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Persistent increases in cocaine-seeking behavior after acute exposure to cold swim stress

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Abstract

Background—Acute and chronic stress reinstates drug-seeking behavior. Current animal models show that these effects are contingent (either temporally, contextually, or both) on the drug-conditioning environment. To date, no paradigm exists to model the common human situation in which stressors that are distinct from the experience of drugs can lead to relapse.

Methods—Rats were allowed to self-administer cocaine or saline over eight days. Then, they underwent extinction training, during which responding was not reinforced with drug infusions. After 16 days of extinction, rats were submitted to a brief cold swim stress and then tested for seeking behavior (responding not reinforced with drug infusions) for four days.

Results—All rats developed self-administration behavior. Following extinction, cold swim stress induced reinstatement of drug-seeking behavior in cocaine-trained rats, an effect that was still present three days after stress exposure.

Conclusions—This study indicates that cold swim stress can have long-term effects on drug-seeking behavior and may provide us with a suitable model to study the latent effects of stress on relapse to drug abuse.

Keywords

cocaine; relapse; reinstatement; stress; cold swim; self-administration

Introduction

Stress is a major factor precipitating relapse to drug addiction in humans (1). Elements of this interaction between stress and drugs have been successfully modeled in rodents; thus, exposure to a variety of acute and chronic stressors triggers drug-seeking for many drugs

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including cocaine, nicotine, heroin, and ethanol (1–4). In these models, rodents trained to self-administer drugs are subjected to an extinction procedure, whereby conditioned responding is no longer reinforced with drug infusions. The ability of stress to reinstate drug-seeking after this extinction period is then evaluated. To date, these models have used stressors that are linked to the drug-seeking test temporally and contextually. In most studies, the stressor is *temporally* linked to the test because it is either actively present or administered shortly before the drug-seeking test. In studies that have introduced a short delay (1–3 h) between stress and test, it has still been necessary to administer the stress in the test environment to produce reinstatement; thus the stressor remains *contextually* linked to the drug-taking environment (5,6).

However, such models do not account for the common human situation where relapse may occur in response to stressors that are separated in time and context from the drug-taking environment.

In this study we examined whether exposure to an acute stressor that was both temporally and contextually distinct from the drug-taking environment could induce reinstatement of drug-seeking behavior. Rats were tested for reinstatement at several time points after exposure to a brief cold water swim. This stressor is a modified form of the Porsolt forced swim test and is known to activate the secretion of stress hormones without producing immobilization associated with learned helplessness (7). We show that this stressor is able to trigger reinstatement of drug-seeking behavior, and that these effects persist for up to three days after stress exposure.

Methods and Materials

Procedures are described in detail in Supplement 1. Briefly, rats self-administered saline (n=19) or cocaine (600 µg/kg/infusion, n=23) using nose pokes as the operant response. After eight self-administration sessions, rats underwent an extinction phase. During extinction, rats were placed in the self-administration chambers for 16 additional sessions during which nose-poking in the active hole did not result in drug delivery. Rats that did not reach the extinction criteria were eliminated from the study (see Supplement 1). One to two hours following the last extinction session, rats were subjected to a 4.0–4.5 min cold swim stress. The next day, they were placed back in the self-administration chambers to assess reinstatement of drug seeking behavior, using procedures identical to those used in the extinction phase. Behavior was monitored for three additional days to determine the duration of the effect. Data were analyzed as described in Supplement 1. Only rats that successfully completed all phases of the experiment (see Supplement 1) were included in the statistics (n=17 in the saline group; n=18 in the cocaine group).

Results

Self-administration training and extinction phase

All rats nose-poked preferentially in the active hole vs. the inactive hole to obtain infusions of either cocaine or saline (Hole effect $F_{1,33}=61.5$, $p<0.001$). Average daily intake of cocaine was 35 ± 1.4 infusions (i.e. 21 mg/kg/day) whereas it was 8.1 ± 1.4 for saline (Drug effect $F_{1,33}=163.3$, $p<0.001$). As expected, active/inactive hole discrimination was greater in the cocaine vs. saline group (Drug $\times$ Hole interaction $F_{1,33}=35.6$, $p<0.001$). In addition, rats with access to cocaine responded far more in the active hole than rats with access to saline (Drug effect $F_{1,33}=50.0$, $p<0.001$) and, for the inactive hole, there was a tendency for greater responding (Drug effect $F_{1,33}=3.9$, $p=0.06$). During the extinction phase, responding in the previously-active hole gradually decreased in both cocaine- and saline-trained rats (Figure

1). During the last four days of extinction responding in the active and inactive holes was similar across groups (Drug effect $F_{1,33}=1.4$, n.s.).

Test for reinstatement

Exposure to swim stress almost doubled nose-poking in the previously active hole (Figure 2), demonstrating reinstatement of the previously extinguished seeking behavior in the cocaine-trained group (Stress effect: $F_{1,17}=12.4$, $p<0.003$) but not in the saline-trained group (Stress effect: $F_{1,16}=0.6$, ns; Drug $\times$ Stress interaction: $F_{1,33}=7.7$, $p<0.01$). The effects of swim stress were strongest one day after the end of the stressor and decreased thereafter (Newman Keul's comparison with last extinction day, $p<0.001$, $p<0.01$, $p=0.05$, ns, for days 1, 2, 3, and 4 respectively).

Discussion

Our results demonstrate that a brief stressor administered outside the self-administration environment is able to reinstate extinguished cocaine-seeking behavior after the stress itself had ended. This is the first time, to our knowledge, that a stressor both temporally and contextually separated from the drug-paired environment has been shown to induce reinstatement. The effects of cold swim stress on drug-seeking behavior persisted for up to three days after exposure to the stress. Swim stress did not increase responding in animals that had learned to self-administer saline, indicating that its effects were specific to cocaine.

Several types of stress-related stimuli are known to induce reinstatement of drug-seeking behavior. These include administration of the stress hormone corticosterone (8,9), the peptide corticotrophin releasing factor (CRF) (10,11), and the pharmacological stressor yohimbine (12–14). Similarly, acute exposure to footshock and food deprivation reinstate drug-seeking behavior in self-administration models (6,11,12,15), and cold swim stress reinstates seeking in a place preference paradigm (16). However, the stressors utilized in these models were either on-board or were administered in close temporal proximity to the reinstatement test (for review, see 4). Thus, these paradigms do not reproduce the common human situation, whereby stressors that are distinct from the experience of drugs can lead to relapse. Some studies have shown that either the pharmacological stressor CRF or intermittent footshock cause reinstatement even if a delay exists between exposure to stress and testing (5,6). These studies also removed the animals from the drug taking context for a time between the exposure to the stressor and the reinstatement trial. However, despite achieving temporal separation, this delay was short, approximately three hours or less, and crucially, the stressor itself was still administered in the testing chamber. The stressor, therefore, remained contextually linked to experience of drugs. It was thus suggested that stress produces conditioned excitation to the context in which it is administered; this conditioned excitation overrides the inhibitory processes that govern reduced responding during extinction (5). In the present study, however, the stressor was wholly separate from the drug-paired context and it caused reinstatement for up to three days after the stressor had ended. This suggests that the effects of cold swim stress are independent of such conditioned excitation. Although the effects of swim stress were significant, it should be noted that the magnitude of the effect was relatively small compared with other stressors, which produce higher levels of reinstatement (3,4).

A number of candidate mechanisms could underlie this phenomenon. Elevation of the stress hormone corticosterone has been shown to produce reinstatement of seeking behavior (8). One possibility is that swim stress leads to a persistent elevation of circulating corticosterone such that the animal remains in a “stressed” state until testing. However, this is unlikely to be the case because it has been shown that corticosterone returns to baseline levels two hours after the end of cold swim procedure (7). Extra-hypothalamic corticotrophin releasing

factor (CRF) and/or noradrenaline, have also been heavily implicated in stress-induced reinstatement of cocaine-seeking behavior (2,17). These studies also involve the acute elevation of the modulator and the rapid production of a reinstatement response. Whether a prolonged elevation in either of these transmitters contributes to our effect is not certain as, to our knowledge, the length of time they remain elevated has not been studied after cold swim stress. Furthermore, this time course could be altered in cocaine-treated rats (18). Therefore, although one possibility is that prolonged elevation of CRF and/or noradrenaline reinstates drug-seeking, the long delay between the stressor and reinstatement suggests a more complex explanation. One possibility is that the stressful experience could produce neuroadaptations that prime the system to respond more strongly when re-exposed to the drug-paired context at later time points. A key locus of such changes could be ventral tegmental area (VTA) dopamine neurons. Activation of VTA dopamine neurons has been linked to reinstatement of drug-seeking behavior (for review see (19)). Importantly, a persistent long-term potentiation-like phenomenon can be induced in these cells by the same cold swim stress used in the current study (20). This result suggests that exposure to cold stress may lead to a persistent elevation in synaptic strength in the VTA which, when paired with an increase in excitatory input caused by re-exposure to the drug-paired context, would lead to strong excitation of VTA dopamine neurons and re-instatement of drug-seeking behavior.

In conclusion, we show that reinstatement of drug-seeking behavior may be produced by a stressor that is both temporally and contextually distinct from the drug-paired environment. The relevance of this model to the human situation may make it useful for studying the mechanisms underlying stress-induced relapse with a view to creating better treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Acquisition and extinction of self-administration behavior. During the self-administration sessions (left-hand panels) rats learned to nose-poke preferentially in the active hole (top) vs. the inactive hole (bottom) to obtain infusions of either cocaine (filled symbols, $n=18$) or saline (open symbols, $n=17$). During extinction sessions (right-hand panels), nose-poking in the active hole was no longer reinforced with infusions. All animals gradually reduced their nose-poking behavior and, during the last four days of extinction, responding in the active and inactive holes was similar across groups.

Extinction and Reinstatement

Figure 2.

Stress-induced reinstatement of drug-seeking behavior. Cold swim stress increases responding in the hole previously paired with drug delivery in cocaine-trained rats (filled symbols, $n=18$) but not saline-trained rats (open symbols, $n=17$). This increase in responding in the cocaine group persists for 3 days after stress (** $p<0.001$, ** $p<0.01$, * $p=0.05$ compared with last day of extinction).