Behavioural Brain Research 244 (2013) 137–141

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Short communication

Systemic or intra-prelimbic cortex infusion of prazosin impairs fear memory reconsolidation

Fabricio H. Do Monte[a,*], Rimenez R. Souza[a], Ting T. Wong[b], Antonio de Padua Carobrez[a]

[a] Departamento de Farmacologia, Centro de Ciências Biológicas, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil
[b] Christian Brothers University (CBU), Memphis, TN, USA

HIGHLIGHTS

- Post-retrieval infusion of prazosin impairs subsequent retrieval of fear memory.
- Impairment in fear memory induced by prazosin is dependent of memory reactivation.
- Impairment in fear memory induced by prazosin does not spontaneously recover with time.
- Intra-prelimbic cortex infusion of prazosin impairs fear memory reconsolidation.

ARTICLE INFO

Article history:
Received 8 December 2012
Received in revised form 19 January 2013
Accepted 25 January 2013
Available online 1 February 2013

Keywords:
Prazosin
Memory reconsolidation
Prelimbic cortex

ABSTRACT

The alpha-1 adrenergic antagonist prazosin has been used to alleviate the symptoms of PTSD, but the mechanism remains unclear. One possibility is that prazosin may disrupt fear memory reconsolidation, leading to attenuation of fear responses. To test this hypothesis, we administered a single systemic injection of prazosin during the reconsolidation of olfactory fear conditioning in rats. We found that a post-retrieval injection of prazosin disrupted subsequent retrieval of fear. Similarly, intra-prelimbic cortex infusion of prazosin during the reconsolidation period also disrupted subsequent retrieval of fear. These findings suggest that fear memory undergoes reconsolidation through activation of alpha-1 adrenergic receptors in the prelimbic cortex.

Fear learning is an essential ability for survival in a threatening environment. However, dysregulation of fear circuits may cause the persistence of fear responses resulting in excessive fear and anxiety [1]. Recent research has focused in developing strategies for suppressing these maladaptive fear responses [2]. Currently, the extinction based therapy is considered one of the most common treatments for anxiety disorders such as post-traumatic stress disorder (PTSD) [3,4]. However, it has the inconvenient that fear memories may reappear with the passage of time or may reinstate toward stressful situations [5]. Pioneer studies have demonstrated that during a short period after fear retrieval, previously consolidated fear memories can become labile and subjective to pharmacological interference, particularly by drugs that inhibit the molecular mechanism involved in memory formation [6–8]. This disruptive process initiated after memory retrieval is referred to as "reconsolidation blockade", and has been suggested as a novel therapeutic strategy to reduce fear in PTSD patients with the promise of avoiding the reappearance of fear [9,10].

The noradrenergic system has long been involved in the modulation of emotional memories [see 11 for a review]. Several clinical studies in humans have demonstrated the efficacy of alpha-1 adrenergic antagonist prazosin in alleviating the symptoms of PTSD [12–15], but the mechanism involved in the attenuation of fear responses remains to be elucidated. One possible explanation could be that prazosin facilitates the mechanisms of fear extinction. However, contrary to this assumption, previous studies in rodents have demonstrated that the blockade of alpha-1 adrenergic receptor with prazosin disrupts the mechanisms of fear extinction [16,17]. Another possibility is that prazosin treatment would disrupt the reconsolidation of fear memories, leading to a reduction in PTSD symptoms, but no study has addressed the role of alpha-1 adrenergic receptors in fear memory reconsolidation.

Since olfaction is the most important sensory system in rodents [18], fear conditioning toward olfactory stimuli results in robust and long-lasting fear responses [19,20]. In the present study, we took advantage of the olfactory fear conditioning paradigm in rats to investigate the role of alpha-1 adrenergic receptors in fear memory reconsolidation. We then focused in the medial prefrontal cortex (mPFC) as a potential substrate mediating the effects of

* Corresponding author at: Laboratory of Fear Learning, Department of Psychiatry, School of Medicine, University of Puerto Rico, UPR, PO Box 365067, San Juan, PR 00936, USA. Tel.: +1 787 9993057; fax: +1 787 9993057.
E-mail address: fabriciodomonte@gmail.com (F.H. Do Monte).

0166-4328/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbr.2013.01.031

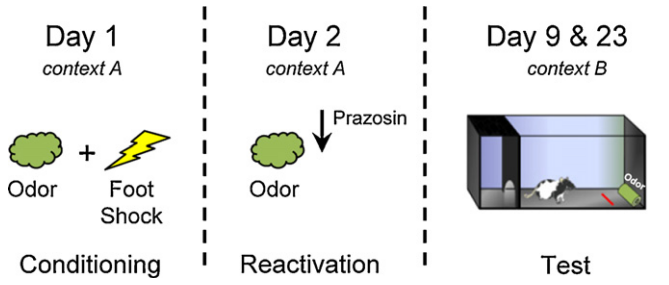

Fig. 1. Schematic representation of the olfactory fear conditioning paradigm. On day 1, rats received 5 pairings of amyl acetate odor and electrical footshock during a 4 min session in context A. On day 2 (reactivation session), animals were returned to the same conditioning chamber in the presence of amyl acetate for 2 min (without footshock) and were systemically or intra-mPFC injected with vehicle or prazosin immediately after being removed from the chamber. Additional control groups were fear conditioned as previously mentioned and received vehicle or prazosin injections in the home cage during day 2 (not reactivated). The retention of olfactory fear conditioning was assessed in a different context (context B) one week later (test) or three weeks (spontaneous recovery) after reactivation, in which a cloth impregnated with the conditioned odor amyl acetate was used as an odor source. We measured the percentage of time rats spent hiding in a different compartment away from the conditioned odor cloth (compartment on the left) and the percentage of time rats spent close to the odor cloth (drawing of cloth on right with red line indicating 7 cm from odor cloth).

prazosin, since this brain region has been shown to be essential for the encoding of olfactory-based emotional learning [21,22].

Male Long-Evans rats were fear conditioned in a conditioning chamber (context A) saturated with amyl acetate odor receiving 5 electrical footshock (day 1). The next day, subjects were returned to the same chamber in the presence of the conditioned odor for a 2 min reactivation session, which was immediately followed by a systemic or intra-mPFC injection of vehicle or prazosin. The retention of olfactory fear conditioning was assessed one week later in an odor box (context B), where rats were initially habituated in the absence of the conditioned odor. On the next day (test) and two weeks later (spontaneous recovery test), a cloth impregnated with the conditioned odor was used as an odor source in one side of the chamber. A one week period between reactivation and test was kept to ensure that prazosin or any active metabolites were completely cleared out during test (Fig. 1; see supplemental material for more details).

The percentage of time spent freezing was used as a memory retention parameter during the reactivation session on day 2. The following behavioral responses were measured during the exposure to the context B: the percentage of hide time (time hiding in a different compartment away from the conditioned odor cloth) and the percentage of approach time (time when rats are within 7 cm of the odor cloth). The freezing response during conditioned odor presentation in context B was not significantly high (less than 10% of the time) compared to other studies using freezing as a measure of fear. Therefore, freezing behavior was not considered in the context B. In fact, previous studies in rats have demonstrated that freezing is elicited only in situations where a flight route is not available or when rats are not able to maintain a defensive distance from the threatening stimulus [23].

In the first set of experiments, rats were randomly divided to receive a single systemic injection of vehicle (Veh, $n = 10$) or prazosin (Pz, 1.5 mg/Kg; $n = 10$) immediately after the reactivation session. Two additional groups that were not submitted to the reactivation session received vehicle ($n = 8$) or prazosin (1.5 mg/kg; $n = 8$) and remained in the home cage. A student's t-test for independent samples did not reveal differences in freezing time during the reactivation session between groups (Veh: 54%; Pz: 51%, $t_{20} = 0.24$; $p = 0.81$), suggesting that both groups acquired the same levels of fear conditioning. A one-way ANOVA performed

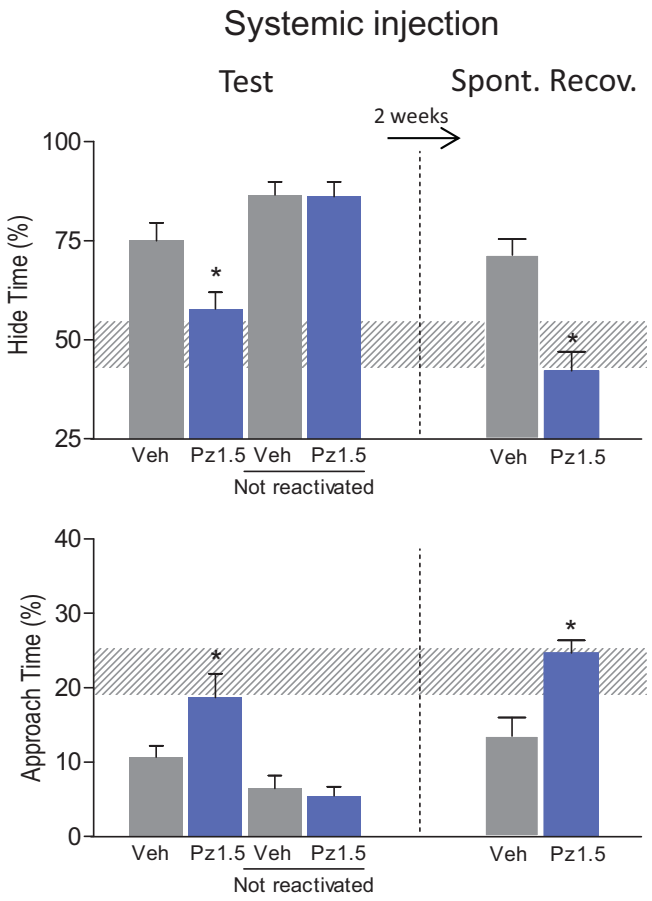

Fig. 2. Systemic post-retrieval infusion of prazosin disrupts fear memory reconsolidation. A single injection of prazosin (1.5 mg/Kg) immediately after reactivation session impaired subsequent retrieval of olfactory fear memory, as indicated by a significant reduction in the percentage of hide time and an increase in the percentage of approach time. This effect was dependent of fear reactivation, since prazosin treated rats that did not receive fear reactivation exhibited levels of fear similar to vehicle group. When re-tested in context B two weeks later, prazosin treated rats still showed impairment in fear retrieval, indicating that fear did not spontaneously recover three weeks after disrupting reconsolidation. Hatched horizontal bars represent the mean and the confidence limits (±95%) for all the subjects during the familiarization session in context B. *$p < 0.05$ compared to vehicle group. One way ANOVA followed by Tukey's test. Data are expressed as mean ± SEM ($n = 8$–10 per group).

during a familiarization session in context B did not reveal statistical differences between the groups in the parameters hide time ($F_{(3,36)} = 0.6$; $p = 0.56$) and approach time ($F_{(3,36)} = 1.39$; $p = 0.26$). Thus, data obtained during the familiarization session for all groups were merged and expressed as the mean and the confidence limits (±95%) for all the subjects (see Fig. 2, hatched horizontal bars). In general, rats spent ~50% of the time in the hide compartment and ~50% of the time in the opened area, indicating that they did not generalize the olfactory conditioned fear when exposed to the novel context.

However, during the odor test, an ANOVA overall comparison revealed a significant treatment effect between the groups for the parameters hide time ($F_{(3,32)} = 11.23$; $p = 0.00003$) and approach time ($F_{(3,32)} = 9.59$; $p = 0.0001$). Further analysis using Tukey's test revealed a significant ($p < 0.05$) effect in the reactivated group treated with prazosin when compared to the vehicle group (see Fig. 2). Prazosin-treated rats showed a decreased time in the hide box and an increased time spent near the conditioned odor source, suggesting that post-reactivation blockade of alpha-1 adrenergic receptors impaired the retrieval of olfactory fear conditioning one week later. Contrary, non-reactivated rats treated with the same

dose of prazosin did not show impairment in the retention of olfactory fear when compared to non-reactivated control group (all p's > 0.05), demonstrating that the disruptive effect of prazosin depends on prior memory reactivation.

Evidences from literature have shown that memories may follow two distinct processes after being triggered by memory retrieval: extinction or reconsolidation. Differences between these processes seem to be dependent on the retrieval time: while short retrieval sessions lead to reconsolidation, long retrieval sessions lead to extinction mechanisms [24–26]. Although previous studies have demonstrated that a short reactivation session promotes fear reconsolidation instead of fear extinction, it is possible that, under our experimental conditions, prazosin is reducing fear retrieval by facilitating the mechanisms of fear extinction. It has been shown that spontaneous recovery of fear occurs over the course of few weeks after fear memory extinction [27]. Therefore, to investigate if fear memory would reappear with the passage of time, rats were re-tested in context B two weeks later.

Our results showed that prazosin pretreatment reduced the hide time ($t_{20} = 4.6$; $p = 0.005$) and increased the approach time ($t_{20} = -3.61$; $p = 0.003$) during the spontaneous recovery test performed two weeks later, when compared to vehicle control group (Fig. 2). These findings suggest that prazosin impairs the reconsolidation of olfactory fear, since fear memory fail to re-emerge three weeks following treatment. Another explanation could be that prazosin-treated rats spent more time around the odor source during the first test, which would result in some extinction of the shock-odor association and consequent reduction of fear during the following test. However, it is little likely since previous findings from our laboratory showed that rats restricted close to the conditioned odor needed more than three extinction sessions of ten minutes to extinguish fear (unpublished data).

The present findings agree with a previous study in which blockade of alpha-1 adrenergic receptors during the post-retrieval period disrupted memory reconsolidation in a paradigm involving drug-associated cues in rats [28]. In a recent study, Olson et al. (2011) showed that prazosin reduced the expression of fear potentiated startle, aggression and social interaction in mice previously exposed to a traumatic experience of stress [29]. Our results, however, provide the first evidence that post-retrieval blockade of alpha-1 adrenergic receptors may result in disruption of the fear memory reconsolidation.

Activation of alpha-1 adrenergic receptors triggers an intracellular cascade that results in increased levels of the enzyme protein kinase C (PKC). It has been recently shown that many PKC substrates are involved in the biochemical pathways that are critical for memory reconsolidation [30]. Therefore, reduction in neuronal PKC levels after prazosin could explain the disruption of fear memory reconsolidation observed in the present study.

Among brain regions implicated in the control of aversive emotional states, the mPFC, more specifically the prelimbic (PL) subregion, has been shown to be an essential neural site for the acquisition of olfactory fear conditioning [31]. Previous neuroanatomical studies have demonstrated that PL is strongly interconnected with the basolateral nucleus of the amygdala [32,33], another key structure in the aversive association that occurs between footshock and olfactory stimulus [34]. In addition, the mPFC, including PL, has a substantial concentration of alpha-1 adrenergic receptors [35], which makes this region a potential neural substrate mediating the disruptive effects of prazosin on fear reconsolidation.

We started investigating this possibility by injecting vehicle PBS ($n = 8$), prazosin 0.3 μg ($n = 6$) or prazosin 0.6 μg ($n = 6$) directly into PL immediately after the reactivation session. A one-way ANOVA comparing the percentage of time freezing during the reactivation session did not reveal significant differences between groups (Veh: 63%; Pz 0.3 = 74%; Pz 0.6 = 72%, $F_{(2,17)} = 1.8$; $p = 0.18$), suggesting that all groups acquired the same levels of fear conditioning. Likewise, no statistical differences were observed between the groups in the parameters hide time ($F_{(2,17)} = 0.3$; $p = 0.70$) and approach time ($F_{(2,17)} = 0.6$; $p = 0.55$) during the familiarization in the context B. Similar to the previous experiment, group data obtained during the familiarization day was merged and expressed as the mean and the confidence limits (±95%) for all the subjects (see Fig. 3A, hatched horizontal bars).

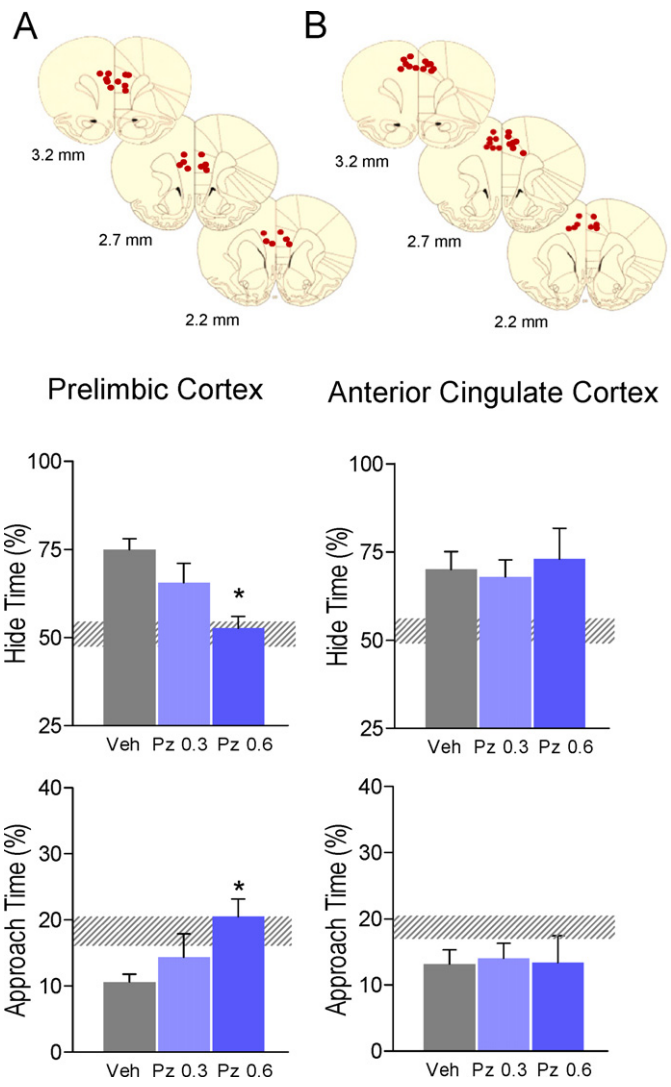

Fig. 3. Intra-prelimbic cortex infusion of prazosin disrupts fear memory reconsolidation. Post-retrieval infusion of prazosin (0.6 μg/side) into the prelimbic cortex (A), but not into the anterior cingulate cortex (B), impaired subsequent retrieval of olfactory fear memory, as indicated by a significant reduction in the percentage of hide time and an increase in the percentage of approach time. Hatched horizontal bars represent the mean and the confidence limits (±95%) for all the subjects during the familiarization session in context B. *$p < 0.05$ compared to vehicle group. One way ANOVA followed by Tukey's test. Data are expressed as mean ± SEM ($n = 6$–12 per group).

During the odor test, an ANOVA overall comparison showed a significant treatment effect between the groups for the parameters hide time ($F_{(2,17)} = 7.8$; $p = 0.002$) and approach time ($F_{(2,17)} = 4.39$; $p = 0.02$). Further analysis using Tukey's test revealed a significant ($p < 0.05$) effect in the group treated with prazosin 0.6 μg in the above parameters when compared to the vehicle control group (see Fig. 3A). Rats treated with an intra-PL infusion of prazosin 0.6 μg showed a decreased time in the hide box and an increased time spent near the conditioned odor source, indicating that

post-reactivation blockade of PL-alpha-1 adrenergic receptors impaired the retrieval of olfactory fear conditioning one week later. These data suggest that fear memory undergoes reconsolidation through activation of alpha-1 adrenergic receptors in PL, and that prazosin impairs this process.

Drug backflow along the cannula track can occur during intracerebral infusion resulting in non-specific targeting effects. We therefore investigated if the anterior cingulate cortex (ACC), another subregion of the mPFC located immediately above PL, could also be mediating the disruptive effects of prazosin on fear memory. To test this, another group of rats was microinjected with either vehicle PBS ($n = 12$), prazosin 0.3 μg ($n = 10$) or prazosin 0.6 μg ($n = 7$) within the ACC immediately after the reactivation session. A one-way ANOVA did not reveal significant differences between the groups in the percentage of time freezing during the reactivation session (Veh: 52%; Pz 0.3: 63%; Pz 0.6: 60%, $F_{(2,26)} = 0.48$; $p = 0.62$). In addition, no statistical differences were observed between the groups in the parameters hide time ($F_{(2,26)} = 1.05$; $p = 0.36$) and approach time ($F_{(2,26)} = 0.39$; $p = 0.67$) during the familiarization session in context B. Thus, group data obtained during familiarization day was again merged and expressed as the mean and the confidence limits (±95%) for all the subjects (see Fig. 3B, hatched horizontal bars).

Contrary to intra-PL infusion of prazosin (0.6 μg), intra-ACC infusion of prazosin at both doses (0.3 μg or 0.6 μg) did not affect the hide time ($F_{(2,26)} = 0.15$; $p = 0.85$) and the approach time ($F_{(2,26)} = 0.03$; $p = 0.97$) during the odor test, when compared to vehicle control group (Fig. 3B). One could argue that the lack of effect in fear reconsolidation after intra-ACC infusion of prazosin is due to a fewer number of alpha-1 adrenergic receptors in this area. However, the concentration of alpha-1 adrenergic receptors in the ACC is comparable to those described in PL [35]. A recent study showed that infusion of protein synthesis inhibitor anysomicin into the ACC blocked fear reconsolidation [36]. Differences between our study and Einarsson and Nader (2012) may be attributed to differences between the conditioned stimuli, since we used an olfactory cue, and they used a contextual cue. Nevertheless, both studies suggest that fear reconsolidation occurs in the mPFC, although the specific subregion that is recruited may depend on the conditioned stimuli.

In conclusion, our findings suggest that impairment in fear memory reconsolidation induced by blockade of alpha-1 adrenergic receptors is specific to PL. This is the first study showing that the PL subregion of the mPFC is part of the neural system modulating fear memory reconsolidation. Taken together, the present results support the idea that the beneficial effects of prazosin treatment in PTSD patients may be due to impairment in fear reconsolidation, rather than facilitation in fear extinction. This speculation is also sustained by previous studies in rodents showing that prazosin treatment impairs the mechanisms of fear extinction [16,17]. In this way, a precise control in the session duration during cognitive behavioral therapy seems to be critical to determine the fear memory progression in patients with anxiety disorders receiving prazosin treatment.

Conflict of interest

The authors declare no conflict of interest.

Contributions

F.H.M., R.R.S. and T.T.W. designed and conducted all experiments. F.H.M wrote the manuscript. A.P.C. supervised the project. All authors edited and accepted the final version of the manuscript.

Acknowledgments

This work was supported by CAPES, PRONEX, FAPESP, NIH (NIH 5-T37-MD001378-06)-CBU, and CNPq from which F.H.M.M. and R.R.S. received a doctoral fellowship and A.P.C. a research fellowship. Authors would like to thank Jose Rodriguez-Romaguera for critical reading of the manuscript and helpful suggestions.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2013.01.031.

References

[1] Jovanovic T, Norrholm SD. Neural mechanisms of impaired fear inhibition in posttraumatic stress disorder. Frontiers in Behavioral Neuroscience 2011;5:44.
[2] Dunlop BW, Mansson E, Gerardi M. Pharmacological innovations for posttraumatic stress disorder and medication-enhanced psychotherapy. Current Pharmaceutical Design 2012;18:5645–58.
[3] McLean CP, Foa EB. Prolonged exposure therapy for post-traumatic stress disorder: a review of evidence and dissemination. Expert Review of Neurotherapeutics 2011;11:1151–63.
[4] Barrera TL, Mott JM, Hofstein RF, Teng EJ. A meta-analytic review of exposure in group cognitive behavioral therapy for posttraumatic stress disorder. Clinical Psychology Review 2012;33:24–32.
[5] Perez Benitez CI, Zlotnick C, Stout RI, Lou F, Dyck I, Weisberg R, et al. A 5-year longitudinal study of posttraumatic stress disorder in primary care patients. Psychopathology 2012;45:286–93.
[6] Przybyslawski J, Sara SJ. Reconsolidation of memory after its reactivation. Behavioural Brain Research 1997;84:241–6.
[7] Nader K, Schafe GE, Le Doux JE. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 2000;406:722–6.
[8] Milekic MH, Alberini CM. Temporally graded requirement for protein synthesis following memory reactivation. Neuron 2002;36:521–5.
[9] Soeter M, Kindt M. Erasing fear for an imagined threat event. Psychoneuroendocrinology 2012;37:1769–79.
[10] Agren T, Engman J, Frick A, Bjorkstrand J, Larsson EM, Furmark T, et al. Disruption of reconsolidation erases a fear memory trace in the human amygdala. Science 2012;337:1550–2.
[11] Roozendaal B, McGaugh JL. Memory modulation. Behavioral Neuroscience 2011;125:797–824.
[12] Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. American Journal of Psychiatry 2003;160:371–3.
[13] Dierks MR, Jordan JK, Sheehan AH. Prazosin treatment of nightmares related to posttraumatic stress disorder. Annals of Pharmacotherapy 2007;41:1013–7.
[14] Taylor HR, Freeman MK, Cates ME. Prazosin for treatment of nightmares related to posttraumatic stress disorder. American Journal of Health-System Pharmacy 2008;65:716–22.
[15] Germain A, Richardson R, Moul DE, Mammen O, Haas G, Forman SD, et al. Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US Military Veterans. Journal of Psychosomatic Research 2012;72:89–96.
[16] Do-Monte FH, Allensworth M, Carobrez AP. Impairment of contextual conditioned fear extinction after microinjection of alpha-1-adrenergic blocker prazosin into the medial prefrontal cortex. Behavioural Brain Research 2010;211:89–95.
[17] Bernardi RE, Lattal KM. A role for alpha-adrenergic receptors in extinction of conditioned fear and cocaine conditioned place preference. Behavioral Neuroscience 2010;124:204–10.
[18] Brennan PA, Keverne EB. Neural mechanisms of mammalian olfactory learning. Progress in Neurobiology 1997;51:457–81.
[19] Otto T, Cousens G, Herzog C. Behavioral and neuropsychological foundations of olfactory fear conditioning. Behavioural Brain Research 2000;110:119–28.
[20] Kroon JA, Carobrez AP. Olfactory fear conditioning paradigm in rats: effects of midazolam, propranolol or scopolamine. Neurobiology of Learning and Memory 2009;91:32–40.
[21] Tan H, Lauzon NM, Bishop SF, Chi N, Bechard M, Laviolette SR. Cannabinoid transmission in the basolateral amygdala modulates fear memory formation via functional inputs to the prelimbic cortex. Journal of Neuroscience 2011;31:5300–12.
[22] Laviolette SR, Lipski WJ, Grace AA. A subpopulation of neurons in the medial prefrontal cortex encodes emotional learning with burst and frequency codes through a dopamine D4 receptor-dependent basolateral amygdala input. Journal of Neuroscience 2005;25:6066–75.
[23] McNaughton N, Corr PJ. A two-dimensional neuropsychology of defense: fear/anxiety and defensive distance. Neuroscience and Biobehavioral Reviews 2004;28:285–305.

[24] Pedreira ME, Maldonado H. Protein synthesis subserves reconsolidation or extinction depending on reminder duration. Neuron 2003;38:863–9.
[25] Suzuki A, Josselyn SA, Frankland PW, Masushige S, Silva AJ, Kida S. Memory reconsolidation and extinction have distinct temporal and biochemical signatures. Journal of Neuroscience 2004;24:4787–95.
[26] Bustos SG, Maldonado H, Molina VA. Disruptive effect of midazolam on fear memory reconsolidation: decisive influence of reactivation time span and memory age. Neuropsychopharmacology 2009;34:446–57.
[27] Quirk GJ. Memory for extinction of conditioned fear is long-lasting and persists following spontaneous recovery. Learning and Memory 2002;9:402–7.
[28] Bernardi RE, Ryabinin AE, Berger SP, Lattal KM. Post-retrieval disruption of a cocaine conditioned place preference by systemic and intrabasolateral amygdala beta2- and alpha1-adrenergic antagonists. Learning and Memory 2009;16:777–89.
[29] Olson VG, Rockett HR, Reh RK, Redila VA, Tran PM, Venkov HA, et al. The role of norepinephrine in differential response to stress in an animal model of posttraumatic stress disorder. Biological Psychiatry 2011;70:441–8.
[30] Bonini JS, Da Silva WC, Bevilaqua LR, Medina JH, Izquierdo I, Cammarota M. On the participation of hippocampal PKC in acquisition, consolidation and reconsolidation of spatial memory. Neuroscience 2007;147:37–45.
[31] Lauzon NM, Ahmad T, Laviolette SR. Dopamine D4 receptor transmission in the prefrontal cortex controls the salience of emotional memory via modulation of calcium calmodulin-dependent kinase II. Cerebral Cortex 2012;22:2486–94.
[32] McDonald AJ. Organization of amygdaloid projections to the prefrontal cortex and associated striatum in the rat. Neuroscience 1991;44:1–14.
[33] Vertes RP. Differential projections of the infralimbic and prelimbic cortex in the rat. Synapse 2004;51:32–58.
[34] Walker DL, Paschall GY, Davis M. Glutamate receptor antagonist infusions into the basolateral and medial amygdala reveal differential contributions to olfactory vs. context fear conditioning and expression. Learning and Memory 2005;12:120–9.
[35] Pieribone VA, Nicholas AP, Dagerlind A, Hokfelt T. Distribution of alpha 1 adrenoceptors in rat brain revealed by in situ hybridization experiments utilizing subtype-specific probes. Journal of Neuroscience 1994;14:4252–68.
[36] Einarsson EO, Nader K. Involvement of the anterior cingulate cortex in formation, consolidation, and reconsolidation of recent and remote contextual fear memory. Learning and Memory 2012;19:449–52.