Neurobiology of Learning and Memory **78,** 539–552 (2002)
doi:10.1006/nlme.2002.4082

Amygdala Modulation of Memory Consolidation: Interaction with Other Brain Systems

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There is a strong consensus that the amygdala is involved in mediating influences of emotional arousal and stress on learning and memory. There is extensive evidence that the basolateral amygdala (BLA) is a critical locus of integration of neuromodulatory influences regulating the consolidation of several forms of memory. Many drug and stress hormone influences converge in activating the release of norepinephrine (NE) within the BLA. Evidence from studies using in vivo microdialysis and high-performance liquid chromatography indicates that increases in amygdala NE levels assessed following inhibitory avoidance training correlate highly with subsequent retention. Other evidence indicates that NE influences on memory consolidation require muscarinic cholinergic activation within the BLA provided by projections from the nucleus basalis magnocellularis (NB). Evidence from several experiments indicates that activation of the BLA plays an essential role in modulating memory consolidation processes involving other brain regions. These findings provide strong support for the hypothesis that the BLA plays a critical role in regulating the consolidation of lasting memories of significant experiences.

Although the first evidence suggesting the involvement of the amygdala in learning and memory was published over 65 years ago (Klüver & Bucy, 1937), it is only in recent years that the amygdala has become a central focus of inquiry in studies of learning and memory. There is now extensive evidence suggesting that the amygdala is involved in the effects of attention and reward (Easton & Gaffan, 2000 Gallagher, 2000; Everitt, Cardinal, Hall, Parkinson, & Robbins, 2000) and that the amygdala may be a locus of the neural changes underlying the acquired association of cues with emotional responses, especially the autonomic and motoric responses elicited by fearful stimuli (Davis, 2000; LeDoux, 2000). In addition, there is a strong consensus that the amygdala is involved in mediating the effects of emotional arousal on memory. Findings of many studies indicate

Supported by an NRSA from NIMH MH12646 (J.L.M., and C.K.M.) and a USPHS Research Grant from NIMH, MH12526 (J.L.M.). We thank Benno Roozendaal for comments on a previous draft of this paper and Nancy Collett for her assistance in the preparation of the manuscript.

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1074-7427/02 $35.00

that the amygdala modulates the consolidation of long-term explicit memories of emotionally arousing experiences by influencing other brain regions involved in memory consolidation (Cahill & McGaugh, 1998; McGaugh, 2000; McGaugh, Ferry, Vazdarjanova, & Roozendaal, 2000).

AMYGDALA INVOLVEMENT IN MEMORY CONSOLIDATION

Interest in the involvement of the amygdala in influencing memory consolidation was originally stimulated by Goddard's finding (1964) that, in rats, electrical stimulation of the amygdala administered immediately after training impaired memory of an aversive training experience. As it had been known for many years that electroconvulsive shock induces retrograde amnesia in rodents as well as human subjects (McGaugh & Herz, 1972; Zubin & Barrera, 1941), Goddard's findings suggested that the amygdala may be a brain region critically involved in memory consolidation. Subsequent studies demonstrated that amygdala stimulation delivered after inhibitory avoidance training can *enhance* as well as impair memory consolidation (Kesner & Doty, 1968; McGaugh & Gold, 1976; Kesner & Wilburn, 1974; Gold, Macri, & McGaugh, 1973). For example, low intensity footshock with low intensity amygdala stimulation produces memory enhancement (Gold, Hankins, Edwards, Chester, & McGaugh, 1975). The evidence that posttraining amygdala stimulation can either enhance or impair memory clearly indicates that alteration of activity in the amygdala does not simply disrupt local neural circuits involved in memory consolidation. Rather, such findings suggest that the amygdala *modulates* the consolidation of recently acquired information.

To investigate whether such modulation of memory consolidation involves amygdala interactions with other brain regions, a number of studies have examined the effects of lesions of the stria terminalis (ST), a major pathway carrying projections to and from the amygdala. An initial study using inhibitory avoidance training found that ST lesions blocked the memory-impairing effects of electrical stimulation of the amygdala but otherwise did not affect learning or memory (Liang & McGaugh, 1983). Infusions of the opiate antagonist naloxone into the bed nucleus of the stria terminalis (BNST) also blocked the amnestic effects of posttraining amygdala stimulation (Liang, Messing & McGaugh, 1983). Although these findings were consistent with the hypothesis that amygdala efferents carry modulatory influences to other regions of the brain involved in consolidating memory, they did not exclude the possibility that the ST lesion and BNST drug infusion effects may have been due to disruption of amygdala afferents. Subsequent studies discussed below provided additional evidence that the effects resulted, at least in part, from disruption of amygdala efferents.

DRUG AND STRESS HORMONE INFLUENCES ON MEMORY CONSOLIDATION: MEDIATION BY THE AMYGDALA

It is now well established that drugs and stress hormones administered shortly after training modulate the consolidation of memory for many kinds of learning tasks, including tasks using appetitive as well as aversive motivation (Bohus, 1994; de Kloet, 1991; Gold & van Buskirk, 1975; Izquierdo & Dias, 1985; Liang, 2000; McGaugh, 1966,1989a,b, 2000;

Roozendaal, 2000; Williams & McGaugh, 1994; McGaugh & Gold, 1989; Sandi & Rose, 1994). Furthermore, considerable evidence indicates that these modulatory influences involve the amygdala. ST lesions block the memory-modulating effects of peripherally administered epinephrine and glucocorticoids (Liang & McGaugh, 1983; Roozendaal & McGaugh, 1996) as well as those of drugs affecting opioid peptidergic (McGaugh, Introini-Collison, Juler, & Izquierdo, 1986) and cholinergic (Introini-Collison, Arai, & McGaugh, 1989) systems. Lesions of the amygdala block the memory-enhancing and -impairing effects of epinephrine (Cahill & McGaugh, 1991), benzodiazepines (Tomaz, Dickinson, & McGaugh, 1992), and glucocorticoids (Roozendaal & McGaugh, 1996). More specifically, the effects are blocked by selective lesions of the basolateral complex of the amygdala (BLA) (Roozendaal & McGaugh, 1996; Tomaz et al., 1992). These findings, as well as those of other studies discussed below, provide extensive evidence that the BLA is critically involved in stress hormone and drug influences on memory consolidation (McGaugh et al., 2000).

INVOLVEMENT OF NORADRENERGIC ACTIVATION WITHIN THE AMYGDALA

An involvement of amygdala adrenoceptors in memory consolidation was first suggested by the findings that β-adrenoceptor antagonists infused into the amygdala after inhibitory avoidance training impaired memory consolidation and that concurrent administration of norepinephrine (NE) attenuated the impairment (Gallagher, Kapp, Musty, & Driscoll 1977; Gallagher, Kapp, Pascoe, & Rapp, 1981). The subsequent finding that infusions of the β-adrenoceptor antagonist propranolol into the amygdala blocked the memory-enhancing effects of epinephrine administered peripherally after training (Liang, Juler, & McGaugh, 1986) provided the first evidence that peripheral stress hormone influences on memory consolidation involve activation of β-adrenoceptors in the amygdala. Other findings of that study indicated that NE infused into the amygdala enhanced retention and blocked the memory-impairing effect of adrenal demedullation. In addition, propranolol administered together with NE blocked the memory-enhancing effects of the NE infusions (Liang et al., 1986). Importantly, ST lesions also blocked the memory-enhancing effects of a low dose of NE as well as the memory-impairing effects of a high dose of NE infused into the amygdala posttraining (Liang, McGaugh, & Yao, 1990). These findings rule out the possibility that ST lesions block modulatory influences by reducing the release of NE in the amygdala. In contrast, lesions of the ventral amygdalofugal pathway which have been reported to reduce amygdala NE (Emson et al., 1979) attenuated, but did not block the memory-enhancing effects of posttraining intra-amygdala infusions of NE; a higher dose of NE was required to induce memory enhancement. Thus, in addition to providing evidence that NE in the amygdala influences memory consolidation, these findings provide additional support for the view that amygdala efferents are critically involved in mediating amygdala influences on memory consolidation.

Recent studies have provided extensive additional evidence that selective activation of adrenoceptors in the BLA modulates memory consolidation. Posttraining intra-BLA infusions of β-adrenoceptor agonists enhance memory for water-maze spatial training (Hatfield & McGaugh, 1999) as well as inhibitory avoidance (Ferry & McGaugh, 1999; Ferry, Roozendaal, & McGaugh, 1999a,b). Amygdala noradrenergic activation plays a

critical role in mediating several neuromodulatory influences on memory consolidation. Infusions of β-adrenergic antagonists into the amygdala, or selectively into the BLA, block the memory modulating effects of drugs affecting GABAergic, opioid peptidergic and glucocorticoid receptors (McGaugh, Introini-Collison, Cahill, Castellano, Dalmaz, Parent, & Williams, 1993; McGaugh, Cahill, Parent, Mesches, Coleman-Mesches, & Salinas, 1995; McGaugh et al., 2000, Roozendaal, 2002). Such findings suggest that these drugs have a common influence on memory mediated by noradrenergic activation within the amygdala. Findings of several studies using *in vivo* microdialysis and high-performance liquid chromatography provide strong support for this implication. Naloxone, an opiate receptor antagonist found to enhance memory consolidation (Gallagher et al., 1981; Introini et al., 1989), increases NE release in the amygdala and an opiate agonist decreases release (Quirarte, Galvez, Roozendaal, & McGaugh, 1998). Similarly, picrotoxin, a GABA receptor antagonist known to enhance memory consolidation (Breen & McGaugh, 1961), increases NE release in the amygdala and muscimol, a GABA receptor agonist, decreases release (Hatfield, Spanis, & McGaugh, 1999). Importantly, peripherally administered epinephrine also increases NE release in the amygdala (Williams, Men, Clayton, & Gold, 1998; Williams & Clayton, 2001).

Research investigating the effects of training on NE release in the amygdala has provided additional support for the hypothesis that noradrenergic activation in the amygdala is involved in modulating memory consolidation. Footshock of the kind typically used in inhibitory avoidance training induces NE release in the amygdala that varies directly with footshock intensity (Galvez, Mesches, & McGaugh, 1996; Quirarte et al., 1998). We have also examined NE release induced by inhibitory avoidance training (McIntyre, Hatfield, & McGaugh, in press). As expected on the basis of our previous studies of the effects of footshock stimulation (Galvez et al., 1996; Quirarte et al., 1998), NE levels were increased following training (see Fig. 1). However, perhaps somewhat surprisingly, the duration of the increased NE levels was greater than that previously found with footshock stimulation

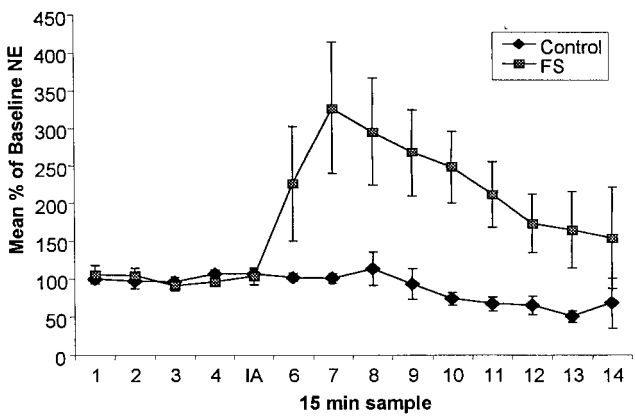

FIG. 1. Effects of inhibitory avoidance training on norepinephrine levels in the amygdala. Rats in the footshock group received a 0.55 mA, 1 s footshock during training. Microdialysis samples were collected every 15 min and automatically injected into an HPLC system optimized for norepinephrine detection. Norepinephrine levels (mean ± SEM) are expressed as a percent change from average baseline levels. A repeated measures ANOVA revealed a significant group effect ($p < .0001$) and a significant effect of trial in the footshock groups ($p < .005$), but not in the control group ($p > .5$) McIntyre, Hatfield & McGaugh, 2002.

given without inhibitory avoidance training (Galvez et al., 1996; Hatfield et al., 1999; Quirarte et al., 1998). These findings suggest that the combination of the footshock and novel contextual information provided by the training may have increased amygdala noradrenergic activation. Additionally, as is shown in Fig. 2, the amount of increase in amygdala NE after the training predicted the rats' 24-h retention performance. Animals with larger increases in NE release after training had longer retention latencies than those with smaller increases in NE release. These findings, considered together with those of studies of drug effects on NE levels, provide strong support for the hypothesis that NE release in the amygdala may play a critical role in modulating memory consolidation (McGaugh, 2000).

INVOLVEMENT OF CHOLINERGIC ACTIVATION WITHIN THE AMYGDALA

Muscarinic cholinergic activation within the amygdala also appears to be critical for enabling memory-modulatory influences. Muscarinic cholinergic antagonists infused into the amygdala, or more specifically into the BLA, block the memory-modulating effects of peripherally administered epinephrine as well as adrenoceptor and glucocorticoid receptor agonists infused into the amygdala posttraining (Introini-Collison, Dalmaz, & McGaugh, 1996; Power, Roozendaal, & McGaugh, 2000). Posttraining intra-BLA infusions of muscarinic cholinergic agonists enhance memory for several kinds of training, including inhibitory avoidance, contextual fear conditioning, and changes in reward magnitude (Power & McGaugh, 2002; Vazdarjanova & McGaugh, 1999; Salinas, Introini-Collison, Dalmaz, & McGaugh, 1997). Furthermore, β-adrenoceptor antagonists do not block the memory-enhancing effects of cholinergic agonists infused after training into the amygdala (Introini-Collison et al., 1996; Salinas et al., 1997). These findings strongly suggest that memory influences induced by BLA noradrenergic activation require muscarinic cholinergic activation within the BLA and that noradrenergic activation is not required for muscarinic

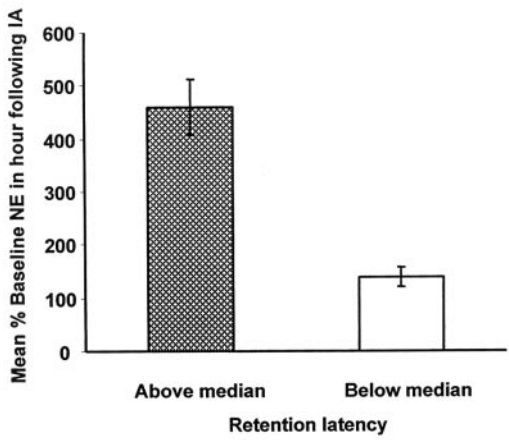

FIG. 2. Mean (+SE) percentage of baseline norepinephrine in the hour following inhibitory avoidance training with footshock. Rats receiving training footshock (0.55 mA/1 s) were divided by 24-h retention latencies (above median vs below median latency). Posttraining levels of norepinephrine in rats with latencies above the median were significantly greater than norepinephrine levels in rats with latencies below the median ($p < .0002$).

cholinergic influences. Thus, the cholinergic effects may occur at a step subsequent to noradrenergic activation.

The nucleus basalis (NB) provides the major source of cholinergic input to the BLA (Mesalum, Mufson, Wainer, & Levey, 1983; Nagai, Kimura, Maeda, McGeer, Peng, & McGeer, 1982; Woolf & Butcher, 1982). To examine the role of this cholinergic pathway in memory modulation, a recent study investigated the effect of unilateral phthalic acid-induced lesions of the NB projections to the BLA (Power & McGaugh, 2002). These relatively selective lesions impaired inhibitory avoidance learning and retention. However, as is shown in Fig. 3, posttraining intra-BLA infusions of either the cholinergic agonist oxotremorine or the acetylcholinesterase inhibitor physostigmine into the ipsilateral BLA attenuated the memory impairment. These findings strongly suggest that projections from the NB provide the cholinergic activation that is essential for amygdala modulation of memory consolidation. These findings provide further evidence that disruption of neuromodulatory systems within the BLA produce greater memory impairment than those produced by ST or BLA lesions. Although ST and BLA functioning do not appear to be required for inhibitory avoidance learning and retention, considerable evidence indicates that they are required for BLA neuromodulatory influences on memory consolidation.

INVOLVEMENT OF OTHER BRAIN REGIONS IN AMYGDALA INFLUENCES ON MEMORY CONSOLIDATION

As discussed briefly above, ST lesions block many memory-modulatory influences, including those induced by intra-amygdala NE infusions. These findings suggest that

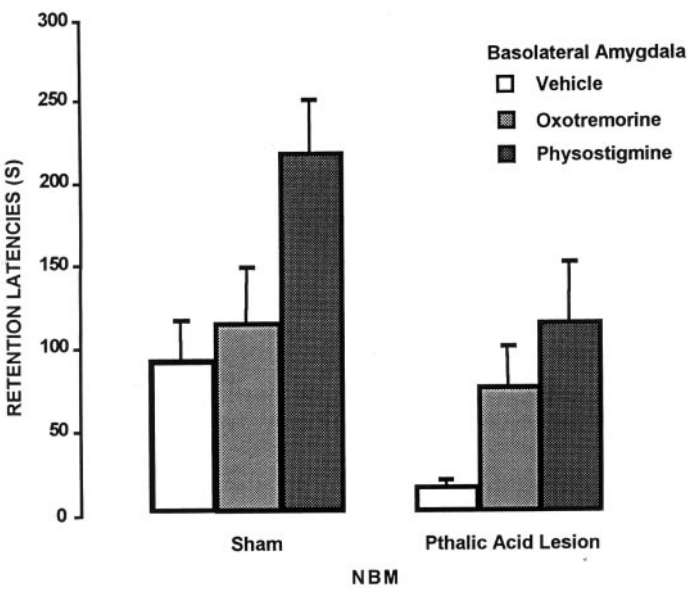

FIG. 3. Retention latencies (mean +SE) in seconds of rats with sham or phthalic acid lesion of the nucleus basalis and with intra-BLA infusions of cholinergic agonists, oxotremorine or physostigmine immediately after training. Phthalic acid-induced lesions impaired inhibitory avoidance retention ($p < .05$). Infusions of oxotremorine or physostigmine rescued normal memory in lesioned rats. The physostigmine infusions enhanced memory in nonlesioned rats ($p < .05$) (Power & McGaugh, 2002).

amygdala efferents to other brain regions, including cortical regions, may be critical in mediating such influences. Interestingly, this possibility was proposed several years before the first experiments investigating the involvement of the amygdala in memory consolidation. Gerard (1961, p. 30) suggested that ". . . 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."

Extensive evidence suggests that muscarinic cholinergic activation of the cortex by NB projections is essential for learning-induced cortical plasticity (Metherate & Weinberger, 1990; Weinberger, 1998; Miasnikov, McLinn & Weinberger, 2001). The BLA projects to the NB (Russchen, Amaral, & Price, 1985), at least partially through the ST (Price, 1981). Stimulation of the BLA desynchronizes cortical activity as assessed by electroencephalographic (EEG) recordings, enhances the duration of the cortical EEG response evoked by somatosensory stimulation, and potentiates the NB influence on cortical activation (Dykes, 1997; Dringenberg, Saber, & Cahill, 2001). BLA activation of cortical EEG is blocked by systemic administration of the muscarinic cholinergic antagonist scopolamine as well as by infusions of lidocaine into the NB (Dringenberg & Vanderwolf, 1996). Such findings suggest that BLA activation may influence learning and memory by stimulating cholinergic activation of the cortex. To examine this implication, we investigated the effects of BLA influences on memory consolidation in animals with selective lesions of NB cortical projections induced by 192-IgG saporin (Power, Thal, & McGaugh, 2002). As is shown in Fig. 4, 192-IgG saporin-induced lesions did not impair inhibitory avoidance retention but completely blocked the memory-enhancing effects of NE infused into the

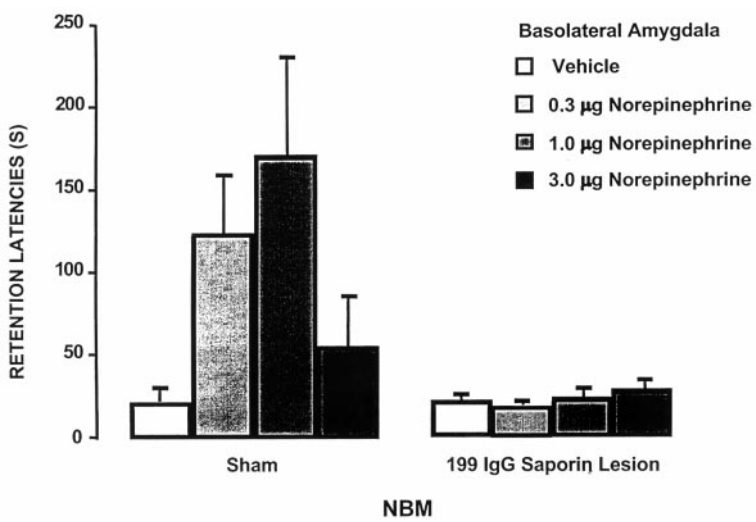

FIG. 4. Retention latencies (+SE) in seconds for rats receiving intra-BLA norepinephrine posttraining and sham or 192 IgG-saporin-induced lesions of the nucleus basalis. Both 0.3 and 1.0 (g doses of norepinephrine enhanced inhibitory avoidance retention in non-lesioned rats ($p < .01$ and .001 respectively). Lesions of the nucleus basalis did not impair retention ($p > .05$) but blocked intra-BLA norepinephrine memory enhancement ($P < 0.05$ and 0.001 vs respective non-lesioned groups and p's $> .05$ vs vehicle group) (Power, Thal & McGaugh, 2002).

BLA posttraining. These findings are consistent with the view that NB cholinergic projections to the cortex may play a critical role in enabling BLA modulation of memory consolidation.

As noted above, the amygdala sends direct and indirect projections to many brain regions including the caudate nucleus (via the ST) and the hippocampus (Pikkarainen, Ronko, Savander, Insausti, & Pitkanen, 1999). The findings of many "double-dissociation" studies indicate that the hippocampus and the caudate nucleus are involved in mediating different forms of learning (McDonald & White, 1993; Packard & McGaugh, 1992). In rats trained in a water maze, posttraining infusions of amphetamine into the hippocampus enhanced memory for spatial training but not cued training and amphetamine infused into the caudate nucleus selectively enhanced memory for cued training (Packard, Cahill, & McGaugh, 1994). In contrast, amphetamine infused into the amygdala after training enhanced memory for both kinds of training. Lidocaine infused into the hippocampus or caudate prior to the retention test blocked the enhancing effects of amphetamine on retention of spatial or cued learning, respectively. However, lidocaine infused into the amygdala prior to testing did not block the enhancing effect of posttraining intra-amygdala amphetamine infusions on the retention of either task. These findings clearly indicate that a functionally intact amygdala is not required for the expression of memory for training in these tasks and, by inference, that the amygdala is not the locus of the neural changes mediating the enhanced memory for either kind of training (Packard et al., 1994; Packard & Teather, 1998). The issue of whether the amygdala may be a locus of other forms of memory, including cued and contextual fear conditioning, is, at present, unresolved (Vazdarjanova & McGaugh, 1998; Cahill et al., 1999; Schafe et al., 2001).

The finding that lesions of the ST block the memory enhancement induced posttraining muscarinic cholinergic activation of the caudate nucleus (Packard, Introini-Collison, & McGaugh, 1996) provides further evidence that amygdala efferents influence memory processing in the caudate nucleus. Recent research using *in vivo* microdialysis has shown that acetylcholine levels increase in the amygdala as rats perform a hippocampus-dependent spontaneous alternation task. Although performance on this task is not affected by lesions of the amygdala, acetylcholine release in the amygdala correlates positively with performance, further indicating a role for the amygdala in modulating memory processing that occurs in the hippocampus (McIntyre, Marriott, & Gold, in press).

Other recent findings have provided additional evidence that the BLA is the critical region of the amygdala involved in modulating memory storage in other brain regions. Several experiments have found that posttraining intrahippocampal infusions of a glucocorticoid receptor agonist enhance inhibitory avoidance retention (Roozendaal & McGaugh, 1997; Roozendaal, 2000, 2002). However, selective lesions of the BLA or intra-BLA infusions of a β-adrenoceptor antagonist block the enhancement induced by intrahippocampal drug infusions (Roozendaal & McGaugh, 1997; Roozendaal, Nguyen, Power, & McGaugh, 1999). These findings clearly indicate that memory-modulatory influences within the hippocampus require a functionally intact BLA and suggest that projections from the BLA either potentiate consolidation processes or serve as a "cofactor" to enable them.

Findings of several experiments suggest that projections mediated by the ST are essential for glucocorticoid effects on memory consolidation. The nucleus accumbens (NAc) receives a strong projection from the BLA, mostly via the ST (Mogenson & Yang, 1991; Everitt & Robins, 1992). As we previously found with lesions of the ST, bilateral lesions

of the NAc block the memory enhancement induced by posttraining systemic injections of the synthetic glucocorticoid dexamethasone (Setlow, Roozendaal, & McGaugh, 2000). The involvement of BLA–NAc projections was examined in rats with unilateral NAc lesions as well as ipsilateral or contralateral lesions of the BLA. Dexamethasone administered posttraining enhanced memory in animals with ipsilateral lesions (i.e., rats with one intact BLA–NAc pathway) but did not enhance memory in rats with contralateral (i.e., asymmetrical) BLA–NAc lesions. Another study investigated the effects of posttraining intra-BLA or intrahippocampal infusions of a glucocorticoid receptor agonist on memory in rats with bilateral lesions of either the ST or NAc. Lesions of either the ST or NAc blocked the memory-enhancing effects of the glucocorticoid receptor agonist infused into the BLA or hippocampus (Roozendaal, de Quervain, Ferry, Setlow, & McGaugh, 2001). Considered together, the findings of these studies clearly suggest that an intact BLA–NAc pathway is required for enabling the memory-enhancing effects of glucocorticoids on memory consolidation. It has not, as yet, been determined whether this pathway is involved in mediating other neuromodulatory influences on memory consolidation.

The BLA projects directly to the entorhinal cortex (Krettek & Price, 1974; Pikkarainenen et al., 1999). Posttraining infusions of drugs into the entorhinal cortex modulate the consolidation of memory for inhibitory avoidance training (Izquierdo & Medina, 1997). This influence is likely not due to a direct effect of the entorhinal cortex on hippocampal activity, as lesions of the perforant path do not block the retention enhancement induced by posttraining electrical stimulation of the entorhinal cortex (Gauthier & Destrade, 1984). Recent experiments examined whether an intact BLA is critical for enabling memory enhancement induced by intraentorhinal cortex infusions (Roesler, Roozendaal, & McGaugh, 2002). Posttraining unilateral infusions of the synthetic cAMP analog 8-bromo-cAMP into the entorhinal cortex enhanced memory for inhibitory avoidance training. As is shown in Fig. 5, a unilateral lesion of the BLA ipsilateral to the drug infusion blocked the memory enhancement. A unilateral BLA lesion contralateral to the entorhinal cortex

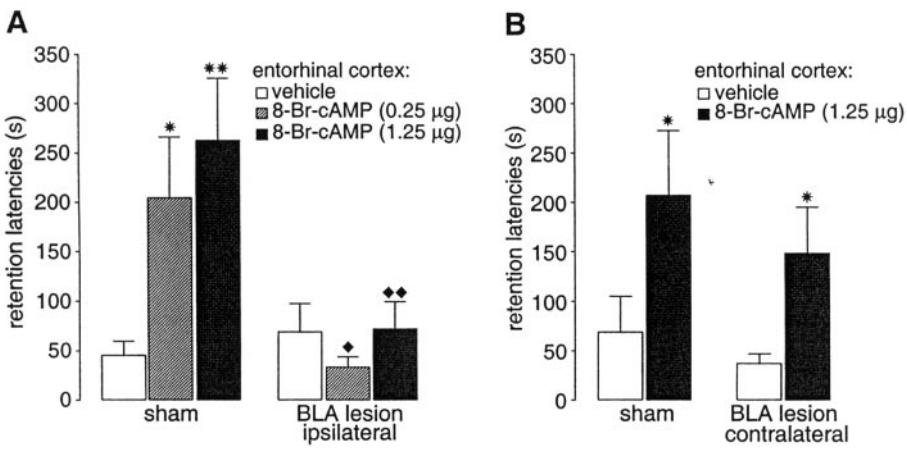

FIG. 5. Retention latencies (mean + SE) in seconds of rats with unilateral sham or NMDA-induced lesions of the basolateral amygdala (BLA) given 8-Br-cAMP (0.25 or 1.25 μg) into the entorhinal cortex immediately after inhibitory avoidance training. A, ipsilateral BLA lesions. B, contralateral BLA lesions $^{*}p < .05$ and $^{**}p < .01$ compared to the corresponding vehicle group, $n = 7$–14 per group) (Roesler, Roozendaal, & McGaugh, 2002).

infusion did not block the memory enhancement. Thus, as we have found with studies of other BLA interactions with other brain regions in influencing memory consolidation, an intact BLA is required for modulation of memory consolidation involving the entorhinal cortex. These effects may be mediated by direct projections between the BLA and the entorhinal cortex (Paré, Dong & Gaudreau, 1995). However, the specific pathway involved has not as yet been investigated.

CONCLUDING COMMENTS

The BLA is involved in mediating many aspects of arousal, stress, emotion, and memory. The findings summarized in this paper provide strong evidence that the BLA provides two important functions in memory. First, the BLA is a locus of interaction of arousal-activated neuromodulatory systems regulating memory consolidation. Second, the BLA modulates the functioning of other brain regions involved in the consolidation of different types or forms of memory. The evidence strongly suggests that BLA is relatively nonselective in modulating the consolidation of different aspects of memory. And, the evidence is consistent with that of many other studies suggesting that different brain regions are involved in the consolidation of different kinds of information. Although any specific learning task no doubt engages many brain systems, memory for each task appears to depend selectively on a subset of systems. Although our research suggests that no specific form of memory *requires* amygdala processing, an intact amygdala is essential in enabling the modulation of many forms of memory. Through this action, the BLA plays a central role in regulating the consolidation of memories of emotionally arousing experiences.

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