Priority Communication

Biological Psychiatry

Compulsive Addiction-like Aggressive Behavior in Mice

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ABSTRACT

BACKGROUND: Some people are highly motivated to seek aggressive encounters, and among those who have been incarcerated for such behavior, recidivism rates are high. These observations echo two core features of drug addiction: high motivation to seek addictive substances, despite adverse consequences, and high relapse rates. Here we used established rodent models of drug addiction to determine whether they would be sensitive to "addiction-like" features of aggression in CD-1 mice.

METHODS: In experiments 1 and 2, we trained older CD-1 mice to lever press for opportunities to attack younger C57BL6/J mice. We then tested them for relapse to aggression seeking after forced abstinence or punishment-induced suppression of aggression self-administration. In experiment 3, we trained a large cohort of CD-1 mice and tested them for choice-based voluntary suppression of aggression seeking, relapse to aggression seeking, progressive ratio responding, and punishment-induced suppression of aggression self-administration. We then used cluster analysis to identify patterns of individual differences in compulsive "addiction-like" aggressive behavior.

RESULTS: In experiments 1 and 2, we observed strong motivation to acquire operant self-administration of opportunities to aggress and relapse vulnerability during abstinence. In experiment 3, cluster analysis of the aggression-related measures identified a subset of "addicted" mice (~19%) that exhibited intense operant-reinforced attack behavior, decreased likelihood to select an alternative reinforcer over aggression, heightened relapse vulnerability and progressive ratio responding, and resilience to punishment-induced suppression of aggressive behavior.

CONCLUSIONS: Using procedures established to model drug addiction, we showed that a subpopulation of CD-1 mice demonstrate "addiction-like" aggressive behavior, suggesting an evolutionary origin for compulsive aggression.

Keywords: Addiction, Aggression, Mice, Motivation, Relapse, Reward

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Aggression is evolutionarily advantageous, critical to survival, and well-conserved across species (1,2). However, voluntarily seeking aggression against members of one's own species, and finding the experience reinforcing, has been described as an almost entirely human occurrence, representing a "perversion" of a hunting instinct that can be unmasked in the general population under permissive circumstances and may thereafter be repeated compulsively (3–5). The phenomenology of this appetitive aggression is similar to that of other rewarding experiences, such as sexual pleasure or drug intoxication; accordingly, aggression is sometimes pursued despite immediate or long-term adverse consequences (6,7). Unsurprisingly, relapse (recidivism) rates among violent offenders are as high as relapse rates in drug addiction (7–9). Therefore, appetitively driven human aggression appears to mimic core features of drug addiction: high motivation to seek the rewarding stimulus, often despite adverse consequences, and high relapse rates. In addition, like drug addiction, which develops in only about 20% of people who use addictive drugs (10), pathological aggression develops only in a minority of people who engage in aggressive encounters during their lifetime (11–13).

If appetitive aggression against conspecifics is modulated by reward mechanisms similar to those that drive drug addiction, it may be observable across species in an analogous manner (14). There is already some evidence for this. Dominant mice will lever press or nose poke for the opportunity to attack subordinate intruder mice (15–17), as well as form persistent conditioned place preference to aggression-paired contexts (18,19). However, self-administration and conditioned place preference are not sufficient to show that a rewarding stimulus is being sought maladaptively, addictively, or pathologically (14,20,21). In models of drug addiction, those criteria have been operationalized as self-administration despite adverse consequences (compulsive drug self-administration) and relapse to drug seeking during abstinence (20,22). To our knowledge, no

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published reports have evaluated these behaviors in preclinical studies on aggressive behavior.

In the present study, we first determined relapse to aggression seeking by combining a mouse operant model of self-administration of aggression (15,23) with rodent drug relapse models in which drug seeking is assessed after forced abstinence in the home cage (24,25), after punishment-induced abstinence (26), or after choice-based voluntary abstinence (27). We then used an experimental procedure inspired by a DSM-IV–based rat model of addiction (14,20), in which we trained a large cohort of male CD-1 mice for aggression self-administration and then tested them for choice-based voluntary suppression, relapse to aggression seeking, responding under a progressive ratio reinforcement schedule, and aggression self-administration despite adverse consequences (punishment).

The results of our first set of experiments demonstrate robust relapse to aggression seeking (operationally defined as persistent lever pressing under extinction conditions) after prolonged abstinence or suppression of aggression seeking, whether forced, punished, or choice-based, in nearly all aggressive mice. The results of our follow-up experiment, using previously established metrics for an "addicted" rodent (14,20), identify a subset of "aggression-addicted" mice (~19%) that exhibited intense operant-reinforced attack behavior, decreased likelihood to select an alternative palatable food reward over aggression, heightened relapse vulnerability and progressive ratio responding, and resistance to punishment-induced suppression of aggression self-administration.

METHODS AND MATERIALS

A detailed description of experimental subjects, apparatus, and procedures are provided in Supplemental Methods and Materials. We describe the specific experiments below.

Experiment 1: Relapse to Aggression Seeking After Forced Abstinence

The goal of experiment 1 was to determine the persistence of nonreinforced aggression seeking (relapse) after cessation of self-administration (Figure 1A). We trained 32 mice for

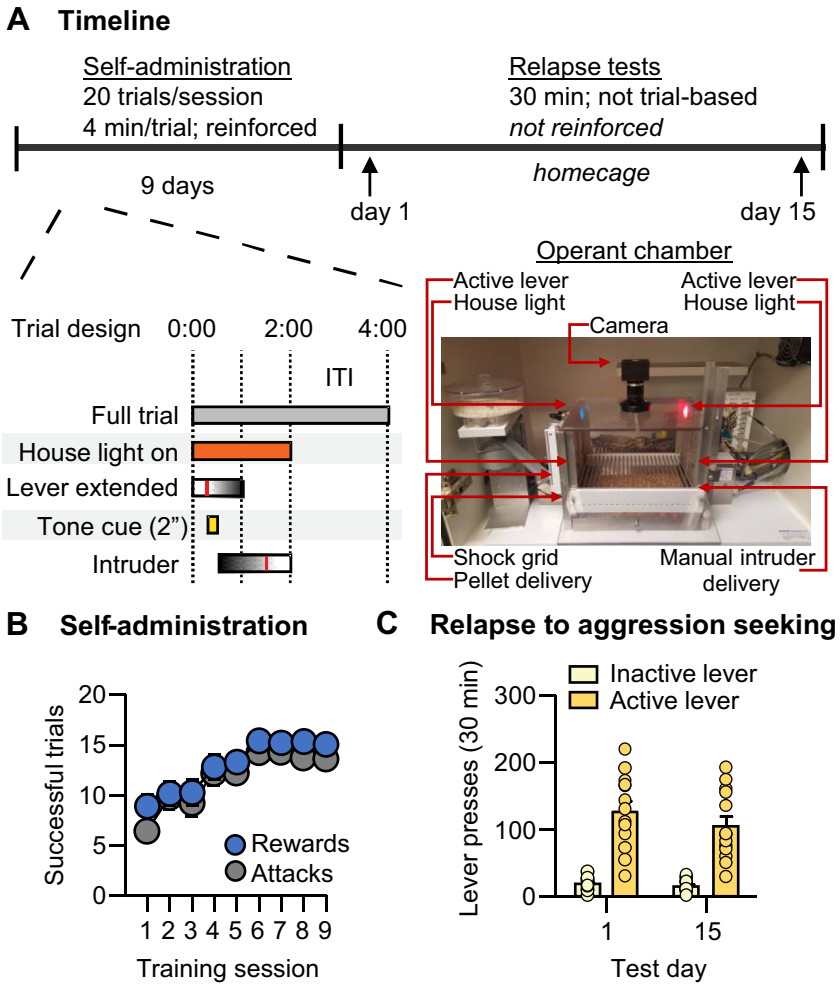

Figure 1. Relapse to aggression seeking after forced abstinence. **(A)** Time course schematic for training and testing (top) and for individual trials (bottom). Vertical red lines within the "lever extended" and "intruder" bars indicate an active lever press and removal of an intruder after an attack bout, respectively, relative to total possible durations. **(B)** Number of rewarded and attack trials over 9 days (80-minute session/day) of aggression self-administration under a trial design fixed-ratio 1 reinforcement schedule ($n = 26$). **(C)** Number of nonreinforced "active" lever and inactive lever presses during a 30-minute relapse to aggression-seeking test under extinction conditions on day 1 ($n = 13$) or day 15 ($n = 13$) of forced abstinence. Individual data denoted with circles. Data are mean ± SEM. ITI, intertrial interval.