Role of the Basolateral Amygdala in Memory Consolidation

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ABSTRACT: Memories of emotionally arousing events tend to be more vivid and to persist longer than do memories of neutral or trivial events. Moreover, memories of emotionally influenced information may endure after a single experience. Recent findings strongly suggest that the influence of emotional arousal on memory consolidation is mediated by the release of adrenal stress hormones (epinephrine and glucocorticoids) and neurotransmitters that converge in modulating the noradrenergic system within the amygdala. Considerable evidence also indicates that amygdala activation influences memory by regulating consolidation in other brain regions. The findings suggest further that this memory-modulatory system may be involved in the formation of traumatic memories and posttraumatic stress disorder in human subjects.

KEYWORDS: long-term memory; norepinephrine; stress hormones; glucocorticoids; acetylcholine; memory modulation; epinephrine

ADRENERGIC EFFECTS ON MEMORY CONSOLIDATION

It has long been known that emotionally arousing experiences activate the release of epinephrine from the adrenal medulla. Gold and van Buskirk's report[1] that post-training systemic injections of epinephrine enhanced retention of inhibitory avoidance training was the first to provide evidence suggesting that this stress-released hormone influences memory consolidation. This finding suggested that the consolidation of memories over time following learning may have an important adaptive role in enabling endogenous processes activated by experience to modulate memory consolidation and thus regulate memory strength.[2] Subsequent findings indicating that adrenalectomy, or selective removal of the adrenal medulla, impaired retention performance in rats[3–5] provided additional evidence suggesting that endogenous arousal-related release of adrenal stress hormones influences the storage of long-term memories for emotionally significant experiences.

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Ann. N.Y. Acad. Sci. 985: 273–293 (2003).

Although epinephrine must ultimately affect memory consolidation through actions on the brain, it does not readily cross the blood-brain barrier.[6] The finding that systemic administration of sotalol, a peripherally acting β-adrenoceptor antagonist, blocks epinephrine-induced memory enhancement[7] indicates that epinephrine's effects on memory consolidation are initiated by activation of peripheral β-adrenoceptors. The evidence that β-adrenoceptors are located on vagal afferents to the nucleus of the solitary tract (NTS) in the brain stem[8] suggests that systemic epinephrine may modulate neural processes through actions mediated by the NTS. Several findings support this suggestion. Temporary inactivation of the NTS with lidocaine immediately after training impairs retention on an inhibitory avoidance task[9] and blocks the memory-enhancing effects of systemic posttraining injections of epinephrine.[10] As will be discussed, the influence of the NTS on the amygdala is critically involved in epinephrine regulation of memory consolidation.

Shortly after Gold and van Buskirk reported that posttraining systemic administration of epinephrine enhanced memory consolidation, Gallagher and colleagues[11,12] found that β-adrenoceptor antagonism within the amygdala immediately after inhibitory avoidance training impaired retention performance and that concurrent administration of norepinephrine attenuated the impairment. Subsequent findings indicated that posttraining infusions of the β-adrenoceptor antagonist propranolol administered into the amygdala also blocked the memory enhancement induced by systemic administration of epinephrine and that posttraining infusions of norepinephrine into the amygdala enhanced retention and attenuated the impairment induced by adrenal demedullation.[13]

These findings very strongly suggest that noradrenergic activation in the amygdala plays a critical role in mediating epinephrine-induced memory enhancement. Extensive evidence now indicates that noradrenergic projections from the NTS to the amygdala are critically involved in mediating adrenergic influences on memory consolidation.[14–16] The NTS may also influence activation of the noradrenergic system in the amygdala through an indirect pathway going from the NTS to the nucleus paragigantocellularis, which in turn activates locus coeruleus (LC) neurons that project to the amygdala.[17–20] For example, infusions into the LC region of clonidine, a drug that suppresses LC activity through activation of α_2-adrenergic autoreceptors, block the memory enhancement seen with systemic injections of epinephrine, but they do not block the memory enhancement found with intra-amygdala infusions of norepinephrine.[21]

Interactions of Norepinephrine with Other Neuromodulatory Systems in the Basolateral Amygdala

Many recent findings indicate that the basolateral complex of the amygdala (BLA) is the critical region of the amygdala involved in regulating memory consolidation.[22–29] Posttraining intra-BLA infusions of norepinephrine or β-adrenoceptor agonists enhance retention of inhibitory avoidance as well as water-maze spatial training.[28,30] Moreover, selective lesions of the BLA or intra-BLA infusions of β-adrenoceptor antagonists block memory enhancement induced by a variety of drugs administered either systemically or into other brain regions.[31–33]

Although much of the research examining the role of the adrenergic system in the BLA focuses on β-adrenoceptors, the BLA also contains a high density of α-adreno-

ceptors.[34,35] Like β-adrenoceptors, α-adrenoceptors have been implicated in regulating memory consolidation processes. Selective activation of the postsynaptic α_1-adrenoceptor in the BLA dose-dependently enhances inhibitory avoidance retention performance.[27] The influence of α-adrenoceptors on memory consolidation appears to be mediated by an interaction with β-adrenoceptors in the BLA as posttraining intra-BLA infusions of the β-adrenoceptor antagonist atenolol block memory enhancement induced by selective activation of α_1-adrenoceptors.[27] Furthermore, posttraining intra-BLA infusions of the α_1-adrenoceptor antagonist prazosin shift to the right the dose-response effects on memory consolidation produced by concurrent intra-BLA infusions of the β-adrenoceptor agonist clenbuterol.[36] Although 8-Br-cAMP infusions into the BLA enhance retention in a manner similar to that found with clenbuterol, prazosin does not shift the dose-response memory enhancement induced by 8-Br-cAMP.[36] When considered together with pharmacological evidence indicating that β-adrenoceptors modulate memory storage through direct coupling to adenylate cyclase, these findings suggest that α-adrenoceptors may act indirectly on memory processing by influencing β-adrenergic-induced effects on the synthesis of cAMP.[37,38]

Several neurotransmitter systems influence memory consolidation through actions on the noradrenergic system within the amygdala or, more specifically, the BLA. Studies using several types of training tasks have found that posttraining systemic injections of GABAergic compounds modulate memory. The GABAergic antagonist picrotoxin enhances, whereas the GABAergic agonist muscimol impairs memory.[39–41] Administration of the opioid peptidergic antagonist naloxone enhances memory,[42–44] and administration of the opioid agonist β-endorphin impairs memory consolidation.[45] Importantly, 6-hydroxydopamine–induced lesions of the dorsal noradrenergic forebrain bundle block the memory-enhancing effects of systemic or intra-amygdala infusions of naloxone.[43] Additionally, lesions of the amygdala or intra-amygdala infusions of the β-adrenoceptor antagonist propranolol block memory modulation produced by systemic injections of GABAergic and opioid peptidergic drugs.[44,46,47] As will be discussed, the adrenocortical stress hormone corticosterone also influences memory consolidation by affecting noradrenergic activation of the BLA. Infusions of the synthetic glucocorticoid dexamethasone enhance memory when given posttraining, but intra-BLA infusions of the β-adrenoceptor antagonist propranolol, atenolol, or zinterol block the glucocorticoid-induced memory enhancement.[31]

Amygdala Norepinephrine Release during Aversive Stimulation and Drug Treatment

In an early study examining the relation between brain norepinephrine levels and memory, Gold and van Buskirk[48] reported evidence suggesting that the activity of norepinephrine in the brain (telencephalon, diencephalon, and brain stem) was increased in rats given a memory-enhancing dose of epinephrine immediately after training. More recent studies have examined levels of norepinephrine within the amygdala in behaving rats with the use of *in vivo* microdialysis combined with high-performance liquid chromatography (HPLC). Several studies reported that stress induced by prolonged immobilization or tail pinch increased amygdala norepinephrine levels.[49,50] Considerable evidence now also indicates that norepinephine levels in-

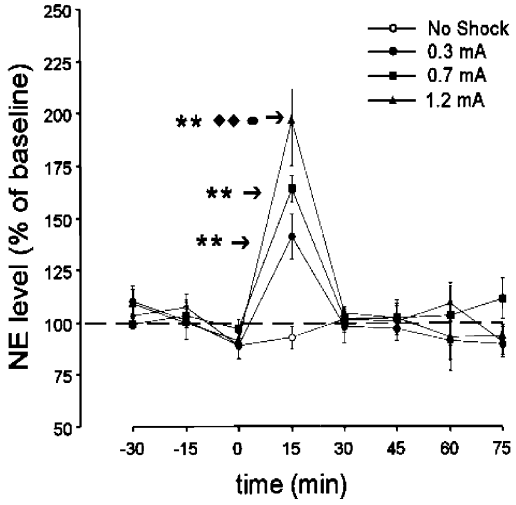

FIGURE 1. Effects of footshock intensity on amygdala norepinephrine levels as assessed by *in vivo* microdialysis and HPLC. Rats were given single 3-second footshock at an intensity of 0.3 mA, 0.7 mA, or 1.2 mA. Microdialysis samples were collected at 15-minute intervals throughout the session. Norepinephrine levels (mean ± SEM) are represented as percentage change from average basal levels prior to footshock. Amygdala norepinephrine levels immediately following footshock vary directly with stimulus intensity. $^{**}P < 0.01$ as compared to nonshock group. $^{◆◆}P < 0.01$ as compared to 0.3 mA group; $^{•}P < 0.05$ as compared to 0.7 mA group. (From Quirarte *et al*., 1998.)

crease after a single mild footshock of the kind typically used in inhibitory avoidance training.[51] Furthermore, as shown in FIGURE 1, amygdala norepinephrine levels assessed after a single footshock vary directly with stimulus intensity.[52]

As just discussed, pharmacological evidence indicates that the modulatory effects of drugs affecting several neurotransmitter systems on memory consolidation depend on β-adrenoceptor activation in the amygdala. Drugs that affect memory when administered systemically also influence norepinephrine release in the amygdala. As shown in FIGURE 2, injections of memory-enhancing doses of the opioid peptidergic antagonist naloxone significantly increase norepinephrine levels in the amygdala and potentiate the increase induced by footshock.[52] By contrast, systemic injections of β-endorphin, which impair memory consolidation,[45] reduce norepinephrine levels in the amygdala and completely block the footshock-induced increase in norepinephrine levels.[52] Similarly, systemic injections of the memory-enhancing GABAergic antagonist picrotoxin produce a large and prolonged increase in norepinephrine levels in the amygdala, even in the absence of footshock, whereas the memory-impairing GABAergic agonist muscimol decreases norepinephrine levels to 72% of mean baseline values[53] (FIG. 3). Additionally, Williams and colleagues[14] reported that systemic administration of memory-enhancing doses of epinephrine significantly increased norepinephrine levels in the amygdala. Thus, evidence from these studies indicates that memory-enhancing drugs increase levels

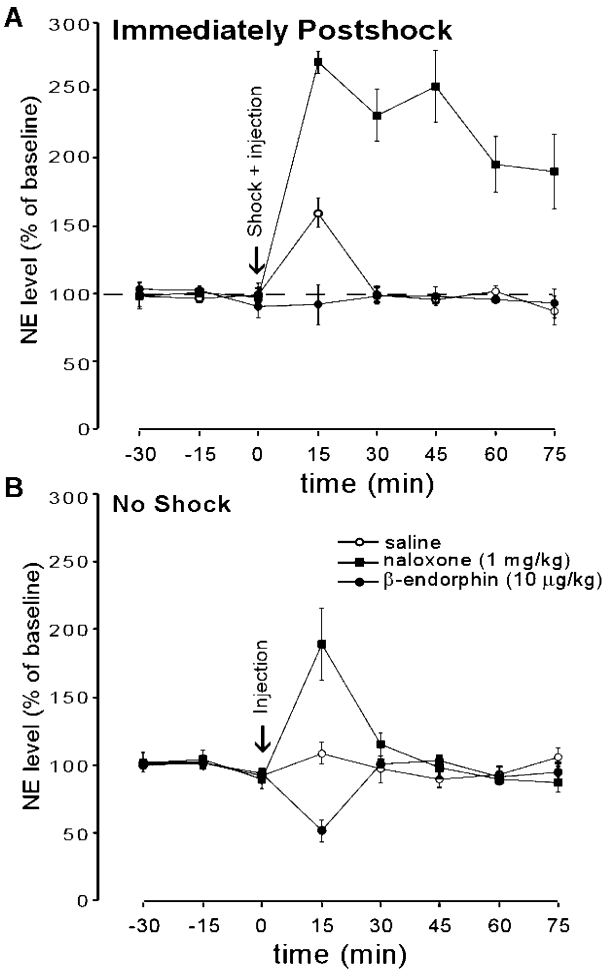

FIGURE 2. Effects of systemic injections of the opioid peptidergic naloxone and the antagonist β-endorphin on norepinephrine in release in the amygdala with (**A**) and without (**B**) footshock, as assessed by *in vivo* microdialysis and HPLC. Microdialysis samples were collected at 15-minute intervals throughout the session. Norepinephrine levels (mean ± SEM) are presented as percentage change from average basal levels prior to footshock. (**A**) Amygdala norepinephrine levels in rats receiving naloxone after footshock were greater than levels seen in saline- and β-endorphin–injected rats. Norepinephrine levels remained elevated for 75 minutes in rats receiving naloxone following footshock. Norepinephrine levels increased above baseline following footshock in saline-injected, but not β-endorphin–injected rats. (**B**) Without footshock, amygdala norepinephrine levels increased and decreased after naloxone and β-endorphin injections, respectively, compared with those seen in saline-injected rats. (From Quirarte *et al.*, 1998.)

TABLE 1. Effects of drugs on inhibitory avoidance retention and amygdala norepinephrine release

Drug	Effect on long-term memory	Effect on amygdala norepinephrine
Naloxone	Enhancement	Increase
β-endorphin	Impairment	Decrease
Picrotoxin	Enhancement	Increase
Muscimol	Impairment	Decrease
Epinephrine	Enhancement	Increase

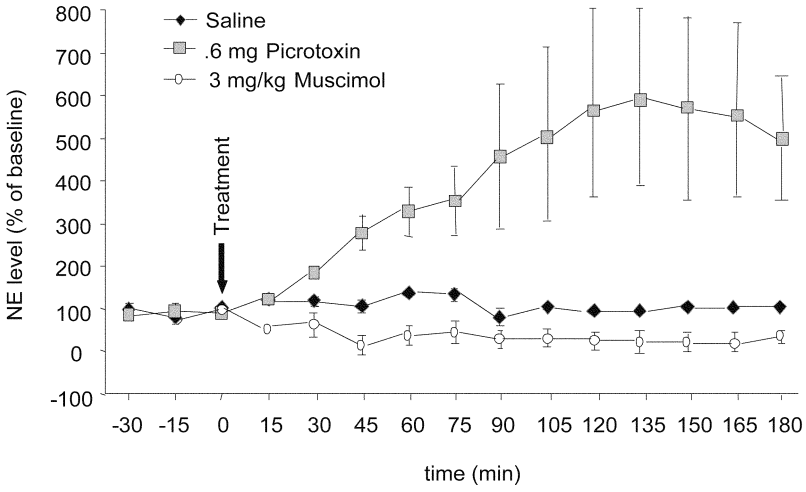

FIGURE 3. Effects of systemic injections of the GABAergic antagonist picrotoxin and the agonist muscimol on amygdala levels of norepinephrine, as assessed by *in vivo* microdialysis and HPLC. Microdialysis samples were collected at 15-minute intervals. Norepinephrine levels (mean ± SEM) are represented as a percentage change from average basal levels taken before treatment. Systemic picrotoxin injections increased and muscimol injections decreased norepinephrine levels in the amygdala for 180 minutes when compared to levels seen in saline-treated rats. (From Hatfield *et al*., 1999.)

of norepinephrine in the amygdala, whereas memory-impairing drugs block activation of the amygdala noradrenergic system (TABLE 1). Such findings provide strong support for the hypothesis that noradrenergic activation in the BLA is critically involved in modulating memory consolidation and that several neurotransmitters converge on the noradrenergic system in the BLA in mediating their effects on memory consolidation.

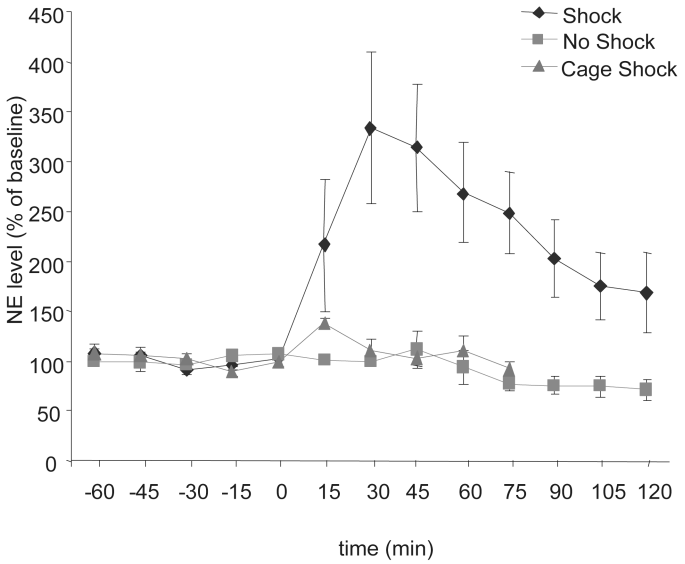

FIGURE 4. Effect of inhibitory avoidance training on amygdala norepinephrine levels as assessed by *in vivo* microdialysis and HPLC. Norepinephrine levels (mean + SEM) are represented as a percenage change from average baseline values taken before training. Amygdala norepinephrine levels increased following inhibitory avoidance training. This increase was greater and more long-lasting than was the increase following the same footshock in a holding cage. Norepinephrine levels did not increase above baseline in rats that were trained (placed in inhibitory avoidance chamber and blocked in the dark compartment for 10 seconds) without footshock. (From McIntyre *et al*., 2002.)

Amygdala Norepinephrine Release during Inhibitory Avoidance Training

In recent experiments we used *in vivo* microdialysis techniques to examine changes in amygdala norepinephrine levels in individual rats as they acquire and consolidate new, emotionally influenced memories. With this method, it is possible to relate the training-induced increase in norepinephrine levels to the subsequent retention performance of individual animals.[54] A surprising finding was that the mean percentage and duration of the increase in amygdala norepinephrine levels assessed after inhibitory avoidance training greatly exceeded that seen in rats shocked in a holding cage.[51,54] The critical difference between animals that were trained and those that received shock in a holding cage was the exposure to the novel context of an inhibitory avoidance apparatus. Therefore, the pattern of amygdala norepinephrine release appears to be influenced by context. However, novelty alone cannot explain the enhanced increase in norepinephrine, inasmuch as exposure to the inhibitory avoidance apparatus in the absence of footshock did not increase norepinephrine levels. It is important to note that manipulations of the amygdala as much as 6 hours after training can affect consolidation of emotionally influenced memories.[22] These findings fit well with previous pharmacological results, suggest-

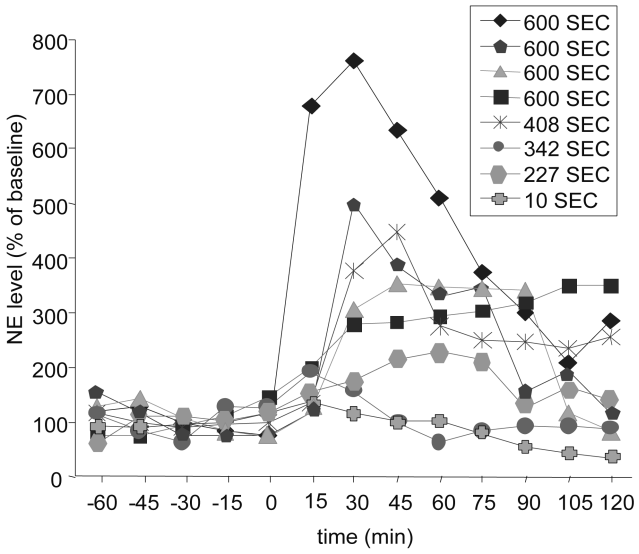

FIGURE 5. Norepinephrine release, as assessed by *in vivo* microdialysis and HPLC, in individual rats following inhibitory avoidance training with footshock. Percentage of baseline norepinephrine following inhibitory avoidance training is graphed for each individual rat. The key notes retention score on the following day. Amygdala norepinephrine levels correlate with 24-hour retention performance. Correlation values for the first five posttraining samples varied from +0.75 to +0.92. (From McIntyre *et al*., 2002.)

ing that prolonged posttraining activation of noradrenergic receptors in the amygdala plays a critical role in modulating memory consolidation.[55,56]

Further analysis examined the relation between training-induced release of amygdala norepinephrine and subsequent retention performance of individual animals. As shown in FIGURE 5, amygdala norepinephrine levels assessed after training are highly correlated with inhibitory avoidance performance tested 24 hours after training. The rats that exhibited the best retention (i.e., those that did not enter the shock compartment on the testing day) were also the rats in which the increase in amygdala norepinephrine levels in the samples following training were greatest.

NORADRENERGIC-CHOLINERGIC INTERACTIONS ON MEMORY CONSOLIDATION

Extensive evidence indicates that activation of muscarinic receptors within the BLA is a requirement for norepinephrine-induced memory enhancement. Systemic injections of the muscarinic cholinergic antagonist atropine attenuate the memory-enhancing effects of the β-adrenoceptor agonist clenbuterol as well as those of epinephrine.[57] Intra-amygdala infusions of propranolol do not attenuate the memory enhancement induced by systemic injections of the cholinergic agonist oxotremorine, whereas a subeffective dose of atropine infused into the amygdala prevents the

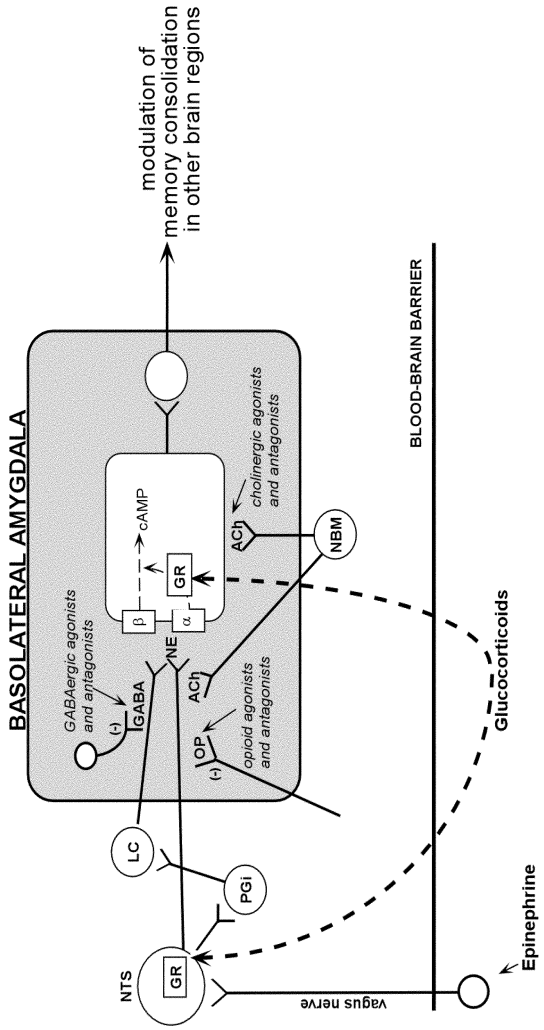

FIGURE 6. Schematic of the basolateral complex of the amygdala and peripheral influences adapted from McGaugh.[70] The interactions of neuromodulators on memory consolidation are represented as indicated from pharmacological and lesion data. ACh, acetylcholine; GR, glucocorticoid receptor; LC, locus coeruleus; NBM, nucleus basalis magnocellularis; NE, norepinephrine; NTS, nucleus of the solitary tract; PGi, nucleus paragigantocellularis; α,$\alpha_1$adrenoceptor; β, β-adrenoceptor; cAMP, cyclic 3′, 5′–adenosine monophosphate; OP, opioid peptide.

memory-enhancing effects of oxotremorine as well as those of the β-adrenoceptor agonist clenbuterol.[57] In a recent study we found that depletion of acetylcholine in the amygdala with relatively selective phthalic acid-induced lesions of cholinergic projections from the nucleus basalis magnocellularis to the amygdala impairs rats' performance on the inhibitory avoidance task. The impairment is reversed by intra-BLA infusions of either oxotremorine or the acetylcholinesterase inhibitor physostigmine immediately after training.[58] Infusions of cholinergic antagonists into the amygdala, or the BLA, also block the memory modulation produced by systemic injections of opioid peptidergic, GABAergic, and glucocorticoid receptor agonists.[29,59] Recent neuroanatomical findings indicate that cholinergic fibers contact noradrenergic terminals in the BLA. Noradrenergic terminals also form synapses with dendrites or spines of intrinsic cholinergic neurons in the BLA.[60] Together, these findings suggest that converging neuromodulatory systems influence noradrenergic and cholinergic activation in the BLA. A schematic model of BLA modulation of memory consolidation is represented in FIGURE 6.

GLUCOCORTICOID EFFECTS ON MEMORY CONSOLIDATION

Like epinephrine, glucocorticoids are released from the adrenal glands (epinephrine from the adrenal medulla; glucocorticoids from the adrenal cortex) in response to emotionally arousing experiences. Posttraining administration of the natural ligand corticosterone or the synthetic glucocorticoid dexamethasone enhances memory consolidation in a dose- and time-dependent manner.[23,61] Glucocorticoids are highly lipophilic and directly activate mineralocorticoid and glucocorticoid receptors in the brain. Memory-modulating glucocorticoid receptors are activated only when circulating glucocorticoid levels are significantly above basal levels. Infusion of a glucocorticoid receptor antagonist impairs memory consolidation.[5,62] Furthermore, a point mutation in the mouse glucocorticoid receptor that selectively prevents dimerization and DNA binding of the glucocorticoid receptor impairs spatial memory performance.[63] As found with other neuromodulatory systems, glucocorticoid-induced memory enhancement is intimately linked to activation of the noradrenergic system within the BLA.[31] Glucocorticoid effects on memory consolidation may involve activation of glucocorticoid receptors in brain-stem noradrenergic cell groups that innervate and activate the BLA. These noradrenergic neurons have high densities of glucocorticoid receptors.[64] Glucocorticoids can enhance the norepinephrine synthesis rate in the LC during emotionally arousing conditions.[65] Furthermore, intra-NTS administration of a glucocorticoid receptor agonist enhances memory via a mechanism that depends on noradrenergic activation in the BLA.[66] Glucocorticoid receptor antagonism in the NTS does not block memory enhancement induced by systemic dexamethasone treatment, but it does increase the dose required for inducing memory enhancement.[66] These findings are consistent with the hypothesis that glucocorticoids may activate noradrenergic neurons and stimulate the release of norepinephrine in the BLA during emotionally arousing situations.

Recent findings have suggested that glucocorticoid-induced memory enhancement further requires coactivation of β-adrenoceptors and muscarinic cholinergic receptors within the BLA. Memory enhancement induced by posttraining administration of a glucocorticoid receptor agonist infused directly into the BLA is blocked

by infusions of the β-adrenoceptor antagonist atenolol or the muscarinic cholinergic antagonist atropine into the BLA.[24,29,67] Moreover, glucocorticoid-induced memory modulation involves an interaction with intracellular norepinephrine signaling cascades in the BLA, possibly through effects on G-protein–mediated events on cAMP accumulation.[67,68] Glucocorticoid receptor antagonist administration attenuates the enhancing effects of intra-BLA infusions of a β-adrenoceptor agonist on memory consolidation, but it does not affect retention enhancement induced by intra-BLA infusions of 8-Br-cAMP, a synthetic cAMP analog. Memory enhancement induced by intra-BLA infusions of the glucocorticoid receptor agonist RU 28362 is blocked by β-adrenoceptor antagonism or cAMP inhibition in the BLA. Therefore, glucocorticoids may exert rapid (nongenomic) effects on BLA activation via interaction with the β-adrenoceptor-cAMP cascade.[67] These findings are consistent with evidence just summarized, indicating that stress hormones and neuromodulators converge in the BLA to participate in the enhancement of consolidation of emotionally influenced memories.

BASOLATERAL AMYGDALA MODULATION OF EFFERENT NEURAL SYSTEMS

Findings of many experiments from our laboratory and others have indicated that after memories have been consolidated, the BLA is no longer involved in the expression of long-term memories.[69,70] For example, lesions of the BLA or drug infusions into the BLA 1 day to 1 month after training do not block inhibitory avoidance retention performance.[22,55,56,71] This evidence that the BLA may not be a site of long-term memory storage suggests that BLA activity influences other neural systems during the consolidation phase of memory storage. Further evidence that the BLA participates in the consolidation of memory through its influence on efferent neural systems includes the findings that lesions of the stria terminalis, a major output pathway of the amygdala, block memory enhancement induced by posttraining injections of epinephrine[72] as well as enhancement induced by intra-amygdala infusions of norepinephrine or glucocorticoids.[13,73] Consistent with this finding, bilateral lesions of the nucleus accumbens, which receives a strong projection from the BLA, via the stria terminalis, also block the memory enhancement seen with systemic or intra-BLA administration of glucocorticoids.[73,74]

Studies of amygdala influences on different forms of memory have provided further evidence that the BLA interacts with other neural systems during consolidation of long-term memories. For example, posttraining injections of amphetamine into the hippocampus or the caudate nucleus selectively enhance memory for the hippocampus-dependent water-maze spatial task or the caudate nucleus-dependent cued version of the water-maze task, respectively. Importantly, amphetamine-infused posttraining into the amygdala enhances memory for both tasks[75] (TABLE 2). Furthermore, inactivation of the hippocampus or the caudate nucleus, but *not* the amygdala, before retention testing selectively attenuated amphetamine-induced memory enhancement[76] (TABLE 2). This evidence strongly suggests that the amygdala is not the locus of the enhanced memory, but, rather, it serves to modulate memory consolidation through its influence on processes in other brain areas, including the hippocampus and the caudate nucleus. Recent experiments have also

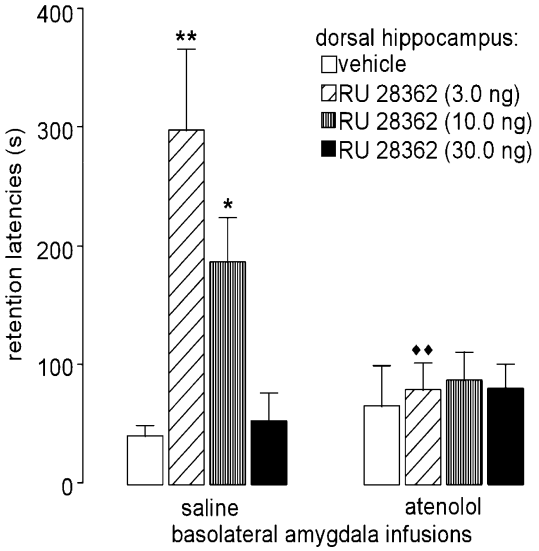

FIGURE 7. Step-through latencies (mean + SEM) for a 48-hour inhibitory avoidance test. Effects of immediate posttraining unilateral infusions of the glucocorticoid receptor agonist RU28362 (3.0, 10.0, or 30.0 ng) into the dorsal hippocampus and pretraining unilateral infusions of either saline or the β-adrenoceptor antagonist atenolol (0.5 μg) into the ipsilateral basolateral amygdala. *P <0.05; **P <0.01 as compared with the corresponding intra-hippocampal vehicle group; ◆◆P <0.01 as compared with the corresponding intra-basolateral amygdala saline group. (From Roozendaal *et al*., 1999.)

TABLE 2. Amygdala modulation of hippocampus- and caudate nucleus-dependent memory tasks

	Spatial task retention	Cued task retention
Posttraining infusions		
d-amphetamine, hippocampus[a]	Enhanced	No effect
d-amphetamine, caudate nucleus[a]	No effect	Enhanced
d-amphetamine, amygdala[a]	Enhanced	Enhanced
d-amphetamine, amygdala; lidocaine, hippocampus[b]	Enhancement blocked	Enhanced
Posttraining and pretesting infusions		
Post: d-amphetamine, hippocampus[b] Pre: lidocaine, hippocampus[b]	Enhancement blocked	(Not tested)
Post: d-amphetamine, caudate nucleus Pre: lidocaine, caudate nucleus[b]	(Not tested)	Enhancement blocked
Post: d-amphetamine, amygdala Pre: lidocaine, amygdala[a]	Enhanced	Enhanced

[a]Packard, Cahill & McGaugh, 1994; Packard & Teather, 1998.
[b]Packard & Teather, 1998.

indicated a role for β-adrenoceptor activation within the BLA in modulating memory consolidation in the hippocampus. Posttraining intrahippocampal infusions of a glucocorticoid receptor agonist enhance retention performance on an inhibitory avoidance task, whereas infusions of the β-adrenoceptor antagonist atenolol into the ipsilateral BLA block this memory enhancement.[32] These findings indicate a direct involvement of BLA β-adrenoceptors in the facilitation of hippocampal processing of newly acquired information (FIG. 7).

Neuroanatomical and electrophysiological findings indicate that there are direct interactions between the amygdala and the hippocampus. High-frequency stimulation of the BLA has been reported to facilitate population spike long-term potentiation in the dentate gyrus of the hippocampus.[77] This potentiation depends on activation of β-adrenoceptors in the BLA.[78] Moreover, dentate gyrus long-term potentiation is reinforced in the presence of appetitive or aversive stimuli, or BLA stimulation, administered within 30 minutes before or after perforant path tetanization.[79,80] This long-term potentiation reinforcement is blocked by β-adrenoceptor or muscarinic receptor antagonists.[80]

Recent findings indicate that the BLA also interacts with cortical areas during memory consolidation. Direct, unilateral infusions of the cAMP analog 8-Br-cAMP into the entorhinal cortex immediately after training on an inhibitory avoidance task enhance memory retention, but lesions of the ipsilateral BLA block this enhancement[33] (FIG. 8). Lesions of the BLA alone did not impair memory retention performance, and BLA lesions contralateral to the entorhinal cortex infusion site did not block the 8-Br-cAMP–induced memory enhancement, indicating that this effect

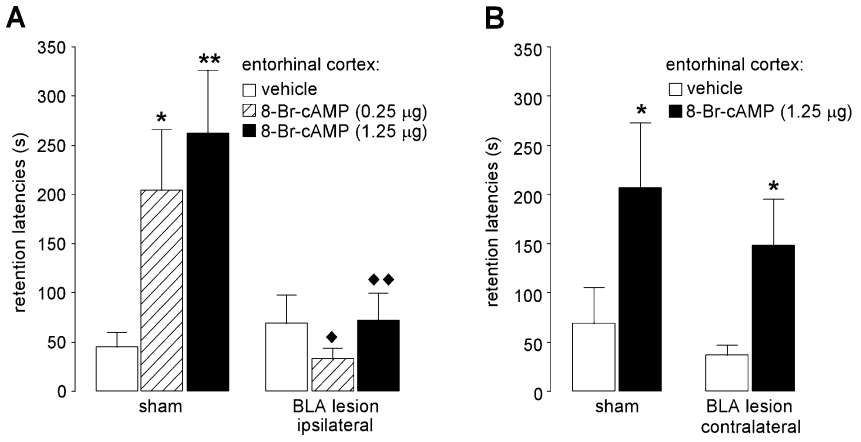

FIGURE 8. Step-through retention latencies (mean + SEM) in seconds of rats with unilateral sham or neurotoxic lesions of the basolateral amygdala given 8-Br-cAMP (0.25 or 1.25 μg) into the entorhinal cortex immediately after inhibitory avoidance training. Lesions of the ipsilateral (**A**), but not the contralateral (**B**) basolateral amygdala block the memory-enhancing effects of intra-entorhinal cortex infusions of 8-Br-cAMP. *P <0.05, **P <0.01, as compared with the corresponding vehicle group, ◆P <0.05, ◆◆P <0.01 compared with the corresponding sham lesion group. (From Roesler *et al.*, 2002.)

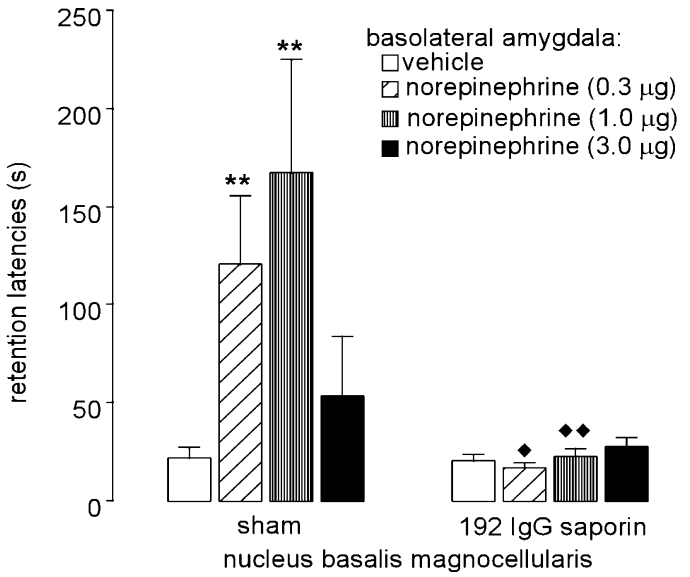

FIGURE 9. Step-through retention latencies (mean + SEM) in seconds for rats with sham or 192-IgG saporin lesions of the nucleus basalis magnocellularis (NBM) given post-training intra-basolateral amygdala infusions of vehicle or norepinephrine (0.3, 1.0, or 3.0 μg). 192 IgG-saporin-induced lesions of the NBM block memory enhancement produced by posttraining, intra-BLA infusions of norepinephrine. $^{**}P < 0.01$ compared with the corresponding vehicle group, $^{\blacklozenge}P < 0.05$, $^{\blacklozenge\blacklozenge}P < 0.01$ compared with the corresponding sham lesion group. (From Power, Thal, and McGaugh, 2002.)

was due to the loss of the anatomical interaction between the BLA and the entorhinal cortex.[33] Electrophysiological findings also indicate a coupling between these two neuroanatomical regions. Neuronal activity in the BLA oscillates in phase with entorhinal cortex neuronal activity,[81] and spontaneous discharges of BLA neurons induce short-latency "sharp potentials" in the entorhinal cortex.[82]

Memory enhancement due to activation of BLA β-adrenoceptors appears to depend on intact projections from the nucleus basalis magnocellularis (NBM) to the neocortex. In a recent experiment, we found that selective lesions of corticopetal NBM cholinergic projections with 192 IgG-saporin block memory enhancement induced by intra-BLA infusions of norepinephrine[30] (FIG. 9). BLA activation may modulate memory consolidation processes in the neocortex by influencing the activity of corticopetal NBM neurons or through a coincident interaction in the neocortex of BLA and NBM efferents. Consistent with this view, stimulation of the BLA produces scopolamine-sensitive, NBM-dependent neocortical desynchronization of EEG patterns.[83,84]

These findings indicate that the BLA interacts with other brain regions in modulating memory consolidation.[13,30,32,33,72,73,75,76] Complementary electrophysiological findings have provided strong support for this view.[77–84] Furthermore, the cortical and subcortical regions implicated in memory storage processes receive sig-

nificant direct and indirect input from the BLA.[85–88] Additionally, pharmacological stimulation of the amygdala induces expression of the protein FOS, indicative of neuronal activation,[89,90] as well as mRNA for the activity-regulated cytoskeletal-associated immediate early gene *Arc* in the ipsilateral hippocampus and the caudate nucleus.[91] The findings that *Arc* protein and mRNA are localized selectively to activated synapses and that inhibition of *Arc* expression in the hippocampus with antisense oligonucleotides impairs spatial memory and maintenance of long-term potentiation suggest that *Arc* may be a marker for encoding processes.[92,93] Activation of BLA neurons projecting to other neural regions may modulate local processes underlying memory consolidation. Alternatively, or additionally, reciprocal projections from these areas to the BLA may be critical for enabling the long-term storage of new information.

SOME THOUGHTS ON POSSIBLE THERAPEUTIC IMPLICATIONS

The findings suggesting that the release of stress hormones and activation of the BLA regulate the strength of long-term memory, as well as the evidence that, in human subjects, administration of the β-adrenoceptor blocker propranolol attenuates the enhanced long-term memory induced by emotionally arousing information without affecting memory for neutral information[94] has suggested that overactivation of this modulatory system may contribute to the development of posttraumatic stress disorder (PTSD).[95] In support of this suggestion, Pitman *et al.*[96] reported that chronic administration of a β-blocker to individuals who had experienced trauma reduced the subsequent incidence of PTSD assessed weeks after the traumatic experience. Additionally, the total dose of epinephrine administered to patients treated in intensive care for traumatic injury or disease was, among many measures assessed, the single best predictor for the number of traumatic memories reported months later.[97] Importantly, the results of a recent investigation of the effects of treatment with noradrenergic drugs on memory storage in healthy human control subjects were consistent with the findings in animal studies. Administration of yohimbine, and α_2-adrenoceptor agonist or β_1-adrenoceptor antagonist metoprolol to subjects prior to their viewing of a narrated slide show significantly improved or impaired, respectively, retention performance assessed 1 week later.[98]

Glucocorticoid administration selectively enhances memory for emotionally arousing material in human subjects.[99] These findings are consistent with the findings from animal studies indicating that glucocorticoid's effects on memory consolidation require coactivation of arousal-induced noradrenergic mechanisms.[68] Glucocorticoid treatments also influence the number of memories reported by patients recovering from traumatic intensive care experiences. Patients given glucocorticoids during intensive care treatment had better memory than that of patients not given glucocorticoids for the intensive care experiences.[97,100] However, Schelling *et al.*[101] reported that septic shock patients given prolonged hydrocortisone treatment during their stay in the intensive care unit subsequently displayed a reduced risk of developing PTSD symptoms. It is not yet clear what factors are responsible for the differential effects of glucocorticoid treatments and endogenous levels on memories of intensive care experiences and PTSD. However, some evidence indicates that although elevated glucocorticoid levels can enhance memory consolida-

tion, they may, especially when chronically elevated, impair memory retrieval processes.[68,102,103] As PTSD is a slowly developing condition that may require continuous retrieval and consolidation of emotionally arousing information, these seemingly paradoxical effects of glucocorticoids on memory formation and PTSD may be due to differential influences on consolidation and retrieval.

CONCLUDING REMARKS

In a prescient suggestion offered over four decades ago, and a decade before publication of the first studies investigating the role of the amygdala in memory consolidation, Ralph Gerard wrote: "…the amygdala (may act) directly on cortical neurons to alter…their responsiveness to the discrete impulses that reach the cortex…these deep nuclei could easily modify the ease and completeness of experience fixation even if the nuclei were not themselves the loci of engrams."[104] The findings summarized in this paper indicate that there is now considerable evidence consistent with Gerard's suggestion that the amygdala is part of a memory modulatory system. The research reviewed in this chapter provides strong evidence suggesting that: (1) adrenal stress hormones modulate memory consolidation, (2) stress hormones and other neuromodulators influence memory by influencing the activation of β-adrenoceptors within the BLA, (3) the modulation requires concurrent muscarinic cholinergic activation in the BLA, (4) BLA activity modulates memory consolidation in other brain regions, and (5) recent investigations of the roles of stress hormones in memory formation in human subjects may have important implications for understanding and treating trauma-related memory.

ACKNOWLEDGMENTS

The authors thank Nancy Collett for assistance in preparing this manuscript. This research was supported by National Institute of Mental Health NRSA Grant MH12646 (C.K.M.), a Schneiderman graduate fellowship (A.E.P.), and a USPHS Research Grant from NIMH, MH12526 (J.L.M.).

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