Rapid extinction of cocaine craving: toward a novel cue exposure therapy

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Cocaine does not only evoke intense rewarding sensations but also induces craving for more cocaine. This latter effect is especially obvious in addicted individuals and is thought to contribute together with other factors to trigger relapse after abstinence[1-3]. Cocaine-induced craving can be studied in animals in the drug reinstatement model[4]. In this model, responding for the drug (e.g., pressing a lever) is first extinguished by discontinuing drug reinforcement and then reinstated by drug priming (i.e., non-contingent re-exposure to the drug) or stress. Importantly, during reinstatement testing, responses continue to be unrewarded as during extinction and, therefore, reflect genuine drug seeking[5]. Here we show that reinstatement of cocaine seeking can be rapidly extinguished with daily repeated cocaine priming. The extinction of cocaine seeking fully generalized to stress, another major trigger of drug craving and relapse. These findings suggest that cocaine and stress induce drug craving by generating similar conditioned interoceptive effects. The targeted extinction of these effects by repeated drug priming under medical supervision may represent a novel behavioral therapy against relapse in abstinent cocaine addicts.

Over the past two decades, great strides have been made in understanding the neurobiology of cocaine-induced reinstatement[6-13], yet to date this knowledge has not translated into significant treatment advances. In contrast, little progress has been made in clarifying its underlying behavioral mechanisms. According to an interoceptive conditioning hypothesis, with repeated

cocaine use, some of the peripheral interoceptive effects of cocaine would acquire strong conditioned properties for signaling drug availability and for eliciting drug seeking[14-19]. During reinstatement testing, the acute re-experience of these conditioned interoceptive effects would contribute to reinstate cocaine seeking, a phenomenon that has been demonstrated very recently[18]. Interestingly, this hypothesis is consistent with recent research involving the interoceptive insular cortex in drug craving in both humans[20] and animals[21,22].

One unique prediction of the interoceptive conditioning hypothesis – with major translational implications – is that repeated re-exposure to cocaine during extinction should eventually lead to a progressive loss of its conditioned interoceptive effects. Indeed, during extinction, since the interoceptive cues generated by cocaine no longer predict response reinforcement, animals should progressively learn to disregard these cues and refrain from responding to them. In addition, if stress reinstates cocaine seeking by mimicking some of the drug's interoceptive effects, as has been proposed previously[16], the extinction of cocaine-induced reinstatement should generalize to stress-induced reinstatement. The goal of this study was to test these predictions.

Following extinction of stable cocaine self-administration (0.75 mg/kg/injection, 2 h per day during 3 weeks), rats (n = 7) were tested with repeated daily, passive re-exposure to cocaine or drug priming (15 mg/kg, i.p.; for other details, see Methods). Cocaine strongly reinstated cocaine seeking during the first priming, as compared to vehicle (Fig.1a). As predicted from

the interoceptive conditioning hypothesis of drug reinstatement, this reinstating effect decreased with repeated cocaine priming (Fig.1a). To assess whether this loss of cocaine effects on reinstatement generalizes to stress, two separate groups of rats were tested as in the first experiment, except that they were tested for stress-induced reinstatement both before and after repeated daily re-exposure to cocaine (group COC, $n = 5$) or vehicle (group VEH, $n = 6$) (Fig.1b). As shown in Fig.1c, stress dramatically reinstated cocaine seeking above the extinction baseline in a similar manner in both groups of rats. However, after repeated daily re-exposure to cocaine and resulting loss of efficacy (Fig.1d), stress totally lost its ability to reinstate cocaine seeking (Fig.1e).

This study clearly demonstrates that the ability of cocaine to trigger drug seeking can be extinguished rather rapidly and that this effect generalizes to stress, another well-known powerful precipitant of drug craving and relapse in human cocaine addicts[23]. These results strongly support the interoceptive conditioning hypothesis of drug reinstatement[14-18] and suggest a novel cue exposure therapy against relapse after abstinence. Traditional cue exposure therapies attempted to extinguish the conditioned effects of exteroceptive cues predictive of drug reinforcement (e.g., pictures of drug paraphernalia) with mixed clinical efficacy[24]. However, in real life, the interoceptive cues generated by the drug itself are more contiguous to and more predictive of drug use than exteroceptive predictive stimuli[18]. In the laboratory, these differences would explain why drug- or stress-induced reinstatement is generally more intense than reinstatement induced by re-exposure to conditioned

exteroceptive cues. Thus, the extinction of the conditioned interoceptive effects of cocaine in abstinent individuals should considerably increase the efficacy of traditional cue exposure therapies. Such extinction could be achieved under medical supervision either by passive re-exposure to priming doses of cocaine without response reinforcement or to a cocaine analog that mimics the peripheral interoceptive effects of cocaine without crossing the blood-brain barrier (e.g., cocaine-methiodide[18]). Additional research will be necessary to determine the identity of the conditioned peripheral interoceptive cues of cocaine, the mechanisms by which they lose their ability to induce craving and, finally, how this extinction of drug-induced craving can be accelerated and maintained persistently to reliably protect abstinent individuals against relapse. Nevertheless, based on recent research, we predict that the extinction of drug-primed craving and its generalization to stress will involve long-lasting changes in neuronal activity within the interoceptive insular cortex[20-22].

Methods

Animals and housing. Eighteen male Wistar rats (Charles River, Hollister, CA), weighing 320-430g at the start of the behavioral training, were used. The rats were housed in groups of two or three and maintained in a light- and temperature-controlled vivarium. All behavioral testing occurred during the dark phase of the light-dark cycle. Food and water were freely available. Three days after their arrival in the laboratory, rats were prepared with catheters for cocaine self-administration in the jugular vein, as described previously[16]. All procedures were conducted in conformity with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Acquisition and extinction of cocaine self-administration. Cocaine self-administration was conducted in standard operant chambers[16]. One week after surgery, operant-naïve rats were trained to self-administer intravenous cocaine (0.75 mg/kg per injection) during 3 weeks on a fixed-ratio 1 time-out 20s schedule of reinforcement, as described elsewhere[16]. Each daily self-administration session lasted 2 h. Following acquisition and stabilization of cocaine self-administration (variation between the last three self-administration sessions less than 15%), rats were tested under extinction. Briefly, during extinction, responding on the active lever was no longer rewarded by cocaine. Each daily extinction session lasted 2h. Extinction testing continued until average responding on the active lever decreased below 20 responses per hour (i.e., within a maximum of 18 extinction days).

Footshock stress. Footshock (alternating current; 0.86 mA; 0.5 s trains) were delivered through a scrambler (Coulbourn Instruments) to the grid floor of the operant chamber. They were administered during 15-min in an intermittent manner according to a variable interval schedule (mean interval: 40 sec; range: 10-70 sec).

Drug. Cocaine HCl was obtained from the National Institute on Drug Abuse and was dissolved in sterile physiological saline (0.9%).

Effects of repeated cocaine on cocaine-induced reinstatement. Seven rats were tested in this experiment. The effects of repeated cocaine on cocaine-induced reinstatement took place after extinction of cocaine self-administration. On the first day, rats received a vehicle injection (1 ml/kg, i.p.) immediately before the regular daily 2-h extinction session. On the following 5 days, they received one priming dose of cocaine (15 mg/kg, i.p.) immediately before extinction testing.

Effects of extinction of cocaine priming on stress-induced reinstatement

Eleven rats were tested in this experiment. After extinction, one group of rats (n = 6) was tested for stress-induced reinstatement of cocaine seeking both before and after repeated cocaine priming (as described above). Stress-induced reinstatement was precipitated by exposing rats to intermittent electric footshock during 15 min immediately before the regular daily 2-h extinction session. Each stress testing day was preceded by a baseline day during

which the 15-min period of intermittent footshock was replaced by a 15-min period without footshock. Another group of rats (n = 5) was tested as the first group, except that they received vehicle instead of cocaine between the two tests of stress-induced reinstatement.

Data analysis. Behavioral data were submitted to a square root transformation to meet the requirements of homogeneity of error variance. Square-root transformed data were then subjected to one-way or two-way analysis of variance (ANOVA), followed by appropriate post-comparisons using the Newman-Keuls's test.

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Figure legend.

Fig. 1. Rapid extinction of cocaine craving. **(A)** Decrease in cocaine-induced reinstatement with repeated daily re-exposure to the drug. Vehicle or cocaine (15 mg/kg, IP) was administered immediately before the onset of each extinction session. Vehicle was administered the day before the first cocaine administration. #, different from vehicle ($F_{1,6}$ = 31.23, $p < 0.01$, one-way ANOVA); *, different from the first re-exposure to cocaine ($p <$ 0.05, Newman-Keuls's test following one-way ANOVA). **(B)** Treatment timeline for group COC and group VEH in the stress-induced reinstatement experiment. During baseline days (B), the extinction session was preceded by a 15-min period without electric footshock. During stress days (S), the extinction session was preceded by a 15-min period of intermittent electric footshock (see Supporting Online Material). Following the first exposure to stress, animals were re-baselined during 3 consecutive regular extinction sessions (E) before receiving repeated administration of cocaine (C) or vehicle (V). **(C)** Stress-induced reinstatement before repeated re-exposure to cocaine. *, different from baseline (main effect of stress: $F_{1,9} = 5.79$, $p < 0.05$). **(D)** Decrease in cocaine-induced reinstatement with repeated daily re-exposure to the drug. #, different from group VEH ($p < 0.05$, Newman-Keuls's test following a two-way ANOVA). **(E)** Stress-induced reinstatement after repeated re-exposure to cocaine. #, different from group VEH ($p < 0.05$, Newman-Keuls's test following a two-way ANOVA); *, different from baseline ($p < 0.01$, Newman-Keuls's test following a two-way ANOVA). Statistical analyses were conducted on square-root transformed data to meet the requirement of homogeneity of error variance.

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