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Post-conditioning propranolol disrupts cocaine sensitization

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Abstract

Antagonists of β -adrenergic receptors (β -ARs) have previously been demonstrated to impair long-term memory in a variety of animal behavioral paradigms. Surprisingly little is known about the ability of β -ARs to modulate initial memory formation in drug conditioning paradigms. The current study examined whether the post-training administration of the β -AR antagonist, propranolol, would disrupt single-trial cocaine-induced sensitization. Rats received 10 mg/kg propranolol immediately following a 30-min cocaine or vehicle exposure in a conditioning context and were later tested for their locomotor response to a cocaine challenge. Rats that received propranolol following cocaine conditioning showed an impairment of locomotor sensitization during testing. However, this effect was only seen in animals with an initial sensitivity to the locomotor effects of cocaine. Rats that failed to show a locomotor response to cocaine during conditioning were not affected by propranolol. We discuss the implications of these findings as they relate to drug conditioning and memory consolidation studies.

Keywords

consolidation; cocaine; sensitization; memory; propranolol

1. Introduction

Norepinephrine (NE) is critically involved in a variety of cognitive processes, including attention, arousal, emotion, learning, and memory consolidation (Sara, 2009). NE facilitates memory consolidation primarily via β -adrenergic receptors (β -ARs). Because of the important role of NE and β -ARs in mediating stressful and/or emotional experiences, specifically fear-motivated memories, it is perhaps not surprising that consolidation studies involving β -ARs have primarily utilized aversive learning paradigms. For example, in rodent studies, post-training injections of NE or β -AR agonists have been shown to enhance memory in inhibitory avoidance (Introini-Collison et al., 1991; Ferry and McGaugh, 1999) and fear conditioning (LaLumiere et al., 2003; Berlau and McGaugh, 2006) paradigms. Furthermore, β -AR antagonists impair consolidation of aversive memories (Berlau and McGaugh, 2006; Adamec et al., 2007; Qu et al., 2008; Kroon and Carobrez, 2009). Norepinephrine has also been demonstrated to be involved in the consolidation of spatial

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(Cahill et al., 2000; Row and Dohanich, 2008) and object recognition (Dornelles et al., 2007; Roozendaal et al., 2008) memories.

Interestingly, little is known about the role of β -ARs following a learning experience using drug conditioning paradigms. However, it is becoming clear that adrenergic modulation has a critical influence on drug cue-mediated behaviors. For example, Otis & Mueller (2011) recently reported that propranolol impaired the retrieval, or expression, of a cocaine conditioned place preference (CPP) in rats. Furthermore, the norepinephrine reuptake inhibitor, atomoxetine, was shown to impair recovery of drug-seeking behavior in cocaine self-administration when administered during extinction training (Janak et al., 2012). We have previously shown using the cocaine CPP paradigm that β -AR antagonists administered following retrieval trials altered cue-induced responding during subsequent trials (Bernardi et al., 2006; Bernardi et al., 2009). These findings are consistent with those in aversive paradigms, such as fear conditioning (Debiec and Ledoux, 2004) and inhibitory avoidance (Przybylski et al., 1999), and suggest mechanistic similarities in the processing of drug and fear memories. In fact, enhanced arousal is a feature of both stress and the physiological actions of psychostimulants (Berridge, 2008), and noradrenergic activation has been hypothesized to enhance associative mechanisms that drive drug-seeking during withdrawal (Koob, 2009).

The purpose of the current study was to determine whether a single-trial cocaine-induced locomotor session is vulnerable to post-trial β -AR modulation. Drug dependence in humans is characterized by high rates of relapse, of which cues previously associated with drugs of abuse are a major contributor (O'Brien et al., 1998; Weiss, 2005). Because locomotor sensitization may model some aspects of drug dependence in humans (Robinson & Berridge, 1993, 2001), and context-dependent, but not context-independent, sensitization can be achieved with a single conditioning trial (Post et al., 1987; McDougall et al., 2007) in rodents, this paradigm is ideal for examining post-training drug memory consolidation. Here we use a 2-day sensitization paradigm to examine the role of β -ARs in the potential consolidation of a cocaine-context memory in rats by administering propranolol or vehicle following cocaine conditioning and testing for locomotor sensitization to a low-dose cocaine challenge dose 72 hr later. We show that post-trial propranolol inhibited a subsequent sensitized locomotor response to cocaine specifically in rats initially responsive to the locomotor activating effects of cocaine that may be indicative of an impairment of drug memory consolidation.

2. Methods

2.1 Subjects

Seventy-two male Sprague Dawley rats (Harlan, Indianapolis, Indiana) weighing 250–300 grams served as subjects. Rats were housed three per cage in a temperature-controlled (21 °C) environment maintained on a 12-hr light-dark cycle (lights on at 6 a.m.). Food and water was available *ad libitum*. All experiments were performed in accordance with the National Institutes of Health guidelines for the care and use of laboratory animals. All behavioral testing was conducted during the light phase between 0800 h and 1700 h.

2.2 Apparatus

Locomotor activity was assessed in six Opto-Varimex-3 automated activity monitors (Columbus Instruments, Columbus, OH). Each monitor consists of a clear acrylic plastic test cage (40 × 40 × 30 cm) placed inside a monitoring unit that records ambulatory beam interruptions from 15 evenly-spaced infrared photocell emitter/detector pairs evenly spaced along each axis and located 2 cm above the chamber floor. Monitors and test cages were housed in black acrylic plastic chambers lined with a sound-attenuating foam material

designed to eliminate noise from the external environment. Inside each chamber, a fluorescent light and a fan were on during testing to provide illumination, ventilation and a low level of masking noise.

2.3 Drugs

Cocaine HCl was obtained from Sigma (St. Louis, MO) and dissolved in physiological saline (0.9% NaCl) for intraperitoneal (IP) injection (1 ml/kg). Cocaine was administered in doses of 30 mg/kg (conditioning) and 15 mg/kg (testing), doses chosen based on previous work from our and others' laboratories (Post et al., 1987; Bernardi et al., 2007). Propranolol (Sigma) was dissolved in saline for IP injection (1 ml/kg) and administered in a dose of 10 mg/kg. This dose of propranolol has been used frequently in previous memory studies (e.g., Bernardi et al., 2006; Otis and Mueller, 2011).

2.4 Behavioral Procedures

Cocaine conditioning (Session 1)—Rats were placed into the activity monitors, which served as the conditioning context, for a 30-min habituation period designed to reduce possible stress-induced increases in locomotor activity. Thirty minutes later rats were administered an injection of cocaine (30 mg/kg IP) or vehicle and immediately placed back into the activity monitors for 30 min. Following this conditioning trial, rats were immediately administered an injection of 10 mg/kg IP propranolol or vehicle. Activity monitors were thoroughly cleaned with a 10% isopropanol solution between rats.

Locomotor sensitization testing (Session 2)—Seventy-two hours later, rats were tested with a cocaine challenge to examine the effect of post-conditioning propranolol on locomotor sensitization. Rats were placed into the activity monitors for 30 min, then given an injection of cocaine (15 mg/kg IP) and placed back into the activity monitors for 30 min to measure the locomotor response to cocaine.

2.5 Data analysis

Statistical analyses were conducted with SPSS software (Chicago, IL). Significant ANOVAs were followed by Student's t-test, where specified. Significance was set at $p < .05$.

3. Results

There was a clear difference in locomotor activity during conditioning between cocaine- and vehicle-treated rats. Figure 1 (left) shows the mean ($\pm$ SEM) ambulation counts during conditioning for the four groups, based on pre- (cocaine vs. vehicle) and post-conditioning treatment (propranolol vs. vehicle). Thus, the four groups are cocaine-vehicle ($n = 18$), cocaine-propranolol ($n = 18$), vehicle-vehicle ($n = 18$), and vehicle-propranolol ($n = 18$). A two-way ANOVA revealed a significant effect of pretreatment [$F(1,68) = 48.9, p < .001$], but no effect of posttreatment and no interaction [$F(1,68) < 2.5, ps > .12$]. Thus, cocaine-treated animals showed higher locomotor activity during conditioning than their vehicle-pretreated counterparts.

Rats that received propranolol following cocaine conditioning showed less locomotor activity during testing compared to vehicle-treated rats. Figure 1 (right) shows the mean ($\pm$ SEM) ambulation counts during testing. There was a significant effect of pretreatment [$F(1,68) = 11.2, p < .005$] and a significant effect of posttreatment [$F(1,68) = 4.5, p < .05$], but no pretreatment $\times$ posttreatment interaction [$F(1,68) = 1.6, p = .21$]. Thus, animals treated with cocaine during conditioning showed a higher locomotor response to cocaine—locomotor sensitization—during testing as compared to animals treated with saline during

conditioning. Furthermore, propranolol impaired the locomotor response to cocaine during testing.

In a subsequent analysis we separated cocaine-treated animals based on their locomotor response to cocaine during conditioning into responders and non-responders, and reanalyzed the effects of postconditioning propranolol based on this separation. To do this, we identified the highest 30-min locomotor activity score (3639) from the 36 animals pretreated with saline during conditioning, and used this as our separation score. This ensured that rats who failed to show a locomotor response to cocaine were matched on activity with saline-treated groups, as can be seen in Figure 2 (left). Thus, cocaine-treated animals with a locomotor activity score lower than 3639 during the 30-min conditioning session were identified as non-responders, while cocaine-treated animals with a locomotor activity score higher than 3639 during the 30-min conditioning session were identified as responders. Non-responders and responders accounted for 13 (36%) and 23 (64%) rats, respectively, of the 36 cocaine-treated animals. This means of data separation was based on previous studies that also characterized high and low responders based on an initial response to cocaine, in which low responders showed no difference in cocaine-induced activation as compared to vehicle-treated animals (Romanova et al., 2010).

Non-responders

Rats identified as non-responders showed identical locomotor activity during both conditioning and testing as compared to rats treated with vehicle prior to the conditioning trial. Figure 2 (left) shows the mean ($\pm$ SEM) ambulation counts during conditioning. A two-way ANOVA revealed no significant interaction or effects of pretreatment or posttreatment [$F(1,45) < 1.1$, $p > .31$], confirming no difference in locomotor activity among the groups.

Figure 2 (right) shows the mean ($\pm$ SEM) ambulation counts during testing for the non-responders. Again, There was no significant interaction [$F(1,45) = 3.2$, $p > .05$] or effects of pretreatment or posttreatment [$F(1,45) < 1.1$, $p > .35$]. Importantly, this confirms no locomotor sensitization in animals pretreated with cocaine prior to conditioning, as the locomotor response in this group was identical to that receiving cocaine for the first time.

Responders

In rats identified as responders, there was a clear difference in locomotor activity following cocaine pretreatment during conditioning as compared to vehicle-treated rats. Figure 2 (left) shows the mean ($\pm$ SEM) ambulation counts during conditioning among the groups. A two-way ANOVA revealed a significant effect of pretreatment [$F(1,55) = 224.3$, $p < .001$], but no significant effect of posttreatment or interaction [$F(1,55) < 3.6$, $p > .05$]. Student's t-test confirmed that cocaine-vehicle and cocaine-propranolol animals showed higher locomotor activity during conditioning than their vehicle-pretreated counterparts [$t(29) = 10.3$, $p < .001$] and [$t(26) = 12.6$, $p < .001$], respectively. Thus, cocaine-treated rats exhibited higher locomotor activity than saline-treated rats.

Rats that received propranolol following cocaine conditioning showed significantly lower locomotor activity during testing than rats that received vehicle following cocaine conditioning. Figure 2 (right) shows the mean ($\pm$ SEM) ambulation counts during testing. A two-way ANOVA revealed a significant pretreatment x posttreatment interaction [$F(1,55) = 5.3$, $p < .05$], as well as significant main effects of both pretreatment [$F(1,55) = 16.6$, $p < .001$] and posttreatment [$F(1,55) = 9.6$, $p < .005$]. Student's t-test confirmed that cocaine-vehicle animals showed higher locomotor activity testing than vehicle-vehicle animals [$t(29) = 4.4$, $p < .001$], confirming a cocaine-induced sensitized locomotor response in animals

pretreated with cocaine during conditioning relative to animals pretreated with vehicle prior to conditioning. Furthermore, cocaine-vehicle animals showed a significantly higher locomotor response than cocaine-propranolol animals [$t(21) = 2.7, p < .05$], and cocaine-propranolol animals showed no difference in locomotor activity during testing relative to the vehicle-vehicle [$t(26) = 0.6, p = .53$] and vehicle-propranolol [$t(26) = 1.3, p = .20$] groups. These results suggest that propranolol administration following cocaine conditioning impaired the sensitized locomotor response. Again, the two groups pretreated with vehicle prior to conditioning did not differ in locomotor activity during testing [$t(34) = 0.8, p = .42$].

We also performed a regression analysis to compare the acute locomotor response to cocaine with the subsequent sensitized response to cocaine in the animals from each of the cocaine-treated groups (Figure 3). The acute locomotor response to cocaine was significantly correlated with the cocaine-induced sensitized locomotor response in the vehicle-posttreated animals only ($p < .005, r^2 = 0.41$; left graph), while no correlation was seen in propranolol-treated animals ($p = .88, r^2 = 0.002$; right graph). This is again reflective of the impairment in the sensitized response to cocaine by propranolol.

4. Discussion

The results presented here demonstrate that locomotor sensitization can be disrupted by propranolol administered following initial cocaine exposure. These findings are consistent with other studies demonstrating behavioral impairments following post-training β -AR antagonist administration, which have been interpreted as effects on memory consolidation (Ferry and McGaugh, 1999; Cahill et al., 2000; LaLumiere et al., 2003; Roozendaal et al., 2008). Our findings of a propranolol effect only in animals with an initial sensitivity to the locomotor effects of cocaine suggest that propranolol interacts with the cellular processes induced by cocaine to alter subsequent sensitized responding.

Cocaine exerts its actions via blockade of reuptake of catecholamines such as dopamine and norepinephrine (Weinshenker and Schroeder, 2007). Because norepinephrine, via β -ARs, is one mediator of salience endowed upon neutral cues by rewarding or aversive unconditioned stimuli (Harley, 2004), it is perhaps not surprising that propranolol would impair cocaine-induced contextual memory consolidation in responders. This may also account for the lack of effect in non-responders, in which cocaine failed to induce a locomotor response. The absence of a cocaine-induced response suggests that the physiological processes that underlie cocaine sensitization (e.g., emotional value, reward, memory) were not induced, so there was no process for propranolol to alter.

The relationship between locomotor sensitization and reward remains a tentative one. For example, in rodents, psychostimulant sensitization and reinforcement may not be correlated (e.g., Ben-Shahar et al., 2005; Marusich et al., 2008; but see Allen, Everitt, Nelson, Gully, & Zahniser, 2007). Furthermore, sensitization phenomena have only sparsely been demonstrated in humans (Bradberry, 2007). Thus, the clinical relevance of sensitization remains unclear. However, the neural mechanisms that produce behavioral sensitization in rodents have long been suggested to model the neurobiological adaptations that induce drug craving following drug use in humans (Robinson and Berridge, 1993; Kalivas et al., 1998; Robinson and Berridge, 2001), especially changes in mesocorticolimbic dopamine circuits that underlie both sensitization and the reinforcing properties of drugs of abuse and drug-associated cues (Robinson and Berridge, 2003; Anderson and Pierce, 2005). In addition, previous work has suggested that sensitization resulting from limited exposure and that resulting from chronic cocaine exposure can be pharmacologically dissociated (Reimer and Martin-Iverson, 1994).

Studies have recently begun to demonstrate the need to analyze behavior in subpopulations that show differing levels of responding (Weber et al., 2007; Bouton et al., 2008; Burgos-Robles et al., 2009), including in drug conditioning paradigms (dela Cruz et al., 2009). In humans, not all drug users progress from drug-taking to addiction, and thus it is critical to understand the mechanisms by which the initial experience to drugs of abuse and the environment in which they are encountered may impact future drug responding. One important finding of the current study is that propranolol-induced impairment occurred only in animals that demonstrated an initial sensitivity to the locomotor activating effects of cocaine. In other words, it is likely that acquisition of the cocaine-context association, which required cocaine-induced locomotor activation, was necessary to detect the impairment induced by propranolol.

An elegant series of previous studies has also examined differences in a variety of measurements based on the initial locomotor responsiveness to a single administration of cocaine (Low and High Responders: LCRs and HCRs, respectively) (e.g., Allen et al., 2007). In these studies, LCRs and HCRs have been demonstrated to differ in intravenous cocaine CPP (Allen et al., 2007) and cocaine self-administration (Mandt et al., 2008), with LCRs but not HCRs exhibiting CPP, and LCRs showing increased responding under a progressive ratio schedule of reinforcement, respectively. Interestingly, a finding consistent across these studies is that only LCRs developed locomotor sensitization with repeated cocaine injections, suggesting an increased sensitivity to the stimulant effects of cocaine, consistent with an increase in sensitivity to cocaine as measured using CPP and self-administration. In contrast, we found that only those rats that responded to an initial administration of cocaine exhibited locomotor sensitization. This again highlights the likely mechanistic differences in cocaine responsiveness with single versus repeated dosing of cocaine (i.e., conditioned vs. unconditioned sensitization), suggesting an early environmental contingency that is later overcome by the effects of repeated cocaine.

One alternative to a propranolol-mediated impairment in consolidation interpretation is a conditioning effect of the post-test drug treatment, which could result in a new association or alter the value of either cocaine itself or the cocaine-context association. A new propranolol-induced CS-US association is not likely. Previous studies have demonstrated that the dose of propranolol used here (10 mg/kg) failed to induce a place preference on its own (Milton et al., 2008), induce a conditioned taste aversion (Freeman et al., 2008), or devalue food reward incentive (Przybylski et al., 1999), suggesting that propranolol fails to serve as a US. Another scenario is that an interaction between propranolol and cocaine diminishes the putative positive value of cocaine that initiates a subsequent sensitized response. Although propranolol has been demonstrated not to impair cocaine-induced locomotor activity (Harris et al., 1996), limited data exist as to whether propranolol affects other behavioral properties of cocaine that may be involved in sensitization. In terms of reinforcement, propranolol systemically administered prior to cocaine priming had no effect on cocaine-primed reinstatement in squirrel monkeys (Platt et al., 2007). This suggests that propranolol does not diminish the reinforcing properties of cocaine. However, further studies are needed to clarify this issue.

In addition to its well-studied rewarding/reinforcing effects, cocaine has also been shown to have acute anxiogenic properties that occur when the rewarding effects subside, an effect demonstrated in both human (Williamson et al., 1997) and rodent (Paine et al., 2002; Hayase et al., 2005; Schank et al., 2008) studies. This aversive component of cocaine may contribute to the locomotor arousal necessary to condition a sensitized response in the current study. This acute effect of cocaine has been demonstrated to be mediated, in part, by increased noradrenergic activity. The anxiogenic effect of cocaine, as measured in mice in the elevated plus maze, was shown to be blocked by propranolol (Schank et al., 2008). Thus, propranolol

may alter the aversive value of cocaine through a mediation of anxiety and subsequently impair cocaine-context conditioning. It is possible that these effects are mediated by the BLA, which has been demonstrated to be critical for the enhancement of memory consolidation for emotional experiences (Ferry et al., 1999; Lalumiere and McGaugh, 2005) as well as memory processing during extinction (Bernardi et al., 2009).

In conclusion, we report here that a cocaine and context association results in a sensitized locomotor response to a subsequent cocaine challenge that can be impaired by post-conditioning administration of propranolol, suggestive of a role for β -ARs in the consolidation of drug memories. These results are consistent with the identified role of β -ARs during memory retrieval (Bernardi et al., 2006; Bernardi et al., 2009; Otis and Mueller, 2011; Janak et al., 2012). In addition, our results suggest that in the paradigm used here, individual difference in the initial responsiveness to cocaine underlie its ability to condition cocaine-induced behavioral responses.

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Highlights

- Propranolol impairs cocaine sensitization in high cocaine responders
- No effect of propranolol in low responders
- Initial locomotor response to cocaine important for effect of adrenergic antagonism
- Adrenergic antagonism may be involved in drug memory consolidation

Figure 1.

Locomotor activity in response to cocaine during conditioning trials and testing. (*Left*) Data represent mean activity ($\pm$ SEM) during the 30-min conditioning trial. The groups that received cocaine prior to conditioning showed higher locomotor activity than vehicle-treated rats. (*Right*) Data represent mean activity ($\pm$ SEM) during the 30-min test. Rats that received vehicle following conditioning show an increased conditioned locomotor sensitized response as compared to rats that received propranolol following conditioning. Propranolol-treated rats showed a locomotor response comparable to rats receiving cocaine for the first time during testing.

Figure 2.

Locomotor activity in response to cocaine during conditioning trials and testing in Responders and Non-Responders. (*Left*) Data represent mean activity ($\pm$ SEM) during the 30-min conditioning trial. Responders showed higher locomotor activity than vehicle-treated rats, while Non-Responders showed activity levels comparable to vehicle-treated rats. (*Right*) Data represent mean activity ($\pm$ SEM) during the 30-min test. Responders that received vehicle following conditioning show an increased conditioned locomotor sensitized response as compared to responders that received propranolol following conditioning. Propranolol-treated responders showed a locomotor response comparable to rats receiving cocaine for the first time during testing. Both vehicle- and propranolol-treated non-responders showed a locomotor response comparable to rats receiving cocaine for the first time during testing. NR = Non-Responders; R = Responders

Figure 3.

Relationship between acute locomotor response to cocaine and conditioned sensitized locomotor response to cocaine. Data represent mean locomotor activity in response to cocaine during conditioning (*x*-axis) and testing (*y*-axis). The Cocaine-Vehicle group demonstrated a significant correlation between conditioning and testing (*left*), while the Cocaine-Propranolol group failed to show such a relationship (*right*).