ARCHIVAL REPORT

Increased Impulsivity Retards the Transition to Dorsolateral Striatal Dopamine Control of Cocaine Seeking

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Background: Development of maladaptive drug-seeking habits occurs in conjunction with a ventral-to-dorsal striatal shift in dopaminergic control over behavior. Although these habits readily develop as drug use continues, high impulsivity predicts loss of control over drug seeking and taking. However, whether impulsivity facilitates the transition to dorsolateral striatum (DLS) dopamine-dependent cocaine-seeking habits or whether impulsivity and cocaine-induced intrastriatal shifts are additive processes is unknown.

Methods: High- and low-impulsive rats identified in the five-choice serial reaction-time task were trained to self-administer cocaine (.25 mg/infusion) with infusions occurring in the presence of a cue-light conditioned stimulus. Dopamine transmission was blocked in the DLS after three stages of training: early, transition, and late-stage, by bilateral intracranial infusions of α-flupenthixol (0, 5, 10, or 15 μg/side) during 15-min cocaine-seeking test sessions in which each response was reinforced by a cocaine-associated conditioned stimulus presentation.

Results: In early-stage tests, neither group was affected by DLS dopamine receptor blockade. In transition-stage tests, low-impulsive rats showed a significant dose-dependent reduction in cocaine seeking, whereas high-impulsive rats were still unaffected by α-flupenthixol infusions. In the final, late-stage seeking test, both groups showed dose-dependent sensitivity to dopamine receptor blockade.

Conclusions: The results demonstrate that high impulsivity is associated with a delayed transition to DLS-dopamine-dependent control over cocaine seeking. This suggests that, if impulsivity confers an increased propensity to addiction, it is not simply through a more rapid development of habits but instead through interacting corticostriatal and striato-striatal processes that result ultimately in maladaptive drug-seeking habits.

Key Words: Cocaine, dopamine, drug addiction, goal-directed, habitual, striatum

Increasing evidence suggests that addiction results from the convergence of various neurobiological adaptations in vulnerable subjects, eventually resulting in the loss of control over maladaptive drug seeking (1–3). Exposure to addictive drugs, such as cocaine, not only impairs executive processes, resulting in impulse control deficits and behavioral inflexibility (4), but it also facilitates the development of drug-seeking habits (3,5,6), thereby rendering instrumental actions that are resistant to their immediate consequences and motivational significance (6,7). Addictive drugs trigger adaptations within corticostriatal circuitry, including reductions in metabolic activity and D2 dopamine receptors, that are initially restricted to the ventral limbic areas of the striatum and prefrontal cortex but eventually encompass the more dorsolateral, associative and cognitive, territories of these structures (8–10). This progressive shift from limbic to cognitive corticostriatal networks that occurs over the course of addiction (11) takes place alongside a transition from the nucleus accumbens to the dorsolateral striatum (DLS) in the locus of control over drug seeking and taking (12) and the associated imbalance in fronto-striatal and striato-striatal functional coupling (13) displayed by former and current addicted individuals.

Studies in animals have further demonstrated that this ventral to DLS shift in the control over drug seeking (14,15) is not only associated with the development of habitual responding for the drug as assessed by devaluation procedures (3,6) but also reflects the emergence of compulsive cocaine seeking (16). The latter, a hallmark feature of addiction (17), is predicted by the behavioral trait of high impulsivity (18), which is associated with low D2/3 dopamine receptor availability in the ventral striatum (19). This has led to hypotheses suggesting that impulsivity and habits, with their striatal dopaminergic substrates, interact during the development of cocaine addiction, but the neurobiological basis of this interaction is unknown. Neurocomputational learning theory-based, actor-critic models of basal ganglia function (20) suggest that high impulsivity and its associated low D2 dopamine receptor availability in the ventral striatum facilitate the transition to DLS control over drug self-administration. However, we and others have suggested that compulsive drug seeking in addiction might instead result from weak inhibitory control over a rather independently established, drug-influenced, maladaptive incentive habit (4,21).

We therefore directly investigated whether high impulsivity interacts with the recruitment of dopamine-dependent DLS control over cocaine-seeking behavior over an extended period of cocaine self-administration. To do this, we investigated the effects of bilateral infusions of the dopamine receptor antagonist

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α-flupenthixol into the DLS of rats identified as high (HI) and low impulsive (LI) in the 5-choice serial reaction-time task (5-CSRTT), on cue-controlled cocaine-seeking behavior at early, transitional, and late stages of training under a second-order schedule of reinforcement for cocaine (22). Under these conditions we have previously shown that cocaine seeking becomes dependent upon dopamine transmission in the DLS (14,18,23), and the functional recruitment of this dopaminergic mechanism is a neurobiological marker of the emergence of drug-seeking habits (3,6).

Methods and Materials

Subjects

Forty male Lister Hooded rats (Charles River Laboratories, Kent, United Kingdom) weighing approximately 300 g on arrival were housed as described previously (23). Experiments were conducted in accordance with the United Kingdom 1986 Animals (Scientific Procedures) Act.

5-CSRTT

Apparatus and Procedure. The 5-CSRTT apparatus has been described in detail elsewhere (24,25) (Supplement 1). The training procedure was identical to that previously described (18). Each training session began with illumination of the operant chamber by a house light and the delivery of a food pellet in the magazine. Pushing open the magazine panel and collecting this pellet initiated the first trial. After a fixed intertrial interval (ITI), a light at the rear of one of the response apertures was briefly illuminated. Responses in this aperture within a limited-hold period (5 sec) were reinforced by the delivery of a food pellet in the magazine (correct responses). Responses in a nonilluminated aperture were recorded as incorrect responses and were punished by a 5-sec time-out period. Failure to respond within the limited-hold period counted as an omission and was likewise punished. Additional responses in any aperture before food collection (perseverative responses) were recorded but not punished. Responses made in any aperture before the onset of the target stimulus, or premature responses, were punished by a 5-sec time-out period. Across training sessions, the ITI was gradually increased, and the stimulus duration was gradually decreased (25). Subjects were considered to have acquired the task when accuracy was > 75% and omissions were fewer than 20% while the stimulus duration was .5 sec with a 5-sec ITI.

After 2 weeks of stable responding, rats underwent three 60-min challenge 7-sec ITI (long intertrial interval [LITI]) sessions, separated by baseline 5-sec ITI sessions (18,26). The LITIs markedly increase premature responding, thereby facilitating the identification of interindividual differences in impulsivity. The number of premature responses during LITI sessions provides an index of impulse control (18,19,24–26), which is used to identify HI or LI rats. Subjects were ranked according to the mean number of premature responses during the last two LITI sessions (10,18). Those with <20 or >50 premature responses were selected as LI and HI rats, respectively ($n = 8$/group) (Figure S1 in Supplement 1).

In addition, premature responses, magazine panel pushes, correct and incorrect responses, omitted trials, and collection latency (milliseconds to collect the food pellet) were averaged across the baseline sessions preceding each of the last two LITI sessions to compare baseline behavioral performance in LI and HI rats.

Surgery

Rats then underwent standard intravenous and intrastriatal surgeries under general anesthesia (Supplement 1). Cannulae were implanted bilaterally 2 mm above the dorsolateral striatum (anterior/posterior+1.2, medial/lateral±3, dorsal/ventral-3 [15]; AP and ML coordinates measured from bregma, DV coordinates from the skull surface, incisor bar at −3.3 mm [27]).

Drugs

Cocaine hydrochloride (Macfarlan-Smith, Edinburgh, United Kingdom) was dissolved in sterile .9% saline. α-Flupenthixol (Sigma Aldrich, Poole, United Kingdom) was dissolved in double-distilled water. Drug doses are reported in the salt form.

Cocaine Self-Administration

Apparatus. Twelve standard operant conditioning chambers described in detail elsewhere (15) were used (Methods in Supplement 1).

Procedure. The timeline of self-administration procedures is shown in Figure 1. Briefly, cocaine self-administration training sessions began 7 days after surgery. Cocaine (.25 mg/infusion; .1 mL/5 sec) was available under a fixed-ratio 1 (FR1) (continuous reinforcement) schedule of reinforcement in which one active lever press resulted in an infusion and initiated a 20-sec timeout. During that 20 sec, the cue-light (conditioned stimulus [CS]) above the active lever was illuminated, the house light was extinguished, and both levers were retracted. Pressing on the inactive lever was recorded to provide an index of general activity but had no programmed consequence. A maximum of 30 cocaine infusions was available at this stage. Active and inactive lever assignment was counterbalanced.

After five training sessions under the FR1 schedule of reinforcement, the dose-dependent effects of striatal dopamine receptor blockade on early-stage cocaine seeking were tested. Bilateral infusions of α-flupenthixol were made into the DLS. These 15-min test sessions [FI15(FR10:S)] instituted a change in contingency in that every active lever press resulted in a 1-sec light CS presentation, and cocaine was only delivered on the first lever press after the 15-min interval (23). Thus, the early performance tests were conducted before and were thus unaffected by self-administered cocaine on these sessions, because they were explicitly assessed for cocaine seeking within the fixed interval rather than a fixed ratio. Each test session was immediately followed by a FR1 cocaine self-administration training session (30 reinforcers over 2 hours), and rats were given a training session between test days so as to confirm and maintain a stable cocaine-taking baseline.

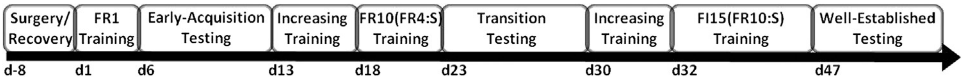

Figure 1. The timeline of self-administration experimentation. Subjects underwent intravenous catheter and central cannulae surgery a week before beginning behavioral training. There were five sessions of fixed-ratio 1 (FR1) training followed by early-acquisition testing. From Days 13 to 17, the response requirement was increased across sessions to the mid-stage training schedule of FR10(FR4:S). Rats remained on that schedule for five sessions before entering mid-stage testing. The response requirement was again increased on Days 30 and 31 to the final second-order training schedule, FI15 (FR10:S). Rats were again tested after 15 training sessions from Days 32 to 46 on the final schedule of reinforcement. Late-stage testing began on Day 37. d, day; FI, fixed-interval.