 53 s either into the NAcc or the DLS, following a Latin-square design. Infusion cannulae were left in place for another 60s to allow for drug diffusion before rats were placed into the operant chambers.

2.5. Drugs

Cocaine hydrochloride (Cooperative Pharmaceutique Française, France) was dissolved in sterile 0.9% saline solution. The D1R agonist (±) chloro-APB hydrobromide (SKF82958), the D1R antagonist R(+)–SCH–23390 hydrochloride (SCH23390), the D2R agonist quinelorane dihydrochloride and the D2R antagonist S(−)-Raclopride (+)-tartrate salt were all dissolved in PBS (all drugs were purchased from RBI-Sigma, USA). The different agonists and antagonists were administered at the following doses: for peripheral administration: saline 1 ml/kg; cocaine at 15 mg/kg/ml; D2R agonist quinelorane at 0.25 mg/kg/ml. For intracerebral administrations: the D1R agonist, SKF82958 at 0.05; 0.1; 0.5 or 1 μg/0.5 μl/side; the D2R agonist, quinelorane at 0.05; 0.1; 1; 1.5; 2.5 or 5 μg/0.5 μl/side; the D2R antagonist raclopride at 5 μg/0.5 μl/side; the D1R antagonist SCH23390 at 1 μg/0.5 μl/side and phosphate-buffered saline (PBS) at 0.5 μl/side. Doses were chosen as referred by Baldo et al. (2002), Dias et al. (2004), and Nowend et al. (2001).

2.6. Experimental designs

2.6.1. Experiment 1: reinstatement produced by D1R or D2R agonist injection in the nucleus accumbens

The first set of rats (n = 29) was submitted to the surgical procedure for intravenous catheter and intracerebral cannula implantation. Once recovered from surgery, the animals underwent the acquisition of SAL (n = 12) or COC (n = 17) SA paradigm, followed by extinction training. After attaining stable responding in the extinction phase, these animals first received intraperitoneal saline (1 ml/kg) and COC (15 mg/kg) challenges in a counterbalanced manner to verify that peripheral COC administration induced reinstatement. Then, animals were randomly assigned into 4 groups in order to receive different doses of either a D1R (SKF82958) or D2R agonist (quinelorane) in the NAcc as follows: SAL SA D1R agonist intra NAcc (n = 6); COC SA D1R agonist intra NAcc (n = 9); SAL SA D2R agonist intra NAcc (n = 6), COC SA D2R agonist intra NAcc (n = 8). The different doses of SKF82958 and quinelorane were administered in a counterbalanced order and each intracerebral injection was followed by at least two extinction sessions before the next administration.

Following each peripheral or intracerebral injections, the rats were immediately positioned in the SA cages in extinction conditions and the number of AL and IL lever presses was recorded during the 2 h long test session (see Fig. 1A for procedure scheme).

2.6.2. Experiment 2: reinstatement produced by D1R or D2R agonist injection in the dorsolateral striatum

A second set of rats (n = 31) was used for Experiment 2 in the same conditions as in Experiment 1; the rats were implanted with intra DLS cannula and run through SAL (n = 12) or COC (n = 19) SA. As in Experiment 1, after attaining stable responding on the extinction phase, all animals first received intraperitoneal saline (1 ml/kg) and COC (15 mg/kg) challenges in a counterbalanced manner to verify that peripheral COC induced reinstatement. Then, four groups of animals were constituted in order to receive different doses of either D1R agonist (SKF82958, same doses as in Experiment 1) or D2R agonist (quinelorane, same doses as in Experiment 1) in the DLS. The numbers of animals per groups were as follows: SAL SA D1R agonist intra DLS (n = 6), COC SA D1R agonist intra DLS (n = 11), SAL SA D2R agonist intra DLS (n = 6), COC SA D2R agonist intra DLS (n = 8) (*see* Fig. 2A for procedure scheme).

Since we found that only the highest dose of the D2R agonist induced a strong reinstatement, an additional set of rats was conducted in the same conditions described above but received intermediate doses of quinelorane in the DLS. In the same conditions as Experiments 1 and 2, rats (n = 11) were submitted to the surgical procedures for i.v. cathether and intra DLS cannula implantations. Once recovered from surgery, the animals underwent the acquisition of SAL (n = 6) or COC (n = 5) SA, followed by extinction training. After attaining stable responding on the extinction phase, these animals first received intraperitoneal saline (1 ml/kg) and COC (15 mg/kg) challenges in a counterbalanced manner to verify that peripheral COC induced reinstatement. Then the two groups of animals received different doses of the D2R agonist in the DLS as follows: SAL SA D2R agonist intra DLS (n = 6), COC SA D2R agonist intra DLS (n = 5). The different doses of

the D2R agonist (quinelorane: 0, 1, or 2.5 μg/0.5 μl/injection) were administered in a counterbalanced order and each injection was followed by at least two extinction sessions before the next intra-cerebral administration.

2.6.3. Experiment 3: Blockade of peripheral D2R agonist effect by a D1R and/or D2R antagonist administration in the dorsolateral striatum and nucleus accumbens

Rats that were run in Experiment 2 and new rats (n = 20) were used for these tests. Rats implanted with cannula into the DLS underwent systemic administration of quinelorane and simultaneous intra-DLS infusion of either the D1R antagonist SCH23390 (1 μg/0.5 μl/injection; n = 11, being SAL SA n = 6; COC SA n = 5) or the D2R antagonist raclopride (5 μg/0.5 μl/injection; n = 31, being SAL SA n = 12; COC SA n = 19; see Fig. 3A; 3D for procedure scheme). Rats implanted with cannula in the NAcc received systemic administration of quinelorane and simultaneous intra-NAcc infusion of either SCH23390 or raclopride, in the same doses (SCH23390 or raclopride n = 9, being SAL SA n = 4; COC SA n = 5. See Fig. 4A for procedure scheme).

2.7. Histology

After completion of behavioral testing, animals received a lethal dose of sodium pentobarbital (Ceva Santé Animale, France) and were perfused transcardially with a 4% formaldehyde solution. The brains were removed and stored in a 30% sucrose-formalin solution for 72 h. Coronal sections (60 μm) were sliced on a freezing microtome, and after being mounted onto gelatin-coated slices, they were left to dry for 24h to be then stained with thionin. Cannula placements were verified under a light microscope, and section reconstructions were drawn in reference to the atlas of Paxinos and Watson (2007; Supplementary Fig. S5). Animals in which at least one of the two cannulae was misplaced were excluded from the experiment. Numbers of animals described in previous sections refer to the final group sizes that were included into statistical analyses, not taking into account animals that were discarded either due to catheter failure and/or cannula misplacement. Altogether the number of rats removed from each experiment due to the aforementioned reasons were as follows: Experiment 1: n = 5; Experiment 2: n = 6; Experiment 3: n = 2.

2.8. Data analyses

Responding during the acquisition and extinction sessions was analysed using a two-way analysis of variance (ANOVA) with days and levers as repeated measures. Responding during the reinstatement phase was analysed using a three-way ANOVA with group as the between-subjects factor (SAL SA versus COC SA) and challenge or doses (SAL versus COC or PBS versus SKF82958, quinelorane, SCH2 3390 or raclopride) and lever (AL *vs.* IL) as within-subjects factors. Following each overall ANOVA, significant main effects were further analysed by multiple comparisons Newman-Keuls *post hoc* tests.

3. Results

3.1. Experiment 1: reinstatement elicited by D1R, but not D2R, agonist infused into the NAcc

3.1.1. Acquisition, extinction and peripheral cocaine challenges

Rats of the COC SA group acquired stable responding on the AL during acquisition and then underwent extinction training (Fig. 1A shows the outline of Experiment 1 and Supplemental Figs. S1 and S2 Experiment 1 show acquisition and extinction data). Next, animals underwent a SAL and a COC challenge (Fig. 1B), to control for relapsing behavior. As this phenomenon has been extensively described in the literature, the statistical data regarding these experiments are described in detail in the supplementary information section.

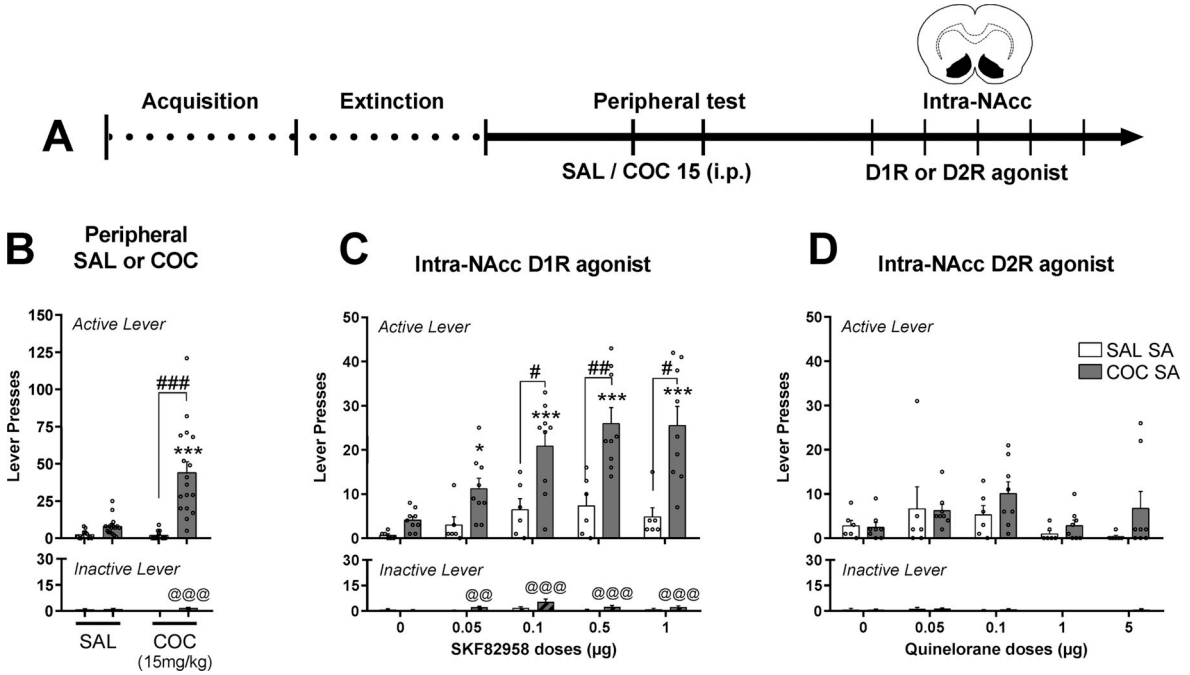


Fig. 1. Intra-NAcc infusion of the D1R agonist, but not D2R agonist, induces reinstatement of cocaine-seeking (Experimental design: A). Active lever responses to cocaine or saline challenges for COC SA (gray bars; n = 17) and SAL SA (white bars; n = 12) animals (B). D1R agonist SKF82958 when injected into the NAcc dose-dependently induces the reinstatement of COC seeking in the COC SA group (gray bars; n = 9) but not in the SAL SA group (white bars; n = 6) (C). Intra NAcc infusion of the D2R agonist quinelorane does not induce reinstatement of COC seeking in the COC SA group (gray bars, n = 8) when compared to the SAL SA group (white bars; n = 6; D). Data are expressed as mean ± SEM. * p < 0.05; *** p < 0.001: dose/treatment effect [versus dose 0 (PBS)]; # p < 0.05; ## p < 0.01; ### p < 0.001: group effect [versus SAL SA]; @@ p < 0.01; @@@ p < 0.001; lever effect (three-way ANOVAs followed by Newman-Keuls *post hoc* tests).

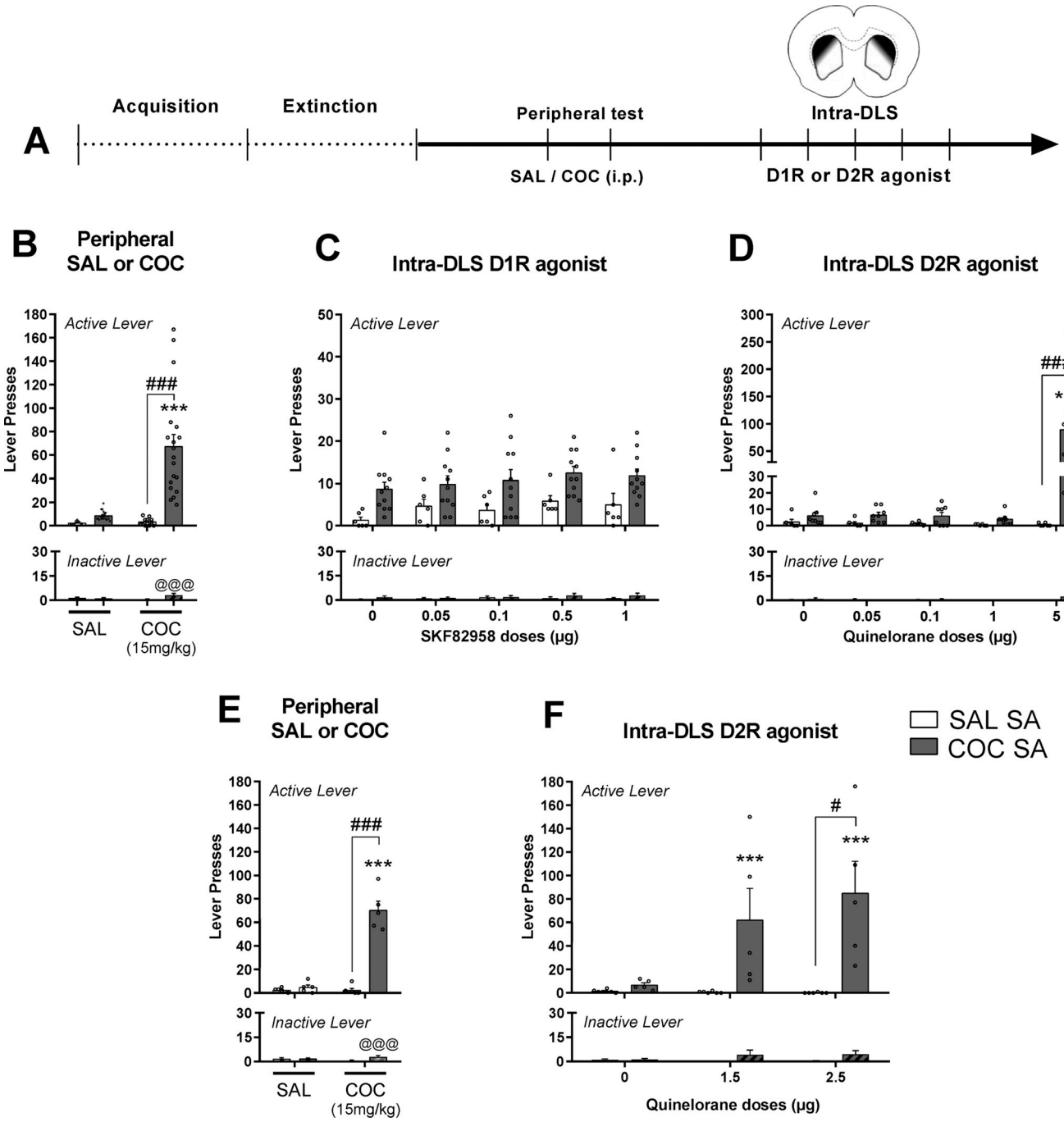


Fig. 2. Intra-DLS infusion of the D2R agonist, but not D1R agonist, induces reinstatement of cocaine-seeking (Experimental design: A). Active lever responses to cocaine or saline challenge for COC SA (gray bars; n = 19) and SAL SA (white bars; n = 12) animals (B). D1R agonist SKF82958 did not induce reinstatement of cocaine seeking in the COC SA group (gray bars, n = 11; SAL SA: white bars, n = 6) when injected into the DLS (C). Intra DLS infusion of the D2R agonist quinelorane induces reinstatement of cocaine seeking in the COC SA group (gray bars, n = 8; SAL SA: white bars, n = 6)with the highest dose tested (D). In another cohort of rats, a second dose response test was performed (E; F): Active lever responses to cocaine or saline challenge for COC SA (gray bars; n = 5) and SAL SA (white bars; n = 6) animals (E). D2R agonist quinelorane dose-dependently induces the reinstatement of cocaine seeking in the COC SA group (gray bars; n = 5) but not the SAL SA group (white bars; n = 6; F). Data are expressed as mean ± SEM. ** $p < 0.01$; *** $p < 0.001$: dose/treatment effect [versus dose 0 (PBS)]; # $p < 0.05$; ### $p < 0.001$: group effect; @@@ $p < 0.001$; lever effect (three-way ANOVA followed by Newman-Keuls *post hoc* tests).

3.1.2. Intra-NAcc challenges

The D1R agonist injected in the NAcc induced a dose dependent reinstatement of lever presses on the AL. The three way ANOVA (group x dose x lever) indicated a significant interaction ($F_{(4,52)} = 4.12$; $p = 0.0056$]). Post hoc analyses on AL data indicated that the D1R agonist SFK 82958 elicited a dose-dependent increased responding within the COC SA group in comparison to the SAL SA group [group × doses interaction $F_{(4,52)} = 5.52$; $p = 0.00087$). Newman-Keuls post hoc analyses indicated that the COC SA group increased AL presses with all doses of the D1R agonist in comparison with the dose 0

[lever × dose interaction $F_{(4,32)} = 12.94$; $p = 0.000002$; Newman-Keuls (NK): dose 0 μg *vs.* 0.05 μg: $p = 0.0173$; 0 μg *vs.* 0.1 μg: $p = 0.0002$; 0 μg *vs.* 0.5 μg: $p = 0.0001$; 0 μg *vs.* 1 μg: $p = 0.0001$) and also in comparison to the IL (NK: dose 0.05 μg: $p = 0.01$; dose 0.1 μg: $p = 0.0001$; dose 0.5 μg: $p = 0.0001$; dose 1 μg: $p = 0.0001$). No differences in IL presses of the COC SA group were found. A dose × lever interaction close to significance was observed within the SAL SA group due to a marginal increase in AL presses [$F_{(4,20)} = 2.70$; $p = 0.05978$] with the 0.1 and 0.5 μg doses of the D1R agonist, in comparison to the dose 0 (Fig. 1C).

Concerning the D2R agonist, the ANOVA conducted on the effects of intra-NAcc administration of the different doses of quinelorane showed a main effect of lever [$F_{(1,12)} = 17.72$; $p = 0.0012$] but no group effect nor group x dose × lever interaction [$F_{(4,48)} = 0.86$; $p = 0.4923$; Fig. 1D].

3.2. Experiment 2: reinstatement elicited by D2R, but not D1R, agonist infused into the DLS

3.2.1. First dose response experiment

3.2.1.1. Acquisition, extinction and peripheral cocaine challenges. Rats of the COC SA group acquired stable responding on the AL during acquisition and then underwent extinction training (Fig. 2A shows the outline of Experiment 2 and Supplemental Figs. S1 and S2 Experiment 2 1st dose response show the acquisition and extinction data). Next, animals underwent a SAL and a COC challenge (Fig. 2B), to control for relapsing behavior. As this phenomenon has been extensively described in the literature, the statistical data regarding these experiments are described in detail in the supplementary section.

3.2.1.2. Intra-DLS challenges. Intra-DLS administration of different doses of the D1R agonist SKF82958 showed a lever × group interaction [$F_{(1,15)} = 5.85$; $p = 0.0288$] and post hoc analyses indicated that the COC SA group showed a general increase on AL compared to SAL SA and to its IL ($p = 0.0015$ and $p = 0.0004$, respectively). However, no group x dose × lever interaction was found [$F_{(4,60)} = 0.18$; $p = 0.9491$]. In addition, no interactions have been observed regarding responding on the IL (Fig. 2C).

For the D2R agonist, the 3 way ANOVA indicated a significant group x dose × lever interaction [$F_{(4,48)} = 5.95$; $p = 0.0006$]. Newman-Keuls post hoc analyses indicated that the COC SA group increased AL presses when injected with the highest dose of quinelorane in comparison with all other doses [$F_{(4,28)} = 8.03$; $p = 0.0002$; NK: dose 5 μg *vs.* 0 μg, 0.05 μg, and 1 μg: $p = 0.0001$; 5 μg *vs.* 0.1 μg: $p = 0.0002$] and also in comparison with the IL (NK: $p = 0.0001$ for all doses). Further two-way ANOVA and post hoc analyses showed that AL presses of COC SA group were also superior in comparison with SAL SA group [dose × group interaction; $F_{(4,48)} = 6.14$; $p = 0.0005$; NK: COC SA dose 5 μg *vs.* SAL SA 0 μg, 0.05 μg, and 0.1 μg: $p = 0.0001$; *vs.* 1 μg: $p = 0.0002$; *vs.* 5 μg: $p = 0.0038$]. No interactions have been observed regarding responding on the IL (Fig. 2D).

3.2.2. Second dose-response experiment

Experiment 2 showed that reinstatement of COC-seeking was produced only by the highest dose of quinelorane administered into the DLS. Therefore, we performed another complementary experiment in which we administered intermediate doses of quinelorane aiming to further investigate the reinstating effects caused by the infusion of the D2R agonist into the DLS. Thus, we trained another set of rats in the same protocol of COC SA as in the previous experiments.

3.2.2.1. Acquisition, extinction and peripheral cocaine challenges. Rats of the COC SA group acquired stable responding on the AL during acquisition and then underwent extinction training. Next, animals underwent a SAL and a COC challenge (Fig. 2E and Supplemental Figs. S1 and S2 Experiment 2 2nd dose response show the acquisition and extinction data) to control for relapsing behavior. As this phenomenon has been extensively described in the literature, the statistical data regarding these experiments are described in detail in the supplementary section.

3.2.2.2. Intra-cerebral challenges. Intra-DLS administration of different doses of the D2R agonist quinelorane showed an interaction of group x dose x lever [$F_{(2,18)} = 6.92$; $p = 0.0059$]. Post hoc analyses indicated that the COC SA group increased AL presses when injected with both doses of quinelorane in comparison with PBS administration [lever × dose interaction; $F_{(2,8)} = 5.56$; $p = 0.0306$; NK: dose 0 μg *vs.* 1.5 μg: $p = 0.0095$; *vs.* 2.5 μg: $p = 0.0035$] and also in comparison with the IL (NK: dose 1.5 μg: $p = 0.0192$; dose 2.5 μg: $p = 0.0073$). Post hoc analyses of group x dose x lever [$F_{(2,18)} = 6.92$; $p = 0.0059$] interaction also showed that AL presses of COC SA group were marginally superior in comparison with SAL SA group in the dose of 1.5 μg [NK: $p = 0.1108$], and were significantly superior for the dose of 2.5 μg [NK: $p = 0.0310$]. No interactions have been observed regarding responding on the IL (Fig. 2F).

3.3. Experiment 3: effects of D1R or D2R antagonists into the DLS or NAcc on cocaine-seeking reinstatement induced by peripheral injection of D2R agonist

3.3.1. D1R antagonist into the DLS blocks, while D2R antagonist attenuates, cocaine seeking induced by peripheral infusion of D2R agonist

Our lab and others have previously shown that a peripheral administration of a D2R agonist induces reinstatement of COC-seeking (Dias et al., 2004; Self et al., 1996; Weissenborn et al., 1996). Given that we demonstrated here that the injection of the D2R agonist quinelorane (but not the D1R agonist SKF82958) into the DLS was able to induce reinstatement of COC-seeking, we tested whether the reinstatement produced by the peripheral administration of quinelorane is due to its action on DLS D2R receptors by questioning its blockade with an intra-DLS administration of a D2R antagonist. Thus, in two sets of rats (taken from experiment 2) we performed a systemic administration of the D2R agonist quinelorane with the simultaneous intra-DLS injection of the D2R antagonist raclopride or the D1R antagonist SCH23390 (see Fig. 3A and D for experimental outlines).

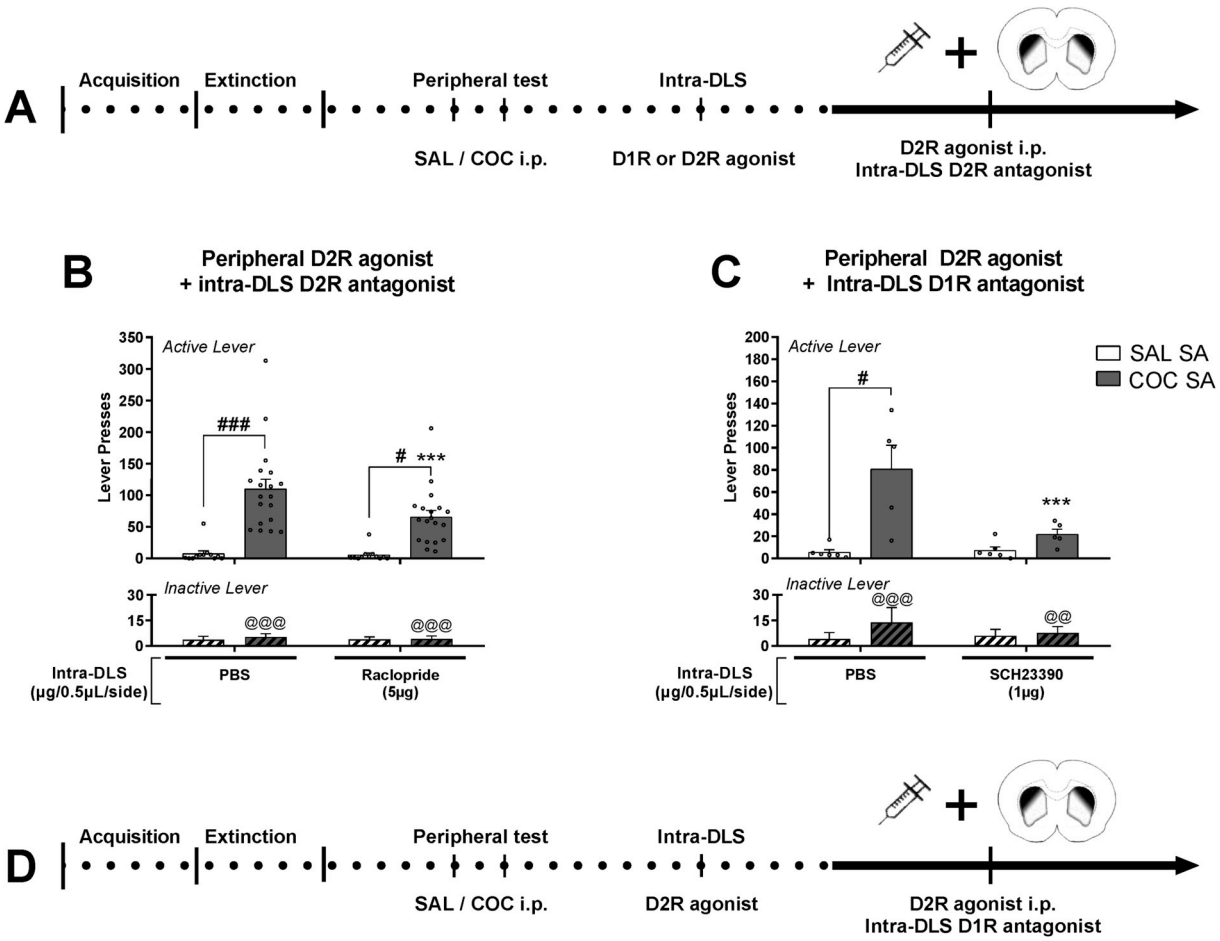


Fig. 3. Intra-DLS injection of the D2R and D1R antagonist decrease D2R agonist-induced reinstatement of COC-seeking. D2R antagonist raclopride attenuates reinstatement induced by systemic injection of D2R agonist quinelorane (0.25 mg/kg) on the COC SA group (A: Experimental design; B: COC SA :gray bars, n = 19; SAL SA: white bars, n = 12). D1R antagonist SCH23390 blocks reinstatement induced by systemic injection of D2R agonist quinelorane (0.25 mg/kg) on the COC SA group (C: COC SA: gray bars, n = 5; SAL SA: white bars, n = 6; D: Experimental design). Data are expressed as mean ± SEM. *** $p < 0.001$: treatment effect (*versus* PBS); # $p < 0.05$; ### $p < 0.001$: group effect; @@ $p < 0.01$; @@@ $p < 0.001$: lever effect (three-way ANOVAs followed by Newman-Keuls *post hoc* tests).

For the group receiving intra-DLS infusion of raclopride, a three-way ANOVA showed a group x lever × antagonist interaction [$F_{(1,29)} = 7.04$; $p = 0.0128$]. Further two-way ANOVA [group × antagonist interaction: $F_{(1,29)} = 7.91$; $p = 0.0087$] and post hoc analyses showed that the peripheral administration of quinelorane induced a strong reinstatement of lever presses on AL in the COC SA group in comparison with SAL SA group (NK: $p = 0.0002$). This confirms previous studies showing the strong reinstating effects of the peripheral infusions of D2R agonists on COC-seeking (Caine et al., 1999; Dias et al., 2004; Khroyan et al., 2000). Post hoc analyses also showed that the simultaneous intra-DLS infusion of D2R antagonist raclopride restrained the reinstatement of AL pressing induced by the peripheral infusion of quinelorane in the COC SA group (NK: $p = 0.0004$), though still being marginally superior in comparison to the SAL SA group (NK: $p = 0.0236$). Responding on IL in both experiments showed no interactions whatsoever (experimental design: Fig. 3A; Fig. 3B).

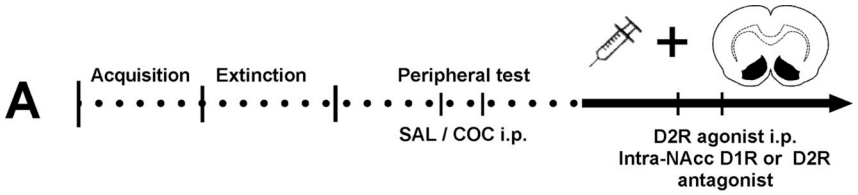
For the group undergoing intra-DLS infusion of the D1R antagonist SCH23390, the three-way ANOVA showed a group x lever × antagonist interaction [$F_{(1,9)} = 9.97$; $p = 0.0116$], while further two-way ANOVA [group × antagonist interaction: $F_{(1,9)} = 10.24$; $p = 0.0108$] and post hoc analyses showed that the peripheral administration of the D2R agonist quinelorane induced the reinstatement of AL presses in the COC SA group compared to the SAL SA group (NK: $p = 0.0041$). Interestingly, post hoc analyses also showed that the simultaneous intra-DLS infusion of the D1R antagonist SCH23390 impeded the reinstatement of AL pressing induced by the peripheral infusion of quinelorane in the COC SA group (NK: $p = 0.0019$), being then comparable to the SAL SA group (NK: $p = 0.3663$). The experimental design is in Fig. 3D and data in Fig. 3C.

These impairments in quinelorane-induced reinstatement by both the D2R and the D1R antagonist injections in the DLS are not due to any locomotor debilitating effects as can be seen from Supplemental Fig. S3 that shows locomotor activity data measured during the reinstatement challenges in the self-administration cages, which are equipped with photocell beams.

3.3.2. D1R or D2R antagonists into the NAcc blocks reinstatement of cocaine-seeking induced by peripheral infusion of D2R agonist

As we have previously observed that the D1R agonist administered in the NAcc induced reinstatement of COC-seeking, we also assessed whether the D1R in the NAcc participated in the process of induction of reinstatement observed with the peripheral injection of this D2R agonist. Thus, with another set of rats we performed the same systemic treatment with quinelorane (0.25 mg/kg; i.p.), this time with either the simultaneous injection of the D1R antagonist SCH23390 or the D2R antagonist raclopride in the NAcc (see Fig. 4A for experimental design).

A three-way ANOVA showed a lever x antagonist × group interaction [$F_{(2,14)} = 10.05$; $p = 0.002$]. Further two-way ANOVAs [antagonist × group interaction: $F_{(2,14)} = 9.44$; $p = 0.0025$] and post hoc analyses showed that the peripheral administration of the D2R agonist quinelorane induced an enhancement of AL responding in the COC SA group in comparison with SAL SA group (NK: $p = 0.0336$). Again, this



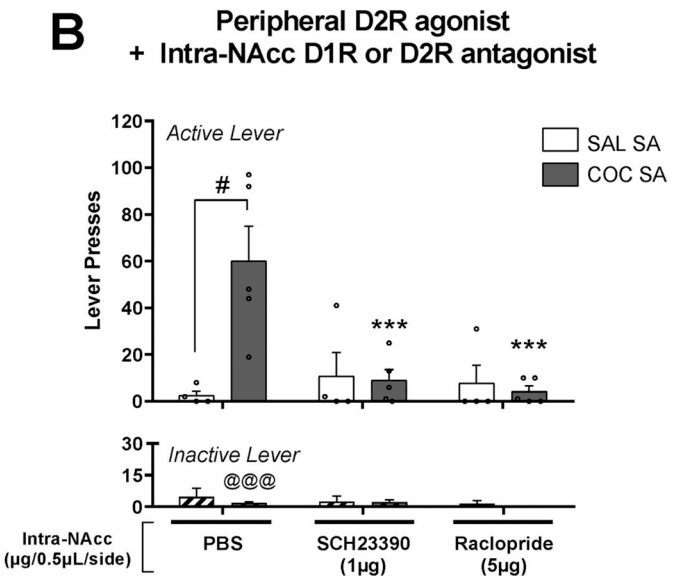


Fig. 4. Intra-NAcc infusion of the D1R antagonist SCH2 3390 or the D2R antagonist raclopride block D2R agonist-induced reinstatement of COC-seeking (Experimental design: A). D1R or D2R antagonists block the reinstatement of cocaine seeking induced by systemic injection of D2R agonist quinelorane (0.25 mg/kg) in the COC SA group (COC SA: gray bars, n = 5; SAL SA: white bars, n = 4; B). Data are expressed as means ± SEM. *** $p < 0.001$: treatment effect (*versus* PBS); # $p < 0.05$: group effect; @@@ $p < 0.001$: lever effect (three-way ANOVA followed by Newman-Keuls *post hoc* test).

confirms a strong reinstating effects of the peripheral infusions of D2R agonists on COC-seeking (Dias et al., 2004; Khroyan et al., 2000; Weissenborn et al., 1996). Post hoc analyses also showed that intra-NAcc infusion of either SCH23390 (NK: $p = 0.0015$) or raclopride (NK: $p = 0.0018$) completely blocked the reinstatement of AL pressing induced by the peripheral infusion of quinelorane on the COC SA group, with the COC SA group showing similar average of AL presses as the SAL SA group, under the same treatments (SCH: NK $p = 0.9037$; Quin: NK $p = 0.8064$). Responding on IL showed no interactions whatsoever (Fig. 4B).

Contrary to the DLS injections, debilitating effects on locomotor activity might have played a role in the impairments of quinelorane induced reinstatement, as decreased locomotion has been observed following intra-NAcc injection of the D1R and D2R antagonists (Fig. S4).

4. Discussion

The aim of the present work was to identify the neural substrates in terms of brain structures and DA receptors that may preside over the reinstatement of COC-seeking behavior. When looking at the specific involvement of either D1R or D2R agonists administered locally in the brain, the present work shows a double dissociation between the actions of D1R and D2R in the ventral (NAcc) and dorsolateral portions of the striatum on the reinstatement of COC-seeking in rats. Our results show that within the NAcc, administration of a D1R but not a D2R agonist induces reinstatement whereas within the DLS, administration of a D2R but not D1R agonist induces reinstatement of drug seeking. This indicates that the two DA receptors are acting differently in the expression of reinstatement.

Since reinstatement of COC-seeking is produced by COC and has been shown to be replicated by a peripheral administration of a D2R agonist (but not by a D1R agonist) (Dias et al., 2004), we verified the respective implication of the D1R and D2R receptor locally in the ventral and dorsal portions of the striatum in the peripheral D2R effects reported. Our hypothesis, regarding the previous findings, was that blockade of the D2R in the DLS will preclude D2R agonist induced reinstatement. Effectively, we found that quinelorane-induced reinstatement was attenuated by a D2 antagonist injection in the DLS but surprisingly also by a D1 antagonist injection. Taking into account that neither of these two antagonists have motor effects, these data indicate that within DLS, complex interactions between these two receptors preside to quinelorane induced reinstatement of cocaine seeking behaviors. Within the NAcc, the reinstating effects produced by the systemic administration of the D2R agonist were also blocked by an intra NAcc infusion of either a D1R or a D2R antagonist. However here, the specificity of the effects can be discussed, since both antagonists show in parallel strong locomotor decreasing effects that might have to some degree prevented expression of reinstatement. Further experiments need to be completed to draw a definitive answer.

Taken together, these studies highlight the complexity of interactions between these two types of DA receptors, whose actions appear to be brain structure-specific in the reinstatement of COC-seeking.

4.1. A D1R but not a D2R agonist in the NAcc reinstates cocaine seeking

Our results showing the reinstating effects of D1R stimulation within the NAcc adds to the literature demonstrating the importance of the D1R bearing medium spiny neuron (MSN) pathway of the NAcc in goal directed behaviors (Lobo et al., 2010; Lobo and Nestler, 2011) and more specifically, on the reinstatement of COC-seeking behavior (Bachtell et al., 2005; Hobson et al., 2013). The intra NAcc administration of the D2R agonist quinelorane, on the other hand, had no effect when injected in the same region. This indicates that, as DA is released in the NAcc, the stimulation of D1R plays a major role in the reinstatement of COC seeking. Indeed, while intra-NAcc COC or DA infusion has been shown to reinstate COC-seeking (Cornish and Kalivas, 2000; Park et al., 2002), here this is replicated in a dose dependent

manner by the sole stimulation of the D1R within the NAcc but not by the D2R stimulation. Different neuroadaptations in D1R-vs D2R-MSNs in the NAcc may take place in response to COC SA. Indeed, a wide array of research has shown differential and often opposing roles of D1R- and D2R-MSNs in motivation and reinforcement (Hikida et al., 2010; Kai et al., 2015; Kravitz et al., 2012; Lobo et al., 2010; Self et al., 1996), which have been linked to their distinguished projections to target regions. Accumbal MSNs differentially contribute to COC-induced neuroadaptations by changing their intrinsic, synaptic, and structural characteristics in a cell type-specific fashion (for a review, see Smith et al., 2013). Repeated COC exposure increased and decreased miniature excitatory post-synaptic currents at D1R-and D2R-MSNs, respectively (Kim et al., 2011). Further, repeated COC exposure has been shown to potentiate transmission at D1R-MSNs, through the strengthening of their glutamatergic inputs onto NAcc D1R-MSNs (Bock et al., 2013; Dobi et al., 2011; Pascoli et al., 2012), while weakening the outputs of D2R-gabaergic MSNs at ventral pallidum (Creed et al., 2016). Altogether, these data indicate that COC exposure reorganizes cell type- and input-specific connectivity in the NAcc possibly rendering signaling from accumbal D1R bearing MSNs more efficient at contributing to the induction of COC-seeking.

Regarding the DAergic mesolimbic circuitry, the inactivation of the DA projection from the VTA to the NAcc leads to a reduction in COC-seeking behavior (See et al., 2007). In fact, as opposed to D2R bearing-MSNs, D1R-MSNs of the NAcc project preferentially to GABAergic neurons within the VTA, which in turn innervate VTA-DA neurons (Bocklisch et al., 2013). This D1R-MSN direct-pathway is potentiated by COC treatment, resulting in an enhancement of GABA release from D1R-MSNs onto VTA-GABA neurons, and thus disinhibiting VTA-DA neurons (Bocklisch et al., 2013). Taking into account the importance of the DAergic input into the NAcc, one can assume that the activation of D1R by the intra-NAcc injection of SKF82958 may indirectly disinhibit DA-VTA neurons, thus enhancing DA levels on the ventral striatum, thus leading to reinstatement of drug-seeking behavior (Bocklisch et al., 2013; Phillips et al., 2003).

Concerning the D2R action within the NAcc, we did not observe any effect despite a dose-dependent response. This absence of effect should be interpreted with caution since some previous studies have shown that intra NAcc D2R agonist administered in the shell of the NACC induces reinstatement of COC-seeking (Bachtell et al., 2005; Schmidt et al., 2006; Schmidt and Pierce, 2006s). Our injections did not differentiate the shell and core parts of the NAcc (most of our injections reached the boundaries of both core and medial shell as shown in Fig. S5, supplementary information) and this might have precluded the observation of more localized effects of the D2R agonist. In addition, the methodology used might play a role in the difference of results we observed. Bachtell et al. (2005) have used a within-session reinstatement procedure, while in our work the animals underwent 2 weeks of extinction sessions before the reinstatement tests. Finally, different pharmacological profiles between the D2R agonists used might also be considered: in our study we used quinelorane while Schmidt et al. (2006) and Bachtell et al. (2005) have used quinpirole and 7-OH-DPAT, respectively. These agonists have been shown to have similar or higher affinity for the D3R vs. D2R as compared with quinelorane (Malmberg et al., 1994; Sautel et al., 1995).

In this work, we used the D2R agonist quinelorane as a follow up of our published study looking at peripheral effects of D1 and D2 agonists on cocaine seeking reinstatement (Dias et al., 2004). Quinelorane exerts low agonistic effects on D3R (Ireland et al., 2005). Indeed, the use of compounds that exhibit marginal selectivity for D3R *vs.* D2R may underlie the elusiveness of the relative role of D2R and D3R in the relapse of COC seeking (Sokoloff and Le Foll, 2017). Nonetheless, the administration of the D3R agonist PD 128.907 into the NAcc failed to induce reinstatement of COC seeking behavior (Schmidt et al., 2006), which seems to argue against the involvement of the D3R of the NAcc in the reinstatement of COC seeking.

Regarding the ineffectiveness of D2R stimulation within the NAcc to induce reinstatement, D2R downstream mechanisms cannot be ruled out. For instance, a significant reduction of the D2R high affinity state is observed within the NAcc after COC SA, likely due to a potentiation by COC of the antagonistic interactions between D2R and the A_{2A} adenosine receptor subtypes within the NAcc (Filip et al., 2012; Pintsuk et al., 2016). This leads to the suggestion that this interaction may hinder any reinstating effects that the D2R agonist may have when administered within the NAcc after COC SA (Bachtell and Self, 2009; Borroto-Escuela et al., 2016; Pintsuk et al., 2016).

Finally, it should be noted that besides being localized post-synaptically, D2R are also found presynaptically on DA projections (Vallone et al., 2000), as well as on corticostriatal inputs in the striatum. On these different sites, many roles have been attributed to D2R, from the modulation of other receptors' function, to the regulation of transmitter (e.g. DAergic and glutamatergic, in the striatum) release (Soares-Cunha et al., 2016). Thus, the use and the interpretation of D2R pharmacology is usually very complex.

4.2. A D2R but not a D1R agonist in the DLS reinstates cocaine seeking

Several works suggest the participation of DAergic inputs to the DLS in COC-seeking and its reinstatement (Gabriele et al., 2012; Gabriele and See, 2011; Pacchioni et al., 2011). Exposure to COC cues induce increases in extracellular DA in the dorsal striatum of rodents and humans, with this increase being positively correlated with self-reports of craving in COC-dependent subjects (Gabriele et al., 2012; Garavan et al., 2000; Ito et al., 2002; Volkow et al., 2006). Hence, the involvement of the DLS DA in COC associated behaviors progressively increases with experience. Within this region, DA mediates cue-controlled COC-seeking (Ito et al., 2002). Whereas inactivation of DLS with GABA agonists after 1, 14 or 60 days of abstinence following COC SA disrupts COC seeking behavior (Pacchioni et al., 2011), reversible inactivation of the DLS impairs COC primed reinstatement, after 14 days of abstinence (Gabriele and See, 2011). Also, while DLS inactivation attenuates COC seeking following exposure to a discrete associated cue or to the context following extinction training (Fuchs et al., 2006), intra-DLS infusion of the DA receptor antagonist α-flupenthixol impairs COC SA under a second-order schedule of reinforcement (Vanderschuren et al., 2005). Importantly, the DAergic input into the DLS is known to be a critical component of drug seeking characterized as habitual or compulsive (Belin and Everitt, 2008; Volkow et al., 2006) and its action has been shown to be critical in habitual COC-seeking behavior (Zapata et al., 2010).

Regarding the DLS indirect pathway, the reinstating effect observed by the intra-DLS infusion of the D2 agonist quinelorane is not likely to be underlain by its actions through D3R. Besides its low agonistic effect on D3R, this receptor subtype is scarcely, if at all, expressed in the DLS (Stanwood et al., 2000). On the other hand, the D2R has been shown to be highly expressed within the dorsal striatum and specifically within the DLS, as compared to DMS (Yin et al., 2009).

4.3. Not that simple: cooperation vs. competition of D1R/D2R in reinstatement

Here we replicated previously published results showing that peripheral administration of a D2R agonist such as quinelorane (but not a D1R agonist) powerfully induces reinstatement of COC-seeking following extinction (Dias et al., 2004). However, our data regarding intracerebral infusions suggests that this effect is not mediated by the D2R of the NAcc alone, since the injection of quinelorane in this region did not induce reinstatement. Intriguingly, our experiments suggest that the reinstating effects of the systemic administration of the D2R agonist are most likely dependent on a complex interaction between D1R and D2R both at NAcc and dorsal striatum. This assumption is based on our results showing that the inhibition of the D1R or D2R within the

dorsolateral or the ventral portion of the striatum blocks or attenuates (respectively) the reinstatement of COC-seeking by peripheral administration of a D2R agonist.

This blockade highlights the importance of the cooperative activity of both D1R and D2R of the striatum on the systemic D2R stimulation-induced reinstatement of COC-seeking. Other examples of the necessary role for D1R on the expression of D2R-mediated effects include the facilitation of conditioned reward by bromocriptine. This D2R agonist has been shown to depend on D1R activity, as the pretreatment with D1R antagonist blocks the aforementioned effect (Ranaldi and Beninger, 1995). The interaction between both DA receptors on the reinstatement of COC-seeking is also evidenced by studies showing that the reinstatement induced by intra-NAcc shell infusion of D2R agonist was completely blocked by either pre- (Schmidt and Pierce, 2006) or simultaneous treatment with D1R antagonist SCH23390 (Bachtell et al., 2005).

In addition, in our study raclopride was not able to block completely the systemic quinelorane-induced reinstatement when injected into the DLS. This suggests that whereas the stimulation of D2R within the DLS can reinstate drug-seeking behavior, the reinstatement induced by systemic D2R agonist may rely on additional mechanisms. Similar effect is observed regarding the participation of D1R within the DLS in our study, not being able to induce reinstatement by itself, but impeding systemic quinelorane reinstatement once pharmacologically blocked.

4.4. Complexity within the ventro/dorsal divides of the striatum

The transition from initial to compulsive drug use correlates with a shift in the striatal subregions controlling drug-related behaviors, from the NAcc to the DLS (Everitt and Robbins, 2013). Cell-type-specific alterations in striatal D1R-MSN versus D2R-MSN signaling in response to COC has also been reported in several studies (Anderson and Pierce, 2005; Lobo and Nestler, 2011; Smith et al., 2013). The consensus is that increased sensitivity to COC and COC-seeking behaviors is associated with a predominance of D1R-MSN activity over D2R-MSN activity (Bock et al., 2013; Lobo et al., 2010). Very recently, Marcott et al. (2018) demonstrated that repeated exposure to COC produced a decrease in the sensitivity of postsynaptic D2R signaling specifically in the NAcc in comparison to the dorsal striatum. On the other hand, COC SA increases the proportion of D2R in the high affinity state within the dorsal region of the striatum (Briand et al., 2008). Differences in neuroadaptations between the ventral and dorsal striatum may thus have contributed to our contrasting data.

In summary, our study highlights the interaction of D1R and D2R within different striatal regions, evidencing that the role of both receptors influence each other's actions on the reinstatement of COC-seeking behavior. It appears that both regions of the striatum act in tandem in the induction of the reinstatement, with the participation of both dopamine receptor subtypes. This might happen in spite of the segregation of the receptors in striatal neurons; one possible mechanism may rely on the collateral connections between D1R- and D2R-MSNs, in which D1R and D2R may modulate the activity of each other and mutually modulating the activity of MSNs, finally influencing behavioral outputs (Philibin et al., 2011; Soares-Cunha et al., 2016).

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CRediT authorship contribution statement

Renan Costa Campos: Conceptualization, Methodology, Data curation, Writing - original draft. **Carine Dias:** Methodology, Data curation, Writing - review & editing. **Florence Darlot:** Methodology, Writing - review & editing. **Martine Cador:** Conceptualization, Methodology, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropharm.2020.108113.

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