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Review

Noradrenergic Regulation of Fear and Drug-Associated Memory Reconsolidation

James M Otis[1], Craig T Werner[2] and Devin Mueller*[,1]

[1]Department of Psychology, University of Wisconsin-Milwaukee, Milwaukee, WI, USA; [2]Department of Neuroscience, Rosalind Franklin University, North Chicago, IL, USA

Emotional and traumatic experiences lead to the development of particularly strong memories that can drive neuropsychiatric disorders, such as posttraumatic stress disorder (PTSD) and drug addiction. Disruption of these memories would therefore serve as a powerful treatment option, and targeting the pathologic emotional, but not declarative, component of a memory would be ideal for clinical intervention. Research reveals that after retrieval of a consolidated memory, the memory can be destabilized, and must then be reconsolidated through synaptic plasticity to allow subsequent retrieval. Disruption of reconsolidation-related plasticity would therefore impair specific, reactivated memories. Noradrenergic signaling strengthens synaptic plasticity and is essential for encoding the emotional components of memory. Consistent with this, investigations have now revealed that noradrenergic signaling is a critical mechanism for reconsolidation of emotional memories in rodent and human models. Here, we discuss these investigations and promising clinical trials indicating that disruption of noradrenergic signaling during reconsolidation may abolish the pathologic emotional, but not declarative, component of memories allowing alleviation of neuropsychiatric disorders including PTSD and drug addiction.
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INTRODUCTION

Memories serve to store relevant information and were originally assumed to be static and inflexible. More recently, evidence has emerged that memories are, in fact, dynamic and modifiable. Initially, memories are acquired and consolidated into long-term representations (McGaugh, 2000; Müller and Pilzecker, 1900). Memory consolidation involves modifications in synaptic efficacy and intrinsic neuronal excitability (eg, Alkon, 1979; Bailey and Chen, 1983; Disterhoft *et al*, 1986; McKernan and Shinnick-Gallagher, 1997; Rogan *et al*, 1997; Whitlock *et al*, 2006; for reviews, see Kandel, 2001; Sehgal *et al*, 2013), and such changes allow subsequent memory retrieval. Following consolidation, memory and memory-related plasticity are dynamically regulated during and after retrieval. Retrieval can result in synaptic destabilization (Kim *et al*, 2010; Lee *et al*, 2008), and ensuing restabilization processes are required for subsequent memory expression across a variety of learning paradigms and species (eg, Kroes *et al*, 2014; Lee *et al*, 2005; Misanin *et al*, 1968; Nader *et al*, 2000; Przybyslawski *et al*, 1999; for a review, see Nader and Hardt, 2009; Reichelt and Lee, 2013). These restabilization processes, known as reconsolidation, involve *de novo* protein synthesis (Nader *et al*, 2000) and synaptic plasticity (Clem and Huganir, 2010). Thus, modification of reconsolidation-related plasticity allows for memory modification and even memory elimination. Reconsolidation is now being studied extensively as disruption of pathologic, emotional forms of memory could alleviate memory-related disorders, such as posttraumatic stress disorder (PTSD; Brunet *et al*, 2008) and drug addiction (Saladin *et al*, 2013; Xue *et al*, 2012).

Converging evidence using rodents and human subjects reveals that noradrenergic signaling is critical for memory reconsolidation. For example, inhibition of α_1- and β-adrenergic receptor (AR) activity during reconsolidation leads to memory disruption within both appetitive and aversive memory paradigms (Bernardi *et al*, 2006, 2009; Do Monte *et al*, 2013; Gazarini *et al*, 2013; Milton *et al*, 2008b; Przybyslawski *et al*, 1999; Wouda *et al*, 2010). Furthermore, disruption of noradrenergic signaling during reconsolidation reduces long-term emotional memory in healthy humans (for a recent meta-analysis, see Lonergan *et al*, 2013), is associated with better quality of life among PTSD patients (Poundja *et al*, 2012), and is capable of reducing cue-induced cravings among patients with cocaine addiction (Saladin *et al*, 2013). Several reviews have discussed the many signaling mechanisms that regulate reconsolidation in general, such as glutamate receptor transmission, cholinergic signaling, MAP kinase activity, protein synthesis, and epigenetic modifications (for a review, see Alberini, 2011; Nader and Hardt, 2009; Reichelt and Lee, 2013; Sorg, 2012). However, none have specifically focused on the large body

*Correspondence: Dr D Mueller, Department of Psychology, University of Wisconsin-Milwaukee, 2441 East Hartford Avenue, Garland Hall 224, Milwaukee, WI 53211, USA, Tel: +1 414 229 6113, Fax: +1 414 229 5219, E-mail: devinm@uwm.edu
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of literature revealing that noradrenergic signaling is critical for reconsolidation across appetitive and aversive memory paradigms. Here we discuss these encouraging findings and also highlight limitations of these studies, future research directions, and recent inconsistent results regarding the efficacy of the most commonly used amnesic, the β-AR antagonist propranolol. Finally, the ethics of reconsolidation blockade for treatment of neuropsychiatric disorders are discussed. We conclude that reconsolidation disruption, particularly by noradrenergic receptor blockade, would serve as a powerful and ethical treatment option as such memory disruption is specific to the pathologic, emotional component of a reactivated memory.

NEUROPHYSIOLOGY

Reconsolidation is regulated by noradrenergic signaling at each of its receptors, specifically α_1-, α_2-, and β-ARs. The effects of α_1-, α_2-, and β-AR activation are complex, but the general principles follow that α_1- and β-AR activation increases intrinsic neuronal excitability, whereas α_2-AR activation has the opposite effect. Simply stated, α_1-AR activation reduces the conductance of non-gated K^+ channels (K^+_{leak}), causing slow membrane depolarization (McCormick and Prince, 1988). Similarly, β-AR activation decreases the conductance of ion-gated K^+ channels, reducing the slow and fast afterhyperpolarization that contribute to spike-frequency adaptation (Foehring *et al*, 1989; Mueller *et al*, 2008; Otis *et al*, 2013). Thus, both α_1- and β-AR activation enhance intrinsic excitability, particularly by increasing the likelihood (α_1) and frequency (β) of evoked action potentials. In contrast, α_2-AR activation enhances inward-rectifying K^+ channel conductance, leading to slow membrane hyperpolarization and reduced intrinsic excitability (Marzo *et al*, 2009).

In addition to the modulation of intrinsic neuronal excitability, α_1-, α_2-, and β-AR activation modulate synaptic transmission. Similar to the effects on intrinsic excitability, α_1- and β-AR activation increase the potential for synaptic plasticity, whereas α_2-AR activation has the opposite effect. Specifically, α_1-AR stimulation leads to the activation of phospholipase C (PLC), which leads to the formation of the second messengers inositol triphosphate (IP_3) and diacylglycerol (DAG; Graham *et al*, 1996; Wu *et al*, 1992). IP_3 and DAG increase cytoplasmic Ca^{2+} through divergent signaling mechanisms, and such Ca^{2+} is critical for synaptic plasticity (Berridge, 1998). β-AR activation also enhances the potential for synaptic plasticity, by stimulation of a G protein (G_s) that is positively linked with adenylyl cyclase (Tesmer *et al*, 1997). Adenylyl cyclase leads to activation of the cAMP-PKA-CREB pathway, which facilitates AMPA receptor trafficking and synaptic plasticity (Nguyen and Woo, 2003). In opposition to β-ARs, α_2-AR activation reduces the potential for synaptic plasticity through stimulation of an inhibitory G protein (G_i) that is negatively linked with adenylyl cyclase (Marzo *et al*, 2009). Moreover, α_2-ARs can act as presynaptic autoreceptors, reducing total noradrenergic synaptic transmission via inhibition of presynaptic Ca^{2+} influx (Hirning *et al*, 1988; Schofield, 1990). Taken together, α_1- and β-AR activation enhances intrinsic excitability and increases the potential for synaptic plasticity. In contrast, α_2-AR activation can reduce intrinsic excitability and synaptic activity at both presynaptic and postsynaptic membranes. Although norepinephrine acts on multiple receptors, each are involved in reconsolidation of aversive and appetitive memories.

NORADRENERGIC REGULATION OF FEAR MEMORY RECONSOLIDATION

Reconsolidation of aversive memories has been studied extensively using fear conditioning. Fear is a powerful emotion, and the memories associated with fear-provoking events are robust (Gale *et al*, 2004; for a review, see Davis, 1997; Ledoux, 2000; Maren, 2001). Fear conditioning involves pairing a conditioned stimulus (CS), such as a distinct cue or environment, with an aversive unconditioned stimulus (US), such as a shock. Following conditioning, presentation of the CS in the absence of the US results in memory retrieval and conditioned fear expression. Furthermore, retrieval can induce subsequent memory destabilization that allows for modification and reconsolidation of the now-labile memory. To assess whether a particular mechanism is critical for memory reconsolidation, two basic experiments should be performed. First, manipulations (eg, pharmacological) should preferably be given after, rather than before, memory retrieval, and the long-lasting effects of these manipulations should be evaluated during a long-term memory retrieval test. The major issues with giving manipulations before retrieval, instead of after, is that such manipulations could affect memory destabilization before reconsolidation (Ben Mamou *et al*, 2006; Lee *et al*, 2008; Milton *et al*, 2013) or could induce memory impairments that are behaviorally similar, but mechanistically distinct from memory reconsolidation disruption (Otis *et al*, 2013). The importance of giving a long-term retrieval test (generally 24 h after the manipulation) is to ensure that reconsolidation is complete and that any pharmacological effects are no longer present (Dudai, 2004). The second experiment serves as a control, wherein the same manipulation is given in the absence of retrieval to ensure that observed effects require memory reconsolidation (for a review, see Nader and Hardt, 2009). Manipulations should have long-lasting effects on memory when given after, but not in the absence of, memory retrieval for investigators to conclude that reconsolidation has been affected. Finally, some investigators have also used a retrieval test briefly after the manipulation (generally 3 h), to provide further support for reconsolidation blockade (eg, Debiec and LeDoux, 2006; Nader *et al*, 2000). In the case that the memory is impaired long, but not briefly, after the initial retrieval test, investigators can be sure that reconsolidation has been affected.

Rodent Studies

Fear memory reconsolidation is regulated by noradrenergic signaling through both α- and β-ARs. Studies using rodent fear conditioning reveal that reconsolidation is disrupted by administration of β-AR antagonists systemically (Przybyslawski *et al*, 1999; Muravieva and Alberini, 2010) or directly into the amygdala (Debiec and Ledoux, 2004, 2006; Debiec *et al*, 2011). The effects of β-AR blockade are long lasting, as

administration of the β-AR antagonist propranolol after reactivation of recent and remote fear memories prevents fear expression for weeks or longer (Abrari *et al*, 2008; Debiec and Ledoux, 2004). Furthermore, propranolol-induced reconsolidation disruption prevents the reinstatement of fear following presentation of a reminder shock (Abrari *et al*, 2008; Debiec and Ledoux, 2004). In contrast, fear memory reconsolidation can be enhanced by amygdalar infusions of β-AR agonists (Debiec *et al*, 2011). Taken together, rodent fear conditioning experiments reveal that β-AR activation is a critical mechanism for control of fear memory reconsolidation.

Data from the inhibitory avoidance paradigm indicate that not all aspects of fear memories are regulated by β-AR activation. Muravieva and Alberini (2010) found that systemic injections of propranolol after retrieval reduced subsequent cue-induced freezing, whereas propranolol had no effect on behavioral avoidance. In contrast to freezing, rodent avoidance learning is thought to require declarative memory (Cammarota *et al*, 2007). Thus, although declarative knowledge cannot be measured in rodents, these data support the idea that β-AR activation specifically regulates reconsolidation for the emotional non-declarative, but not declarative, component of fear memories. This notion is well supported by investigations examining the effectiveness of propranolol for disruption of fear memory reconsolidation in humans (eg, Kindt *et al*, 2009; see below).

Fear memory reconsolidation is also regulated by α-AR activity. Systemic injection of the α_2-AR agonist clonidine, which reduces total noradrenergic signaling, abolishes cue-induced fear memory reconsolidation (Gamache *et al*, 2012). In contrast, systemic injection of the α_2-AR antagonist yohimbine enhances fear memory reconsolidation leading to increased context-induced fear expression (Gazarini *et al*, 2013). Moreover, the effects of yohimbine are prevented by the α_1-AR antagonist prazosin or β-AR antagonist propranolol (Gazarini *et al*, 2013). Thus, α_2-AR activation impairs fear memory reconsolidation by reducing α_1 and β-AR signaling. Recent data also reveal that α_1-AR activity is required for fear memory reconsolidation. Systemic or intraprelimbic medial prefrontal cortex administration of the α_1-AR antagonist prazosin prevents fear memory reconsolidation, an effect that reduces cue-induced fear expression for at least 3 weeks (Do Monte *et al*, 2013). Interestingly, these effects conflict with data revealing that prelimbic β-AR blockade does not disrupt reconsolidation of drug-associated memories (Otis *et al*, 2013), indicating differences between paradigms or between mechanisms required for reconsolidation processes in the prelimbic cortex. Taken together, experiments using rodents reveal that fear memory reconsolidation requires activation of α_1 and β-ARs, whereas reconsolidation is hindered by α_2-AR-dependent inhibition of α_1 and β-AR signaling.

Human Studies

Considerable evidence reveals that noradrenergic signaling at β-ARs regulates reconsolidation of human memories. Kindt *et al* (2009) used human fear conditioning to determine the effects of the β-AR antagonist propranolol on reconsolidation. Propranolol was administered before memory retrieval, with the notion that the orally administered propranolol takes time to reach peak plasma concentrations (Gilman and Goodman, 1996). Propranolol had no immediate effects on conditioned fear, as measured by fear-potentiated startle (eyeblink reflex). In contrast, propranolol induced long-lasting impairments in conditioned fear expression during subsequent retrieval trials when administered before but not in the absence of retrieval. Importantly, propranolol did not disrupt expectation of the aversive US, indicating that β-AR blockade during or after retrieval disrupts the pathologic emotional, but not declarative, component of the fear memory (Kindt *et al*, 2009). This work has been replicated and thoroughly extended within the past several years (Sevenster *et al*, 2012; Soeter and Kindt, 2010, 2011, 2012a, b), and these studies further reveal that propranolol administration during retrieval impairs robust fear memories in humans (Soeter and Kindt, 2012b). Moreover, propranolol-induced memory impairments provide protection against spontaneous recovery of fear 30 days following extinction (Soeter and Kindt, 2010). Crucially, further evidence now reveals that propranolol impairs human fear memories when administered after CS presentation, confirming that the observed effects are specific to reconsolidation blockade (Soeter and Kindt, 2012a, b). Finally, propranolol-induced reconsolidation disruption is specific to a reactivated memory, but not to a similar non-reactivated fear memory (Soeter and Kindt, 2011), confirming that the effect is memory-specific and does not generalize to other memories. These data have been further supported by a recent meta-analysis, confirming that cue-induced fear is reduced by propranolol when given during reconsolidation (Lonergan *et al*, 2013). Taken together, propranolol induces long-lasting disruption of human fear memory reconsolidation in a retrieval-dependent and memory-specific manner. These data indicate that disruption of noradrenergic signaling may be effective for disruption of human fear memories outside of the laboratory, such as memories of real-life trauma.

Clinical Trials

Recent investigations have examined the necessity of β-AR activation for reconsolidation of traumatic memories in patients with PTSD. Brunet *et al* (2008) used script-driven memory retrieval to induce reconsolidation of real-life traumatic memories. Immediately and 2 h after memory retrieval, short- and long-acting formulations of propranolol were administered, respectively. During a follow-up reactivation test a week later, propranolol-treated patients had significantly reduced psychophysiologic responding (heart rate, skin conductance) when compared with placebo-treated patients. Moreover, these physiologic responses were reduced below threshold for PTSD diagnoses (Brunet *et al*, 2008). When administered in conjunction with multiple (6) memory reactivation sessions, propranolol treatment reduced the diagnosis of PTSD by more than 70% and reduced symptom severity by more than 50% (Brunet *et al*, 2011). Finally, propranolol treatment during memory retrieval was associated with improved quality of life and reduced depressive symptoms among patients with PTSD (Poundja

et al, 2012). Although these data are promising and indicate that reconsolidation of traumatic memories may require β-AR activation, each clinical investigation lacks appropriate placebo and/or no-reactivation control groups. Future controlled investigations should fill this critical gap, permitting a better understanding and accurate control of the memory mechanisms involved in PTSD.

NORADRENERGIC REGULATION OF REWARD-RELATED MEMORY RECONSOLIDATION

Appetitive memories are associated with positive feelings, such as the rewarding effects of drugs that reinforce drug-seeking behaviors. Retrieval of these memories induces craving and drives drug seeking. Therefore, disruption of drug-associated memories would limit relapse susceptibility. Despite the differences in valence, similarities have been found between the underlying processes that regulate aversive and appetitive memory reconsolidation. Initial studies using the rodent radial arm maze revealed that systemic (Przybyslawski *et al*, 1999) or intracerebroventricular (Roullet and Sara, 1998) infusions of β-AR antagonists following retrieval disrupted reconsolidation of memories underlying context-driven reward-seeking behavior. Since these pioneering experiments, research has focused on the necessity of noradrenergic signaling for reconsolidation of drug-related memories using the conditioned place preference (CPP) and self-administration (SA) paradigms.

Rodent CPP Studies

The CPP paradigm is commonly used to study appetitive memories. In this paradigm, animals are conditioned to associate one chamber with a drug of abuse, and another with vehicle (control). Following conditioning, CPP retrieval tests are given during which animals are allowed full access to both chambers. An animal that spends significantly more time in the previously drug-paired context at test is said to be drug seeking, and such behavior requires context-driven memory retrieval.

Noradrenergic signaling is critical for CPP memory reconsolidation. Systemic injections of the β-AR antagonist propranolol immediately following a retrieval test (or tests) prevent subsequent expression of a cocaine CPP memory (Bernardi *et al*, 2006; Fricks-Gleason and Marshall, 2008). Propranolol also disrupts morphine CPP memory reconsolidation (Robinson and Franklin, 2007, 2010). Thus, memories associated with both psychostimulants and opiates are susceptible to reconsolidation blockade by propranolol. Furthermore, we and others recently demonstrated that β-AR blockade within the amygdala (Bernardi *et al*, 2009; Otis *et al*, 2013), but not the hippocampus or prelimbic cortex (Otis *et al*, 2013, 2014), prevents cocaine CPP memory reconsolidation. Moreover, specific blockade of amygdalar α_1- or β_2-ARs disrupts cocaine CPP memory reconsolidation (Bernardi *et al*, 2009). The effects of β-AR blockade provide long-lasting protection against drug-induced reinstatement of the CPP (Fricks-Gleason and Marshall, 2008; Robinson and Franklin, 2010), supporting the idea that β-AR blockade does not enhance extinction, but rather impairs CPP reconsolidation. Further investigation also reveals that β-AR blockade disrupts a double-conditioned morphine CPP (8 morphine pairings, instead of 4 pairings) when the CPP memory is reactivated 30 days after training (but not 1 day after training; Robinson and Franklin, 2010). These data are encouraging as they indicate that drug-associated memories can be disrupted by β-AR blockade even if these memories are acquired long before pharmacologic intervention.

Rodent SA Studies

In addition to place conditioning, appetitive memories can be studied using the SA paradigm. In this model, rodents are trained to lever press or nose poke for rewards, such as food, intravenous drug infusion, or intracranial stimulation (eg, of the lateral hypothalamus). Experiments have revealed that systemic propranolol injections administered *after* memory retrieval disrupt context- or cue-driven sucrose seeking (Diergaarde *et al*, 2006; Milton *et al*, 2008b), cocaine seeking (Milton *et al*, 2008b), and ethanol seeking (Wouda *et al*, 2010) within the SA paradigm (but see Milton and Everitt, 2010; Williams and Harding, 2014). However, these convincing experiments have been overshadowed by studies revealing no effect of propranolol when administered *before* memory retrieval (Lee and Everitt, 2008; Milton and Everitt, 2010). The latter experiments were likely performed with preretrieval infusions so that the effects could be compared with those of other pharmacological agents. However, data reveal that β-AR blockade is more effective at impairing memory during the 'late phase' of reconsolidation. Specifically, using the rodent radial arm maze, intracebroventricular infusions of the β-AR antagonist timolol was shown to impair memory reconsolidation when administered 60 min after retrieval (Roullet and Sara, 1998). In contrast, timolol had no effect when infused 5, 30, or 300 min after retrieval. Consistent with this, we found that propranolol injections immediately before cocaine CPP memory retrieval have no effect on reconsolidation (Otis and Mueller, 2011), whereas systemic injections or amygdalar infusions of β-AR antagonists after retrieval disrupt cocaine CPP memory reconsolidation (Bernardi *et al*, 2006, 2009; Fricks-Gleason and Marshall, 2008; Otis *et al*, 2013). Thus, the lack of reconsolidation blockade could be due to metabolism of propranolol before the late phase of memory reconsolidation, which may require β-AR-dependent protein synthesis. Alternatively, preretrieval propranolol may have prevented memory destabilization such that memory reconsolidation was not necessary to maintain the memory. In support of this, β-AR activation facilitates NMDA receptor channel conductance (Huang *et al*, 1998; Ji *et al*, 2008), and NMDA receptor activation is essential for fear memory destabilization (Ben Mamou *et al*, 2006; Milton *et al*, 2013). Thus, β-AR activation may facilitate NMDA receptor signaling for memory destabilization. To assess the necessity of β-AR activation for memory destabilization, future investigations should determine if preretrieval β-AR blockade prevents the memory-impairing effects of protein synthesis inhibition during memory reconsolidation.

To determine the effects of propranolol treatment on reconsolidation of SA memories, experiments were grouped by timing of drug administration and effectiveness of

Table 1 Efficacy of Propranolol for Reconsolidation Disruption Within the Self Administration (SA) Paradigm

Timing	Effect	SA paradigm	Authors (year)
After			
	Impaired	Sucrose (extinction)	Diergaarde *et al* (2006)
	Impaired	Sucrose (CR)	Milton *et al* (2008b)
	Impaired	Cocaine (CR)	Milton *et al* (2008b)
	No effect	Cocaine (reinstatement)	Milton and Everitt (2010)
	Impaired	EtOH (extinction)	Wouda *et al* (2010)
	No effect	EtOH (extinction)	Williams and Harding (2014)
Before			
	No effect	Sucrose (PCA)	Lee and Everitt (2008)
	No effect	Sucrose (PIT)	Lee and Everitt (2008)
	No effect	EtOH (PCA)	Milton *et al* (2012)
	No effect	EtOH (PIT)	Milton *et al* (2012)

Abbreviations: CR, conditioned reinforcement; PCA, Pavlovian conditioned approach; PIT, Pavlovian-to-instrumental transfer.
Summary of findings for research examining the effectiveness of propranolol for reconsolidation blockade within the SA paradigm.

propranolol (as listed in Table 1). When propranolol was administered *after* memory reactivation, 4/6 studies revealed a significant impairment in subsequent context- or cue-driven reward seeking. In contrast, when propranolol was administered *before* memory reactivation, 0/4 studies revealed significant impairments in subsequent cue-driven reward seeking. Thus, propranolol is capable of impairing reconsolidation of reward-related memories in both the CPP and SA paradigms when administered after, but not before, memory reactivation.

An alternative explanation regarding the effectiveness of propranolol for reconsolidation blockade in the SA paradigm is related to the type of memory being investigated. Specifically, experiments have revealed that postretrieval injections of propranolol impair conditioned reinforcement (Milton *et al*, 2008b), whereas preretrieval injections of propranolol have no effect on Pavlovian conditioned approach (PCA) or Pavlovian instrumental transfer (PIT; Lee and Everitt, 2008; Milton *et al*, 2012). In support of the idea that preretrieval propranolol is capable of preventing reconsolidation, preretrieval propranolol disrupts fear memory reconsolidation in humans (Kindt *et al*, 2009; Soeter and Kindt, 2010, 2011; Zhao *et al*, 2011), although this may be because propranolol takes $\sim$90 min to reach peak plasma concentrations when orally administered in humans (Gilman and Goodman, 1996). Taken together, because propranolol was administered before memory retrieval, it is unclear whether PCA or PIT is affected by β-AR blockade during memory reconsolidation.

Human and Clinical Studies

Noradrenergic signaling is also critical for reconsolidation of human drug-related memories. Zhao *et al* (2011) first demonstrated that propranolol impairs memory of heroin-related, but not neutral, words among patients with heroin addiction. Participants learned a list of heroin-related positive words (eg, syringe, foil), negative words (eg, vomit, diarrhea), and neutral words (eg, table, refrigerator). The next day, propranolol was orally administered before a memory retrieval test. Although there was no effect of propranolol on retrieval during this test, 24 h later propranolol-treated patients recalled fewer heroin-related positive and negative words, but not neutral words (Zhao *et al*, 2011). Moreover, propranolol had no effect when administered in the absence of memory retrieval, indicating that the memory-impairing effects of propranolol required memory reactivation. Although follow-up experiments should examine the effects of postretrieval β-AR blockade on memory of heroin-related words, these data indicate that β-AR blockade selectively impaired memory reconsolidation of retrieved heroin-related words, but not neutral words, in patients with heroin addiction.

Recent data suggest that reconsolidation disruption by β-AR blockade also reduces cue-induced cocaine cravings. Saladin *et al* (2013) treated cocaine-dependent subjects with propranolol or placebo immediately after presentation of cocaine-related cues (video and actual cocaine). The next day, the same cues were presented to the subjects in the absence of propranolol. Propranolol-treated individuals had significantly reduced cocaine cravings during cue presentation, indicating that β-AR blockade during memory reconsolidation reduced subsequent cue-induced cocaine cravings. Despite this, follow-up experiments should replicate this study with a no-retrieval control group to confirm that the observed effects are specific to memory reconsolidation. Interestingly, patients were given another follow-up test 1 week after propranolol treatment, and although propranolol-treated individuals reported less cue-induced cocaine cravings overall, this effect did not reach the threshold for significance. However, multiple retrieval sessions followed by propranolol treatment induces more reliable and robust effects on drug-associated memory reconsolidation in rodents (Fricks-Gleason and Marshall, 2008), and is more effective at eliminating symptoms of PTSD in humans (Brunet *et al*, 2011). Thus, follow-up experiments should assess whether multiple cue-reactivation plus propranolol sessions will induce more pronounced and long-lasting memory impairments among patients with drug addiction.

PROPOSED MECHANISMS AND PATHWAYS

Presentation of conditioned stimuli in both aversive and appetitive conditioning paradigms induces norepinephrine release (Cassens *et al*, 1980; Mingote *et al*, 2004), which activates presynaptic (α_2) and postsynaptic receptors (α_1-, α_2-, and β-ARs; Figure 1). Research described above provides convincing evidence that such activity controls memory reconsolidation in a bidirectional manner. Despite this, the particular mechanism by which noradrenergic signaling regulates memory reconsolidation is less clear.

Cellular Mechanisms

Noradrenergic signaling likely regulates memory reconsolidation via modulation of synaptic plasticity (see Figure 1). Synaptic plasticity is a critical mechanism for reconsolidation (Clem and Huganir, 2010). Moreover, NMDA receptor

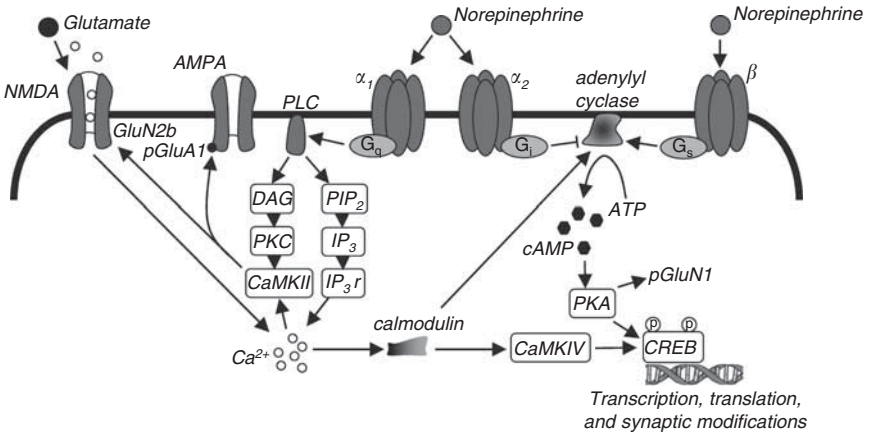

Figure 1 Cellular mechanisms of memory reconsolidation. Postsynaptic noradrenergic signaling strengthens emotional memory reconsolidation by enhancing *N*-methyl-D-aspartate (NMDA) receptor-dependent synaptic plasticity. α_1-Adrenergic receptor (AR) activation enhances phospholipase C (PLC) signaling to activate Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). CaMKII associates with the NMDA receptor subunit GluN2B, and this binding facilitates AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor phosphorylation and promotes NMDA receptor-dependent synaptic plasticity. α_2-AR activation inhibits adenylyl cyclase, whereas β-AR activation stimulates adenylyl cyclase. Adenylyl cyclase activation facilitates protein synthesis and GluN1 phosphorylation via cAMP-PKA-CREB. Thus, NMDA, α_1, and β receptor signaling modifies existing membrane-bound proteins and induces synthesis of new proteins for the orchestration of reconsolidation-dependent synaptic plasticity. In contrast, α_2-ARs function as inhibitory presynaptic autoreceptors (not illustrated) and as postsynaptic receptors (illustrated) to reduce α_1 and β-AR receptor signaling.

activation, a well-known mechanism of synaptic plasticity and learning (Morris *et al*, 1986), is essential for both fear and drug-associated memory reconsolidation (Brown *et al*, 2008; Lee *et al*, 2006; Milton *et al*, 2008a, 2012; Suzuki *et al*, 2004). Noradrenergic signaling enhances NMDA receptor ion channel conductance (Huang *et al*, 1998; Ji *et al*, 2008) and NMDA receptor-dependent synaptic plasticity (Thomas *et al*, 1996). This likely occurs via both α_1- and β-AR signaling. Specifically, PKA downstream of β-ARs promotes phosphorylation of the NMDA receptor 1 subunit (GluN1; Bird *et al*, 2005; Snyder *et al*, 1998). In contrast, CaMKII downstream of α_1-ARs directly binds directly to GluN2B subunits (Leonard *et al*, 1999), and this binding is essential for AMPA receptor phosphorylation (Zhou *et al*, 2007), synaptic plasticity (Barria and Malinow, 2005; Zhou *et al*, 2007), and memory consolidation (Zhou *et al*, 2007). Interestingly, GluN2B-containing NMDA receptor neurotransmission may not be critical for restabilization of memory during reconsolidation (Ben Mamou *et al*, 2006; Milton *et al*, 2013), indicating that the GluN2B subunit may only serve as a scaffolding mechanism for reconsolidation (similar to memory consolidation, see Zhou *et al*, 2007). Considering that norepinephrine is released upon presentation of emotionally salient cues (Cassens *et al*, 1980), and reconsolidation follows presentation of those cues, norepinephrine facilitates NMDA receptor-dependent synaptic plasticity during memory reconsolidation. This is likely to allow for maintenance of cue salience, such that noradrenergic receptor blockade during reconsolidation disrupts the pathologic emotional, but not declarative, components of reactivated memories.

Neural Circuit of Reconsolidation

Much is known regarding the signaling mechanisms underlying memory reconsolidation. Despite this, the neural circuits underlying reconsolidation are less clear. Here, we describe a simplified neural circuit that likely regulates reconsolidation and expression of fear and drug-associated memories (see Figure 2).

Noradrenergic and glutamatergic signaling in the BLA regulate reconsolidation of fear memories (Debiec and LeDoux, 2004; Lee *et al*, 2006; Milton *et al*, 2013) and drug-associated memories (Bernardi *et al*, 2009; Milton *et al*, 2008a; Otis *et al*, 2013). Thus, amygdalar noradrenergic and glutamatergic afferents must be important for reconsolidation. The amygdala receives noradrenergic input from the nucleus tractus solitarius (NTS) and locus coeruleus (LC; Fallon and Ciofi, 1992; Ricardo and Koh, 1978), which are engaged during memory consolidation (for a review, see McIntyre *et al*, 2012). However, whether NTS or LC is important for memory reconsolidation is unknown. The amygdala also receives glutamatergic input from thalamic, hippocampal, and cortical neurons, and these afferents underlie emotional learning and memory (for a review, see LeDoux, 2000). In fact, amygdalar glutamatergic inputs undergo synaptic potentiation following fear conditioning (Rogan *et al*, 1997; McKernan and Shinnick-Gallagher, 1997) and appetitive conditioning (Tye *et al*, 2008), suggesting that potentiation of these synapses may underlie aversive and appetitive memories. Consistent with this, the reconsolidation–extinction procedure, which induces erasure of fear memories and drug-associated memories in rodents and humans (Monfils *et al*, 2009; Schiller *et al*, 2010; Xue *et al*, 2012), causes synaptic depotentiation at thalamoamygdalar synapses (Clem and Huganir, 2010; also see Agren *et al*, 2012). Taken together, the amygdala receives both glutamatergic and noradrenergic input for memory reconsolidation. These data support the idea that noradrenergic inputs to the amygdala restabilize glutamate-dependent plasticity during reconsolidation, allowing for the persistence of emotional memories.

Although the BLA inputs underlying emotional memory reconsolidation for aversive and appetitive behaviors

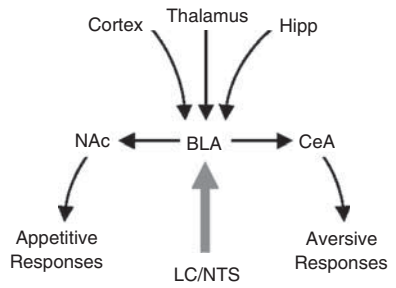

Figure 2 Neural circuit of emotional memory reconsolidation. Noradrenergic (thick gray arrow) and glutamatergic (black arrows) neurons converge in basolateral nucleus of the amygdala (BLA) to control *N*-methyl-D-aspartate (NMDA) receptor-dependent synaptic plasticity for emotional memory reconsolidation. Following reconsolidation, BLA output neurons to nucleus accumbens (NAc) and central nucleus of the amygdala (CeA) control appetitive and aversive responses, respectively, during emotional memory expression. Hipp, hippocampus; LC, locus coeruleus; NTS, nucleus tractus solitarius.

overlap, the outputs for these behaviors are likely distinct. BLA projection neurons innervate the central nucleus of the amygdala (CeA; Pare *et al*, 1995), a structure that has distinct projections for the expression of particular fear responses (LeDoux *et al*, 1988; for a review, see LeDoux, 2000). BLA projection neurons also innervate the nucleus accumbens (NAc; Stuber *et al*, 2011), a pathway that is critical for cue-induced reward seeking (Cador *et al*, 1989; Ambroggi *et al*, 2008; Stuber *et al*, 2011). Taken together, learning-related synaptic potentiation in BLA-CeA projection neurons promotes cue-induced fear, whereas plasticity in BLA-NAc projection neurons promotes cue-induced reward seeking. Furthermore, BLA noradrenergic signaling restabilizes this plasticity during reconsolidation for the maintenance of cue-induced behaviors.

ALTERNATIVE INTERPRETATION: FACILITATION OF EXTINCTION

Extinction is the formation of a new inhibitory memory, wherein conditioned responses to a stimulus are reduced due to repeated omission of the reinforcer (Quirk and Mueller, 2008). Thus, an alternative hypothesis to the research described above is that disruption of noradrenergic signaling facilitates extinction learning, rather than impairs reconsolidation. However, this hypothesis is inconsistent with data revealing that noradrenergic signaling enhances, rather than impedes, formation of new memories (for a review, see McGaugh, 2000). Hence, inhibition of β-ARs impairs, rather than facilitates, extinction learning in appetitive and aversive learning paradigms (eg, LaLumiere *et al*, 2010; Mueller *et al*, 2008).

ETHICAL CONSIDERATIONS FOR CLINICAL INTERVENTION

More than a decade ago, ethical opposition regarding the use of memory elimination for the treatment of neuropsychiatric disorders came from *Beyond Therapy*, a report published by the President's Council on Bioethics (US) (2003). This article sparked debate among ethicists regarding research and potential therapies for the treatment of neuropsychiatric disorders, particularly PTSD (Bell, 2007; Donovan, 2010; Kolber, 2007). The major argument made in *Beyond Therapy* is that 'forgetting therapy' is unethical as 'our happiness depends also on our memory, on knowing who we are in relation to who we have been' (President's Council on Bioethics (US), 2003, p 209). Despite this, research has revealed that memories are naturally dynamic, and therefore memory modification is not as artificial as it may seem. In fact, the primary therapy currently used for treatment of PTSD is extinction-based exposure therapy, which involves the formation of a new inhibitory memory that can overcome original memories (Quirk and Mueller, 2008). Although this has worked well in some patients, a more robust approach may be necessary in certain circumstances (Conklin and Tiffany, 2002). In such cases, the data described here indicates that ablation of the pathologic, emotional component of a memory by inhibition of noradrenergic signaling may be useful.

Ethical arguments made against memory disruption for the treatment of neuropsychiatric disorders (ie, 'forgetting therapy') are outdated and in opposition to current research. First, 'forgetting therapy' is a misnomer, particularly when describing reconsolidation blockade by noradrenergic receptor antagonism. Human research demonstrates that the declarative components of memory remain intact following propranolol-induced reconsolidation blockade, whereas the pathologic, emotional components that drive disordered behaviors are abolished (eg, Kindt *et al*, 2009). Thus, patients given such therapy would not forget their life experiences. Second, reconsolidation disruption by noradrenergic receptor antagonism is memory specific and does not eliminate associated or non-reactivated memories (Bernardi *et al*, 2006; Kindt *et al*, 2009; Otis *et al*, 2013; Przybyslawski *et al*, 1999; Soeter and Kindt, 2011). Third, noradrenergic receptor blockade during reconsolidation has been shown to improve quality of life in patients with PTSD (Brunet *et al*, 2011; Poundja *et al*, 2012). Finally, noradrenergic receptor blockade during reconsolidation is capable of reducing cue-induced drug cravings (Saladin *et al*, 2013), suggesting that such therapy could limit relapse susceptibility. Taken together, memory disruption by noradrenergic receptor antagonism could provide an ethical and powerful option for treatment of memory-related psychiatric disorders.

Although modification of memory reconsolidation via noradrenergic receptor antagonism could alleviate psychiatric disorders, clinicians should be wary of the possible deleterious effects of noradrenergic receptor antagonism when given in conjunction with prolonged memory tests, aimed to induce extinction. Specifically, investigations using rodents reveal that extinction is impaired when noradrenergic receptor antagonists are administered (LaLumiere *et al*, 2010; Mueller *et al*, 2008). Thus, when given in conjunction with prolonged retrieval trials, as opposed to brief retrieval/reconsolidation trials, noradrenergic receptor blockers could potentially promote the persistence of maladaptive behaviors associated with psychiatric dysfunction.

CONCLUDING REMARKS

Strong emotional memories contribute to the persistence of fear disorders and drug addiction, and erasure of the pathologic aspects of these memories is possible. Here we describe preclinical data that reveal that both fear and drug-associated memories are susceptible to disruption by β-AR blockade during reconsolidation. Despite this, well-controlled clinical trials must be completed to firmly conclude whether β-AR activity regulates reconsolidation of real-life human traumatic or drug-associated memories. Studies using rodents also reveal that α_1-AR activity is critical for reconsolidation of fear and drug-associated memories, although such experiments have not been performed with human subjects. Considering that both β-AR and α_1-AR activation are indirectly inhibited by α_2-AR (autoreceptor) stimulation, future preclinical and clinical studies should determine the effectiveness of α_2-AR agonists and α_1-AR antagonists on disruption of human memory reconsolidation. The data demonstrating that the emotional component of a pathologic memory can be selectively disrupted leaving the declarative component intact using β-AR antagonists suggest that these antagonists effectively neutralize the affective strength of the memory without impairing the entirety of the memory. Whereas the data are generally interpreted as demonstrating reconsolidation blockade, an alternative explanation is that the memory has been modified by weakening the affective strength. Thus, β-AR antagonists could serve as targeted therapeutic agents to neutralize pathologic memories, effectively reducing their impact. Overall, the findings described here support the use of noradrenergic pharmacotherapies as efficacious adjuncts for the treatment of pathologic memory disorders, such as PTSD and addiction.

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