



BRAZILIAN JOURNAL
OF MEDICAL AND BIOLOGICAL RESEARCH

www.bjournal.com.br

ISSN 0100-879X
Volume 45 (4) 291-375 April 2012

BIOMEDICAL SCIENCES

Braz J Med Biol Res, April 2012, Volume 45(4) 308-313

doi: 10.1590/S0100-879X2012007500045

The influence of stress on fear memory processes

I.D. Martijena and V.A. Molina

The Brazilian Journal of Medical and Biological Research is partially financed by



Ministério da Ciência e Tecnologia



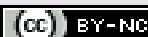
Ministério da Educação



Institutional Sponsors



Explore High - Performance MS Orbitrap Technology In Proteomics & Metabolomics



All the contents of this journal, except where otherwise noted, is licensed under a [Creative Commons Attribution License](http://creativecommons.org/licenses/by-nc/4.0/)

The influence of stress on fear memory processes

I.D. Martijena and V.A. Molina

IFEC-CONICET, Departamento de Farmacología, Facultad de Ciencias Químicas,
Universidad Nacional de Córdoba, Córdoba, Argentina

Abstract

It is well recognized that stressful experiences promote robust emotional memories, which are well remembered. The amygdaloid complex, principally the basolateral complex (BLA), plays a pivotal role in fear memory and in the modulation of stress-induced emotional responses. A large number of reports have revealed that GABAergic interneurons provide a powerful inhibitory control of the activity of projecting glutamatergic neurons in the BLA. Indeed, a reduced GABAergic control in the BLA is essential for the stress-induced influence on the emergence of associative fear memory and on the generation of long-term potentiation (LTP) in BLA neurons. The extracellular signal-regulated kinase (ERK) subfamily of the mitogen-activated protein kinase (MAPK) signaling pathway in the BLA plays a central role in the consolidation process and synaptic plasticity. In support of the view that stress facilitates long-term fear memory, stressed animals exhibited a phospho-ERK2 (pERK2) increase in the BLA, suggesting the involvement of this mechanism in the promoting influence of threatening stimuli on the consolidation fear memory. Moreover, the occurrence of reactivation-induced lability is prevented when fear memory is encoded under intense stressful conditions since the memory trace remains immune to disruption after recall in previously stressed animals. Thus, the underlying mechanism in retrieval-induced instability seems not to be functional in memories formed under stress. All these findings are indicative that stress influences both the consolidation and reconsolidation fear memory processes. Thus, it seems reasonable to propose that the emotional state generated by an environmental challenge critically modulates the formation and maintenance of long-term fear memory.

Key words: Stress; Amygdala; GABA; Memory; Fear

Introduction

There is a broad consensus that memories of emotionally arousing events are robust and long lasting (1). In addition, there are several studies showing that stressful experiences enhance memory formation (2-4). Such a facilitating influence is highly adaptive since it is extremely relevant for the animal's survival to store vital information, which enables it to detect, anticipate and avoid potential dangerous stimuli in future encounters. In addition, contributions to the effect of stress on fear memory are central to elucidating the consequence of stress for brain function. A greater understanding of the mechanisms involved in the effects of stress on cognitive processes can have potential implications in terms of the prevention and treatment of mental disorders, since excessive and inappropriate fear due to memories from traumatic events is a hallmark symptom of several anxiety-related disorders such as post-traumatic stress disorder, phobia

and panic disorder (5).

Involvement of the amygdaloid complex in both stress reaction and formation of fear memory

A growing number of reports have focused on identifying the brain circuitry and the neurobiological mechanisms that underlie the promoting influence of threatening experiences on the emergence of aversive motivated memories (6). An important aspect to note is that the amygdaloid nuclei implicated in fear memory formation are also involved in stress-induced anxiety and fear reactions, further supporting that these processes are interrelated and can influence each other.

The amygdala or the amygdaloid complex is a hetero-

Correspondence: V.A. Molina, IFEC-CONICET, Departamento de Farmacología, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Haya de la Torre y Medina Allende, Ciudad Universitaria, 5000 Córdoba, Argentina. Fax: 54-0351-433-4420. E-mail: vmolina@fcq.unc.edu.ar

Presented at the III Fórum em Neurobiologia do Estresse, Araraquara, SP, Brazil, September 8-10, 2011.

Received November 26, 2011. Accepted March 15, 2012. Available online March 30, 2012. Published April 9, 2012.

geneous collection of nuclei located in the medial temporal lobe rostral to the hippocampus formation. These groups of nuclei have been divided into two broad compartments: the centrocorticomедial area and the region classically known as the basolateral complex (BLA) consisting of the lateral, basolateral and basomedial nuclei (7). The two regions are distinguished on the basis of histological criteria, neurochemical components and neuroanatomical connections to other regions (inputs and outputs). The BLA integrates sensory information from cortical and subcortical projections, is centrally involved in emotional processing and generates the appropriate emotional reaction to environmental threats (7). Thus, this brain region plays an essential role in the processing of emotions (6,8). The central nucleus (CeA) is considered to be a relevant output region to the brainstem for the selective expression of innate and associated emotional reactions (9). Finally, the flow of information from the BLA to the CeA is largely unidirectional and gated in part by inhibitory intercalated neurons. The majority of the inputs to the amygdala are excitatory projections that use glutamate as a neurotransmitter (6,7). They form synaptic connections on dendrites from other excitatory projecting neurons that transmit information to other regions of the amygdala and outside the amygdala. Importantly, it is well recognized that GABAergic interneurons are responsible for controlling the activity of projecting glutamatergic cells through feedforward and feedback inhibition (10,11), providing a powerful inhibitory control of the activity of these projecting neurons in the BLA (12,13). In fact, the low neuronal firing recorded in BLA neurons is caused by this inhibitory modulation (13).

A large number of reports have emphasized that the GABAergic system in the amygdaloid complex is a key component in the modulation of emotional reactions to stressful stimuli. For instance, it has been demonstrated that stress exposure resulted in a decreased chloride uptake mediated by GABA(A) sites in this brain region (14,15), as well as a reduced benzodiazepine binding, and the expression of α -1 GABA(A) receptor mRNA in the BLA (16). Findings from our laboratory have revealed that a single restraint experience elicited BLA neuron hyperexcitability, which resulted from the reduction of recurrent GABAergic inhibition (17). This view was further supported by pharmacological evidence, since intra-BLA infusion of midazolam (MDZ), a positive modulator of GABA(A) sites, prevented the enhanced emotional reactions exhibited by stressed animals (18,19). Moreover, blockade of GABA(A) receptors in the BLA, but not in the adjacent CeA, elicited an emotional response similar to that induced by stress (18). Overall, these findings suggest that stress, by reducing this inhibitory GABAergic control, would result in an unmasked activation of projecting neurons of the BLA, generating robust emotional reactions, such as excessive fear and anxiety, which have been consistently reported in animals subjected to a variety of stressful stimuli (18-20).

The BLA plays a pivotal role in the facilitating influence of stress on the consolidation of emotional memories, including fear memory (see Ref. 1). It is widely accepted that the convergence of the conditioned stimulus (CS), such as a neutral context, tone or light, and the unconditioned stimulus (US), such as an electric footshock, in a classic Pavlovian paradigm of fear occurs in the BLA, leading to synaptic plasticity (6,21-23). The functional link between the generation of long-term potentiation (LTP), a cellular model of synaptic plasticity, in the BLA and the induction of fear conditioning is sustained by a considerable number of reports (18,23-25). Besides, GABAergic inhibitory control seems to play a major role in memory consolidation (12,26,27) and fear conditioning leads to reduced GABAergic neurotransmission in the BLA (28,29). Importantly, the stress-induced promoting influence on the emergence of associative fear memory coincided with GABAergic disinhibition, which facilitated the generation of LTP in BLA neurons (18). Furthermore, stimulating GABA(A) sites with MDZ attenuated both the facilitating influence of stress on fear memory and synaptic excitability in the BLA (18). Collectively, these data support the view that GABAergic disinhibition in the BLA triggers hyperexcitability and enhanced neuroplasticity in BLA neurons (18). Such a mechanism is relevant because it is widely accepted that increased glutamatergic signaling in the BLA is essential for fear memory consolidation. In fact, it is well accepted that NMDA-dependent plasticity processes are crucially implicated in fear conditioning (30). Accordingly, pharmacological manipulation with NMDA antagonists interferes with fear learning (31-33). In summary, BLA can be an essential locus for the GABAergic modulation of stress-induced emotional reactions. Thus, the release of inhibition of the GABAergic inhibitory control of the BLA elicited by exposure to stress could be a critical neurobiological event that promotes the association of the CS and the US during fear conditioning and the emergence of neural plasticity in BLA neurons. Along this line of reasoning, GABAergic neurotransmission in the BLA, regulating BLA glutamatergic activity, would serve as a dynamic gating mechanism, adjusting fear memory encoding according to the emotional state at the moment of the fear learning process.

In addition, extensive evidence indicates that a noradrenergic mechanism in the BLA is also involved in the facilitating influence of stress and stress hormones on the consolidation of aversive motivated memory (1). Activation of β and α -1 adrenoceptors in the BLA enhances memory consolidation (34) and a β -adrenoceptor antagonist in the BLA impaired norepinephrine-induced activation of memory (35). In addition, glucocorticoids, stress-related hormones, also enhanced the emergence of aversive motivated memories (36). Moreover, a noradrenergic mechanism in the BLA plays a relevant role in the modulatory effect of stress hormones (1). Consonant with all these findings, it was shown that β -adrenoceptor activation increased LTP

of cortical afferents to pyramidal neurons from the lateral nucleus (37). Interestingly, stress impaired the facilitating effect of norepinephrine on GABAergic inhibition in the BLA (38) and norepinephrine suppressed the GABAergic inhibitory action on neurons from the BLA, allowing the generation of LTP in thalamus-amygdala synapses (39). Hence, stress-induced activation of noradrenergic mechanisms in the BLA can result, at least in part, from a reduced GABAergic control in this brain area.

Effect of stress on fear memory consolidation

Despite compelling evidence supporting the promoting influence of stress on memory consolidation at the behavioral, electrophysiological and pharmacological levels in the BLA, the molecular mechanism involved in such facilitating influence on fear memory consolidation is not entirely clear. The memory consolidation hypothesis states that the acquisition of new information requires a time-dependent stabilization process for the permanent storage of such information (40). During this period the trace is vulnerable to disruption by diverse amnesic agents, including protein synthesis inhibitors, indicating at this point that the memory trace is in a labile state (40,41). However, once the memory trace is immune to interference it is considered stable and, by definition, consolidated (40,42). The process of synaptic consolidation requires *de novo* protein synthesis and the activation of a successive cascade of molecular events and of numerous signaling systems, which are crucial for the stabilization of the cellular and molecular changes elicited by the acquisition process (42,43). One of the classic tenets of this view is that they lead to changes in synaptic efficacy. Fear learning induces changes in protein phosphorylation and gene expression in BLA neurons, which are essential components of this cascade during fear memory consolidation. Among these molecular events, the extracellular signal-regulated kinase (ERK) subfamily of the mitogen-activated protein kinase (MAPK) signaling pathway in several brain areas, including the BLA, plays a pivotal role in the consolidation process and synaptic plasticity (43-45). A recent study using contextual fear conditioning, evaluated ERK signaling in the BLA following a weak fear training protocol in animals previously subjected to a threatening experience. As expected, stress increased fear retention and activated the ERK pathway in the BLA, whereas systemic administration of MDZ, a positive modulator of GABA(A) sites, attenuated both enhanced fear retention and the increased expression of phospho-ERK (p-ERK) in the BLA (46). The fact that stress elicited an increase expression of pERK in the BLA following fear acquisition is consistent with the view that such threatening stimulus facilitated fear memory consolidation. Importantly, an elevated pERK level was already evident at the time of learning as a consequence of the stress experience. Based on these findings, the authors suggested

that stress-induced activation of pERK in the BLA might have facilitated the further enhancement of pERK by the acquisition procedure and the learning-induced intracellular cascade, strengthening the consolidation process involved in the robust fear memory observed in stressed animals (46). Thus, molecular changes such as the activation of the ERK signaling pathway elicited by stress that persists at least one day may underlie the enhanced association of the CS with the US.

Effect of stress on fear memory reconsolidation

According to the consolidation hypothesis, once the memory trace is consolidated, the trace should be fully stabilized and immune to interference. However, a series of studies using diverse aversive and appetitive tasks such as Pavlovian fear conditioning and drug-related memories revealed that the recall of a memory already consolidated rendered such trace susceptible to disruption (47-49). Consonant with such view, this process has been noted in different species and types of memory (49,50), including procedural and declarative memories in humans (51,52). If the memory was not recalled, the trace remained immune to disruption, thus demonstrating that reactivation of the trace converts such consolidated memory to a phase of fragility. After this post-retrieval phase of instability, memories undergo a period of restabilization dependent on new protein synthesis usually referred to as reconsolidation (47,53-56).

Furthermore, this process was suggested to play a central role in updating the original memory with novel information or to strengthen the original trace (57,58). It should be noted, however, that there are boundary conditions that limit the emergence of both the labile phase and the restabilization process (55,57). One such condition is memory age; indeed, as memory ages it is more difficult to change the memory trace and to induce post-retrieval instability (59-62). Interestingly, and as previously noted for consolidated memories, the GABAergic system also participates in the modulation of memory reconsolidation. For instance, activation of GABA(A) sites by benzodiazepine ligands interfered with fear memory reconsolidation (50,62,63). Therefore, a relevant question is how does stress administered prior to fear learning affect the emergence of retrieval-induced lability and the subsequent restabilization process in recent and remote fear memories. That is, how vulnerable to MDZ a fear memory trace would be when reactivated after different times in stressed subjects. The experiments performed to address this question revealed that MDZ did not influence fear memory reconsolidation in older memories of stressed animals, even after the administration of the higher MDZ dose (64). In contrast, MDZ disrupted memory reconsolidation at all memory ages in unstressed subjects (64). Thus, these data suggest that the

occurrence of reactivation-induced lability is prevented when fear memory is encoded under intense stressful conditions. Interestingly, differential effects of MDZ on moderate and intense conditioned aversive states have been described using other experimental paradigms. For instance, Santos et al. (65) reported that fear-potentiated startle and conditioned freezing induced by moderate fear training were both attenuated by MDZ before testing. This drug was also effective in reducing the high levels of freezing associated with strong conditioning, but did not affect strong footshock-induced fear-potentiated startle (65). Therefore, it seems valid to propose that the attenuating effect of MDZ on aversive memory depends on the memory strength and on the particular protocol used to evaluate such cognitive processes. Besides, the influence of MDZ is also crucially dependent on the timing of drug administration with respect to memory reactivation, a factor that should be considered when evaluating the net effect of this benzodiazepine on aversive memories.

It has been reported that blockade of amygdaloid NMDA sites prior to reactivation causes trace memories to become immune to interference (66), therefore activating NMDA sites before reactivation would be effective in inducing instability after retrieval. Bustos et al. (64) used D-cycloserine (DCS), an allosteric modulator of the NMDA receptor that promotes agonist binding and enhances NMDA receptor function (67), before reactivation to test if such procedure would facilitate vulnerability to MDZ in resistant memories such as those formed in stressed rats. Coincidentally, DCS before reactivation promoted retrieval-induced instability in resistant fear memories since memory reconsolidation was vulnerable to MDZ disruption in DCS-treated animals that were previously exposed to stress (64). Taken together, these lines of evidence indicate that the underlying mechanism in retrieval-induced instability seems not to be functional in memories formed under stress. Thus, the passage of time together with prior stressful experiences can significantly affect both retrieval-induced lability and the dynamic property of the memory trace, making such trace immune to memory reconsolidation disruption. This view opens the possibility that fear memories formed under a negative emotional state, such as that elicited by intense stress exposure, might lose flexibility and in turn remain unchanged even after retrieval, promoting

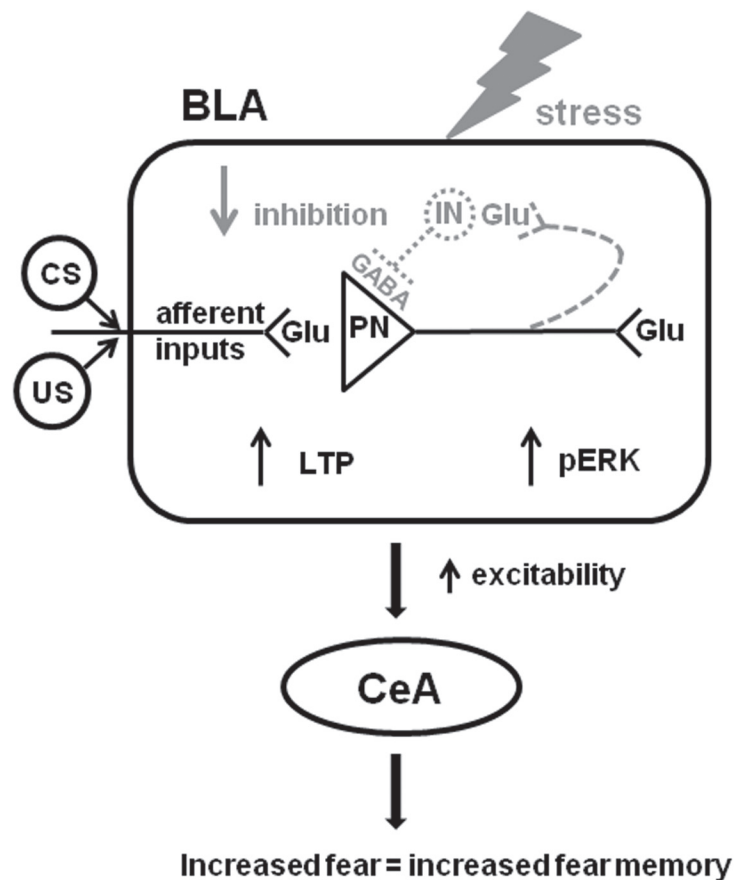


Figure 1. Schematic representation of the mechanisms implicated in the influence of stress on fear memory formation in the basolateral complex (BLA). The convergence of the conditioned stimulus (CS) and the unconditioned stimulus (US) on projection neurons (PN) promotes the occurrence of neuroplasticity such as long-term potentiation (LTP). Stress exposure reduced the inhibitory control of GABAergic interneurons (IN) resulting in an increased excitability of PN, facilitating the onset of LTP and activating the downstream extracellular signal-regulated kinase (ERK) pathway with the concomitant enhancement of phospho-ERK (pERK), a critical step for fear memory consolidation. The BLA output to the central nucleus (CeA) carries increased excitability, which, in turn, will activate target brain structures involved in fear responses, facilitating the expression and the emergence of fear memory.

the emergence of a traumatic memory.

The present review highlights the modulatory role of the inhibitory GABAergic system in a particular subarea of the amygdaloid complex in the stress influence on fear memory formation. Taken together, the findings described in this review support the view that a reduced GABAergic control in the BLA is essential for the stress-induced promoting influence on the emergence of associative fear memory and on the generation of LTP in BLA neurons. The mechanisms involved in the stress-induced effects on the BLA are indicated in Figure 1.

References

1. Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. *Nat Rev Neurosci* 2009; 10: 423-433.
2. Beylin AV, Shors TJ. Stress enhances excitatory trace eyeblink conditioning and opposes acquisition of inhibitory conditioning. *Behav Neurosci* 1998; 112: 1327-1338.
3. Shors TJ. Acute stress rapidly and persistently enhances memory formation in the male rat. *Neurobiol Learn Mem* 2001; 75: 10-29.
4. McGaugh JL, Roozendaal B. Role of adrenal stress hormones in forming lasting memories in the brain. *Curr Opin Neurobiol* 2002; 12: 205-210.
5. Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology* 2010; 35: 169-191.
6. LeDoux JE. Emotion circuits in the brain. *Annu Rev Neurosci* 2000; 23: 155-184.
7. LeDoux JE, Schiller D. The human amygdala. Insights from other animals. In: Whalen PJ, Phelps EA (Editors), *The human amygdala*. New York: Guilford; 2009. p 43-60.
8. Aggleton JP. *The amygdala: a functional analysis*. New York: Wiley-Liss; 2000.
9. Kapp BS, Whalen PJ, Supple WF, Pascoe JP. Amygdala contributions to conditioned arousal and sensory information processing. In: Aggleton JP (Editor), *The amygdala: neurobiological aspects of emotion, memory, and mental dysfunction*. New York: Wiley-Liss; 1992. p 229-254.
10. Sah P, Lopez de AM. Excitatory synaptic transmission in the lateral and central amygdala. *Ann N Y Acad Sci* 2003; 985: 67-77.
11. Dityatev AE, Bolshakov VY. Amygdala, long-term potentiation, and fear conditioning. *Neuroscientist* 2005; 11: 75-88.
12. Ehrlich I, Humeau Y, Grenier F, Ciochi S, Herry C, Luthi A. Amygdala inhibitory circuits and the control of fear memory. *Neuron* 2009; 62: 757-771.
13. Pare D, Collins DR. Neuronal correlates of fear in the lateral amygdala: multiple extracellular recordings in conscious cats. *J Neurosci* 2000; 20: 2701-2710.
14. Martijena ID, Calvo N, Volosin M, Molina VA. Prior exposure to a brief restraint session facilitates the occurrence of fear in response to a conflict situation: behavioral and neurochemical correlates. *Brain Res* 1997; 752: 136-142.
15. Martijena ID, Rodriguez Manzanares PA, Lacerra C, Molina VA. Gabaergic modulation of the stress response in frontal cortex and amygdala. *Synapse* 2002; 45: 86-94.
16. Liu M, Glowa JR. Regulation of benzodiazepine receptor binding and GABA(A) subunit mRNA expression by punishment and acute alprazolam administration. *Brain Res* 2000; 887: 23-33.
17. Isoardi NA, Bertotto ME, Martijena ID, Molina VA, Carrer HF. Lack of feedback inhibition on rat basolateral amygdala following stress or withdrawal from sedative-hypnotic drugs. *Eur J Neurosci* 2007; 26: 1036-1044.
18. Rodriguez Manzanares PA, Isoardi NA, Carrer HF, Molina VA. Previous stress facilitates fear memory, attenuates GABAergic inhibition, and increases synaptic plasticity in the rat basolateral amygdala. *J Neurosci* 2005; 25: 8725-8734.
19. Bignante EA, Paglini G, Molina VA. Previous stress exposure enhances both anxiety-like behaviour and p35 levels in the basolateral amygdala complex: modulation by midazolam. *Eur Neuropsychopharmacol* 2010; 20: 388-397.
20. Calfa G, Volosin M, Molina VA. Glucocorticoid receptors in lateral septum are involved in the modulation of the emotional sequelae induced by social defeat. *Behav Brain Res* 2006; 172: 324-332.
21. Maren S, Quirk GJ. Neuronal signalling of fear memory. *Nat Rev Neurosci* 2004; 5: 844-852.
22. Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. *Neuropsychopharmacology* 2008; 33: 56-72.
23. Pape HC, Pare D. Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. *Physiol Rev* 2010; 90: 419-463.
24. Blair HT, Schafe GE, Bauer EP, Rodrigues SM, LeDoux JE. Synaptic plasticity in the lateral amygdala: a cellular hypothesis of fear conditioning. *Learn Mem* 2001; 8: 229-242.
25. Maren S. Neurobiology of Pavlovian fear conditioning. *Annu Rev Neurosci* 2001; 24: 897-931.
26. Wilensky AE, Schafe GE, LeDoux JE. The amygdala modulates memory consolidation of fear-motivated inhibitory avoidance learning but not classical fear conditioning. *J Neurosci* 2000; 20: 7059-7066.
27. Makkar SR, Zhang SQ, Cranney J. Behavioral and neural analysis of GABA in the acquisition, consolidation, reconsolidation, and extinction of fear memory. *Neuropsychopharmacology* 2010; 35: 1625-1652.
28. Stork O, Ji FY, Obata K. Reduction of extracellular GABA in the mouse amygdala during and following confrontation with a conditioned fear stimulus. *Neurosci Lett* 2002; 327: 138-142.
29. Rea K, Lang Y, Finn DP. Alterations in extracellular levels of gamma-aminobutyric acid in the rat basolateral amygdala and periaqueductal gray during conditioned fear, persistent pain and fear-conditioned analgesia. *J Pain* 2009; 10: 1088-1098.
30. Maren S. Pavlovian fear conditioning as a behavioral assay for hippocampus and amygdala function: cautions and caveats. *Eur J Neurosci* 2008; 28: 1661-1666.
31. Fendt M. Injections of the NMDA receptor antagonist aminophosphonopentanoic acid into the lateral nucleus of the amygdala block the expression of fear-potentiated startle and freezing. *J Neurosci* 2001; 21: 4111-4115.
32. Goosens KA, Maren S. Pretraining NMDA receptor blockade in the basolateral complex, but not the central nucleus, of the amygdala prevents savings of conditional fear. *Behav Neurosci* 2003; 117: 738-750.
33. Goosens KA, Maren S. NMDA receptors are essential for the acquisition, but not expression, of conditional fear and associative spike firing in the lateral amygdala. *Eur J Neurosci* 2004; 20: 537-548.
34. Ferry B, Roozendaal B, McGaugh JL. Basolateral amygdala noradrenergic influences on memory storage are mediated by an interaction between beta- and alpha1-adrenoceptors. *J Neurosci* 1999; 19: 5119-5123.
35. Liang KC, McGaugh JL, Yao HY. Involvement of amygdala pathways in the influence of post-training intra-amygdala norepinephrine and peripheral epinephrine on memory storage. *Brain Res* 1990; 508: 225-233.
36. Roozendaal B, McGaugh JL. Glucocorticoid receptor ago-

- nist and antagonist administration into the basolateral but not central amygdala modulates memory storage. *Neurobiol Learn Mem* 1997; 67: 176-179.
37. Faber ES, Delaney AJ, Sah P. SK channels regulate excitatory synaptic transmission and plasticity in the lateral amygdala. *Nat Neurosci* 2005; 8: 635-641.
 38. Braga MF, Aroniadou-Anderjaska V, Manion ST, Hough CJ, Li H. Stress impairs alpha(1A) adrenoceptor-mediated noradrenergic facilitation of GABAergic transmission in the basolateral amygdala. *Neuropsychopharmacology* 2004; 29: 45-58.
 39. Tully K, Li Y, Tsvetkov E, Bolshakov VY. Norepinephrine enables the induction of associative long-term potentiation at thalamo-amygdala synapses. *Proc Natl Acad Sci U S A* 2007; 104: 14146-14150.
 40. McGaugh JL. Memory - a century of consolidation. *Science* 2000; 287: 248-251.
 41. Davis HP, Squire LR. Protein synthesis and memory: a review. *Psychol Bull* 1984; 96: 518-559.
 42. Dudai Y. The neurobiology of consolidations, or, how stable is the engram? *Annu Rev Psychol* 2004; 55: 51-86.
 43. Sweatt JD. Mitogen-activated protein kinases in synaptic plasticity and memory. *Curr Opin Neurobiol* 2004; 14: 311-317.
 44. Giovannini MG. The role of the extracellular signal-regulated kinase pathway in memory encoding. *Rev Neurosci* 2006; 17: 619-634.
 45. Schafe GE, Atkins CM, Swank MW, Bauer EP, Sweatt JD, LeDoux JE. Activation of ERK/MAP kinase in the amygdala is required for memory consolidation of Pavlovian fear conditioning. *J Neurosci* 2000; 20: 8177-8187.
 46. Maldonado NM, Martijena ID, Molina VA. Facilitating influence of stress on the consolidation of fear memory induced by a weak training: reversal by midazolam pretreatment. *Behav Brain Res* 2011; 225: 77-84.
 47. Nader K, Schafe GE, Le Doux JE. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* 2000; 406: 722-726.
 48. Lee JL, Di Ciano P, Thomas KL, Everitt BJ. Disrupting reconsolidation of drug memories reduces cocaine-seeking behavior. *Neuron* 2005; 47: 795-801.
 49. Pedreira ME, Maldonado H. Protein synthesis subserves reconsolidation or extinction depending on reminder duration. *Neuron* 2003; 38: 863-869.
 50. Bustos SG, Maldonado H, Molina VA. Midazolam disrupts fear memory reconsolidation. *Neuroscience* 2006; 139: 831-842.
 51. Walker MP, Brakefield T, Hobson JA, Stickgold R. Dissociable stages of human memory consolidation and reconsolidation. *Nature* 2003; 425: 616-620.
 52. Forcato C, Burgos VL, Argibay PF, Molina VA, Pedreira ME, Maldonado H. Reconsolidation of declarative memory in humans. *Learn Mem* 2007; 14: 295-303.
 53. Alberini CM. Mechanisms of memory stabilization: are consolidation and reconsolidation similar or distinct processes? *Trends Neurosci* 2005; 28: 51-56.
 54. Dudai Y. Reconsolidation: the advantage of being refocused. *Curr Opin Neurobiol* 2006; 16: 174-178.
 55. Nader K, Hardt O. A single standard for memory: the case for reconsolidation. *Nat Rev Neurosci* 2009; 10: 224-234.
 56. Dudai Y, Eisenberg M. Rites of passage of the engram: reconsolidation and the lingering consolidation hypothesis. *Neuron* 2004; 44: 93-100.
 57. Tronson NC, Taylor JR. Molecular mechanisms of memory reconsolidation. *Nat Rev Neurosci* 2007; 8: 262-275.
 58. Suzuki A, Mukawa T, Tsukagoshi A, Frankland PW, Kida S. Activation of LVGCCs and CB1 receptors required for destabilization of reactivated contextual fear memories. *Learn Mem* 2008; 15: 426-433.
 59. Milekic MH, Alberini CM. Temporally graded requirement for protein synthesis following memory reactivation. *Neuron* 2002; 36: 521-525.
 60. Frankland PW, Ding HK, Takahashi E, Suzuki A, Kida S, Silva AJ. Stability of recent and remote contextual fear memory. *Learn Mem* 2006; 13: 451-457.
 61. Suzuki A, Josselyn SA, Frankland PW, Masushige S, Silva AJ, Kida S. Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *J Neurosci* 2004; 24: 4787-4795.
 62. 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: 446-457.
 63. Zhang S, Cranney J. The role of GABA and anxiety in the reconsolidation of conditioned fear. *Behav Neurosci* 2008; 122: 1295-1305.
 64. Bustos SG, Giachero M, Maldonado H, Molina VA. Previous stress attenuates the susceptibility to Midazolam's disruptive effect on fear memory reconsolidation: influence of pre-reactivation D-cycloserine administration. *Neuropsychopharmacology* 2010; 35: 1097-1108.
 65. Santos JM, Gargaro AC, Oliveira AR, Masson S, Brandão ML. Pharmacological dissociation of moderate and high contextual fear as assessed by freezing behavior and fear-potentiated startle. *Eur Neuropsychopharmacol* 2005; 15: 239-246.
 66. Ben Mamou C, Gamache K, Nader K. NMDA receptors are critical for unleashing consolidated auditory fear memories. *Nat Neurosci* 2006; 9: 1237-1239.
 67. Rouaud E, Billard JM. D-cycloserine facilitates synaptic plasticity but impairs glutamatergic neurotransmission in rat hippocampal slices. *Br J Pharmacol* 2003; 140: 1051-1056.