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Research report

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

Yijing Li, Yanfang Zuo, Peng Yu, Xingjie Ping, Cailian Cui*

Neuroscience Research Institute and Department of Neurobiology, School of Basic Medical Sciences, Peking University, Key Laboratory for Neuroscience, Ministry of Education/National Health and Family Planning Commission, Xueyuan Road 38#, Haidian District, 100191 Beijing, PR China

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

* Corresponding author. Tel.: +86 10 82801120; fax: +86 10 82801120.
E-mail address: clcui@bjmu.edu.cn (C. Cui).

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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