DEPRESSION AND ANXIETY 28:186–193 (2011)

First Place: Donald F. Klein Early Career Investigator Award

NORADRENERGIC ENHANCEMENT OF RECONSOLIDATION IN THE AMYGDALA IMPAIRS EXTINCTION OF CONDITIONED FEAR IN RATS—A POSSIBLE MECHANISM FOR THE PERSISTENCE OF TRAUMATIC MEMORIES IN PTSD

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Background: *Posttraumatic stress disorder (PTSD) is associated with enhanced noradrenergic activity. Animal and human studies demonstrate that noradrenergic stimulation augments consolidation of fear learning. Retrieval of well-established memories by presenting a learned fear cue triggers reconsolidation processes during which memories may be updated, weakened, or strengthened. We previously reported that noradrenergic blockade in the rat amygdala impairs reconsolidation of fear memories. Here we investigated the effects of noradrenergic enhancement on reconsolidation of learned fear.* **Methods:** *Using auditory fear conditioning in rats, we tested the effects of postretrieval intraamygdala infusion of the β-adrenergic receptor agonist isoproterenol or the antagonist propranolol on conditioned fear in the amygdala.* **Results:** *A single intraamygdala infusion of isoproterenol following a retrieval of a well-consolidated memory enhanced fear memory elicited by the learned fear stimulus and impaired extinction of this memory 48 hr later. Intraamygdala infusion of the β-adrenergic receptor antagonist propranolol following a consecutive retrieval trial blocked the enhancing effects of isoproterenol on fear memory.* **Conclusions:** *Postretrieval β-adrenergic stimulation in the amygdala enhances reconsolidation of fear memories, making them resistant to extinction. Noradrenergic augmentation during retrieval of fear memories may thus contribute to persistence and severity of traumatic memories. Reconsolidation may be a useful tool in understanding the pathology of PTSD and may thus help in developing new and in modifying existing treatments of traumatic memories. Depression and Anxiety 28:186–193, 2011.*

Key words: *fear; anxiety; fear conditioning; amygdala; reconsolidation; extinction; isoproterenol; propranolol; posttraumatic stress disorder; PTSD; late-onset PTSD; β-adrenergic receptor; norepinephrine; exposure therapy*

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The authors disclose the following financial relationships within the past 3 years: Contract grant sponsor: NIH; Contract grant numbers: MH046516; MH038774; Contract grant sponsor: NSF; Contract grant number: 0920153.

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DOI 10.1002/da.20803
Published online in Wiley Online Library (wileyonlinelibrary.com).

INTRODUCTION

Posttraumatic stress disorder (PTSD) develops following an emotional trauma and is characterized by the recurrence of intrusive memories, avoidance, and hyperarousal (American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition[1]). One of the most common behavioral treatments for PTSD is exposure therapy.[2] Exposure therapy is based on extinction processes in which repeated exposure to trauma-related cues (thoughts, feelings, and situations) reduces symptoms of posttraumatic stress.[3,4] Pharmacological treatments are also used either alone[3,5–7] or in conjunction with exposure therapy.[3,8] Despite the existence of behavioral and pharmacological treatments, many individuals continue to display symptoms of PTSD several years after an initial diagnosis.[9] Therefore, it is critical to study the mechanisms underlying the persistence of memories for trauma.

Norepinephrine has been implicated in normal and pathological fear and anxiety.[5,10–18] Animal and human studies indicate the involvement of norepinephrine in fear learning and memory.[15,19–23] More specifically, norepinephrine has been found to enhance memory consolidation processes by which new learning, initially labile and susceptible to disruption, is transformed into long-term memories.[15,24,25] Increased noradrenergic activity during trauma has also been implicated in the enhancement of encoding of the memory for traumatic event.[26,27] Further, pilot studies show that the blockade of noradrenergic transmission by the administration of the β-adrenergic receptor antagonist propranolol following trauma decreases the risk of PTSD.[28,29] However, clinical research indicates that the persistence and severity of PTSD symptoms is also associated with increased noradrenergic activity long after the traumatic event.[16,18,30–32] It is possible that norepinephrine is involved not only in the original encoding but also in the maintenance and exacerbation of symptoms associated with traumatic memories.

We addressed this question using a rodent model of fear learning, Pavlovian fear conditioning. Although PTSD is manifested by complex cognitive, emotional and behavioral alterations, and many of these symptoms are unique for humans, ample evidence demonstrates that fear learning contributes significantly to many anxiety pathologies including PTSD.[11,33–37] One of the most commonly used models of fear learning is fear conditioning, the neural basis of which is well understood.[38,39] In fear conditioning, a neutral event (conditioned stimulus, CS), such as tone, is paired with a noxious event (unconditioned stimulus, US), such as electric shock to the foot pads. A key structure involved in fear conditioning is the lateral nucleus of the amygdala (LA), a site where the information about the CS and the US converges.[39,40] Previous studies from our lab indicate that norepinephrine is a major modulator of fear conditioning in the LA. Thus, norepinephrine in the LA is involved in the acquisition, extinction, and reconsolidation of auditory fear conditioning.[41–43] Here, we investigated the role of norepinephrine in memory reconsolidation. Reconsolidation is a process by which well-established (consolidated) memories are rendered labile and susceptible to modification.[44–49] Reconsolidation has been demonstrated in a variety of species using different learning systems and a wide range of learning tasks.[50] In contrast to extinction, where attenuation of learned responding requires prolonged exposure to a learning cue, reconsolidation is triggered by a single exposure to the CS. In a previous study, we found that postretrieval β-adrenergic receptor blockade impairs reconsolidation of auditory fear conditioning in the LA.[42] Here we examined whether enhancing β-adrenergic transmission augments reconsolidation of auditory fear conditioning.

We hypothesized that enhancing noradrenergic signaling immediately following retrieval of conditioned fear will augment the memory and make it resistant to extinction. We tested the effects of isoproterenol on reconsolidation using multiple cue presentations (extinction test) instead of an exposure to a single or few CSs in order to investigate the response of the memory to extinction treatments.

Most of the reconsolidation studies so far used a single reactivation approach to modify the memory.[48,51,52] If each retrieval leads to the release of norepinephrine and the further reconsolidation of the memory, it would help explain why traumatic memories are so persistent. It would also suggest that reconsolidation blockade may be an effective treatment.

We thus further hypothesize that after multiple reconsolidation events it is still possible to block reconsolidation and impair fear memory. In life, as opposed to controlled experimental settings, memories are being constantly retrieved and processed. It is thus important to investigate whether reconsolidating memories may be altered more than once. In other words, it is important to determine the effects of multiple retrievals, each under a different (drug) condition, on a memory. This is especially important if reconsolidation is to be applied to a better understanding of lasting traumatic memories, such as those in PTSD, as PTSD is characterized by recurrent intrusive recollections. Using two distinct memory retrieval sessions separated in time, we asked whether effects of treatments applied during first round of reconsolidation (first retrieval session) could be reversed upon the subsequent memory retrieval.

MATERIALS AND METHODS

SUBJECTS

Adult male Sprague–Dawley rats (Hilltop Laboratories, Scottdale, PA) weighing 275–300 g at the beginning of the procedures were housed individually in clear plastic Nalgene cages in a thermally

controlled colony room. Rats were placed on a 12/12-hr light/dark cycle, and food and water were provided ad libitum throughout the duration of the experiment. All procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Experimental Animals and were approved by the New York University Animal Care and Use Committee.

SURGERY AND HISTOLOGY

Surgery and histology procedures have been the same as in previous study.[44] Under Nembutal anesthesia (45 mg/kg; i.p.), animals were implanted bilaterally with a 22-gauge stainless guide cannulae (Plastics One Inc, Roanoke, VA) aimed at the lateral nuclei of the amygdala (LA) or 2 mm dorsal to the LA. All coordinates were taken from Paxinos and Watson.[53] Coordinates for intra-LA were: 3.0 mm posterior to Bregma, 5.3 mm lateral to the midline, and 8.0 mm ventral to the skull surface. For cannulae implanted 2 mm dorsal to the LA, anterior–posterior and lateral coordinates were the same as for intra-LA implants and the ventral coordinate was 6 mm. The guide cannulae were fixed into the skull with screws and acrylic dental cement. A dummy cannula was inserted into each guide cannula to prevent clogging.

Postsurgical analgesics (2 mg/kg ketoprofen) were given daily for 3 days after all surgeries. Rats had at least 1 week to recover before the start of behavioral procedures.

At the completion of the experiment, rats were euthanized by an overdose of chloral hydrate (600 mg/kg) and were perfused with 10% buffered formalin. Their brains were sectioned at 50 μm thickness. The sections were stained using Cresyl violet and examined under light microscopy for cannula placement. After histological verification, only animals that had placements for both cannulae into the LA (or 2 mm dorsal to the LA) were included in the present report (Fig. 1).

DRUGS AND INFUSIONS

Isoproterenol (ISO; *R*(−)-isoproterenol (+)-bitartrate; Sigma-Aldrich, St. Louis, MO) and propranolol (PRO; DL-Propranolol; Sigma-Aldrich) were both dissolved in saline (SAL) (6.25 μg/μl). Drugs were slowly infused through an infusion cannulae at .25 μl/min using a pump. A total volume of .2 μl of isoproterenol (or propranolol) solution or an equivalent amount of saline vehicle was infused bilaterally into the LA (or 2 mm dorsal to the LA as in the Experiment 2). We have previously shown that the same 1.25 μg dose of propranolol infused bilaterally into the LA impairs reconsolidation of auditory fear conditioning.[42] Infusion cannulae were left in the place for an additional minute to allow the solution to diffuse from the cannulae tips.

APPARATUS AND STIMULI

Auditory fear conditioning was conducted in chamber A; memory reactivation and testing took place in chamber B. Chamber A was a Plexiglas chamber with a metal grid floor (Model E10-10; Coulbourn Instruments, Leigh Valley, PA) that was dimly illuminated by a single house light and enclosed within a sound attenuating chamber (Model E10-20). Chamber B consisted of a distinct conditioning Plexiglas chamber (ENV-001; MedAssociates, Inc., Georgia, VT) and was located in a different room. Chamber B was brightly illuminated by three lights and contained a flat Formica floor that had been scented with peppermint soap. In our previous study, we have shown that this testing environment is distinct enough to minimize generalization from the training environment.[42] The CS was a 30-sec, 5-kHz, 75-dB tone. The US was a 1.0-mA, 1-sec footshock. Behavior during training and testing was videotaped with a camera installed at the top of the chamber.

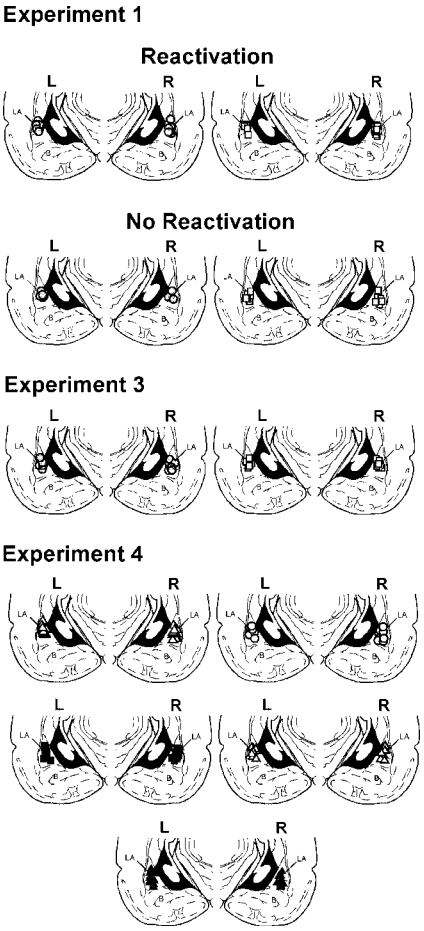

Figure 1. Cannulae placements in the LA. Images show cannulae placements for rats included in Experiments 1, 3, and 4. Symbols indicate injection sites. White squares indicate saline (SAL) groups and gray circles indicate isoproterenol (ISO) groups in Experiments 1 and 3. White triangles indicate saline–saline (SAL-SAL) group, white circles indicate isoproterenol–saline (ISO-SAL) group, black squares indicate propranolol–saline (PRO-SAL), gray triangles indicate isoproterenol–saline (ISO-SAL) group and black triangles indicate propranolol–isoproterenol (PRO-ISO) group in Experiment 4. LA, lateral nucleus of the amygdala; B, basal nucleus of the amygdala. All sections depicted at around 3.8 mm posterior to Bregma.

BEHAVIORAL PROCEDURES

General procedures. On the day before conditioning, rats were habituated for 2 min to handling and for 10 min to conditioning chamber A. For conditioning, after a 2-min acclimatizing period, rats were given a single conditioning trial consisting of one CS that coterminated with the US. After completion of all the procedures, rats were returned to the colony.

Memory retrieval. Memory retrieval was triggered on the day following fear conditioning (in Experiment 4, the second memory retrieval trial took place 48 hr following the first memory retrieval). After a 2-min acclimatization period in chamber B, a single CS was given. The freezing response during the CS presentation was used to measure the conditioned fear response.[41–45] Freezing was videotaped and scored by a blind experimenter, and then used for analysis.

Memory extinction test. Forty-eight hours (or 3 hr for Experiment 3) following the memory reactivation (or following the second memory reactivation session for Experiment 4), rats received nine CS presentations. The mean intertrial interval was 120 sec. Freezing during each CS presentation was videotaped and scored by an experimenter who was blind to the experiment condition. An average of the nine scores for each CS for each rat was subsequently used for the analysis (an average of nine scores was used as there was not any significant treatment × trial interaction). Freezing in all experiments was expressed as a percentage of the total duration of the tone presentation.

Experiment 1. On the day following conditioning, rats were divided into two groups. One group of rats received a memory retrieval (Reactivation group; Fig. 2A) trial followed by intra-LA infusions with ISO ($n = 9$) or SAL ($n = 11$). Another group of rats received either intra-LA infusions of ISO ($n = 5$) or SAL ($n = 6$), without explicit memory retrieval (No Reactivation group; Fig. 2A). On the following day, all animals received an extinction test.

Experiment 2. Procedures were the same as in Experiment 1 except that rats were implanted with cannulae outside of the LA and received drug (or vehicle) infusions 2 mm dorsal to the LA (ISO: $n = 7$; SAL: $n = 7$; Fig. 2B).

Experiment 3. Procedures were the same as in Experiment 1 except that the memory extinction test was performed 3 hr following drug (or vehicle) infusions (ISO: $n = 7$; SAL: $n = 7$; Fig. 2C).

Experiment 4. On the day following training, rats received a memory retrieval trial followed by intra-LA infusions of ISO ($n = 19$), PRO ($n = 19$), or SAL ($n = 10$). Forty-eight hours later, all rats received a second retrieval trial followed by intra-LA drug (or vehicle) infusions. All rats that received SAL infusions during the first retrieval trial were infused with saline again (SAL-SAL: $n = 10$). Half of the rats that had been infused with ISO following the first memory retrieval trial were infused with SAL (ISO-SAL: $n = 9$), whereas the other half were infused with PRO (ISO-PRO: $n = 10$). Rats that received PRO infusions following the first retrieval trial were also divided into two groups following the second memory retrieval. One group was infused with SAL (PRO-SAL: $n = 10$), whereas the other group was infused with ISO (PRO-ISO; $n = 9$).

DATA ANALYSIS

Data were analyzed using Student's *t*-test for independent samples, or a two-way analysis of variance (ANOVA) followed by Tukey's HSD post hoc test, and significance levels were set at $P < .05$.

RESULTS

Fear conditioned rats received bilateral intra-LA infusions of ISO or SAL (Experiment 1; Fig. 2A). One group of rats was presented with a single CS in order to reactivate the memory, (Reactivation group) whereas the other group received infusions without memory reactivation (No Reactivation group). During memory reactivation, both SAL and ISO groups expressed comparable levels of freezing (SAL = 63.9%, ±5.5; ISO = 65.9%, ±5; $P > .05$) (Fig. 2A). Immediately after rats received bilaterally intra-LA infusions of either ISO or SAL. Forty-eight hours later, all rats received an extinction test. Freezing during the CS presentation was measured and scored for analysis. The results from the ANOVA indicated a significant Reactivation × Drug interaction ($F(1,33) = 10.76$, $P < .01$). Post hoc mean

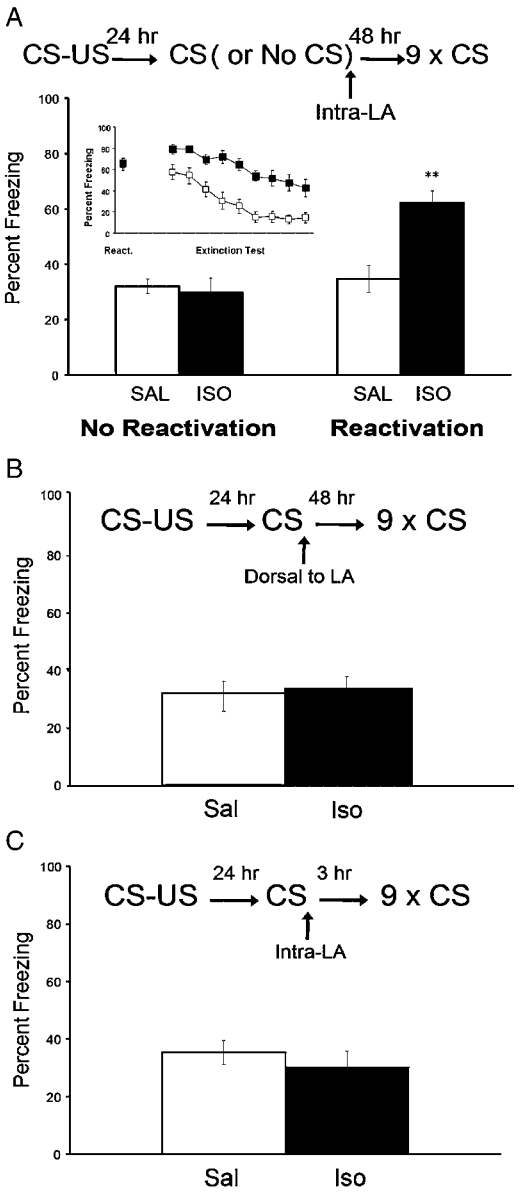

Figure 2. Isoproterenol enhances reconsolidation and prevents extinction of cue conditioned fear. (A) Post-reactivation isoproterenol infusions into the lateral nucleus of the amygdala (LA) enhance fear memory and impair extinction processes forty-eight hours later. The behavioral procedure (top) and freezing to the CS (bottom) during extinction test. Inserted figure shows freezing during reactivation (React.) and 48 hr later during extinction (Extinction Test) in Reactivation SAL (white squares) and Reactivation ISO (black squares) groups. The ISO group extinguishes less. (B) Postreactivation isoproterenol infusions 2 mm dorsal to the LA have no effect on fear memory. The behavioral procedure (top) and freezing to the CS (bottom) during extinction test. (C) Postreactivation isoproterenol infusions into the LA have no effect on memory 3 hr later. The behavioral procedure (top) and freezing to the CS (bottom) during extinction test. (ISO, isoproterenol; SAL, saline; LA, lateral nucleus of the amygdala; CS, conditioned stimulus; US, unconditioned stimulus; **Indicates different from all other groups Tukey's HSD $P < .01$).

comparisons with Tukey's HSD indicated that the freezing scores from the Reactivation–ISO group were significantly different (higher) than all the other groups ($P<.01$), and none of the other groups were significantly different from one another. Based on previous studies,[42,45] the low level of freezing (~20%) during 9 CS alone trials is due to extinction of conditioned fear. Our data demonstrate that postretrieval intra-LA infusions of the β-adrenergic receptor agonist isoproterenol enhance a well-consolidated auditory conditioned fear memory making it resistant to extinction treatments. The results also confirm that a single reactivation trial alone does not affect fear extinction learning 48 hr later.

In order to verify whether the lateral amygdala (LA) was a site of action for ISO on conditioned fear as observed in previous experiment, another group of rats received postretrieval drug or vehicle infusions outside (2 mm dorsal) of the LA (Experiment 2; Fig. 2B). During memory reactivation, both groups showed comparable levels of freezing (SAL = 75.2%, ±5.1; ISO = 73.8%, ±6.6; $P>.05$). There was no statistically significant difference in freezing responding between SAL and ISO groups 48 hr later during the extinction test ($P>.05$; Fig. 2B).

It is possible that exogenous treatments may affect reconsolidation by producing nonspecific effects. In order to control for this condition, it is important to demonstrate that the amygdala is functional following drug infusions before the reconsolidation window is closed (typically few hours following memory recall).[48,50] In order to determine whether postreactivation isoproterenol affects fear memory shortly after reactivation, before reconsolidation processes are completed,[48] another group of rats received an extinction test 3 hr following memory retrieval with postreactivation drug or vehicle infusions (Experiment 3; Fig. 2C). During memory reactivation, both groups showed comparable levels of freezing (SAL = 62.4%, ±4.4; ISO = 62.3%, ±5.4; $P>.05$). There was no statistically significant difference in freezing between SAL and ISO groups ($P=.47$) on freezing during the extinction test 3 hr later. Thus, postretrieval exogenous β-adrenergic stimulation has no effect on the retrieval of auditory conditioned fear 3 hr later.

Experiments described above together with our earlier studies[42,54] demonstrate that the well-consolidated auditory fear memories following a single memory retrieval are susceptible to bidirectional modulation through interference or enhancement of β-adrenergic signaling in the LA.

We next asked whether noradrenergic-dependent reconsolidation of auditory fear conditioning occurs more than once. Five groups of rats implanted with intra-LA cannulae received auditory fear conditioning (Experiment 4, Fig. 3). During the first memory reactivation, all groups expressed similar levels of freezing (SAL-SAL = 64%, ±4.3; PRO-SAL = 60.3, ±2; PRO-ISO = 60.4%, ±5; ISO-SAL = 61.5, ±5.6; ISO-PRO = 62.3, ±5.5; $P>.05$). Forty-eight hours later, all the rats received a second reactivation trial. An ANOVA on freezing levels during the second reactivation trial for the drugs below revealed a significant effect of drug group ($F(4,43) = 11.25$, $P<.01$). Post hoc mean comparisons with Tukey's HSD showed that the PRO-SAL group expressed significantly less freezing than SAL-SAL group ($P<.05$), whereas the ISO-SAL group expressed significantly more freezing than SAL-SAL group ($P<.05$). There was no statistically significant difference between the ISO-PRO and SAL-SAL groups (SAL-SAL = 60.3%, ±5.7; ISO-PRO = 72.6%, ±4.6; $P=.27$); nor was there a statistically significant difference between the PRO-ISO and SAL-SAL groups, although there was a trend toward lower freezing in the PRO-ISO group (SAL-SAL = 60.3%, ±5.7; PRO-ISO = 37.4%, ±9; $P=.11$). Forty-eight hours after the second reactivation, all rats received an extinction test. Statistical analysis revealed a significant Reactivation × Drug interaction effect ($F(1,33) = 10.76$, $P<.01$). Post hoc mean comparisons with Tukey's HSD revealed that the PRO-SAL group expressed significantly less freezing than the SAL-SAL group ($P<.05$), and that the ISO-SAL group demonstrated significantly more freezing than the SAL-SAL group ($P<.05$), whereas the ISO-SAL group showed significantly more freezing than the SAL-SAL group ($P<.05$) and the ISO-PRO group ($P<.01$). Noradrenergic-dependent reconsolidation of conditioned fear occurs more than once and enhancement of noradrenergic transmission impairs extinction of fear memory.

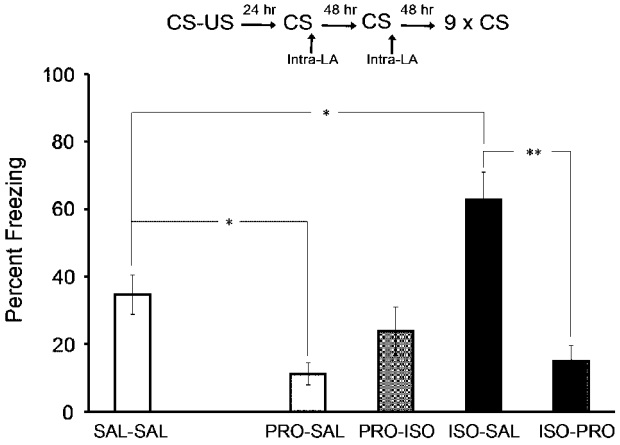

Figure 3. Noradrenergic-dependent reconsolidation of conditioned fear occurs more than once. The behavioral procedure (top) and freezing to the CS (bottom) during extinction test 48 hr following the second reactivation trial. (SAL-SAL, saline–saline; PRO-SAL, propranolol–saline; PRO-ISO, propranolol–isoproterenol; ISO-SAL: isoproterenol–saline; ISO-PRO, isoproterenol–propranolol; *Indicates Tukey's HSD $P<.05$, **indicates Tukey's HSD $P<.01$).

DISCUSSION

In the present study, we examined the role of noradrenergic signaling in the amygdala in the

reconsolidation of auditory fear conditioning. The major finding of this study was that β-adrenergic receptor agonist isoproterenol infused into the lateral amygdala following retrieval of a conditioned fear impaired its extinction 48 hr later (Fig. 2). The failure of ISO in affecting freezing responding without explicit memory retrieval (No Reactivation group), as well as the lack of effect of ISO on memory 3 hr following reactivation (Fig. 2C) is consistent with the memory reconsolidation model, which posits that memory modification is contingent upon memory retrieval and that the modification of a memory is typically not observable until reconsolidation processes are completed several hours postretrieval.[44,48,50] The augmenting effects of postreactivation ISO on fear conditioning infused into the LA but not outside of the amygdala demonstrate that noradrenergic enhancement of reconsolidation is amygdala-dependent (Fig. 2B). These results are consistent with our previous findings (also replicated in this study in Experiment 4) showing that noradrenergic blockade in the amygdala impairs reconsolidation of cue-conditioned fear.[42] Thus, fear memories in the amygdala may be bidirectionally modulated by interference or enhancement with noradrenergic signaling during reconsolidation processes.

Most of reconsolidation studies so far focused on a single memory retrieval (for review[50]). Few studies reported that reconsolidation may occur more than once (e.g.[55,56]). We demonstrated here that noradrenergic-modulated reconsolidation of cue-conditioned fear occurs more than once (Experiment 4). More specifically, we showed that postretrieval ISO-treated fear memory may be ameliorated with PRO upon a subsequent memory reactivation (Fig. 3, group ISO-PRO). Interestingly, we did not observe any statistically significant enhancing effects of ISO on memory that had been attenuated by PRO following a previous memory retrieval (Fig. 3, group PRO-ISO). One explanation is that treatment with PRO attenuates conditioned fear responding to such a degree that subsequent enhancement by exogenous ISO is not possible. An alternative explanation is that enhancement of previously pharmacologically attenuated memories may require more intense noradrenergic stimulation (higher doses of ISO and/or more retrieval trials). A definite answer to these questions requires further studies.

Blocking reconsolidation by interference with noradrenergic signaling has been proposed by us[42,54] and by others[57,58] as a possible tool in the treatment of anxiety disorders such as PTSD or specific phobias. Although existing studies show that postretrieval PRO may disrupt reconsolidation of conditioned fear in humans[59,60] and may ameliorate psychophysiologic responding in PTSD,[57] little is known about the role of noradrenergic signaling in reconsolidation, maintenance, and possible exacerbation of traumatic memories. Clinical studies suggest that enhanced noradrenergic activity during trauma may augment the encoding of the memory.[26] It has been thus proposed that the trauma-induced enhancement of memory encoding contributes to the persistence of traumatic memories (overconsolidation hypothesis).[27] However, clinical research shows that enhanced noradrenergic activity and elevated levels of norepinephrine in the cerebrospinal fluid correlate with severity of symptoms of PTSD.[30,32] Thus, increased noradrenergic activity may be implicated in the maintenance of PTSD symptoms. Our study using a rodent model of fear learning is the first to show that the underlying mechanism of the norepinephrine-related persistence of traumatic memories may be reconsolidation-dependent. If confirmed in humans, these findings may not only be useful in developing novel treatments for PTSD but also be helpful in better understanding and modification of existing therapies, such as an exposure therapy. For example, exposure therapy, especially in its initial stages may cause exacerbation of PTSD symptoms.[61] Such exacerbation of PTSD symptoms may be likely explained in terms of augmenting reconsolidation of trauma-related memories in the context of associated arousal and an increase in noradrenergic signaling. Noradrenergic enhancement of reconsolidation may also serve as a model for delayed-onset PTSD, whereas PTSD symptoms emerge and exacerbate over time.[62,63] Memory reconsolidation is a time-dependent process. Existing data from animal studies suggest that memories are susceptible to modification up to few hours following retrieval. Reconsolidation model may be useful in defining the temporal interval of susceptibility to interference and thus help in a better design of existing therapeutic interventions. Recent studies from our group show that combining reconsolidation and extinction approaches may be more efficient in eliminating learned fear than using extinction alone.[64,65] However, additional preclinical and clinical studies are necessary to better understand the translational value of the reconsolidation model in PTSD.

CONCLUSIONS

Noradrenergic augmentation in the amygdala following retrieval of a traumatic memory enhances memory reconsolidation and makes the memory less susceptible to fear extinction. Elevated noradrenergic activity is associated with persistence and severity of PTSD symptoms. It is thus possible that norepinephrine-modulated reconsolidation processes contribute to the maintenance and exacerbation of trauma-related memories in PTSD.

Acknowledgments. We thank Claudia Farb and Nekee Pandya, Lyndon Luk, and Ian Fabian for their technical assistance. This work was supported by the NIH grants MH046516, MH038774 and NSF grant 0920153 to JEL.

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