Moderate Stress Enhances Memory Persistence: Are Adrenergic Mechanisms Involved?

Article *in* Behavioral Neuroscience · October 2012

DOI: 10.1037/a0029861 · Source: PubMed

5 authors, including:

Gustavo Morrone Parfitt
Fred Hutchinson Cancer Research Center
12 PUBLICATIONS **65** CITATIONS
SEE PROFILE

André Peres Koth
Universidade Federal do Rio Grande (FURG)
3 PUBLICATIONS **39** CITATIONS
SEE PROFILE

Daniela M Barros
Universidade Federal do Rio Grande (FURG)
96 PUBLICATIONS **3,205** CITATIONS
SEE PROFILE

Behavioral Neuroscience
2012, Vol. 126, No. 5, 729–734

0735-7044/12/$12.00 DOI: 10.1037/a0029861

Moderate Stress Enhances Memory Persistence: Are Adrenergic Mechanisms Involved?

Gustavo Morrone Parfitt, Ândrea Kraemer Barbosa, Renan Costa Campos, André Peres Koth, and Daniela Martí Barros
Universidade Federal do Rio Grande

Memory persistence in the inhibitory avoidance (IA) task has been recently shown to require a new event of consolidation 12 hr after acquisition. The immobilization stress (IS) model is largely used to study the effects of stress on memory. In this study we investigated the interactions between stress by immobilization and its effect on the persistence of memory, and also a possible effect mediated by β-adrenergic modulation of stress on memory persistence. An enhancement of long-term memory (LTM) persistence caused by stress through immobilization applied 12 hr after IA training was observed when the animals were submitted to 15 min or 1 hr of IS, but not to 3 hr. The reversal of this memory enhancement caused by IS was observed when the β-adrenergic antagonist propranolol was infused intraperitoneally prior to stress, which implies that β-adrenergic receptors are involved in stress enhancement of LTM persistence.

Keywords: stress, inhibitory avoidance, memory persistence, propranolol

Long-term memory (LTM) requires an initial event of acquisition, undergoing a consolidation process in multiple areas of the brain such as the hippocampus in order to be stored and last for hours, days, or even years. The storage of the traces of LTM is a dynamic process that occurs over its consolidation (Izquierdo, & Medina, 1997; Kandel, 2001; Medina, Bekinschtein, Cammarota, & Izquierdo, 2008). Early studies demonstrated that cortical areas become more active some time after the learning process, probably playing a role in the maintenance of memory trace, while hippocampal activity gradually decreases over time (Bontempi, Laurent-Demir, Destrade, & Jaffard, 1999; Burwell, Bucci, Sanborn, & Jutras, 2004; Frankland, Bontempi, Talton, Kaczmarek, & Silva, 2004). In spite of that, Riedel and collaborators (1999) observed that hippocampal activity is still necessary during the days following acquisition for the memory to be maintained (Riedel et al., 1999).

Recently, a new role for the hippocampus in the maintenance of memory traces was addressed by Bekinschtein and collaborators (2007), who have pointed out a crucial moment for the persistence of memory 12 hr after acquisition. Surprisingly, pharmacological manipulations in the hippocampus during this time point leave LTM formation unaltered, as tested 2 days after acquisition, but leads to impairments on remote memory as tested 7 days post-training. In this late phase, a new event of protein synthesis is required for the establishment of remote memory; brain-derived neurotrophic factor (BDNF) is one of the most crucial proteins for this event. Increased phosphorylation of mitogen-activated protein kinases (MAPKs) and ERK[1/2] is also observed 12 hr postlearning, as well as an increase on the levels of the transcription factors zif268 and c-Fos occurring 24 hr after training (Bekinschtein, et al., 2007; Bekinschtein et al., 2008).

The main physiological consequence for animals subjected to stressful events is the activation of both the amygdala and the hypothalamic–pituitary–adrenal axis (HPA). The activation of the latter causes the release of the stress hormones epinephrine and corticosterone by the adrenal glands (de Kloet, Joëls, & Holsboer, 2005; Herman & Cullinan, 1997). Epinephrine then binds to β-adrenergic receptors on the vagus nerve, which has efferents to the nucleus of solitary tract (NST), leading to an increased norepinephrine influx from NST to the basolateral amygdala nucleus (BLA). Parallel to this event, corticosterone acts in glucocorticoid receptors (GR), enhancing the release of norepinephrine from the NST to BLA, and also reinforcing the related signaling cascade mediated by β-adrenergic receptors (review by McGaugh, & Roozendaal, 2002; Roozendaal, 2002).

Stress can differently influence the stages of memory. For instance, when a GR agonist is administered just before retrieval, an amnestic effect is observed, thus implying inhibition. Conversely, the administration of dexamethasone or epinephrine just before the acquisition of memory enhances the consolidation of LTM. It has been demonstrated that the activation of the noradrenergic neuronal pathways from NST underlies an elevation of the amygdalar modulation on the hippocampus. Hence these

Gustavo Morrone Parfitt, Ândrea Kraemer Barbosa, Renan Costa Campos, André Peres Koth, and Daniela Martí Barros, Laboratório de Neurociências, Instituto de Ciências Biológicas, Universidade Federal do Rio Grande (FURG), Rio Grande, Brazil, and Programa de Pós-graduação em Ciências Fisiológicas, Fisiologia Animal Comparada, FURG, Rio Grande, Brazil.

This study was supported by research grants from the Brazilian National Research Council (CNPq). Daniela Martí Barros is research fellow from CNPq, and Gustavo Morrone Parfitt received a graduate fellowship from CNPq.

Correspondence concerning this article should be addressed to Daniela Martí Barros, Laboratório de Neurociências, Instituto de Ciências Biológicas, Universidade Federal do Rio Grande, Av Itália, Km 8, Rio Grande, RS, 96210-900, Brazil. E-mail: barrosdm@yahoo.com.br

events are primarily responsible for the aforementioned facilitation of LTM consolidation (Izquierdo, Dalmaz, Dias, & Godpy, 1988; Martí Barros et al., 2001; Roozendaal, 2002).

In this study we investigated the interactions between the effects of stress by immobilization on the persistence of memory. Also, we analyzed a possible effect mediated by the β-adrenergic modulation of stress on memory persistence. For this purpose, we administered treatments 12 hr after inhibitory avoidance (IA) training and then had the animals tested 2 or 7 days afterward. To study the influence of stress by immobilization on memory, we immobilized the animals for three different time lapses, namely 15 min, 1 hr, or 3 hr. The participation of β-adrenergic receptors was also verified by the systemic administration of the β-adrenergic antagonist propranolol. Impairments on memory retention observed only 7 days after the training session caused by the administration of the treatment, together with no alterations on memory formation, as measured 2 days after training, demonstrate the involvement of this treatment on memory persistence performance.

Method

Subjects

Male Wistar rats ($n = 170$) (age 2–3 months; weight, 250–280 g) were obtained from a breeding colony of Universidade Federal do Rio Grande (RS, Brazil). The animals were kept in groups of five in each cage, with a 12-hr light/dark cycle, at a temperature of 22°C ± 1°C, with food and water ad libitum. The study followed all the ethical recommendations of the Colégio Brasileiro de Experimentação Animal (COBEA).

Stress Model Procedure and Treatments

The procedures of stress through immobilization were carried out with a 25 × 7 cm plastic tube with an anterior orifice for respiration, sealed with plaster tape on the outside for adjustment to the animal size, so movements were restricted (Fontella et al., 2004). The animals were maintained under movement restriction for 15 min, 1 hr, or 3 hr. In a second series of experiments, the animals were given an IP injection of a β-adrenergic blocker propranolol infusion (25 mg/kg, IP), while the control group received an IP injection of saline. For the reversal experiment, a group submitted to stress for 1 hr received an IP injection of saline or propranolol prior to the stress session. All the treatments were performed 12 hr after the training session in IA.

Behavioral and Statistical Procedures

Inhibitory avoidance (IA). After a week of acclimation, the animals were handled for 3 days to avoid neophobia and then submitted to a one-trial step-down inhibitory avoidance (IA) task. The IA apparatus consists of an acrylic box (50 × 25 × 25 cm), with the floor consisting of parallel stainless steel bars spaced 1.0 cm apart and a 5-cm-wide platform located slightly above the steel bars. On the training section, each animal was placed over the platform, and immediately after stepping down with its four paws on the steel floor, the animal received three 0.7-mA foot shocks, lasting 1 s each, except for the nonshock groups. In the test session no footshock was applied, and the step-down latency was interrupted at 180 s; that is, values equal to or higher than 180 s were counted as 180 s. These data required the use of nonparametric statistics (Kruskal–Wallis analyses of variance followed by Mann–Whitney U test; $p < .05$ was considered to indicate statistical significance). Memory retention was tested 2 or 7 days posttraining; different groups of animals were tested on the 2nd or 7th days to avoid extinction of memory (Bekinschtein et al., 2007).

Elevated plus maze. The animals were also submitted to the elevated plus-maze (EPM) task, 2 or 7 days after the treatments, to determine whether the treatments affected mobility, locomotion, or caused pro- or anticonflict behaviors (Martí Barros, Ramirez, Dos Reis, & Izquierdo, 2004). The EPM apparatus consists of a central platform with two open arms and two enclosed arms in a cross shape. Both open and enclosed arms are in opposition to each other. The maze is located 70 cm above floor level, and tests were carried out under a dim red light. In this test the animals were placed individually on the central platform, and the time spent on the open arms and the total number of entries was recorded during 5 min (de Aguiar et al., 2006). Parametric statistical tests were used. Statistical differences were tested through an analysis of variance (ANOVA) test, followed by the Newman–Keuls posttest. In all comparisons, $p < .05$ was considered to indicate statistical significance.

Results

Training session step-down differences among all groups were not significant in the Kruskal–Wallis analyses of variance (data not shown) ($p = .4532$). Overall median (interquartile range) training session latency was 8.5 (6/12) s.

Stress through immobilization for either 15 min or 1 hr, when carried out 12 hr after the IA training, elicited significant effects on the memory persistence test as shown in Figure 1A. The group stressed for 15 min demonstrated an enhancement of memory 7 days after training ($p = .0042$, $n = 7$–10, Mann–Whitney test), but not 2 days after acquisition of IA. When the stress was induced for 1 hr, the persistence of memory tested 7 days after the training was also improved ($p = .0076$, $n = 10$–12, Mann–Whitney test), and this effect was not observed on the test carried out 2 days after training. However, the group immobilized for 3 hr did not show memory alterations either at the 2nd-day test or at the 7th-day test. In the 7th-day test, a significant difference between the 3-hr group versus 15-min and 1-hr groups was observed ($p < .005$, $n = 7$–12, Mann–Whitney test). The nonshock groups were tested only 7 days after the training, and no differences among them or versus their respective training groups were observed ($p = .9034$. $n = 6$–7, Kruskal–Wallis analyses of variance).

Figure 1B shows the results of the groups submitted to IP infusion of the β-adrenergic blocker propranolol (25 mg/kg) 12 hr after training. The group treated with propranolol presented normal memory formation on the 2nd-day test ($p = .8421$, $n = 10$, Mann–Whitney test); however, when tested 7 days after the IA training, an impaired memory retention was observed ($p = .0030$, $n = 10$, Mann–Whitney test).

Figure 1C shows the results obtained from the groups submitted to IP infusions of propranolol immediately before the 1-hr immobilization stress. The aim of this infusion was to reverse the previously observed facilitation of memory retention on the 7th-day test (Figure 1A). The propranolol/stress group showed a sig-

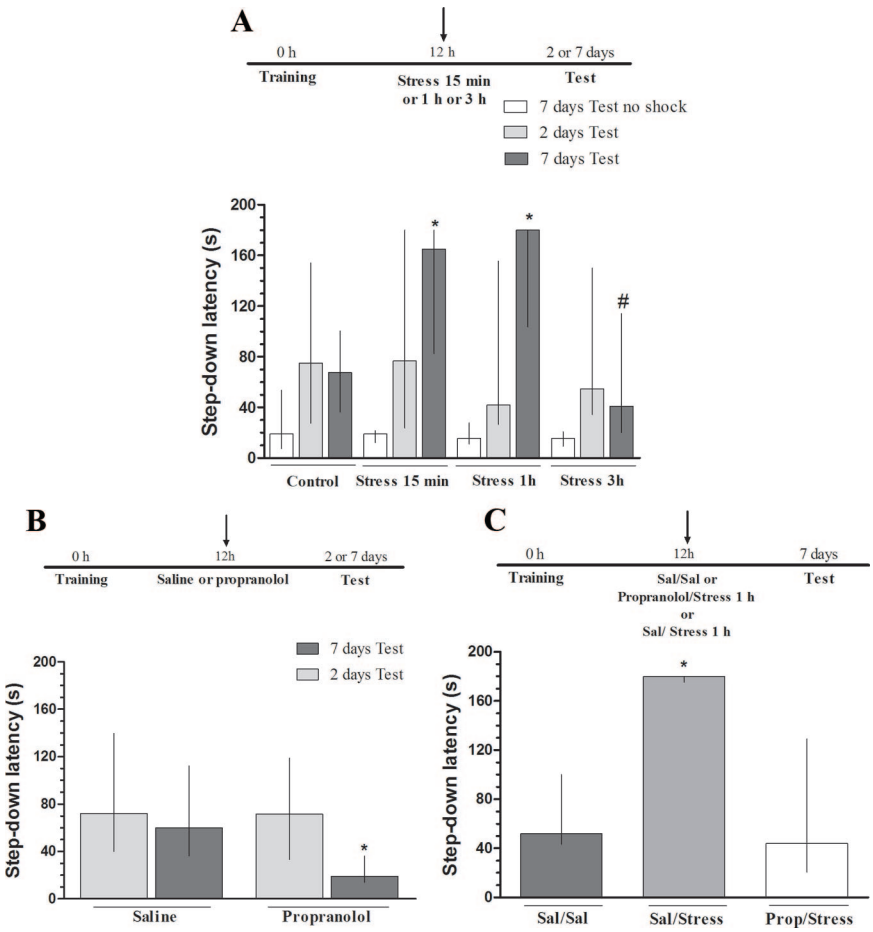

Figure 1. (A) Stress for 15 min or 1 hr, but not 3 hr, enhances memory persistence in inhibitory avoidance (IA). Stress through immobilization, for 15 min or 1 hr, performed 12 hr after learning enhances memory persistence at 7 days, but spares memory formation 2 days after training in IA. * $p < 0.05$, $n = 10$–12; vs. control at 7 days. Three hours of stress performed 12 hr after learning showed no effects on memory at 2 or 7 days. $^{\#}$ $p < 0.05$, $n = 10$–12; vs. stress 15 min and 1 hr at 7 days. The nonshock groups, represented by open bars, did not show differences versus respective nonshock control. (B) Propranolol IP infusions 12 hr after the acquisition on IA task show memory persistence impairment of animals tested on the 7th day but did not alter memory formation as observed on animals tested on the 2nd day after training. * $p < 0.05$, $n = 10$; vs. control tested at 7th day. (C) Propranolol (Prop) injections immediately before 1 hr stress at 12 hr after training reverted memory facilitation caused by 1 hr of immobilization stress and showed no difference when compared with saline (Sal) control group. * $p < 0.05$, $n = 10$; vs. control and Prop/Stress groups. Data are expressed as median and interquartile ranges (25/75).

nificant difference from the stress 1-hr group ($p = .0250$, $n = 10$, Mann–Whitney test), and no difference from the control group, while the saline/stress group demonstrated memory facilitation ($p = .4698$, $n = 7$–10, Mann–Whitney test). Moreover, propranolol/stress group showed no difference from the control group ($p = .4698$, $n = 7$–10, Mann–Whitney test).

The plus maze test was used to assess possible interference of the treatments on IA memory retrieval that might have induced alterations in locomotion or anxiety. It was performed 2 or 7 days after the IP infusion as seen in Table 1. There were no alterations in the percentage of time spent on open arms or in the total of entries among groups ($p > .05$ on one-way analysis of variance, with no posttest significance on Newman–Keuls multiple comparison test).

Discussion

The findings in this report demonstrated an enhancement of LTM persistence caused by stress through immobilization, 12 hr after IA training, with dependence on the exposure time. These data corroborate previous findings by Bekinschtein and collaborators (2007), which point the time window of 12 hr after IA training as crucial for memory persistence in the hippocampus (Bekinschtein et al., 2007). Moreover, it was observed that 15 min or 1 hr, but not 3 hr, of stress enhances memory persistence, not interfering in memory formation. Exposure time dependence was demonstrated, because no enhancement on memory persistence was observed in the group submitted to 3 hr of immobilization, which also was significantly different from the groups stressed for 15 min and

Table 1
Effects on Elevated Plus-Maze Task Performed 2 or 7 Days After Training

Treatment	Total entries	% time open arms
Control 2 days	13.0 ± 0.5	32.0 ± 3.7
Control 7 days	10.4 ± 1.0	43.1 ± 6.6
Control nonshocked	11.6 ± 1.1	44.2 ± 7.1
Stress 15 min 2 days	12.2 ± 1.5	42.5 ± 4.3
Stress 15 min 7 days	12.4 ± 2.4	41.6 ± 4.7
Stress 15 min nonshocked	11.8 ± 1.7	39.4 ± 6.4
Stress 1 h 2 days	9.2 ± 1.4	33.0 ± 5.6
Stress 1 h 7 days	11.0 ± 1.6	35.6 ± 3.6
Stress 1 h nonshocked	11.6 ± 1.5	37.8 ± 5.3
Stress 3 h 2 days	13.2 ± 1.0	40.6 ± 4.5
Stress 3 h 7 days	13.6 ± 1.3	42.3 ± 3.2
Stress 3 h nonshocked	10.2 ± 1.2	42.5 ± 5.1
Saline 2 days	11.4 ± 1.5	43.2 ± 3.7
Saline 7 days	12.6 ± 2.1	36.5 ± 3.0
Propranolol 2 days	11.2 ± 2.2	41.8 ± 5.2
Propranolol 7 days	9.0 ± 1.8	39.4 ± 7.2

Note. There were no alterations in percentage of time spent on open arms or total of entries among groups. Data are expressed as mean and standard error of the mean.

1 hr. Also, the nonshock groups did not learn the IA task, and the stress per se was unable to alter the innate step-down/exploratory behavior.

The immobilization stress model is largely used to study the effects of stress on memory. In this stress model, ACTH and corticosterone levels are rapidly elevated at 1 hr and remain high for at least 3 hr, while a rapid increase in plasma epinephrine concentration is also observed (Marmigère, Givalois, Rage, Arancibia, & Tapia-Arancibia, 2003; Rage, Givalois, Marmigère, Tapia-Arancibia, & Arancibia, 2002; Tajima et al., 1996). In addition, stress through immobilization induces the release of NE in the prefrontal cortex, central nucleus of the amygdala, and hippocampus, and also induces the transcription of enzymes involved in the biosynthesis of NE in the locus coeruleus (LC) (Khoshbouei, Cecchi, Dove, Javors, & Morilak, 2002; Serova et al., 1999; Smagin, Zhou, Harris, & Ryan, 1997).

The effects of stress on memory consolidation were previously evidenced through the demonstration that low doses of glucocorticoids and the GR agonist dexamethasone, when administered immediately after training, enhance memory formation. The involvement of basolateral (BLA) and medial (MEA) amygdalar nuclei in this enhancement has also been observed (Cordero, & Sandi, 1998; Hui et al., 2004; Roozendaal & McGaugh, 1996). However, glucocorticoids affect memory consolidation with an inverted-U-shaped dose response, meaning that high stimulation of GR receptors causes memory impairments (Conrad, Lupien, & McEwen, 1999; Quirarte, Roozendaal, & McGaugh, 1997; Yau, Olsson, Morris, Meaney, & Seckl, 1995). This goes with the observation that the stress caused by 3 hr of immobilization does not elicit the same effect as when it is caused by 15 min or 1 hr, as the rats undergo a longer period of time exposed to high levels of corticosterone. This longer period seems to hinder the enhancement observed with 1 hr of induced stress exposure, thus characterizing the inverted-U-shaped dose response. Reports also showed that the stress caused by 1 hr of immobilization enhances memory acquisition and consolidation, as well as LTP induction (Blank, Nijholt, Eckart, & Spiess, 2002; Nijholt et al., 2004). Moreover, Marmigere and colleagues observed a rapid increase in BDNF levels on the CA1 region 15 and 60 min after immobilization stress (Marmigère, F., Givalois, L., Rage, F., Arancibia, S., & Tapia-Arancibia, L. (2003)). This increase may underlie the enhancement of the stress-induced persistence of memory observed in the aforementioned work, since BDNF is reported to be a crucial protein for this process (Bekinschtein et al., 2008) and its blockade with specific antibody at 12 hr posttraining impairs LTM persistence (Bekinschtein et al., 2007).

In this work we have observed an adrenergic modulation of memory persistence through the administration of propranolol 12 hr after IA training. We also observed the participation of β-adrenergic receptors on LTM persistence at the crucial time point of 12 hr after IA, with no interference on memory formation. These β-adrenergic receptors also appear to be involved in the acquisition of memory when tested in active place avoidance, with participation of the hippocampus in the late phase of consolidation, 3 and 6 hr after IA training (Izquierdo et al., 2006; Stuchlik, Petrasek, & Vales, 2009), and in the retrieval in IA task (Martí Barros et al., 2001). Studies demonstrated that footshocks elevated the release of NE to the amygdala, and this effect is potentiated by peripheral injections of epinephrine (Ferry, Roozendaal, & McGaugh, 1999). Moreover, Katche and collaborators (2010) demonstrated that NE infusions at 12 hr on the CA1 region of the hippocampus induces memory to persist and regulates late c-Fos induction in this region (Katche et al., 2010). The involvement of catecholamines, such as NE, in the late induction of c-Fos caused by the persistent memory provided by strong IA training may be the main correlate on the literature that sustains the participation of β-adrenergic receptors on LTM persistence. In addition, acute stress through immobilization induces c-Fos expression in the hippocampus, while a systemic propanolol injection abolishes stress-induced c-Fos expression on CNS (Herdegen & Leah, 1998; Melia, Ryabinin, Schroeder, Bloom, & Wilson, 1994).

We next investigated the adrenergic implications of stress enhancement on memory persistence. A reversal of this stress enhancement was observed when β-adrenergic antagonist propranolol was injected prior to stress, which implies that β-adrenergic receptors are involved in stress enhancement of LTM persistence. An increase of epinephrine levels in the plasma of animals submitted to stress by immobilization has been reported, and it seems to be related to the enhancement of memory consolidation with systemic epinephrine injections (Ferry et al., 1999; Tajima et al., 1996). This enhancement is hindered by the β-adrenergic blocker propranolol, as well as with the β-adrenergic antagonist sotalol, which does not cross blood–brain barrier when administered systemically (Ferry et al., 1999). Furthermore, β-adrenergic antagonists—propranolol, atenolol, and zinterol, when infused in the BLA—block the enhancement of memory by glucocorticoids (Quirarte et al., 1997). Thus, in this work, we suggest that propranolol injections block both peripheral and central β-adrenergic receptors and then block the enhancement of epinephrine-induced NE release to the amygdala. Also, the injection of propranolol hinders NE-related glucocorticoid effects through the blockage of β-adrenergic receptors in the BLA, which was recently implicated in memory persistence (Ou, Yeh, & Gean, 2010). As a result, it

impedes stress-induced amygdalar modulation in the hippocampus and thus on the memory persistence.

In conclusion, these findings suggest that moderate stress facilitates the persistence of memory and that β-adrenergic receptors are involved in this enhancement. Furthermore, it is suggested that β-adrenergic receptors themselves participate in the process of memory persistence.

References

Bekinschtein, P., Cammarota, M., Igaz, L. M., Bevilaqua, L. R. M., Izquierdo, I., & Medina, J. H. (2007). Persistence of long-term memory storage requires a late protein synthesis- and BDNF-dependent phase in the hippocampus. *Neuron, 53,* 261–277. doi:10.1016/j.neuron.2006.11.025

Bekinschtein, P., Katche, C., Slipczuk, L., Rossato, J. I., Goldin, A., Izquierdo, I., & Medina, J. H. (2008). BDNF is essential to promote persistence of long-term memory storage. *Proceedings of the National Academy of Sciences of the United States of America, 105,* 0–5. doi: www.pnas.org/cgi/doi/10.1073/pnas.0711863105

Blank, T., Nijholt, I., Eckart, K., & Spiess, J. (2002). Priming of long-term potentiation in mouse hippocampus by corticotropin-releasing factor and acute stress: Implications for hippocampus-dependent learning. *Journal of Neuroscience, 22,* 3788–3794.

Bontempi, B., Laurent-Demir, C., Destrade, C., & Jaffard, R. (1999). Time-dependent reorganization of brain circuitry underlying long-term memory storage. *Nature, 400,* 671–675.

Burwell, R. D., Bucci, D. J., Sanborn, M. R., & Jutras, M. J. (2004). Perirhinal and postrhinal contributions to remote memory for context. *The Journal of Neuroscience, 24,* 11023–11028.

Conrad, C. D., Lupien, S. J., & McEwen, B. S. (1999). Support for a bimodal role for type II adrenal steroid receptors in spatial memory. *Neurobiology of Learning and Memory, 72,* 39–46. doi:10.1006/nlme.1998.3898

Cordero, M. I., & Sandi, C. (1998). A role for brain glucocorticoid receptors in contextual fear conditioning: Dependence upon training intensity. *Brain Research, 786,* 11–17. doi:10.1016/S0006-8993(97)01420-0

de Aguiar, R. B., Dickel, O. E., Cunha, R. W., Monserrat, J. M., Martí Barros, D., & Martinez, P. E. (2006). Estradiol valerate and tibolone: Effects on memory. *Pharmacology, Biochemistry, and Behavior, 85,* 689–696. doi:10.1016/j.pbb.2006.10.023

de Kloet, E. R., Jöels, M., & Holsboer, F. (2005). Stress and the brain: From adaptation to disease. *Nature Reviews Neuroscience, 6,* 463–475. doi:10.1038/nrn1683

Ferry, B., Roozendaal, B., & McGaugh, J. L. (1999). Role of norepinephrine in mediating stress hormone regulation of long-term memory storage: A critical involvement of the amygdala. *Biological Psychiatry, 46,* 1140–1152. doi:10.1016/S0006-3223(99)00157-2

Fontella, F. U., Bruno, A. N., Crema, L. M., Battastini, A. M. O., Sarkis, J. J. F., Netto, C. A., & Dalmaz, C. (2004). Acute and chronic stress alter ecto-nucleotidase activities in synaptosomes from the rat hippocampus. *Pharmacology, Biochemistry, and Behavior, 78,* 341–347. doi:10.1016/j.pbb.2004.04.005

Frankland, P. W., Bontempi, B., Talton, L. E., Kaczmarek, L., & Silva, A. J. (2004). The involvement of the anterior cingulate cortex in remote contextual fear memory. *Science* (New York, N.Y.), *304,* 881–883.

Herdegen, T., & Leah, J. D. (1998). Inducible and constitutive transcription factors in the mammalian nervous system: Control of gene expression by Jun, Fos and Krox, and CREB/ATF proteins. *Brain Research Reviews, 28,* 370–490. doi:10.1016/S0165-0173(98)00018-6

Herman, J. P., & Cullinan, W. E. (1997). Neurocircuitry of stress: Central control of the hypothalamo–pituitary–adrenocortical axis. *Trends in Neurosciences, 20,* 78–84. doi:10.1016/S0166-2236(96)10069-2

Hui, G. K., Figueroa, I. R., Poytress, B. S., Roozendaal, B., McGaugh, J. L., & Weinberger, N. M. (2004). Memory enhancement of classical fear conditioning by post-training injections of corticosterone in rats. *Neurobiology of Learning and Memory, 81,* 67–74. doi:10.1016/j.nlm.2003.09.002

Izquierdo, I., Bevilaqua, L. R. M., Rossato, J. I., Bonini, J. S., Medina, J. H., & Cammarota, M. (2006). Different molecular cascades in different sites of the brain control memory consolidation. *Trends in Neurosciences, 29,* 496–505. doi:10.1016/j.tins.2006.07.005

Izquierdo, I., Dalmaz, C., Dias, R. D., & Godpy, M. G. C. (1988). Memory facilitation by posttraining and pretest ACTH, epinephrine, and vasopressin administration: Two separate effects. *Behavioral Neuroscience, 102,* 803–806. doi:10.1037/0735-7044.102.5.803

Izquierdo, I., & Medina, J. H. (1997). Memory formation: The sequence of biochemical events in the hippocampus and its connection to activity in other brain structures. *Neurobiology of Learning and Memory, 68,* 285–316. doi:10.1006/nlme.1997.3799

Kandel, E. R. (2001). The molecular biology of memory storage: A dialogue between genes and synapses. *Science, 294,* 1030–1038. doi:10.1126/science.1067020

Katche, C., Bekinschtein, P., Slipczuk, L., Goldin, A., Izquierdo, I. A., Cammarota, M., & Medina, J. H. (2010). Delayed wave of c-Fos expression in the dorsal hippocampus involved specifically in persistence of long-term memory storage. *Proceedings of the National Academy of Sciences of the United States of America, 107,* 349–354. doi:10.1073/pnas.0912931107

Khoshbouei, H., Cecchi, M., Dove, S., Javors, M., & Morilak, D. A. (2002). Behavioral reactivity to stress: Amplification of stress-induced noradrenergic activation elicits a galanin-mediated anxiolytic effect in central amygdala. *Pharmacology, Biochemistry, and Behavior, 71,* 407–417. doi:10.1016/S0091-3057(01)00683-9

Marmiġere, F., Givalois, L., Rage, F., Arancibia, S., & Tapia-Arancibia, L. (2003). Rapid induction of BDNF expression in the hippocampus during immobilization stress challenge in adult rats. *Hippocampus, 13,* 646–655. doi:10.1002/hipo.10109

Martíi Barros, D., Mello e Souza, T., De David, T., Choi, H., Aguzzoli, A., Madche, C., & Izquierdo, I. (2001). Simultaneous modulation of retrieval by dopaminergic D(1), beta-noradrenergic, serotonergic-1A and cholinergic muscarinic receptors in cortical structures of the rat. *Behavioural Brain Research, 124,* 1–7. doi:10.1016/S0166-4328(01)00208-X

Martí Barros, D., Ramirez, M. R., Dos Reis, E. A., & Izquierdo, I. (2004). Participation of hippocampal nicotinic receptors in acquisition, consolidation and retrieval of memory for one trial inhibitory avoidance in rats. *Neuroscience, 126,* 651–656. doi:10.1016/j.neuroscience.2004.03.010

McGaugh, J. L., & Roozendaal, B. (2002). Role of adrenal stress hormones in forming lasting memories in the brain. *Current Opinion in Neurobiology, 12,* 205–210. doi:10.1016/S0959-4388(02)00306-9

Medina, J. H., Bekinschtein, P., Cammarota, M., & Izquierdo, I. (2008). Do memories consolidate to persist or do they persist to consolidate? *Behavioural Brain Research, 192,* 61–69.

Melia, K. R., Ryabinin, A. E., Schroeder, R., Bloom, F. E., & Wilson, M. C. (1994). Induction and habituation of immediate early gene expression in rat brain by acute and repeated restraint stress. *Journal of Neuroscience, 14,* 5929–5938.

Nijholt, I., Farchi, N., Kye, M., Sklan, E. H., Shoham, S., Verbeure, B., & Blank, T. (2004). Stress-induced alternative splicing of acetylcholinesterase results in enhanced fear memory and long-term potentiation. *Molecular Psychiatry, 9,* 174–183. doi:10.1038/sj.mp.4001446

Ou, L.-C., Yeh, S.-H., & Gean, P.-W. (2010). Late expression of brain-derived neurotrophic factor in the amygdala is required for persistence of fear memory. *Neurobiology of Learning and Memory, 93,* 372–382. doi:10.1016/j.nlm.2009.12.003

Quirarte, G. L., Roozendaal, B., & McGaugh, J. L. (1997). Glucocorticoid enhancement of memory storage involves noradrenergic activation in the

basolateral amygdala. *Proceedings of the National Academy of Sciences of the United States of America, 94,* 14048–14053. doi:10.1073/pnas.94.25.14048

Rage, F., Givalois, L., Marmigère, F., Tapia-Arancibia, L., & Arancibia, S. (2002). Immobilization stress rapidly modulates BDNF mRNA expression in the hypothalamus of adult male rats. *Neuroscience, 112,* 309–318. doi:10.1016/S0306-4522(02)00072-6

Riedel, G., Micheau, J., Lam, A. G., Roloff, E. L., Martin, S. J., Bridge, H., . . . Morris, R. G. M. (1999). Reversible neural inactivation reveals hippocampal participation in several memory processes. *Nature Neuroscience, 2,* 898–905.

Roozendaal, B. (2002). Stress and memory: Opposing effects of glucocorticoids on memory consolidation and memory retrieval. *Neurobiology of Learning and Memory, 78,* 578–595. doi:10.1006/nlme.2002.4080

Roozendaal, B., & McGaugh, J. L. (1996). Amygdaloid nuclei lesions differentially affect glucocorticoid-induced memory enhancement in an inhibitory avoidance task. *Neurobiology of Learning and Memory, 65,* 1–8. doi:10.1006/nlme.1996.0001

Serova, L. I., Nankova, B. B., Feng, Z., Hong, J. S., Hutt, M., & Sabban, E. L. (1999). Heightened transcription for enzymes involved in norepinephrine biosynthesis in the rat locus coeruleus by immobilization stress. *Biological Psychiatry, 45,* 853–862. doi:10.1016/S0006-3223(98)90360-2

Smagin, G. N., Zhou, J., Harris, R. B. S., & Ryan, D. H. (1997). CRF receptor antagonist attenuates immobilization stress-induced norepinephrine release in the prefrontal cortex in rats. *Brain Research Bulletin, 42,* 431–434. doi:10.1016/S0361-9230(96)00368-1

Stuchlik, A., Petrasek, T., & Vales, K. (2009). A dose-response study of the effects of pre-test administration of beta-adrenergic receptor antagonist propranolol on the learning of active place avoidance, a spatial cognition task, in rats. *Behavioural Brain Research, 200,* 144–149. doi:10.1016/j.bbr.2009.01.010

Tajima, T., Endo, H., Suzuki, Y., Ikari, H., Gotoh, M., & Iguchi, A. (1996). Immobilization stress-induced increase of hippocampal acetylcholine and of plasma epinephrine, norepinephrine and glucose in rats. *Brain Research, 720,* 155–158. doi:10.1016/0006-8993(96)00046-7

Yau, J. L., Olsson, T., Morris, R. G., Meaney, M. J., & Seckl, J. R. (1995). Glucocorticoids, hippocampal corticosteroid receptor gene expression and antidepressant treatment: Relationship with spatial learning in young and aged rats. *Neuroscience, 66,* 571–581. doi:10.1016/0306-4522(94)00612-9

Received May 19, 2011
Revision received July 30, 2012
Accepted July 31, 2012 ■