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Research report

Effects of nucleus accumbens amphetamine administration on performance in a delay discounting task

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HIGHLIGHTS

- Chronic cocaine can increase both impulsive choice and nucleus accumbens (NAc) dopamine (DA) release.
- Thus, enhanced NAc DA release could mediate chronic cocaine-induced impulsive choice.
- Intra-NAc amphetamine increased choice of large rewards in an ascending delay discounting task.
- Intra-NAc amphetamine decreased choice of the large rewards in a descending delay discounting task.
- NAc DA may be important for flexible decision making.

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ABSTRACT

Chronic administration of cocaine can cause pronounced and enduring cognitive alterations such as increases in impulsive choice. Chronic cocaine can also result in enhanced dopamine (DA) release in the nucleus accumbens (NAc) in response to reward-related cues. It is possible that this enhanced DA release in the NAc is a mechanism by which cocaine increases impulsive choice. To date, however, the specific role of DA in the NAc in impulsive choice is unclear. To begin to address this, rats received acute microinjections of the indirect DA agonist amphetamine directly into the NAc prior to testing in a delay discounting task in which rats chose between a small, immediate and a large, delayed food reward. When delays to the large reward increased within test sessions, amphetamine increased choice of the large reward. When delays decreased within test sessions, however, amphetamine decreased choice of the large reward. These findings suggest that, rather than specifically mediating impulsive choice, DA neurotransmission in the NAc is necessary for flexible adaptation of choice strategies in the presence of shifting reward contingencies. These results further indicate that enhancements in NAc DA release likely do not account for lasting increases in impulsive choice caused by chronic cocaine.

1. Introduction

Substance use disorders are associated with cognitive and neurobiological impairments that can persist long after cessation of substance use [1]. One facet of cognition that is severely impacted is intertemporal decision making. Substance users typically display an exaggerated preference for immediate rewards, such as substances themselves, over delayed, but more beneficial rewards, such as prolonged abstinence, health and employment. Such preference for smaller, sooner over larger, more delayed rewards, or "impulsive choice," is commonly assessed with delay discounting procedures in which subjects choose between two options, one which yields a small immediate reward and the other which yields a large reward that is delivered after varying delays [2]. All subjects decrease their choice of large rewards as the delays to their delivery increase; however, chronic users of alcohol, cocaine, and opioids, among other substances, show a steeper decrease in pref-

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erence for large, delayed rewards than nonusers (i.e., steeper delay discounting, or increased impulsive choice; [3–5]). Despite numerous demonstrations of this phenomenon, the mechanisms by which chronic substance, and particularly cocaine, use increases impulsive choice remain poorly elucidated.

Aside from cognitive deficits, another consequence of chronic cocaine, either passively or self-administered, is enhanced dopamine (DA) release in the nucleus accumbens (NAc) in response to rewards and reward-related stimuli [6,7]. Studies in rodents have shown that this sensitized DA release is associated with increases in non-drug reward-directed behavior [8] as well as cocaine-dependent behaviors such as psychomotor sensitization [9]. Given the co-occurrence of increased impulsive choice and sensitized NAc DA release following chronic cocaine administration, changes in NAc DA release may be a mechanism by which cocaine could cause increased impulsive choice. Evidence for this hypothesis includes the fact that both sensitized NAc DA release and cocaine-induced increases in impulsive choice are long-lasting phenomena (they can persist for months if not longer) [7,10]. Additionally, artificially augmented NAc DA release enhances other aspects of reward-directed behavior, such as Pavlovian-instrumental transfer [11,12]. Berridge [13] proposed that enhancements in DA release in the NAc may augment the incentive salience attributed to smaller, more immediate rewards over larger, delayed rewards, thus biasing choice toward more immediate gratification. Indeed, human neuroimaging data show that greater activity in the NAc is associated with choice of smaller, more immediate over larger, delayed monetary rewards [14], possibly reflecting greater salience ascribed to the immediate rewards. Together, these lines of evidence suggest that enhanced DA activity in the NAc may play a causal role in increased impulsive choice caused by chronic cocaine, possibly by enhancing the salience of more immediate gratification.

To determine whether enhanced NAc DA release could account for increased impulsive choice observed following chronic cocaine administration, we microinjected the indirect DA agonist amphetamine acutely into the NAc of rats prior to testing in a delay discounting task. This manipulation has been shown to increase incentive salience attributed to reward cues [8] in a manner similar to that produced by chronic cocaine administration [15]. Further, acute (although not chronic) systemic amphetamine has been shown to alter impulsive choice in a rodent delay discounting task [16–23]. However, the effects of amphetamine directly into the NAc on impulsive choice have yet to be tested. Based on previous work, we predicted that intra-NAc amphetamine would increase impulsive choice, and that this would be due to enhancement of the salience of the small, immediate reward.

2. Methods

2.1. Subjects

Male Long-Evans rats (n = 73; 70 days old upon arrival; Charles River Laboratories, Raleigh, NC) were individually housed in a temperature controlled vivarium and kept on a 12 h light/dark cycle. Rats received free access to food and water except as noted. During behavioral training, rats were maintained at 85% of their free-feeding weight, with target weights adjusted upward by 5 g/week to account for growth. All animal procedures were conducted in accordance with the University of Florida Institutional Animal Care and Use Committee and followed the guidelines of the National Institutes of Health.

2.2. Apparatus

Behavioral testing was conducted in eight computer-controlled operant test chambers (Coulbourn Instruments, Harvard Apparatus). Each chamber was housed in a sound-attenuating cabinet and was equipped with a recessed foot pellet delivery trough with a photobeam to detect nosepokes and a 1.12 W lamp to illuminate the food trough. The food trough was located in the center of the front wall of the chamber, 2 cm above the floor. Two retractable levers were positioned to the left and right of the trough, 11 cm above the floor of the chamber. An additional 1.12 W lamp served as the houselight and was located on the back wall of the sound-attenuating cabinet. The floor of the chamber consisted of stainless steel rods and an activity monitor was positioned on the ceiling of the chamber to record locomotor activity during the test session. This monitor consisted of an array of infrared (body heat) detectors focused over the entire test chamber; movement in the chamber (in *x*, *y*, or *z* planes) was defined as a relative change in the infrared energy falling on the different detectors. The operant test chambers were interfaced with a computer running Graphic State 3.0 software (Coulbourn Instruments, Harvard Apparatus), which recorded task events and controlled the components of the chamber (e.g., lever insertion, food pellet delivery) based on the task parameters.

2.3. Surgical procedures

After a week of acclimation on a free feeding regimen, rats were anesthetized with isoflurane gas (1–5% in O_2) and were administered buprenorphine (0.05 mg/kg), Meloxicam (1 mg/kg) and sterile saline subcutaneously (10 mL). After being placed into a stereotaxic apparatus (David Kopf), the scalp was cleaned with a chlorohexidine/isopropyl alcohol swab and an adhesive surgical drape was placed over the rat's body. The scalp was then incised and retracted. Three small burr holes were drilled into the skull for jeweler's screws such that one screw would be anterior to the guide cannulae and two would be posterior to the guide cannulae. Prior to implanting guide cannulae, the skull was leveled to ensure that bregma and lambda were in the same horizontal plane. Finally, two additional burr holes were drilled for bilateral implantation of guide cannulae (22 gauge; Plastics One) above the NAc (AP: +1.7, ML: ±1.8, DV: −6.0 from skull surface). Cannulae were anchored in place with dental cement, and sterile stylets were inserted into the cannulae. After surgery, rats were given additional sterile saline subcutaneously (10 mL) and placed on a heating pad to recover prior to being returned to their home cage. Rats were given one week for recovery before food restriction in preparation for behavioral testing.

2.4. Behavioral procedures

Rats were first shaped to perform the different components of the task (lever pressing for food, nosepoking into food trough) as described previously [24]. They then began training in the delay discounting task, which consisted of five 12-trial blocks and lasted 60 min in duration. Each 40 s trial was initiated by the illumination of both the houselight and trough light. A nosepoke into the trough extinguished the trough light and triggered extension of either a single lever (forced choice trials) or both levers (free choice trials) into the chamber. If rats failed to nosepoke within 10 s, both lights were extinguished and the trial was scored as an omission. A press on one lever (left or right; randomized across rats) always delivered 1 food pellet immediately and a press on the other lever delivered 3 pellets after a variable delay. In one group of rats (n = 15), the delay to the large reward increased across successive blocks of trials ("ascending" group; 0, 4, 8, 16, and 32 s). In a second group of rats (n = 11), the delay decreased across successive blocks of tri-