



Drug Seeking Becomes Compulsive After Prolonged Cocaine Self-Administration

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like behavior appears only in a few). It is thus the interaction between a long exposure to drug and a vulnerable phenotype, not one or the other factor in itself, that seems to determine the development of addiction.

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Drug Seeking Becomes Compulsive After Prolonged Cocaine Self-Administration

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Compulsive drug use in the face of adverse consequences is a hallmark feature of addiction, yet there is little preclinical evidence demonstrating the actual progression from casual to compulsive drug use. Presentation of an aversive conditioned stimulus suppressed drug seeking in rats with limited cocaine self-administration experience, but no longer did so after an extended cocaine-taking history. In contrast, after equivalent extended sucrose experience, sucrose seeking was still suppressed by an aversive conditioned stimulus. Persistent cocaine seeking in the presence of signals of environmental adversity after a prolonged cocaine-taking history was not due to impaired fear conditioning, nor to an increase in the incentive value of cocaine, and may reflect the establishment of compulsive behavior.

Compulsive drug seeking and drug taking distinguishes drug addicts from casual drug users. Addicts display drug-dominated, inflexible behavior and are unable to shift their thoughts and behavior away from drugs and drug-related activities. Even with awareness of the deleterious consequences of this drug-centered behavior, addicts have enormous difficulty in abstaining from drug seeking and use (1, 2). Several hypotheses try to explain the occurrence of compulsive drug use; it may reflect the establishment of an automatic stimulus-response habit (3, 4), drug-induced loss of impulse control (5), sensitization of an

incentive (“wanting”) system (6), or disruption of hedonic homeostasis (7). Remarkably, there is little evidence from animal studies demonstrating the actual progression from casual to compulsive drug use, although drug intake in rats escalates after weeks of prolonged drug self-administration (8). Modeling compulsive drug seeking in animals would clarify our understanding of the neuropsychology of drug addiction and may also lead to the development of novel treatments.

Here, we tested the hypothesis that an extended drug-taking history renders drug seeking impervious to environmental adversity (such as signals of punishment), capturing one element of its compulsive nature (1). Appetitive behavior for natural and drug rewards is readily suppressed by aversive environmental stimuli or outcomes, a phenomenon termed conditioned suppression (9–11). We investigated whether the ability of a footshock-paired conditioned stimulus (CS)

to suppress cocaine-seeking behavior diminishes after a prolonged cocaine-taking history and whether this reduced susceptibility to conditioned suppression also followed a similarly prolonged history of seeking sucrose, a high-incentive natural reinforcer.

In experiment 1, 21 rats were trained to self-administer cocaine under a heterogeneous seeking-taking chain schedule (12), in which drug seeking and taking are separate acts (13). Thus, meeting a response requirement on one lever (the seeking lever) in an operant chamber never resulted in drug, but instead gave access to a second lever (the taking lever), responding on which resulted in an intravenous infusion of cocaine. Immediately after the rats reached training criterion on this schedule—that is, after a limited cocaine-taking history—12 rats received tone-footshock pairings (the CS-shock group), whereas the other nine rats received presentations of the same tone not paired with footshock (the control group). Several days later, conditioned suppression of drug seeking was assessed in a session in which the rats had access to the seeking lever only and the footshock CS was presented for three 2-min periods interspersed with three 2-min periods when no CS was presented (13). The CS-shock group showed a profound conditioned suppression of drug seeking during presentation of the CS [$F(\text{CS}) = 5.32$, $P < 0.05$; $F(\text{CS} \times \text{group}) = 25.65$, $P < 0.001$] (Fig. 1A). There was also a marked increase in the time taken to make the first seeking response (seeking latency) in the CS-shock group [$F(\text{group}) = 7.43$, $P < 0.01$] (Fig. 1B). Thus, in rats with limited cocaine self-administration experience, drug seeking was greatly suppressed by presentation of an aversive CS, showing that it was sensitive to an adverse outcome.

Next, we tested whether cocaine seeking would become less susceptible to an aversive CS after prolonged cocaine self-administration

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experience. The same 21 rats were therefore allowed a further 20 cocaine self-administration sessions. These included eight “extended-access” sessions in which the rats could respond for cocaine under a simple continuous reinforcement (FR1) schedule for a maximum of 80

infusions, thereby greatly increasing the extent of cocaine-taking experience and cocaine exposure. Subsequently, the rats were reconditioned (CS-shock pairings) and tested under the circumstances identical to those in the previous phase of the experiment. Rats with

an extended cocaine-taking history showed virtually no conditioned suppression of drug seeking [$F(\text{CS}) = 0.47$, not significant (n.s.); $F(\text{CS} \times \text{group}) = 1.55$, n.s.] (Fig. 1C), although the response latency in the CS-shock group was still somewhat increased [$F(\text{group}) = 8.39$, $P < 0.01$] (Fig. 1D).

An advantageous characteristic of the seeking-taking chain schedule used is that the rate of responding on the seeking lever is a function of reinforcer magnitude. Thus, rats responding for higher unit doses of cocaine or higher concentrations of sucrose show increased rates of responding on the seeking lever (12); seeking rate can therefore be used as a measure of the incentive value of the reinforcer. A plausible explanation for the reduced susceptibility of cocaine seeking to presentation of the footshock CS is that the incentive value of cocaine increases after prolonged cocaine exposure. Therefore, rats may have been less prepared to reduce their cocaine-seeking rates when faced with signals of an adverse environmental event because cocaine had become a more valuable commodity. To test this possibility, we compared cocaine-seeking rates after limited and extended cocaine exposure but before CS-shock conditioning. Remarkably, the seeking rates were not different under these conditions; that is, they were not affected by the amount and duration of cocaine exposure [$F(\text{experiment phase}) = 0.01$, n.s.] (Fig. 1E), suggesting that the incentive value of cocaine had not changed over the course of the extended self-administration history.

In experiment 2, we aimed to exclude the possibility that different degrees of between-session extinction of the footshock CS ac-

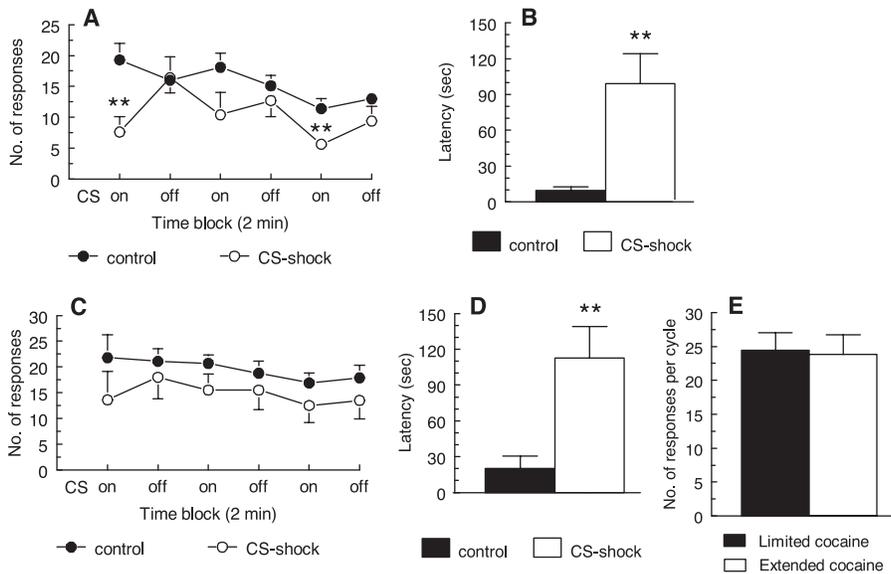
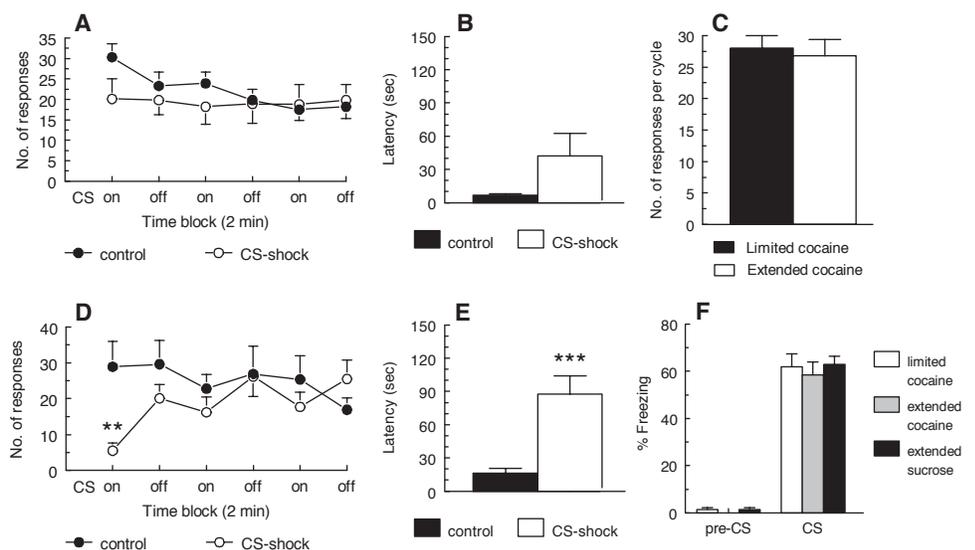


Fig. 1. Presentation of an aversive CS suppresses cocaine seeking after limited (A and B) but not prolonged (C and D) cocaine self-administration, independent of changes in the incentive value of cocaine (E). (A) Mean (\pm SEM) cocaine-seeking responses per 2-min interval in the CS-shock and control groups after limited cocaine exposure, with the aversive CS on or off during alternating 2-min periods. $**P < 0.01$ (Student-Newman-Keuls). (B) Latency to make the first seeking response during the test for conditioned suppression of cocaine seeking in the CS-shock and control groups after limited cocaine exposure. $**P < 0.01$ [analysis of variance (ANOVA)]. (C) Mean (\pm SEM) cocaine-seeking responses per 2-min interval in the CS-shock and control groups after extended cocaine exposure, with the aversive CS on or off during alternating 2-min periods. (D) Seeking latency during the test for conditioned suppression of cocaine seeking in the CS-shock and control groups after extended cocaine exposure. $**P < 0.01$ (ANOVA). (E) Mean (\pm SEM) number of cocaine-seeking responses per seeking-taking chain cycle after limited and extended cocaine self-administration.

Fig. 2. Presentation of an aversive CS does not suppress cocaine seeking after prolonged cocaine self-administration (A and B), independent of changes in the incentive value of cocaine (C). Presentation of an aversive CS suppresses sucrose seeking after prolonged sucrose self-administration (D and E). The differences in conditioned suppression were not the result of differences in conditioned fear (F). (A) Mean (\pm SEM) cocaine-seeking responses per 2-min interval in the CS-shock and control groups after extended cocaine exposure, with the aversive CS on or off during alternating 2-min periods. (B) Seeking latency during the test for conditioned suppression of cocaine seeking in the CS-shock and control groups after extended cocaine exposure. (C) Mean (\pm SEM) number of cocaine-seeking responses per seeking-taking chain cycle after limited and extended cocaine self-administration. (D) Mean (\pm SEM) sucrose-seeking responses per 2-min interval in the CS-shock and control groups after extended sucrose exposure, with the aversive CS on or off during alternating 2-min periods. $**P < 0.01$ (Student-Newman-Keuls). (E) Seeking latency during the test for conditioned suppression of sucrose seeking in the CS-shock and control groups after extended sucrose exposure. $***P < 0.001$ (ANOVA). (F) Conditioned freezing to a



footshock CS in rats with limited cocaine, extended cocaine, and extended sucrose self-administration experience. Percentage of time spent freezing was scored for 2 min before (pre-CS, left panel) and during 2 min of presentation of the CS (right panel).

counted for the diminished conditioned suppression seen after extended, as compared to limited, cocaine exposure—that is, that rats had learned during the suppression tests, when the CS was repeatedly presented, that it no longer predicted footshock when subsequently presented in the self-administration environment. Therefore, rats (CS-shock group, $n = 11$; control group, $n = 12$) were trained to self-administer cocaine under conditions identical to those in experiment 1. However, the first suppression test was omitted, so that rats were conditioned and tested only after extended cocaine exposure, including eight extended-access sessions (13). Unlike the limited-exposure rats, and identical to the extended-exposure rats in experiment 1, cocaine seeking in the CS-shock group was not suppressed at all during presentation of the footshock CS [$F(\text{CS}) = 2.53$, n.s.; $F(\text{CS} \times \text{group}) = 4.40$, $P < 0.05$] (Fig. 2A). Moreover, the seeking latency in the CS-shock group was no different from that in the control group [$F(\text{group}) = 2.15$, n.s.] (Fig. 2B). Consistent with experiment 1, there was also no change in the incentive value of cocaine, as assessed by the rates of seeking before and after the eight extended-access sessions [$F(\text{experiment phase}) = 0.08$, n.s.] (Fig. 2C). Thus, cocaine seeking is greatly suppressed by a footshock CS, but only in rats with a limited cocaine-taking history. This indicates that the flexibility of drug seeking strongly depends on the extent of drug self-administration experience.

Conditioned suppression of appetitive behavior has been readily observed in a variety of settings and is commonly used as an index of conditioned fear in animals responding for natural reinforcers, such as food (9, 10). However, it is not known whether food seeking can also become insensitive to the suppressive effects of an aversive CS after prolonged experience. In experiment 3, we therefore replicated experiment 2 with rats trained to seek and ingest sucrose (13). Rats (CS-shock group, $n = 11$; control group, $n = 11$) were trained to respond for a sucrose solution under the same seeking-taking chain schedule. To make an optimal comparison between cocaine and sucrose self-administration, we chose a unit amount and concentration of sucrose that led to rates of responding on the seeking lever comparable to those in experiment 2 (experiment 3 versus experiment 2: sucrose seeking, 13.9 ± 1.8 responses/min; cocaine, 12.6 ± 1.7 responses/min). In addition, the sucrose-trained rats were trained for a comparable number of sessions and received a comparable number of total reinforcer presentations before assessing conditioned suppression (total number of sucrose reinforcers in experiment 3: 1148 ± 29 ; total number of cocaine reinforcers in experiment 2: 1110 ± 14). After extended experience of sucrose seeking, profound conditioned suppres-

sion during presentation of the footshock CS was still observed [$F(\text{CS}) = 5.31$, $P < 0.05$; $F(\text{CS} \times \text{group}) = 8.35$, $P < 0.01$] (Fig. 2D), together with a marked increase in the seeking latency in the CS-shock group [$F(\text{group}) = 17.27$, $P < 0.001$] (Fig. 2E). Thus, lengthy training under this seeking-taking chain schedule does not itself result in diminished sensitivity of appetitive behavior to presentation of an aversive CS. Rather, these data suggest that the nature of the reinforcer (drug versus natural) determines whether compulsive behavior resistant to adverse environmental events will develop after similarly prolonged periods of self-administration (14, 15).

It is important to exclude the possibility that the failure to observe conditioned suppression in the extended cocaine exposure group reflected weaker fear conditioning. Therefore, the long-term sucrose-trained rats from experiment 3, the long-term cocaine-trained rats from experiment 2, and a new group of rats with limited cocaine exposure (as in experiment 1) all underwent fear conditioning and were tested for conditioned freezing to a discrete auditory (clicker) CS (9, 13, 16). Twenty-four hours after conditioning, the rats were placed in the training context and after 2 min, the clicker CS was played for 2 min (13). Rats in all three groups exhibited profound freezing during the CS [$F(\text{CS}) = 552.2$, $P < 0.01$], and there were no differences in fear behavior among the three groups during the pre-CS or CS periods [$F(\text{CS} \times \text{group}) = 0.77$, n.s.; pre-CS freezing: $F(\text{group}) = 0.003$, n.s.; CS freezing: $F(\text{group}) = 0.82$, n.s.] (Fig. 2F). Thus, the differences in conditioned suppression cannot be attributed to altered pain sensitivity or an inability to encode or express a CS-footshock association after extended cocaine exposure. Conditioned suppression and conditioned freezing are well known to be highly correlated (9), but this correlation between freezing and the suppression of cocaine-seeking behavior was lost in rats with a prolonged cocaine-taking history because they were still fearful, yet their appetitive behavior was not affected by an aversive CS during the unflagging pursuit of drug.

Dysfunction of prefrontal cortical-striatal systems is likely to underlie loss of control over drug use. These systems subserve the coordination of goal-directed and habitual appetitive behavior (17, 18) and have been implicated in both obsessive-compulsive disorder (19) and drug addiction (20). Indeed, animal studies suggest a critical role for the prefrontal cortex in drug seeking (21). Moreover, functional neuroimaging studies in human drug addicts have consistently shown activation of the orbitofrontal and dorsolateral prefrontal cortex during cocaine craving (20), and cocaine addicts are impaired in

cognitive and decision-making abilities that depend on the orbital and other prefrontal cortical areas (22).

Our results show that cocaine seeking can be suppressed by presentation of an aversive CS, but after extended exposure to self-administered cocaine, drug seeking becomes impervious to adversity. Interestingly, inflexible drug seeking appears to develop with prolonged drug-taking experience independently of alterations in the incentive value of cocaine. The attenuated conditioned suppression of seeking does not occur after identically prolonged exposure to sucrose, which suggests that appetitive behavior may more readily become resistant to aversive environmental events when directed toward obtaining drugs rather than natural reinforcers. We therefore conclude that a prolonged cocaine self-administration history endows drug seeking with an inflexible, compulsive dimension.

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