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Naloxone attenuates incubated sucrose craving in rats

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Abstract

Rationale—Cue-induced craving precedes drug relapse and contributes to eating disorders. Opiate antagonists have been demonstrated to be effective at reducing cravings for drugs and food. Craving, as defined as responding for a stimulus previously associated with a reward, increases, or incubates, over forced abstinence in an animal model of relapse.

Objectives—This paper aims to determine anticraving effects of the opiate antagonist, naloxone, on the incubation of sucrose craving.

Methods—106 male Long-Evans rats lever pressed for 10% sucrose solution 2 h/day for 10 days. On either day 1 or 30 of forced abstinence, rats responded in extinction for 6 h and then were injected (ip) with either saline or naloxone (0.001, 0.01, 0.1, 1, or 10 mg/kg). The rats then responded for 1 h for presentation of a tone+light cue previously presented with every sucrose delivery during self-administration training.

Results—The rats responded more in extinction and following saline on day 30 vs day 1 (an incubation of craving). Except for a trend for a decrease in responding following 10 mg/kg on day 1, naloxone was primarily effective on day 30. On day 30, naloxone significantly reduced responding at all doses except for 0.1 mg/kg.

Conclusions—The time-dependent increase in sensitivity to an opiate antagonist is consistent with time-dependent changes in the opiate system following forced abstinence from sucrose. These changes may partly underlie the incubation of sucrose craving. In addition, these findings could be used to support the use of naloxone as an anticraving medication in protracted abstinence.

Keywords

Addiction; Eating; Naltrexone; Obesity; Opiate; Reinforcement; Relapse

Introduction

Addiction to drugs and addictive behaviors attached to food are prevalent (O'Brien 2003; Sobik et al. 2005; CDC 2007). Obesity, in many cases a result of overeating, is a particularly salient public health crisis as rates in the USA have doubled in the past 20 years (CDC). To alleviate such addiction-related problems, it is therefore critical to understand processes that contribute to excessive drug and food intake.

Food and drug rewards are mediated by similar neural circuitry (Volkow and Wise 2005). While the long-term consequences of drug abuse likely differ from maladaptive food habits in terms of ultrastructural brain changes (Crombag et al. 2005), neural adaptations mediating

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learning about rewards of different classes (e.g., food vs drug) are probably similar (Volkow and Wise 2005). Such adaptations, and the behavioral changes (learning) they correspond to, are often studied using animal models of addiction behavior (Shalev et al. 2002).

Cue-induced relapse to reward seeking is one model that has provided insight into the neurobiology of drug seeking (Shalev et al. 2002) and most recently insight into food seeking (Grimm et al. 2005, 2006; Bossert et al. 2005). In this animal model, rats respond for the presentation of a stimulus (tone+light) that was previously associated with self-administration of a reward. The magnitude of responding is taken as a measure of reward seeking and serves as a measure of "craving". Using this model, we and others have identified and characterized a time-dependent increase in responding for drug and food cues during abstinence from self-administration (Lu et al. 2004; Bossert et al. 2005 for reviews). In addition to the finding that the "incubation" of craving for sucrose is resistant to manipulations designed to reduce it (e.g., satiation with sucrose; Grimm et al. 2005), we have found that rats are less sensitive to the response-potentiating effects of cocaine at 1 month of forced abstinence vs 1 day (Grimm et al. 2006). This finding suggests time-dependent changes in the sensitivity of brain reward systems and has led us to consider how such transmitter systems might be affected by, or contribute to, the incubation of sucrose craving.

The opiates are one candidate system. Opiate antagonists (usually naloxone or naltrexone) have been found to decrease food craving and food intake by food bingers and/or obese individuals (Drewnowski et al. 1995; Marrazzi et al. 1995). They also decrease craving for cigarettes and alcohol (Epstein and King 2004; O'Malley et al. 2002). In studies with rats, naltrexone decreases responding for cocaine cues (Burattini et al. 2007), alcohol following alcohol cue exposure (Pickering and Liljequist 2003), and responding in the presence of an alcohol-paired discriminative stimulus (Ciccocioppo et al. 2002). In addition, in cocaine-trained rats, Lu and Dempsey (2004) found that heroin had greater effects later in abstinence vs early on reinstating cocaine seeking behavior—a cross-sensitivity suggesting that either the DA or opiate system (or both) is altered over the incubation of craving. DA release in the nucleus accumbens (NAcc) is increased/decreased by microinjection of an opiate agonist/antagonist into the ventral tegmental area (VTA; Spanagel et al. 1992; Devine et al. 1993) and endogenous opiates mediate food intake in rats (Reid 1985) including motivation to consume food (Glass et al. 1999). Therefore, as we have observed an effect of forced abstinence on DA sensitivity related to responding for a sucrose-paired cue (Grimm et al. 2006), we hypothesized that we would also see a time-dependent effect of a manipulation to affect the opiate system on responding for a sucrose-paired cue.

In the present study, we assessed the effects of the opiate antagonist naloxone on the incubation of sucrose craving. As the effects of opiate antagonism on conditioned reward, let alone incubation of reward craving, have not as yet been extensively characterized, we selected a broad dose range for our study. Previous researchers (Glass et al. 1999; Ciccocioppo et al. 2002; Colantuoni et al. 2002; Powell et al. 2002; Pickering and Liljequist 2003; D'Anci and Kanarek 2004; Leri and Burns 2005; Olmstead and Burns 2005) have described behaviorally relevant effects of naloxone and the similar naltrexone in the ultralow (down to 1 pg/kg), very low (30 ng/kg), and moderate (1–5 mg/kg) to relatively high dose range (up to 20 mg/kg). We chose doses in the submoderate to high range as doses into the very low/ultralow range may antagonize by nonclassic (non receptor-blocking) mechanisms (Olmstead and Burns 2005).

Materials and methods

Animals

Subjects were 106 male Long-Evans rats (350–450 g) bred in the Western Washington University Psychology Department vivarium. The rats were weighed each Monday,

Wednesday, and Friday for the duration of the experiment. The rats were maintained on Mazuri Rodent Pellets, and water was provided ad libitum except as noted in General procedures. The pellets and water were also available ad libitum in the self-administration chambers except as noted in general procedures. All the rats remained singly housed in the vivarium except during daily training or testing sessions when they were brought to the self-administration chambers. The rats were maintained on a reversed 12:12 h light–dark cycle with lights off at 7 A.M. All procedures performed on the rats followed the NIH guidelines for animal care and were approved by the Western Washington University Animal Care and Use Committee.

Apparatus

The self-administration chambers, controlled by a Med Associates (Georgia, VT) system, had two levers, but only one lever (an active, retractable lever) activated the infusion pump. Presses on the other lever (an inactive, stationary lever) were also recorded. The 10% sucrose solution was delivered into a liquid drop receptacle for oral consumption (Med Associates). The chambers had four infrared emitters and detectors (Med Associates) aligned in a tic-tac-toe pattern (front beams each 10.5 cm from wall; side beams each 6 cm from the wall) across the self-administration chamber, each 4.5 cm above the stainless steel bar floor. The emitters/detectors were affixed to the plexiglass of the door or back wall or on plexiglass inserts in the side walls. The beams were set to count the number of complete breaks. The locomotor activity system was integrated into the Med Associates data collection system.

General procedures

The rats were deprived of water in their home cages 17 h before the first training session. Water was not available in the self-administration chambers initially, but was returned to the self-administration chambers when rats learned to reliably respond for sucrose (>20 sucrose deliveries/day), or after 3 days of self-administration training for rats that were slow to learn to press for sucrose. Water was returned to home cages after 48 h of deprivation. The experiment included three phases: training, abstinence, and testing. As described in the Introduction, responding in the testing phase (reinstatement conditions) is taken as an index of craving. Lever presses during testing were never reinforced with sucrose. Training and testing started at 8:30 A.M.

Training phase—Rats were trained to self-administer sucrose (0.2 ml) delivered into a liquid drop receptacle. Training was conducted in 10 daily 2-h sessions under a continuous reinforcement schedule (each lever press was reinforced) with a 40-s timeout after each earned reward. Lever presses were counted during timeouts but were without consequence. Each session began with the insertion of the active lever and the illumination of a red houselight that remained on for the entire session. A 5-s tone (2,900 Hz, 20 dB above background)+light (7.5 W white light above the active lever) discrete compound cue accompanied each reward delivery. At the end of each session, the houselight was turned off and the active lever retracted. There was no limit on the number of rewards earned.

Forced-abstinence phase—At the end of the training phase, rats (n=8–11 rats/group) were randomly assigned to one of the forced-abstinence periods (1 or 30 days). Training behaviors (sucrose intake, active, and inactive lever responding) were compared between groups to ensure groups did not significantly differ from one another during training. The rats lived in the vivarium for the duration of forced abstinence. Saline was administered in the afternoons of the 2 days before testing to acclimate the animals to injections.

Testing phase: Extinction responding—On the test day, all rats were given 6, 1-h extinction sessions that were separated by 5 min until they reached an extinction criterion of less than 15 responses/1 h on the previously active lever. The tone+light discrete cue was not

present during these sessions. Each 1-h session began with the introduction of the active lever and illumination of the houselight. At the end of each session, the houselight was turned off, and the active lever retracted. Two rats were given an additional 1-h extinction session to reach the 15-responses/1 h criterion.

Testing phase: Responding for cue—This session started 5 min after the last 1-h extinction session. Intraperitoneal injection of saline or naloxone (0.001, 0.01, 0.1, 1, or 10 mg/kg) occured immediately before this session. The test for cue-induced sucrose craving consisted of a 1-h session wherein responses on the previously active lever led to the presentation of the tone+light cue on a continuous reinforcement schedule with a 40-s timeout.

Testing phase: Locomotor activity—Locomotor activity was collected throughout the testing phase.

Data analyses

Training phase

Daily sucrose presentations (infusions), active lever responses, and inactive lever responses were analyzed with separate repeated measures ANOVAs (RM ANOVAs) using Time (days 1–10 of training) and the additional between-group factors of Day (1 or 30) and Dose (saline, 0.001, 0.01, 0.1, 1, or 10 mg/kg naloxone) to verify that the rats tested at different time points and with different doses of naloxone received equivalent training.

Testing phase

Data from the extinction sessions (Extinction responding) and tests for cue-induced sucrose seeking (Responding for cue) were analyzed separately for total nonreinforced responses on the previously active lever and responses on the inactive lever. These data were analyzed using ANOVA with the between-group factors of Day (1 or 30) and Dose (saline, 0.001, 0.01, 0.1, 1, or 10 mg/kg naloxone). A subsequent RM ANOVA was conducted on Extinction responding active lever responding to confirm that groups to be tested with saline or naloxone did not differ before the drug manipulation. In this ANOVA, Time was the 6, 1 h extinction sessions. Total locomotor counts from Extinction responding and Responding for cue sessions were also analyzed with separate ANOVAs using the factors of Day and Dose. Paired-samples *t* tests were performed between active lever responding in the sixth hour of extinction and the Responding for cue session for the saline-treated groups to verify that the reinstatement procedure produced robust cue-induced responding at both forced abstinence time points. An independent-samples *t* test was performed with active lever responding in the Responding for cue session between the saline-treated day 1 group and the saline-treated day 30 group to verify an incubation of sucrose craving.

All statistical comparisons were made using SPSS version 12.0. Post hoc comparisons following ANOVA were made using the LSD test. Group data are presented as the mean±SEM in the text and figures.

Results

Training phase

The five rats that failed to demonstrate consistent self-administration behavior (average infusions over training were greater than 2 standard deviations below the mean) were removed from the study. Of those that acquired self-administration (N=106), the number of sucrose deliveries increased over the ten daily training sessions [effect of Time, F (9, 846)=22.9, p<0.001]. In addition, responding on the active lever increased over the course of training

[effect of Time, F (9, 846)=8.4, p<0.001] while responding on the inactive lever decreased [effect of Time, F (9, 846)= 56.8, p<0.001] indicating strong discrimination between levers. Rats pressed an average of 167±11.4 times on the active lever and 3.4±0.5 times on the inactive lever on the final day of training. There were no significant main effects or interactions of Day or Dose for any of the measures indicating that all groups were equivalent before actual manipulations of Day and Dose for testing.

Testing phase: Extinction responding

The rats tested for extinction on day 30 of forced abstinence responded more on the active lever than rats tested on day 1 [effect of Day, F (1, 94)=47.1, p<0.001], demonstrating an incubation of sucrose craving. Active lever responding on day 1 averaged 63.3±5.2 responses over 6 h compared to 135±8.9 responses over 6 h on day 30. As indicated in the Materials and methods, a subsequent RM ANOVA of lever responding over the 6 h of Extinction responding (6, 1-h sessions) confirmed a time-dependent increase in overall responding with a main effect of Day, F (1, 94)=47.1, p<0.001 and a significant Day by Time interaction, F (5, 470)=10.1, p<0.001. This interaction along with a significant main effect of Time, F (5, 470)=157.6, p<0.001 confirmed a significant decrease in responding over the 6 h of Extinction responding. There were no significant effects of Dose, nor any significant interactions other than the Day by Time interaction, indicating that groups on day 1 or day 30 subsequently injected with saline or naloxone were statistically similar before the drug manipulation. On both days, the time course of the 6-h Extinction responding was a dramatic decrease in rate of responding with responding in hour 1 (36.6±3.5 vs 64.6±4.9 responses, day 1 vs day 30) much greater than in hour 6 (3.0 ±0.4 vs 7.8±1.1 responses, day 1 vs day 30).

Inactive lever responding was also slightly higher on day 30 with an average of 7.4±1.8 vs 20.2 ±1.7 responses over 6 h, days 1 and 30, respectively, F (1, 94)=26.6, p<0.001. There were also more photobeam breaks during Extinction responding testing on day 30 vs day 1 with an average of 3,154.4±113.1 vs 3,932.8±111.4 photobeam breaks over 6 h, days 1 and 30, respectively, F (1, 94)=24.1, p<0.001. There were no significant effects of DOSE and no significant interactions for either inactive lever responding or locomotor behavior (p values ranging from 0.2 to 0.8) further demonstrating that treatment groups did not differ before saline or naloxone injection.

Testing phase: Responding for cue

For the saline-treated groups, active lever responding was greater in the Responding for cue session vs the sixth hour of extinction on both days 1 and 30 of forced abstinence. The t values were t (10)=−2.6, p<0.05 for day 1 and t (6)= −5.8, p<0.001 for day 30 (data not shown). Therefore, the rats in the saline condition were reliably responding for the sucrose-paired cue. ANOVA of active lever responding during Responding for cue sessions revealed a significant effect of Day, F (1, 94)=86.1, p<0.001, Dose, F (5, 94)= 4.6, p<0.01, and a Day by Dose interaction, F (5, 94)=3.8, p<0.01. This, coupled with identification of a significant difference between saline day 1 vs saline day 30 responding, t (16)=−6.1, p<0.001, and inspection of the data (Fig. 1) indicated an incubation of craving for the sucrose-paired cue. As indicated in the Materials and methods, this single t test was done as a manipulation check verifying that incubation of craving was observed in saline-treated rats. It was then necessary to remove the effects of incubation to examine the effects of naloxone at each time point. We did this using two methods. First, we simply examined data on days 1 and 30 independently. ANOVA of active lever responding on day 1 revealed no main effect of naloxone, F (5, 46)=1.6, p=0.2. However, a comparison between the saline group and the 10 mg/kg group indicated a trend toward naloxone attenuating responding (p=0.06). ANOVA of active lever responding on day 30 revealed a significant main effect of naloxone, F (5, 48)=4.7, p<0.01. Significant post hoc differences are indicated on Fig. 1. Second, to attempt to explicitly compare the effectiveness

of naloxone on day 1 vs day 30, we removed the effects of incubation by transforming the data to percent of average saline responding (day 1 responding as a percent of day 1 saline and day 30 responding as a percent of day 30 saline). ANOVA was then performed with these transformed data using the between-group factors of Day (1 or 30) and Dose (0.001, 0.01, 0.1, 1, or 10 mg/kg naloxone). ANOVA revealed a significant effect of Day, F (1, 78)=4.7, $p<0.05$, Dose, F (4, 78)=2.6, $p<0.05$, and a nearly significant Day by Dose interaction, F (4, 78)=2.4, $p=0.05$. As this was a between-subjects design, this approach does not provide as much statistical power as comparing a subject's drug-affected behavior to its own baseline (within-subjects design); however, it does provide a statistical method to compare drug effects in groups that already differ due to the effects of another variable. As indicated in Fig. 2, naloxone was more effective on day 30 vs day 1 at the 2 lowest doses tested (0.001 and 0.01 mg/kg). Figure 2 presents percent of saline data subtracted from 100 to convey the effectiveness of naloxone at attenuating Responding for cue active lever responding (100% would be a complete elimination of responding).

Inactive lever responding was higher on day 30 vs day 1, F (1, 94)=8.8, $p<0.01$, but there was no effect of Dose, and there was no significant interaction. The "incubation" of inactive lever responding was actually quite small, with an average of 0.8±0.4 responses on day 1 and 2.4 ±0.4 responses on day 30.

Locomotor activity during Responding for cue, as with inactive lever responding, was higher on day 30 vs day 1, F (1, 94)=4.4, $p<0.05$. Likewise, there was no effect of DOSE and there was no significant interaction. Locomotor activity averaged 516±53.3 photobeam breaks on day 1 vs 672±52.5 photobeam breaks on day 30.

Discussion

The present study examined the effectiveness of the opiate antagonist, naloxone, on attenuating responding for a sucrose-paired cue at both an early and a later time point in forced abstinence. Naloxone was found to attenuate responding almost exclusively at 1 month vs 1 day of forced abstinence (Fig. 1). In addition, a dose-effect relationship was observed on day 30 where naloxone attenuated responding at fairly low doses (0.001 and 0.01 mg/kg) and higher doses (1 and 10 mg/kg), but not at an intermediate dose (0.1 mg/kg; Fig. 1). These results support our hypothesis that naloxone would be effective at reducing responding for a food-paired cue. This further leads us to consider that there is a time-dependent change in some aspect(s) of the opiate system over several weeks of forced abstinence from sucrose self-administration that parallels the incubation of sucrose craving. Overall, as the rats were more sensitive to low doses of naloxone on day 30 (Fig. 2), we conclude that some aspect of the opiate system becomes increasingly sensitive over 1 month of forced abstinence from sucrose self-administration.

The decrease in craving by naloxone in this rat model of relapse parallels described anticraving effects of naloxone upon exposure to cigarette, alcohol, and food cues in humans (Drewnowski et al. 1995; Marrazzi et al. 1995; O'Malley et al. 2002; Epstein and King 2004). In effect, the animal model is validated. However, a recent study of the effect of a single dose of naltrexone on responding in the presence of a discriminative stimulus, previously indicating the availability of sucrose, did not find any effect of naltrexone on conditioned responding (Burattini et al. 2007). This inconsistency is likely due to several methodological issues. First, we are studying relapse due to contingent presentation of a discrete cue formerly paired with sucrose, while Burattini et al. (2007) evaluated the effects of a discriminative stimulus. The processing of these different types of cues appears to require different neural substrates (Phillips and LeDoux 1992; Holland and Bouton 1999). Second, we observed the most reliable effects of naloxone at day 30 of forced abstinence while Burattini et al. (2007) tested responding after about 15 days of extinction. There is also the consideration of differences in efficacy to

explain the discrepancy between naloxone and naltrexone; however, this is unlikely as the naltrexone dose (2.5 mg/kg) was similar to our higher doses. Other than the longer half life of naltrexone, doses of naloxone and naltrexone are comparable to each other (Julien 2001).

We do not believe that the effects of naloxone in the present study were due to behavioral suppression by precipitating somatic withdrawal symptoms. Our rats did not display any obvious somatic signs of opiate dependence either before or after naloxone administration. Although not evaluated systematically, we did not observe classic opiate withdrawal (piloerection, diarrhea, teeth chatter or other tremor/shaking) either during forced abstinence or on test days. Furthermore, body weights increased over forced abstinence and locomotor activity was not affected by naloxone (data not shown). Such somatic signs of naloxone-precipitated withdrawal have been described following a regimen of glucose intake (Colantuoni et al. 2002). However, that regimen (12 h 25% glucose in chow alternating with 12 h forced fasting daily for 8 days) differed substantially from the present study both in terms of amount of sugar and food deprivation conditions (our rats got less sugar and were never food deprived). In addition, Colantuoni et al. (2001) used a dose of naloxone twice as large, 20 mg/kg, as our highest dose.

One limitation of the present study for interpreting time-dependent effects of naloxone was the relatively low responding for the sucrose-paired cue on day 1. While this highlights the incubation of craving effect when comparing it to day 30, it leaves open the possibility that a general lack of effect on naloxone on day 1 responding was due to a dependence of naloxone's efficacy on rate of responding and/or a "floor effect." Both of these alternative hypotheses cause us to lend caution to our interpretation of the effectiveness of naloxone in the present study; however, studies on rate dependency support the generalization that lower rates of responding should actually be more susceptible to disruption (Gonzalez and Goldberg 1977; Phillips et al. 1991). In addition, while not statistically significant, there was a trend for the high dose of naloxone to reduce Responding for cue on day 1 (p=0.06, 10 mg/kg vs saline, overall ANOVA n.s.; see Fig. 1). This indicates a lack of a floor effect.

The dose-effect curve for naloxone on Responding for cue on day 30 was peculiar. The fact that the drug was effective at very low doses and at higher doses, but not at a middle dose, could indicate multiple mechanisms for attenuating responding for the sucrose-paired cue.

A mechanism for the biphasic effect might be regional effectiveness of the antagonist over the doses we tested. For example, there are more opiate receptors in the NAcc vs the VTA (Mansour et al. 1987; McBride et al. 1998) and microinjection studies directing opiate agonists (Zhang and Kelley 1997; Macdonald et al. 2003) into NAcc and VTA have observed site-specific opiate receptor subtype and general dose-effectiveness differences. It could be lower doses of naloxone are more effective in one of these regions, while at the higher doses both regions are affected. The middle dose could produce an "imbalance" in the overall inhibition of the DA system connecting these brain regions. In effect, this could produce an increase in the variability of motivated responding. This was what we observed following the 0.1 mg/kg dose. Inspection of response data revealed, from the ten rats in the group, three rats in the 0.1 mg/kg group made 70 or more responses (70, 70, 72) while three rats made fewer than 25 responses (15, 18, 24). The remaining rats in that group responded 29–41 times (29, 32, 38, 41), whereas the saline mean was 46.4. So overall, the trend from inspection of data from individual rats was for a decrease in responding vs saline following 0.1 mg/kg while some rats actually demonstrated a potentiation of responding.

Finally, although naloxone fairly selectively attenuated cue-induced responding on day 30, it did not decrease day 30 responding to day 1 levels (Fig. 1). Therefore, we may have observed only a partial attenuation of whatever overall neuroadaptations underlie the incubation of

sucrose craving. Other transmitters systems as modulators of the incubation of craving are candidates for further study. Glutamate is a likely choice as Uejima et al. (2007) have very recently found that inhibition of glutamate release with the glutamate autoreceptor agonist LY379268 attenuates incubation of sucrose craving when administered either systemically or directed to the central nucleus of the amygdala (Uejima et al. 2007). GABA is another possible target as VTA GABA neurons likely inhibit mesolimbic DA neurons (Spanagel et al. 1992;Devine et al. 1993); therefore, GABA receptors would be a target for affecting motivated behavior. Finally, DA itself would be a good candidate, especially given our previous observation of a time-dependent decrease in the effects of cocaine-potentiated responding for a sucrose-paired cue (Grimm et al. 2006).

Conclusions

As naloxone was most effective later in forced abstinence, it may be a desirable potential treatment option for reducing food cravings. For example, over 90% of dieters fail in reaching weight reduction goals (Grodstein et al. 1996). The present results also complement clinical studies using naloxone and naltrexone to reduce relapse to food craving and bulimia, alcohol intake, and cigarette smoking (Drewnowski et al. 1995; Marrazzi et al. 1995; O'Malley et al. 2002; Epstein and King 2004). These findings support a general role of the opiate system in relapse, including craving behaviors, related to several reward classes.

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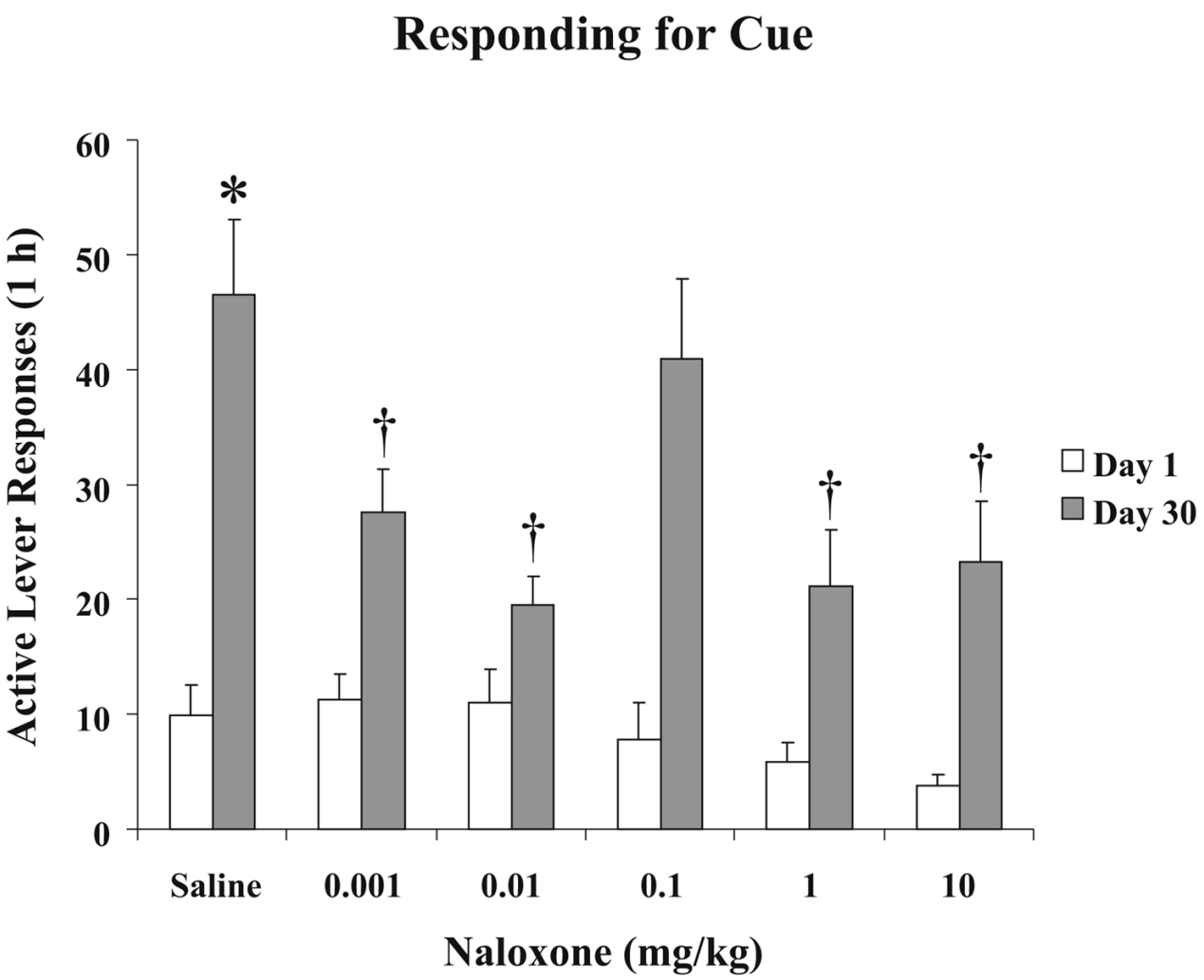

Fig. 1.

Effects of naloxone on Responding for the sucrose-paired cue on day 1 vs day 30. Means±SEMs are indicated for active lever responding. Asterisk indicates significant difference from day 1 (indicated only for saline groups to highlight the incubation of sucrose craving) and *dagger* indicates significant difference from Saline, $p<0.05$. The day 1, 10 mg/kg naloxone group was nearly significantly different from saline ($p=0.06$)

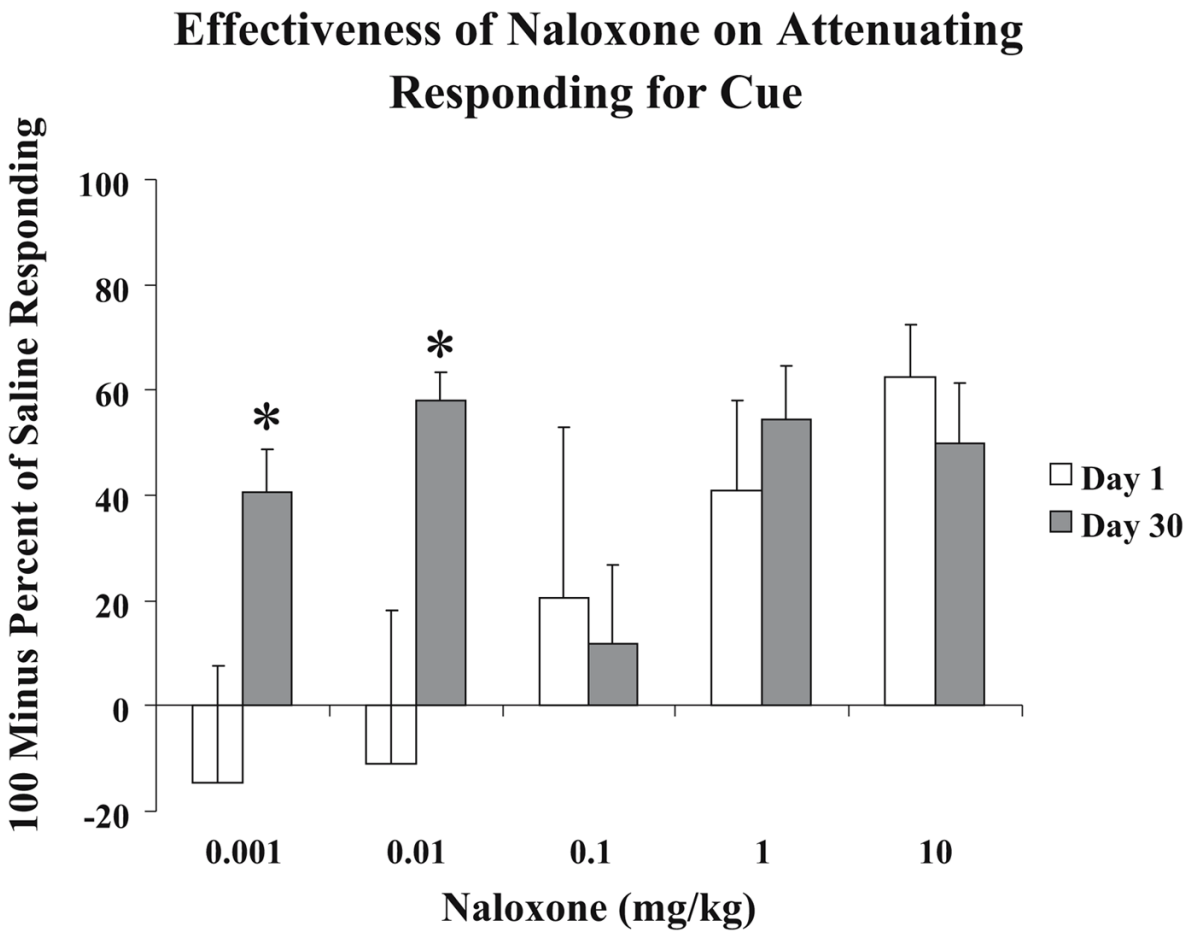

Fig. 2.

Effectiveness of naloxone on Responding for the sucrose-paired Cue on day 1 vs day 30. Means ±SEMs are indicated for 100 minus percent of saline responding (percent of Saline calculated for each group as Responding for cue divided by saline responding for cue at that forced abstinence time point). *Asterisk* indicates significant difference from day 1, $p<0.05$