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Research report

Role of basolateral amygdala dopamine D2 receptors in impulsive choice in acute cocaine-treated rats

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HIGHLIGHTS

- Acute cocaine dose-dependently decreased the impulsive choice in rats.
- D2 receptor blockade had no effect on impulsive choice.
- D2 receptor blockade in the basolateral amygdala reversed the cocaine-induced impulse inhibition.

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ABSTRACT

Psychostimulant substances have been found to either increase or inhibit impulsive choice (preference to choose small immediate reward over large delayed reward) in laboratory animals. Although central dopamine transmission has been demonstrated to be involved in impulsivity and drug addiction, little is known regarding dopaminergic neurotransmission in addictive drug-induced alteration of impulse control. In this study, we used a delay discounting model to measure impulsive choice in rats and found that acute cocaine dose-dependently decreased impulsive choice in rats. Intraperitoneal injection (i.p.) of D1 receptor antagonist SCH23390 (0.02 mg/kg) could increase the impulsive choice but had no effect on the inhibition of impulsive choice induced by acute cocaine exposure. D2 receptor antagonist eticlopride (0.06 mg/kg) had no effect on the choice behavior itself, but it reversed acute cocaine-induced impulse inhibition. Moreover, bilateral microinjection of eticlopride (1 μg/side) into the basolateral amygdala (BLA) but not the nucleus accumbens (NAc) core reversed the inhibitory effect of acute cocaine on impulsive choice. These data suggest important but dissociable roles of dopamine D1 and D2 receptors in impulse control. The preference of delayed rewards depends on D1 receptors, whereas acute cocaine inhibited impulsive choice by activating D2 receptors in the BLA.

1. Introduction

Impulsivity is a heterogeneous phenomenon, which includes impaired inhibitory control of inappropriate behavior, preference for immediate over delayed rewards and premature decision making [1].

In addition to being part of normal behavior, impulsivity is tightly associated with many psychiatric disorders, such as drug addiction. Drug addicts and animals chronically exposed to opiates or cocaine often chose the small immediate reward instead of a large delayed reward [2–10]. High impulsivity could be a consequence of drug addiction as well as a risk factor for developing substance dependence [11]. Impulsivity can be an important predictor of craving [12], and former drug abusers who relapse after abstinence are characterized by impulsivity [13].

The high degree of overlap between impulsivity and drug addiction suggests that similar neurobiological mechanisms may be involved in these processes [11,14]. As one facet of impulsive behavior, impulsive choice is preferred for an immediate smaller reward instead of a delayed larger reward [15]. Previous studies have demonstrated the modulatory role of specific dopamine (DA) receptors in impulse choice. Systemic administration of D1 or D2 receptor antagonist could increase impulsive choices [16–18]. Endogenous D1/D5 receptor stimulation in the medial prefrontal cortex (mPFC) promoted the choice of large delayed rewards [19]. Infusion of D1 or D2 receptor antagonist into orbitofrontal cortex tended to decrease the choice of a large reward if the delay to its delivery was signaled by a cue light [20]. It is well known that drugs

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of abuse (cocaine, amphetamine, morphine, nicotine) increase the extracellular DA concentrations in the nucleus accumbens (NAc), despite their diverse pharmacological mechanism [21–23]. Several studies have proved that addictive drugs, such as amphetamine, can reduce impulsive behavior on the delay discounting task [16,17,24–26], although conflicting results have also been reported [27–29]. However, the role of DA in drug-induced alteration of impulsive choice has not been confirmed, as well as the contributions of DA receptor subtypes and brain regions.

Beyond the dopaminergic pathway from the ventral tegmental area (VTA) to NAc, the basolateral amygdala (BLA) receives dopaminergic projections from the VTA [30,31]. Furthermore, the BLA sends glutamatergic fibers to the NAc, interacts with DA terminals [32–35] and presynaptically modulates NAc DA efflux [36,37]. The VTA, BLA and NAc form a functionally interconnected network that is critical for processing the primary rewarding effects of natural rewards (*e.g.*, food) and addictive drugs, as well as reward-related memory [38–40]. The NAc and BLA have been strongly implicated in impulse control. Excitotoxic lesions or the inactivation of the NAc core or BLA in rats can increase impulsive choice behavior in delay-discounting procedure [41–46].

Therefore, we postulated that the dopaminergic system within the BLA or NAc may be a point of convergence for the impulsive choice and addiction. Uncovering the role of DA in the drug-induced alteration of impulse control will help us to understand the neurobiological basis of impulsivity and drug addiction.

The aim of this study was (1) to determine the effect of acute cocaine exposure on impulsive choice, (2) to compare the contribution of DA D1 and D2 receptors to acute cocaine-induced impulse control behavior and impulsive behavior itself and (3) to pinpoint further the roles of DA D2 receptors within the NAc core and BLA in the cocaine's effect on impulsive choice.

2. Materials and methods

2.1. Subjects

Sixteen male Sprague–Dawley rats were used (Grade I, purchased from Animal Center of Peking University, Beijing), weighing 250–300 g at the beginning of the experiment. Each rat was housed individually, maintained on a 12:12-h light–dark cycle (lights off at 08:00 a.m.) and had access to food *ad libitum*. Rats were habituated to the environment for at least 1 week before the behavior training. The experiments were performed in a quiet room with the temperature maintained at 20–25 °C. All experiments were conducted in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (National Research Council 1996) and approved by the Peking University Committee on Animal Care and Use (No: LA2010-053). All efforts were made to minimize animal suffering and to reduce the number of animals used.

2.2. Delay discounting task

2.2.1. Apparatus

Training and testing occurred in operant chambers (40 cm × 20 cm × 40 cm) contained within light- and sound-insulated boxes. Each chamber was fitted with two retractable levers positioned equidistantly on one wall. Levers were 4 cm wide, 5 cm from the Plexiglas floor and 10 cm apart, and equally distant to the sidewall. A nose-poke and an extended liquid receptacle, which were 2 and 4 cm from the floor, respectively, were centrally located between the two levers. Liquid reward (40 μl water per drop) was delivered by a pump. There was a 3 W cue light inside the nose-poke and a 6 W house light above each operant chamber. Each box was equipped with a video camera and a monitor to provide a view of the chamber, and the output from each camera was recorded into a digital video file for off-line analysis. Two computers were located in an adjacent room, one of which programmed the operant equipment and collected the data and the other was used for video recording.

2.2.2. Procedure

The delay discount model used in our study was modified from the experiment model used by Evenden and Ryan [47] and has been reported in Zuo et al. [48].

The rats first learned to nose-poke to trigger presentation of the levers and to press the levers for water reward, and then they were trained to perform an active choice task until a stable behavioral performance was achieved. To judge whether subjects had successfully acquired the task and reached stable baseline behavior, data from seven consecutive sessions were analyzed by repeated-measures ANOVA with two within-subject factors (session and delay). If the effect of 'delay' was significant at the $P < 0.05$ level but there was no main effect of 'session', animals were considered to have reliably acquired the task. Rats were trained or tested for only one session per day. Each session consisted of 6 blocks of 12 trials. Each block began with two forced-choice trials, only one lever was extended (either left or right, randomizes in pairs), permitting rats to learn the unique outcomes associated with each lever press. The remaining 10 trials were free choice (both levers were presented).

A trial began with the onset of both the house light and cue light, if the rat nose-poke occurred within 10 s, the cue light went out and two levers were extended in the other side of the chamber 1.5 s later. Animals were required to respond on either lever within 10 s. A press on one lever (either left or right, counterbalanced across groups) resulted in the immediate delivery of one drop of water (40 μl, the small, immediate reward); a press on the other lever resulted in the delivery of five drops of water after varying delays (200 μl, the large, delayed reward). The two levers were retracted after the rat succeeded to press one. The house light remained on throughout the delay period and turned off 8 s after the reward was delivered, and the chamber entered into the inter-trial interval (ITI) state until the start of next trial. There are no cues during the delay period. An omission was recorded if the rat failed either to nose-poke or to press the subsequently extended levers within 10 s, and the program returned to the inter-trial interval state with the cue light and house light extinguished until the next trial was scheduled to begin. The delay to large reward remained constant within each block and increased from 0 to 2, 4, 8, 12 and 16 s across blocks. Each trial lasted 50 s no matter what the choice that was made by the subject. Because the rats chose the different delayed reward, the ITI duration was [50–(latency of nose poke and lever press + delay)] seconds. The rats drank about 10 ml of water during the sessions and they had free access to water for 20 min after the finish of each session, followed by approximately 23 h of water deprivation before the start of the next session. They could drink about 40–50 ml of water per day. It is enough to meet their daily need and the body weight of rats did not have significant loss. The same fluid restriction scheme has been used in previous study [48].

2.3. Drugs

Cocaine, D1 receptor antagonist SCH23390 hydrochloride (Sigma-Aldrich, St. Louis, MO, USA) and D2 antagonist eticlopride hydrochloride (Sigma-Aldrich) were used in our study. All drugs were dissolved in 0.9% saline and protected from light. The effects were tested according to Latin square designs. Each rat accepted one pattern of administration before the behavior test in each session. Following a drug test day, rats were retrained for approximately 3–4 days until the behavior stabilized (data from the 3 days

were analyzed by repeated-measures ANOVA, no change was found over time), after which subsequent drugs were administered.

2.4. Experimental design

2.4.1. Experiment 1: effect of acute cocaine exposure on impulsive choice in rats

Using an adopted Latin square design, different doses of cocaine [5, 10, 15, and 20 mg/kg, intraperitoneal injection (i.p.)] were administered in rats trained to perform a delay discounting task for 1 month until stable baseline behavior was attained. Behavior testing began immediately after cocaine injection.

2.4.2. Experiment 2: effects of SCH23390 and eticlopride on the inhibition of impulsive choice caused by acute cocaine treatment

First, we investigated the effects of D1 and D2 receptor antagonists on impulsive choice in rats. Different doses of D1 receptor antagonist SCH23390 (0, 0.01, 0.02 mg/kg, i.p.) and D2 receptor antagonist eticlopride (0, 0.06, 0.09 mg/kg, i.p.) were given 5 min before the behavior testing, respectively. The doses of D1 and D2 receptor antagonists used in this study were selected based on previous studies [16].

Then, to explore whether the inhibitory effect of acute cocaine on impulsive choice in rats depends on DA D1 and D2 receptors, SCH23390 (0.02 mg/kg, i.p.), eticlopride (0.06 mg/kg, i.p.) and saline were administered 10 min before the injection of 10 mg/kg cocaine, respectively.

2.4.3. Experiment 3: effects of microinjection of D2 receptor antagonist into the NAc core and BLA on acute cocaine-induced impulse inhibition

2.4.3.1. Microinfusion surgery. All sixteen rats were surgically implanted with guide cannulae in the NAc and BLA. Rats were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) and secured in a Kopf stereotaxic apparatus with the incisor bar set at −3.3 mm relative to the interaural line in flat skull position. Small burr holes (1 mm in diameter) were drilled on the skull for bilateral placement of stainless-steel guide cannulae (OD 0.80 mm) into the NAc core [anterior/posterior (AP) +2.2 mm, medial/lateral (ML) ±1.5 mm, dorsal/ventral (DV) −6.5 mm] and BLA (AP −2.8 mm, ML ±4.7 mm, DV −7.8 mm). The tip of the guide cannulae was directed to 1 mm above the intended sites of injection. Cannulae were secured to the skull with dental acrylic cement. To prevent clogging, a stainless steel stylet (OD 0.56 mm) was placed in the guide cannulae. All animals were allowed to recover for 1 week before retraining in the delay discounting task.

2.4.3.2. Microinfusion. The influence of D2 receptor antagonist eticlopride in the NAc core and BLA on impulsive choice and cocaine-induced alteration of impulse control was tested by intracerebral microinfusions of eticlopride into these brain regions after the behavior restabilized.

One day before the microinfusion test day, obdurators were removed and a sham infusion procedure (injector was placed in the guide cannulae for 2 min, but no infusion was administered) was conducted to habituate the rats to the routine of infusions. During the microinfusion of eticlopride (0.3, 1, 2 μg/side), obturators were removed, and infusion cannulae (OD 0.4 mm) were extended 1.0 mm below the guide cannulae. The injection was performed through an infusion pump (0.4 μl, 0.1 μl/min, with Harvard syringe pump), while the rat was gently held. The injector was left in place for 2 min to ensure drug diffusion. The obturators were then replaced, and the rats were placed back to their home cage. The animals' behavior was tested 5 min after the infusion. Drug doses for eticlopride were based on previous studies in which similar doses were infused intracranially and were identified to increase the impulsive choice in rats [49]. In Fig. 5, the delay discounting performance with sham infusion on the day before ETI test day was used as the pre-ETI baseline control.

2.5. Histology

Histological verification of the cannulae location was performed after behavioral testing. Rats were anesthetized with chloral hydrate (35 mg/kg, i.p.) and perfused transcardially with 0.9% saline (200 ml) followed by 4% formalin solution (300 ml). After removal from the skull, the brains were post-fixed in 4% formalin solution overnight and transferred into 20 and 30% sucrose solution (in 0.01 M PBS) until sectioning. Coronal sections (30 μm thick) were cut on a cryostat (−19 °C) and wet-mounted on glass microscope slides. Only those animals with cannulae that were correctly placed were used for data analysis (see Fig. 1).

2.6. Data analysis

The percentage of trials in which the animal chose the large delayed rewards was calculated both separately for each delay and across all the delays in each session. All the statistical analyses and graphics were performed with IBM SPSS (version 20, IBM Corporation, Armonk, NY, USA). Data were presented as the mean ± standard error of the mean (SEM). Repeated-measures ANOVA were used for analyses of the effect of cocaine, SCH23390 or eticlopride on percent choice of the large reward. LSD *post hoc* test was used for pairwise comparisons. The average percent choice across all delays was compared by one-way ANOVA followed by LSD *post hoc* test or paired *t*-test. If the delay × dose interaction was significant, further ANOVA was used to examine the effect of drug at different delays. In order to assess the effect of SCH23390 or eticlopride on the cocaine-induced alteration of impulsive choice, data were analyzed by repeated-measures with antagonist (two-level: present or absent), drug (two-level: present or absent) and delay as within-subject variables. If the antagonist × drug × delay interaction was significant, paired *t*-test was used to examine the effect of antagonist at different delays. Graphs were produced using GraphPad PRISM 5.0 (GraphPad Software, San Diego, CA, USA).

Statistical significance was set at $P < 0.05$. Only the significant effects that were critical for the data interpretation are reported in Section 3.

Four rats were excluded from the data analyses because of incorrect cannulae placement. Two rats died during the experiment. Sometimes, the rats failed to finish more than 50% of the trials; therefore, the data were also excluded. Animal numbers are depicted in the figure captions.

3. Results

3.1. Acute cocaine exposure dose-dependently decreased impulsive choice in rats

As shown in Fig. 2, a typical delay discounting behavior was established. Rats preferred the large reward if the reward delivery was immediate and they shifted their preference to the small reward gradually as the delay to the large reward was increased. A single cocaine exposure (10, 15 and 20 mg/kg, i.p.) dose-dependently increased the choice of the large delay reward [dose, $F(4, 63) = 5.306$, $P = 0.001$] in a delay-dependent manner [delay × dose interaction, $F(20, 315) = 1.770$, $P < 0.05$], indicating that cocaine could reduce the impulsive decision making. Further comparisons showed that 10 and 15 mg/kg cocaine increased the choice of the large reward at the delay of 4, 8 and 12 s, whereas

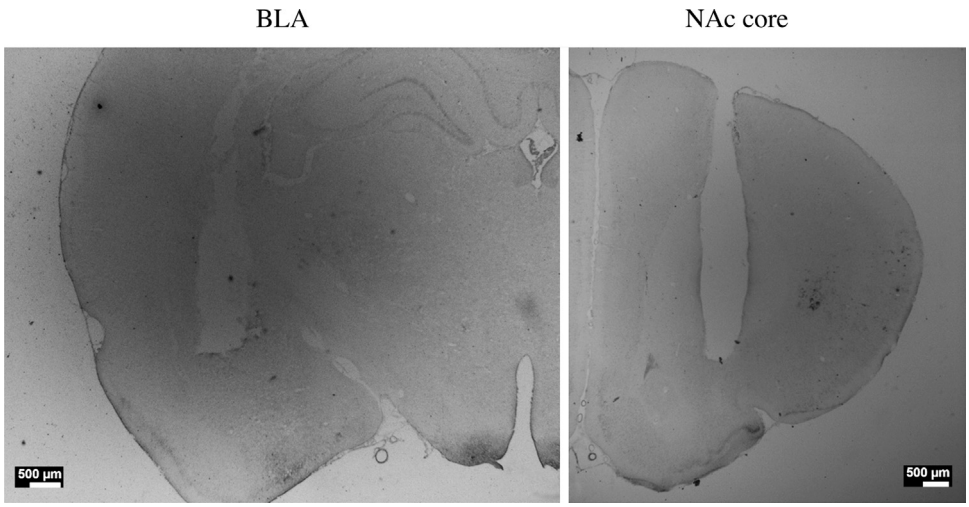

Fig. 1. Representative photomicrograph of cannulae placements in the BLA and NAc core.

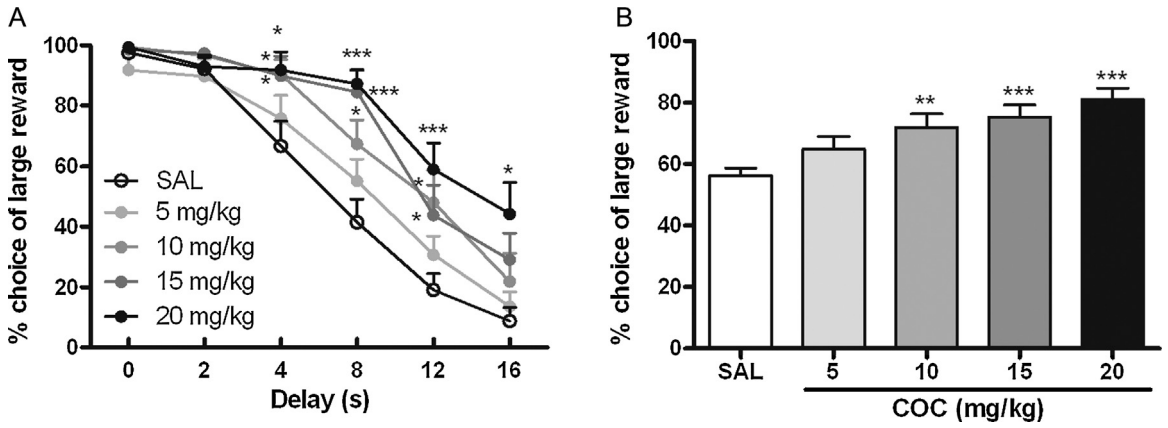

Fig. 2. Acute cocaine (COC) dose-dependently increased the choice of the large reward in rats. In all figures, the category graphs with symbols and lines (panel A) show percent choice of the large reward for each delay, and the column bar graphs (panel B) show average percent choice of the large reward across all delays, subdivided according to the given treatment. $n = 16$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, compared with saline treatment (SAL).

20 mg/kg cocaine increased the choice of the large reward when the delay was 4–16 s.

3.2. Effects of SCH23390 and eticlopride on the inhibition of impulsive choice caused by acute cocaine treatment

As shown in Fig. 3, 0.02 mg/kg SCH23390 obviously increased the impulsive choice, although the effect of dose did not reach the statistical significance [dose, $F(2, 42) = 3.124$, $P = 0.054$]. No delay × dose interaction was found [delay × dose interaction, $F(10, 210) = 1.335$, *ns*]. If the effect of 0.02 mg/kg SCH23390 was compared with saline, significant effect of antagonist [antagonist, $F(1, 29) = 6.921$, $P < 0.05$] could be found, and the antagonist × delay interaction in non-significant [$F(5, 145) = 1.767$, ns]. In contrast to SCH23390, eticlopride had no effect on impulsive choice [Fig. 3C and D, delay × dose interaction, $F(10, 200) = 0.155$, ns; dose, $F(2, 40) = 0.084$, ns].

Then, we investigated whether D1 and D2 receptors were involved in the acute cocaine-induced inhibitory effect on impulsive behavior in rats. As shown in Fig. 4, cocaine significantly increased the choice of the large reward [Fig. 4C, drug, $F(1, 9) = 5.995$; $P < 0.05$; delay × drug interaction, $F(5, 45) = 2.582$, $P < 0.05$]. A significant antagonist × drug interaction was observed, indicating that prior administration of 0.06 mg/kg eticlopride could reverse the acute cocaine-induced impulse inhibition [Fig. 4C, antagonist × drug interaction, $F(1, 9) = 5.846$, $P < 0.05$]. SCH23390 did not markedly change the behavior performance of cocaine treated rats (Fig. 4A and B, antagonist × drug × delay interaction, $F(5, 35) = 0.542$, ns). Moreover, cocaine significantly increased the choice of the large reward in rats pretreated with SCH23390 (Fig. 4 B, SCH/SAL *versus* SCH/COC, $P < 0.05$). These results suggested that D2 but not D1 receptors were implicated in cocaine's inhibitory effect on impulsive choice.

3.3. Effects of microinjection of D2 receptor antagonist into the NAc core and BLA on impulsive choice and acute cocaine-induced inhibition of impulsive choice

In this study, we assessed the roles of D2 receptors within the NAc core and BLA in impulsive choice. Three doses of D2 receptor antagonist eticlopride (0.3, 1, 2 μg/side) were microinjected, respectively, into the NAc core and BLA 5 min before behavior testing. As shown in Fig. 5, no doses of eticlopride could produce significant influences on impulsive choice either in the NAc core (Fig. 5A, C and E) or BLA (Fig. 5B, D and F).

To further determine whether the D2 receptors in the NAc core and BLA were involved in the acute cocaine-induced impulse inhibition in rats as depicted in Fig. 4, D2 receptor antagonist eticlopride (1 μg/side) was microinjected into the NAc core or BLA 5 min before acute cocaine exposure. Microinfusion of eticlopride in the NAc

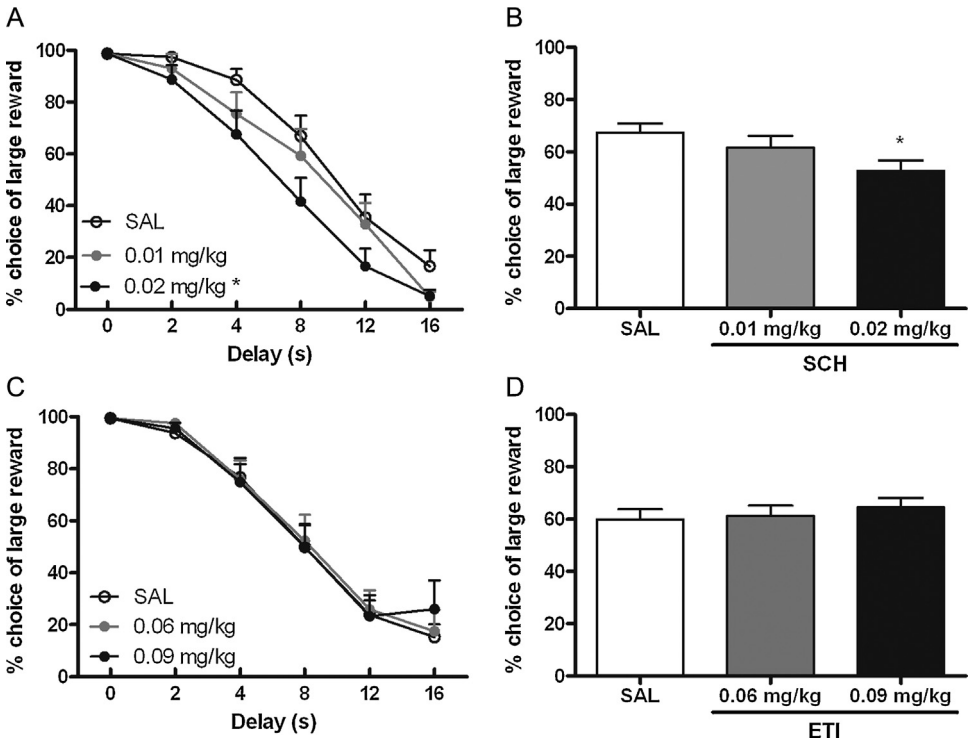

Fig. 3. Different effects of D1 and D2 receptor antagonists on impulsive choice in rats. (A, B) SCH23390 (0.02 mg/kg, i.p.) decreased the choice of the large reward. (C, D) Eticlopride had no effect on the choice preference. SCH indicates SCH23390 and ETI indicates eticlopride. $n = 16$, $^{*}P < 0.05$, compared with saline treatment.

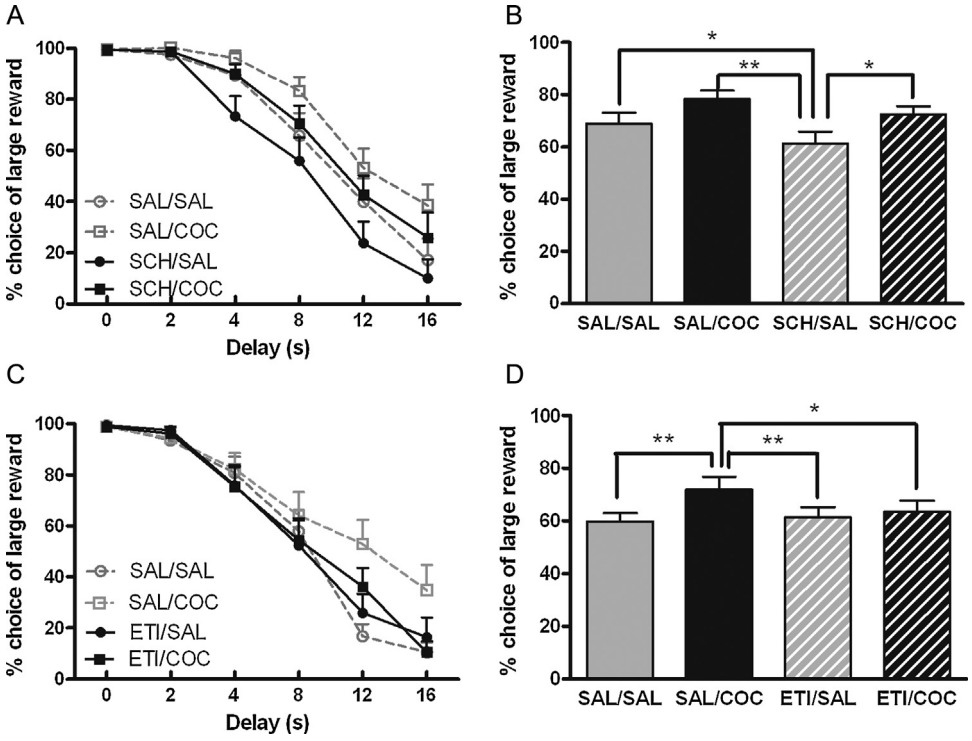

Fig. 4. Different effects of D1 and D2 receptor antagonists on impulsive choice in acute cocaine-treated rats. (A, B) Cocaine increased the choice of the large reward, whereas 0.02 mg/kg SCH23390 did not block it, $n = 16$. (C, D) Injection of 0.06 mg/kg eticlopride significantly reversed the cocaine-induced impulse inhibition. $n = 16$. SCH/COC indicates an injection of SCH23390 10 min before cocaine injection. The same logic for SAL/SAL, SAL/COC, SCH/SAL, ETI/SAL and ETI/COC. $^{*}P < 0.05$, $^{**}P < 0.01$, compared by paired t-tests.

core had no effect on the impulsive behavior in cocaine-treated rats (Fig. 6A; antagonist × drug × delay interaction, $F(5, 25) = 1.593$, ns). Whereas in the BLA, eticlopride markedly decreased the inhibitory effect of acute cocaine on impulsive choice. A significant antagonist × drug × delay interaction was observed (Fig. 6B; antagonist × drug × delay interaction, $F(5, 20) = 4.038$, $P < 0.05$). Further comparisons showed that the effect of intra-BLA microinfusion of eticlopride was evident at the delay of 2 and 8 s ($P < 0.05$). This result indicated that the cocaine-induced inhibition of impulsive choice depends on BLA D2 receptor activation.

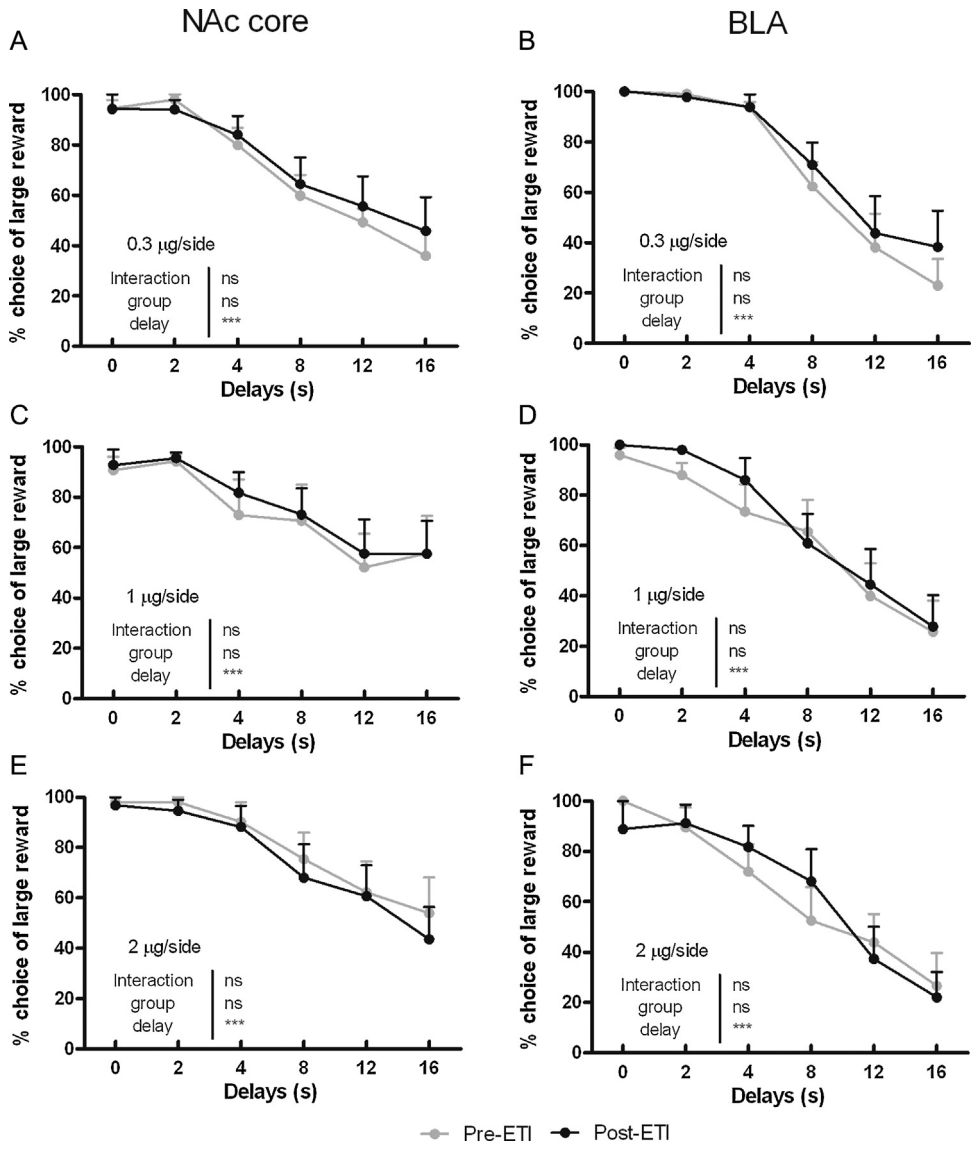

Fig. 5. Effects of microinjection of eticlopride into the NAc core or BLA on impulsive choice. All three doses of eticlopride had no effect on the impulsive choice when microinjected into the NAc core (A, C, E) and BLA (B, D, F), $n = 9–10$. SCH indicates SCH23390, ETI indicates eticlopride, Pre indicates before the drug injection and Post indicates after the injection.

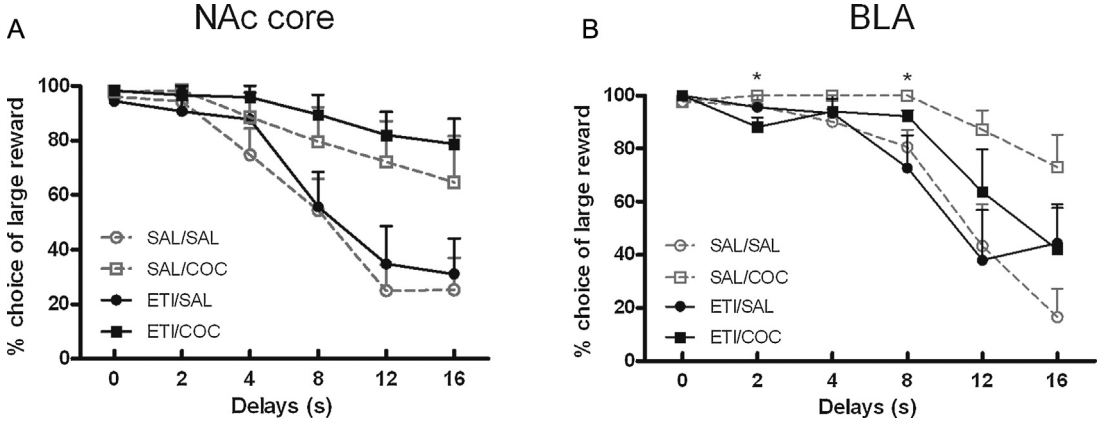

Fig. 6. Microinjection of 1 μg/side eticlopride into the BLA (B) but not the NAc core (A) reversed the cocaine-induced impulse inhibition. In all figures, ETI/COC indicates microinjection of eticlopride 5 min before cocaine injection. The same logic for SAL/SAL, SAL/COC, and ETI/SAL. $n = 10$ in panel A and $n = 5$ in panel B. $^*P < 0.05$, compared with ETI/COC by paired t-tests.

4. Discussion

In the present study, we found that a single systemic administration of cocaine increased the choice of the large delayed reward in the delay discount task, which was partly blocked by D2 receptor antagonist eticlopride in the BLA, but not in the NAc core. D1 receptor antagonist SCH23390, however, did not reverse the cocaine's effect but did increase the impulsive choice itself if systemically administered. The findings provide evidence for the dissociable roles of DA D1 and D2 receptors in impulsive choice and acute cocaine-induced inhibition of impulsive choice. The findings that D1 and D2 receptors play important but distinct roles in impulsive choice and the acute cocaine-induced impulse inhibition were consistent with the report of van Gaalen et al. [16]. They found that tolerance to the delay of reward depends on DA D1 receptor activation, whereas stimulation of DA D2 receptors mediates the inhibitory effects of amphetamine on impulsive decision making.

Contrary to our results, previous studies showed that systemic administration of DA D2 receptor antagonist raclopride or D1/D2 receptor antagonist flupenthixol generally increased the impulsivity on delay discounting procedure, whereas blocking D1 receptors with SCH23390 did not affect the impulsive choice [17,50]. These conflicting results may be related to the different animal models in respective studies. First, rats had to choose between a constant 150 μl water with 4 s delay and an immediate delivery of variable amount of water in Wade et al.'s study. The indifference point was used to indicate the subjective value of the delay reward and the impulsivity [17]. Second, a stimulus light or tone was turned on just before the reward delivery in the previous studies, which might become a conditioned reinforcer [50]. However, if there is no stimulus in the delay period, rats mainly depend on working memory to associate the lever-press with the delayed rewards. Because D1 receptor activity but not D2 receptor is necessary for maintaining working memory [51–54], it is reasonable to find that D1 receptor activation was needed in van Gaalen et al.'s and this study's delay discounting procedures.

Additionally, our work showed that acute cocaine treatment decreased impulsive choice *via* D2 receptors, which is consistent with many reports [55–60] that also suggest that the therapeutic effects of psychostimulant drugs in Attention Deficit Hyperactivity Disorder (a disorder that is associated with high levels of impulsivity) [61] involve the activation of D2 receptors.

The results in the present study showed that D2 receptors in the BLA, but not the NAc core, are critical to reverse the cocaine-induced impulse inhibition in rats. It is documented that BLA is necessary for the impulsive control and the reward-seeking behaviors [48,62,63]. Excitotoxic lesions or the inactivation of BLA increased the delay discounting and effort discounting, rendering rats less likely to choose the larger reward with increasing delays or required multiple presses on the lever [45,46]. The BLA receives the dopaminergic projections from the VTA [30,31] and expresses both D1- and D2-like receptor families [64,65]. The role of BLA DA receptors in drug seeking has also been evaluated before. Previous findings suggest that intra-amygdala infusions of D1/D2 receptor antagonist flupenthixol blocked the expression of ethanol induced CPP [66]. Intra-BLA infusion of DA D1 receptor antagonist SCH23390 inhibited the reinstatement of drug-seeking behavior [67].

According to our knowledge, this study is the first to demonstrate the different role of BLA D2 receptor in the impusle control, as well as the acute cocaine-induced inhibition on impulsive choice. Electrophysiological studies indicate that BLA D1 and D2 receptor activation has different effects on neuronal activity. DA D1 receptor activation could suppress spontaneous postsynaptic potentials, whereas DA D2 stimulation could enhance the excitability of BLA projection neurons. Therefore, DA may suppress spontaneous or weaker signals by D1 receptor activation and enhance large, coordinated inputs *via* D2 receptor stimulation [68]. Therefore, although the underlying mechanism remains to be elucidated, the cocaine's effect on delay discounting behavior may be related to potentiating the inputs to the BLA.

The inhibition of impulsive choice induced by acute cocaine was only partially resumed by D2 receptor antagonist in BLA, but other brain regions might be involved. The BLA sends glutamatergic projections to the mPFC pyramidal and GABAergic interneurons [69,70]. Approximately 20% of mPFC neurons exhibit excitatory responses after BLA stimulation, whereas most of the neurons display inhibition of spontaneous activity through GABAergic interneuron activation. DA could suppress the inhibitory transmissions of the BLA-mPFC pathway by mPFC D2 receptor activation [71]. Acute amphetamine attenuated BLA-evoked inhibition of mPFC neurons, which can be mimicked by selective D2 agonists [72]. Additionally, the mPFC has been implicated in maintaining responses over longer durations for larger magnitude rewards [73]. Disconnection of the mPFC and BLA led rats to select a small immediate reward instead of the large delayed reward [74]. Recent studies showed that intra-mPFC infusion of eticlopride increased impulsive choices [49]. Therefore, we postulated that the largely increased DA level after cocaine administration may activate the D2 receptors and attenuate the BLA-evoked inhibitory responses in the mPFC neurons, therefore causing rats to tolerate the delay of the large reinforcement. Apparently, full elucidation of the exact mechanism underling the DA receptor actions in the BLA-mPFC circuit on impulsive behaviors needs further investigation.

The finding that NAc core D2 receptor antagonism did not alter the impulsive choice, as well as acute cocaine-induced impulse inhibition, is in agreement with previous studies by Winstanley et al. [75]. They found that dopamine depletion within the NAc had no effect on the delay discounting of rats with or without amphetamine treatment. Furthermore, they noted the important role of DA and 5-HT system interaction in amphetamine's effect on impulsive choice. The 8-OH-DPAT (decreasing 5-HT level by activating presynaptic 5-HT_{1A} receptors) induced blockade of amphetamine's effect could be attenuated by a 6-OHDA NAc lesion. The findings that inactivation of D2 receptors in the NAc core had no effect on the acute cocaine-induced impulse inhibition might be due to the lack of control of the NAc 5-HT system in this study. Approximately 95% of the striatum and the NAc neurons in rodents are GABAergic medium-sized spiny neurons (MSNs). According to their projection and DA receptor types, these MSNs can be subdivided into two populations: D1-expressing MSNs (D1-MSNs) and D2-expressing MSNs (D2-MSNs) [76–79]. Activation of these two MSN subtypes would trigger different intracellular signaling cascades and exert different actions on behaviors [80,81]. For example, stimulating D1-MSN in the NAc could induce persistent reinforcement or enhance the cocaine-induced CPP, whereas D2-MSN activation suppresses the CPP [81–83]. Studies have shown that acute cocaine injection (20 mg/kg) induced c-fos expression predominantly in D1-MSN and slightly in D2-MSN in the NAc [78]. Therefore, another possible explanation for the absent effect of the NAc core D2 receptor blockade on cocaine's inhibition of impulsive behavior might be the predominant activation of D1 receptors (lesser extent in D2 receptors) in the NAc core to mediate the rewarding effect after acute cocaine exposure. Further studies examining the effects of intra-NAc core/BLA infusion of selective D1 and D2 receptor agonists, as well as 5-HT antagonists, would be helpful to verify the present findings.

There are some limitations that should be considered in the present work. First, the delay discounting task has a lot of the key features of a response reversal task. Given that acute cocaine and dopamine receptor antagonists have been shown to alter response learning [84–86], it is important to detect whether the effect we found is really a drug-induced change in preference for the large

reward or an alteration in reversal learning. Therefore, we reviewed the behavioral performance of each rat. After cocaine or/and antagonists treatment, the behavior pattern in rats was similar with their baseline performance. Rats shifted their preference to the small reward gradually as the delay to the large reward was increased, but they made more/fewer choices of the large delayed reward at the same delay time compared with the control condition. This finding may exclude the possibility that the curves in Figs. 2–4 reflect an increasing/decreasing proportion of rats that rapidly switch from the large reward lever to the small reward. Second, gliosis and scarring are likely to occur after repeated intracerebral infusions. In our experiment, drugs were microinjected according to the Latin square design. In addition, intra-BLA infusion of eticlopride markedly decreased cocaine-induced impulse inhibition (as depicted in Fig. 6B). Therefore, the absent effect of the intra-NAc core infusion of eticlopride on cocaine-induced impulse inhibition should not be due to the gliosis or scarring. Last, the cannulae were targeted into the NAc core and BLA. Although the injection sites have been confirmed and the microinjection speed and volume were limited, we could not totally rule out the possibility that the drugs may spread beyond the intended brain region.

Altogether, our studies suggest that impulsive choice in rats is controlled by tonic activation of DA D1, rather than D2 receptors. Moreover, D2 receptor activation in the BLA instead of the NAc core mediates the enhanced impulse control caused by acute cocaine.

Conflict of interest

The authors declare that they have no financial relationship with the organization that sponsored the research. No conflict of interest exits in this manuscript.

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