Inhibition of protein synthesis but not β-adrenergic receptors blocks reconsolidation of a cocaine-associated cue memory

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Previously consolidated memories have the potential to enter a state of lability upon memory recall, during which time the memory can be altered before undergoing an additional consolidation-like process and being stored again as a long-term memory. Blocking reconsolidation of aberrant memories has been proposed as a potential treatment for psychiatric disorders including addiction. Here we investigated the effect of systemically administering the protein synthesis inhibitor cycloheximide or the β-adrenergic antagonist propranolol on reconsolidation. Rats were trained to self-administer cocaine, during which each lever press resulted in the presentation of a cue paired with an intravenous infusion of cocaine. After undergoing lever press extinction to reduce operant responding, the cue memory was reactivated and rats were administered systemic injections of propranolol, cycloheximide, or vehicle. Post-reactivation cycloheximide, but not propranolol, resulted in a reactivation-dependent decrease in cue-induced reinstatement, indicative of reconsolidation blockade by protein synthesis inhibition. The present data indicate that systemically targeting protein synthesis as opposed to the β-adrenergic system may more effectively attenuate the reconsolidation of a drug-related memory and decrease drug-seeking behavior.
Inhibition of protein synth blocks reconsolidation

Results

Effect of low dose (1.0 mg/kg) of cycloheximide on reconsolidation

We first tested whether a low dose of the protein synthesis inhibitor cycloheximide could block reconsolidation. Rats were trained in cocaine self-administration in which each lever press resulted in one infusion of cocaine (0.5 mg/kg) paired with the conditioned stimulus (CS). Lever pressing was subsequently extinguished to reduce responding. Memory reactivation occurred 24 h after the last day of lever extinction and consisted of three non-contingent CS presentations in the absence of any cocaine or levers. Rats received injections of vehicle or cycloheximide (1.0 mg/kg; s.c.) immediately following CS memory reactivation, and cue-induced reinstatement was tested 72 h later (Fig. 1A).

Across the 10 d of cocaine self-administration training, there were no differences in number of cocaine infusions (Fig. 1B), active lever presses, or inactive lever presses between rats that would be injected following memory reactivation with cycloheximide \( N = 8 \) or vehicle \( N = 9 \); \( P > 0.05 \). Likewise, no differences were found between groups across the 8 d of lever extinction on the number of active (Fig. 1C) or inactive lever presses \( (P > 0.05) \). A main effect of session (last day of extinction versus reinstatement) was obtained on active lever presses \( (F_{1,15} = 18.16, P = 0.001, \eta^2_p = 0.55) \), such that rats pressed the active lever more on reinstatement when compared with the last day of extinction, but there was not a significant drug by session interaction on active lever presses \( (P > 0.05) \). No main effects or interaction between session and drug on inactive lever presses was obtained \( (P > 0.05) \). These data indicate that a 1.0 mg/kg dose of cycloheximide is insufficient to reduce reconsolidation or cue-induced reinstatement.

Figure 1. A low dose of cycloheximide (1.0 mg/kg) does not affect reconsolidation or cue-induced reinstatement. (A) Schematic representation of the experimental procedures. (B) Total number of cocaine infusions received across each day of self-administration. (C) Total number of active lever presses during lever extinction. (D) Active lever presses on the last day of extinction and on the cue-induced reinstatement test. \( (N_s = 8 \text{ VEH}, 9 \text{ CHX}). \)
Effect of high dose (2.2 mg/kg) of cycloheximide on reconsolidation

In order to examine whether a higher dose of cycloheximide could block reconsolidation, rats previously trained in cocaine self-administration received injections of vehicle or cycloheximide (2.2 mg/kg, s.c.) immediately following CS memory reactivation and were tested on cue-induced reinstatement 72 h later (Fig. 2A). Across the 10 d of cocaine self-administration acquisition, no differences were found between rats that would be injected following memory reactivation with vehicle (N = 9) or cycloheximide (N = 9) on number of cocaine infusions (Fig. 2B), active lever presses, or inactive lever presses (P values >0.05). Likewise, the number of active lever presses (Fig. 2C) and inactive lever presses across the 8 d of extinction did not differ between groups (P values >0.05).

A significant main effect was found of session (last day of extinction versus reinstatement) on inactive lever presses (F(2,1,16) = 6.71, P = 0.020, η² = 0.30), such that inactive lever presses increased on reinstatement (M = 4.89 ± 0.94) versus last day of extinction (M = 2.33 ± 0.58). There was also a significant main effect of drug on inactive lever presses during the last day of extinction and reinstatement (F(1,16) = 5.34, P = 0.035, η² = 0.25), such that vehicle-injected rats (M = 5.00 ± 0.85) pressed the inactive lever more than cycloheximide-injected rats (M = 2.22 ± 0.85). Importantly, however, there was no significant interaction between session and drug on inactive lever presses (P < 0.05), indicating that the main effects on inactive lever presses were not due to administration of the drug but due to preexisting differences between groups.

A significant main effect of session on active lever presses was also obtained (F(2,1,16) = 40.40, P < 0.01, η² = 0.72), such that rats pressed the active lever more on reinstatement when compared with the last day of extinction (Fig. 2D). Additionally, a significant main effect of drug on active lever presses during the last day of extinction and reinstatement was found (F(1,1,16) = 8.01, P = 0.012, η² = 0.33), such that rats receiving cycloheximide pressed the active lever less than rats receiving vehicle; however, this main effect was qualified by a significant interaction between session and drug (Fig. 2D; F(1,1,16) = 9.42, P < 0.01, η² = 0.37). Whereas both groups responded equivalently on the active lever on the last day of extinction (P > 0.05), on the cue-reactivation test rats that received post-reactivation cycloheximide had significantly fewer active lever presses than vehicle-injected rats (F(1,1,16) = 8.89, P < 0.01, η² = 0.36). These data indicate that post-reactivation cycloheximide (2.2 mg/kg) selectively decreases reinstatement to cocaine seeking on the lever previously associated with cocaine through interfering with reconsolidation.

Figure 2. Cycloheximide (2.2 mg/kg) blocks reconsolidation and reduces cue-induced reinstatement. (A) Schematic representation of the experimental procedures. (B) Total number of cocaine infusions received across each day of self-administration. (C) Total number of active lever presses during lever extinction. (D) Active lever presses on the last day of extinction and on the cue-induced reinstatement test. *, Statistically significant (P < 0.05). (Ns = 9 (VEH), 9 (CHX)).

Effect of high dose (2.2 mg/kg) of cycloheximide in the absence of reactivation

To investigate whether the effect of cycloheximide on reinstatement depends upon reactivation and to rule out nonreconsolidation-based mechanisms of cycloheximide’s effect, rats received cycloheximide or vehicle treatment following exposure to the novel context without the presence of cocaine-related CSs, and rats were tested 24 h later on cue-induced reinstatement (Fig. 3A). No differences were seen across the 10 d of cocaine self-administration acquisition between nonreactivated rats that would later be injected with vehicle (N = 8) or cycloheximide (N = 8) on number of cocaine infusions (Fig. 3B), active lever presses, or inactive lever presses (P values >0.05). Similarly, no between-groups differences in active lever presses (Fig. 3C) or inactive lever presses were found across the 8 d of lever extinction (P values >0.05).

A significant main effect of session (last day of extinction versus reinstatement) on active lever presses was found (F(1,1,14) = 60.05, P < 0.01, η² = 0.81), such that responding was higher on reinstatement when compared with the last day of extinction (Fig. 3D). However, no interaction was seen on active lever presses during the last day of extinction and the cue-induced reinstatement test for vehicle- and cycloheximide-injected rats (Fig. 3D; F(1,1,14) = 2.82, P = 0.12, η² = 0.17). Furthermore, no significant main effect or interaction was found for inactive lever presses on reinstatement and the last day of extinction (P values >0.05). These data indicate that cycloheximide’s effect of decreasing cue-reactivation requires memory reactivation, a critical component for reconsolidation blockade.

Effect of propranolol (10 mg/kg) on reconsolidation

In order to test whether the β-adrenergic receptor antagonist propranolol blocks memory reconsolidation, propranolol (10 mg/kg) or vehicle was administered immediately following CS memory reactivation, and cue-induced reinstatement was tested 24 h later (Fig. 4A). Across the 8 d of cocaine self-administration, no differences were found between rats that would be injected following...
memory reactivation with vehicle (N = 9) or propranolol (N = 9) on number of cocaine infusions (Fig. 4B), active lever presses, or inactive lever presses (P values >0.05). Likewise, no differences were found between groups across the 8 d of lever press extinction for active lever presses (Fig. 4C) or inactive lever presses (P values >0.05). A significant main effect of session (last day of extinction versus reinstatement) on active lever presses was found, such that rats pressed the active lever significantly more on reinstatement compared with the last day of extinction (Fig. 4D; F(1,16) = 57.91, P < 0.01, ηp² = 0.78). A significant main effect of session (last day of extinction versus reinstatement) on inactive lever presses was also found, such that rats pressed the inactive lever significantly more on reinstatement (M = 6.22 ± 1.03) when compared with the last day of extinction (M = 3.28 ± 0.68; F(1,16) = 17.78, P < 0.01, ηp² = 0.53). However, no interaction between session and drug on active lever presses (Fig. 4D; F(1,16) = 0.038, P = 0.85, ηp² < 0.01) or inactive lever presses (F(1,16) = 0.513, P = 0.48, ηp² = 0.03) was obtained. These data indicate that propranolol does not affect reconsolidation of a cocaine-cue memory.

In light of the null findings, no control experiments were performed using propranolol. Additional doses of propranolol were not tested because nearly all previous studies that have demonstrated an effect of propranolol on the reconsolidation of appetitive as well as aversive behaviors have utilized a 10 mg/kg dose (Przybyslawski et al. 1999; Debiec and LeDoux 2004; Bernardi et al. 2006; Diergaarde et al. 2006; Robinson and Franklin 2007; Milton et al. 2008; Robinson et al. 2011b; Achterberg et al. 2012; Wei and Li 2014; Schramm et al. 2015). Furthermore, a previous pilot study in our laboratory using a higher dose of propranolol (40 mg/kg) also revealed no propranolol-induced deficits in reinstatement or reconsolidation (data not shown), providing additional evidence that experiments using this higher dose may not be warranted.

**Discussion**

The results of the present study indicate that post-reactivation injection of cycloheximide dose-dependently (2.2 mg/kg but not 1.0 mg/kg) blocks cue-induced reinstatement. The effect of cycloheximide depends upon retrieval of the drug-related CS, indicating that cycloheximide interferes with memory reconsolidation. In contrast to the original hypothesis, post-reactivation propranolol had no effect on cue-induced reinstatement, indicative of no effect on

**Figure 3.** The effect of cycloheximide (2.2 mg/kg) is dependent upon cue reactivation. (A) Schematic representation of the experimental procedures for rats that did not receive light/tone reactivation. (B) Total number of cocaine infusions received across each day of self-administration. (C) Total number of active lever presses during lever extinction. (D) Active lever presses on the last day of extinction and on the cue-induced reinstatement test. (Nₜ = 8 (VEH), 8 (CHX)).

**Figure 4.** Propranolol (10 mg/kg) has no effect on reconsolidation or cue-induced reinstatement. (A) Schematic representation of the experimental procedures. (B) Total number of cocaine infusions received across each day of self-administration. (C) Total number of active lever presses during lever extinction. (D) Active lever presses on the last day of extinction and on the cue-induced reinstatement test. (Nₜ = 9 (VEH), 9 (CHX)).
Inhibition of protein synthesis blocks reconsolidation. Thus, protein synthesis inhibition, but not \( \beta \)-adrenergic inhibition, blocks reconsolidation of a drug-related cue memory in a rodent model of cocaine self-administration.

It is not surprising, however, that propranolol failed to block reconsolidation as measured by cue-induced reinstatement. Previous research indicates that propranolol is not always effective at interfering with reconsolidation in both rodents (Lee and Everitt 2008; Font and Cunningham 2012; Milton et al. 2012; Williams and Harding 2014) and humans (Tollenaar et al. 2009; Bos et al. 2014; Pachas et al. 2015; Spring et al. 2015; Wood et al. 2015), and replications of experiments even within the same laboratory have produced differing results (Kindt et al. 2009; Bos et al. 2014). Some explanations for these inconsistencies include the ability of propranolol to preferentially affect emotional memories over neutral memories (Schwabe et al. 2012a,b), individual differences in participants (Soeter and Kindt 2013), and the mnemonic paradigm under investigation (Muravieva and Alberini 2010; Wei and Li 2014). Furthermore, prior experience with drugs of abuse may engender memories resistant to propranolol blockade (Robinson et al. 2011a; Ortiz et al. 2015), which could explain the present results.

It cannot be ruled out that alterations to the design of the present paradigm might reveal an effect of propranolol on reconsolidation of a cocaine-cue memory. For example, some prior studies have found that repeated reactivation sessions followed by propranolol are required to block reconsolidation (Frickles-Gleason and Marshall 2008; Wouda et al. 2010), yet the present study utilized only a single reactivation session. In addition, it is possible that administering propranolol prior to memory reactivation may induce deficits in reinstatement. However, only drugs administered after memory reactivation can be said to interfere with the reconsolidation phase of reconsolidation (Milton et al. 2013). Compounds administered prior to reactivation, conversely, may interfere with memory due to an enhancement of memory destabilization or through interfering directly with memory recall (Ben Mamou et al. 2006; Hong et al. 2011). The ability of propranolol to reduce cue-induced reinstatement through either of these alternative processes may be an interesting avenue for future investigation.

Additionally, while it is possible that propranolol may decrease reinstatement at a different dose, nearly all studies demonstrating propranolol’s ability to block reconsolidation systemically have used the same dose (10 mg/kg) as was used here in both aversive (Przybyslawski et al. 1999; Debic and LeDoux 2004) and appetitive paradigms (Bernardi et al. 2006; Diergaard et al. 2006; Robinson and Franklin 2007; Milton et al. 2008; Robinson et al. 2011b; Achtenberg et al. 2012; Wei and Li 2014; Schramm et al. 2015). Reports of lower effective doses (1 or 5 mg/kg) of propranolol have only been shown to block reconsolidation of drug CPP in stress-exposed mice (Hymel et al. 2014) or of contextual fear memories after very high shock-conditioning sessions in rats (Abraini et al. 2008). Higher doses have not generally been used in reconsolidation studies; however, a 40 mg/kg dose of propranolol given subcutaneously was reported to reduce morphine CPP (Robinson et al. 2011b). The use of a higher dose was not required, as a 10 mg/kg dose also impaired morphine CPP in the same study. Additionally, when we ran a pilot study using this high dose (40 mg/kg), we found no propranolol-induced deficits in reinstatement or reconsolidation (AB Dunbar and JR Taylor, unpubl.). Use of systemic propranolol at these higher doses is also problematic in terms of possible nonspecific mnemonic or molecular consequences. Thus, it is unlikely that the null effect of propranolol seen here is due to dosage, though this hypothesis would need to be experimentally evaluated.

The instrumental behavior of cue-induced reinstatement is modulated by three main Pavlovian processes: conditioned reinforcer, conditioned approach, and conditioned motivation (Milton and Everitt 2010). While post-reactivation propranolol has been shown to reduce conditioned reinforcement in a rodent model of cocaine self-administration (Milton et al. 2008), preliminary data from the same laboratory indicate that under the same conditions post-reactivation propranolol may not block cue-induced reinstatement (Milton and Everitt 2009, 2010), which is supported by the present results. Furthermore, while alcohol conditioned reinforcement is blocked by post-reactivation propranolol similarly to cocaine (Milton et al. 2008; Schramm et al. 2015), alcohol conditioned motivation and approach are not (Lee and Everitt 2008; Milton et al. 2012), and the effect of propranolol on cue-induced reinstatement to alcohol-seeking is unclear (Wouda et al. 2010; Williams and Harding 2014). Thus, it is likely that propranolol selectively or preferentially modifies the reconsolidation of conditioned reinforcement. Blocking a conditioned reinforcement memory may not be sufficient to decrease cue-induced reinstatement if conditioned motivation and approach memories are intact. Conversely, protein synthesis inhibitors administered intracranially (anisomycin; Barak et al. 2013; Sorg et al. 2015) and systemically (cycloheximide; present results) do block reinstatement to drug seeking, and intra-amygdalar protein synthesis inhibition (anisomycin) also blocks conditioned reinforcement (Lee et al. 2005). The role of protein synthesis inhibition in conditioned motivation and approach has yet to be examined. Protein synthesis inhibition may, thus, modulate the memories of different or additional drug-related psychological processes when compared with propranolol, which enables cycloheximide and anisomycin to block reinstatement to drug seeking. Additional research is needed to directly test the ability of propranolol and cycloheximide to interfere with the reconsolidation of different aspects of cocaine-related memories.

The present finding that post-reactivation cycloheximide attenuates cue-induced reinstatement to cocaine seeking is a valuable contribution to the field as it demonstrates that systemic protein synthesis inhibition blocks reconsolidation. The only systemic agents that have previously been found to block reconsolidation as measured by decreased reinstatement are dopamine and NMDAR antagonists (Yan et al. 2014; Exton-McGuinness and Lee 2015). Understanding how reconsolidation can be blocked systemically is essential for improving the translational potential of reconsolidation-based relapse-prevention therapies. Although cycloheximide is not itself suitable for use in humans, future research should investigate the efficacy of other protein synthesis inhibitors with reduced human toxicity, such as antibiotics that target protein synthesis (McCoy et al. 2011; Sutcliffe 2011), at blocking reconsolidation of drug-related memories. The role of protein synthesis inhibition on blocking memory reconsolidation as measured by reduced reinstatement to drug-seeking behavior deserves further investigation as a potential treatment for addiction.

### Materials and Methods

#### Subjects
One hundred male Sprague Dawley rats (250–275 g; Charles River Laboratories) were individually housed on a 12-h light cycle in a temperature and humidity controlled room. All procedures were conducted during the light phase of the cycle. Rats were allowed to acclimate for 7 d prior to the start of the experiment. All procedures were conducted in accordance with the policies of the Yale University Institutional Animal Care and Use Committee and conformed to National Institutes of Health Guidelines on the Care and Use of Laboratory Animals.
Surgery
Animals were anesthetized with ketamine (100 mg/kg, i.p.) and xylazine (5 mg/kg, i.p.) and injected with carprofen (5 mg/kg, s.c.) and saline (5 mL, s.c.). Rats were implanted with a chronic, indwelling catheter (0.51 × 0.94 mm, Dow Corning) in the right jugular vein. The catheter tubing connected to a cannula (22 gauge, Plastics One) mounted on the back of the animals. The intravenous catheter was flushed with 0.4 mg gentamicin (0.2 mL, Sagent) at surgery and patency was maintained post-surgery by infusion of 0.2 mL of saline containing heparin (35 U/mL, Sagent) and gentamicin (0.08 mg/mL, Hospira) every 2 d. Patency was verified by the infusion of 2 mg of methoxohexitol sodium (0.2 mL, Par). Animals were allowed to recover for 5–7 d before the start of behavioral procedures.

Behavioral apparatus
Behavioral procedures took place in sound-attenuating operant chambers (Med Associates). Context A contained a metal rod floor, two inactive nose ports, an inactive magazine, two retractable levers positioned on the same side of the box, two cue lights positioned directly above the levers, and a fan that provided background noise (65 dB). A metal arm (Med Associates) attached to the operant box held up a spring tether that attached to the back mount on the rats for intravenous cocaine delivery through the catheter. A syringe pump placed outside of the sound-attenuating chamber was connected to the other end of the spring tether by polyethylene tubing (Plastics One) to deliver cocaine infusions. Context B contained an opaque white plastic floor, an illuminated house light, and no fan, levers, nose ports, or magazine. Context B was additionally scented with 1% almond extract.

Behavioral procedures
Rats were restricted to 90% of their free-feeding weight and fed daily to maintain that weight throughout the experiment. Behavioral procedures are similar to those used in previous studies (Sanchez et al. 2010; Wan et al. 2014). Animals underwent acquisition of cocaine self-administration in Context A for 8 d (propranolol experiment) or 10 d (cycloheximide experiments) in daily 1-h sessions. Rats were placed in the operant chamber and secured to the spring tether by polyethylene tubing (Plastics One) to deliver cocaine infusions. Context B contained an opaque white plastic floor, an illuminated house light, and no fan, levers, nose ports, or magazine. Context B was additionally scented with 1% almond extract.

Statistical analysis
Rats that did not acquire self-administration (<50 total cocaine infusions or <10 infusions on the final day of self-administration) or whose catheters were not patent at the end of self-administration training were excluded from all statistical analyses. All analyses were carried out using SPSS version 23. Acquisition of self-administration was analyzed with repeated-measures analyses of variance (rm-ANOVAs) across the 8 or 10 d of self-administration on number of cocaine infusions, number of active lever presses and number of inactive lever presses. Lever extinction was analyzed with rm-ANOVAs across 8 d on number of active and inactive lever presses. To analyze reinstatement results, rm-ANOVAs across session (last day of extinction versus reinstatement test) were conducted on number of active and inactive lever presses. Following significant rm-ANOVAs, planned comparisons (one-way ANOVAs) were performed on active lever presses between groups during extinction and reinstatement.

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