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THE AMYGDALA MODULATES THE CONSOLIDATION OF MEMORIES OF EMOTIONALLY AROUSING EXPERIENCES

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■ **Abstract** Converging findings of animal and human studies provide compelling evidence that the amygdala is critically involved in enabling us to acquire and retain lasting memories of emotional experiences. This review focuses primarily on the findings of research investigating the role of the amygdala in modulating the consolidation of long-term memories. Considerable evidence from animal studies investigating the effects of posttraining systemic or intra-amygdala infusions of hormones and drugs, as well as selective lesions of specific amygdala nuclei, indicates that (*a*) the amygdala mediates the memory-modulating effects of adrenal stress hormones and several classes of neurotransmitters; (*b*) the effects are selectively mediated by the basolateral complex of the amygdala (BLA); (*c*) the influences involve interactions of several neuromodulatory systems within the BLA that converge in influencing noradrenergic and muscarinic cholinergic activation; (*d*) the BLA modulates memory consolidation via efferents to other brain regions, including the caudate nucleus, nucleus accumbens, and cortex; and (*e*) the BLA modulates the consolidation of memory of many different kinds of information. The findings of human brain imaging studies are consistent with those of animal studies in suggesting that activation of the amygdala influences the consolidation of long-term memory; the degree of activation of the amygdala by emotional arousal during encoding of emotionally arousing material (either pleasant or unpleasant) correlates highly with subsequent recall. The activation of neuromodulatory systems affecting the BLA and its projections to other brain regions involved in processing different kinds of information plays a key role in enabling emotionally significant experiences to be well remembered.

INTRODUCTION

Emotionally arousing experiences tend to be well remembered. Studies of the past several decades have provided considerable evidence suggesting that stress hormones released by emotional experiences play an important role in mediating the

effects of emotional arousal on lasting memory. Moreover, there is also substantial evidence that neuromodulatory influences occurring selectively within the basolateral amygdala (BLA) regulate the consolidation of memory for various kinds of experiences through BLA projections to many other brain regions involved in storing newly acquired information. This review focuses explicitly on evidence from studies investigating the role of the amygdala in modulating memory consolidation. The role(s) of the amygdala in other aspects of learning, memory, and behavior are considered in other recent reviews (Davis et al. 2003, Everitt et al. 2003, Gallagher 2000, LeDoux 2000, Sah et al. 2003, Schafe et al. 2001, See et al. 2003, Stork & Pape 2002).

THE BASOLATERAL AMYGDALA MODULATES MEMORY CONSOLIDATION

Although studies published over six decades ago of the effects of brain lesions suggested a possible involvement of the amygdala in learning and memory (e.g., Klüver & Bucy 1937, Weiskrantz 1956), studies of the effects of electrical stimulation of the amygdala on learning and memory (Goddard 1964) were the first to suggest that the amygdala plays a role in influencing memory consolidation. Electrical stimulation of the amygdala administered shortly after rats were trained on an aversively motivated task impaired their memory of the training. The conclusion that the amygdala stimulation disrupted the consolidation of the memory of the training was confirmed by many subsequent findings from other laboratories (Kesner & Wilburn 1974, McGaugh & Gold 1976). One possible interpretation of these findings is that the stimulation disrupted the consolidation of memory processes occurring within the amygdala. However, several subsequent findings suggested that amygdala stimulation modulates memory consolidation and does so through influences mediated by amygdala efferents. The finding that posttraining electrical stimulation of the amygdala can either enhance or impair memory for aversive training (inhibitory avoidance), depending on the stimulation intensity and the training conditions (Gold et al. 1975), clearly indicates that the effects are modulatory, not simply memory impairing. Further, the finding that lesions of the *stria terminalis* block the impairing effects of posttraining electrical stimulation of the amygdala on memory for inhibitory avoidance training (Liang & McGaugh 1983) strongly suggested that the modulation involves projections from the amygdala to other brain regions.

Experiments by Ellis & Kesner (1983) and Gallagher et al. (1981) were the first to use posttraining drug infusions to investigate the involvement of the amygdala in memory consolidation. β-adrenoceptor antagonists infused into the amygdala impaired rats' retention of inhibitory avoidance, and concurrent infusion of norepinephrine (NE) blocked the memory impairment (Gallagher et al. 1981). These investigators also found that posttraining intra-amygdala infusions of opioid peptidergic agonists impaired memory and that antagonists enhanced memory. The

use of posttraining drug treatments, which were introduced in early studies of drug influences on memory (Breen & McGaugh 1961, McGaugh & Petrinovich 1965), excluded direct influences of the drugs on acquisition or retrieval. Thus, the findings provided compelling evidence suggesting that the amygdala infusions affected memory by influencing memory consolidation (McGaugh 1989, 2000).

Subsequent research has provided extensive confirming evidence that posttraining treatments affecting amygdala functioning influence memory consolidation. The finding that posttraining intra-amygdala infusions of drugs influence retention performance tested 24 h or longer after the training, but do not affect performance tested within a few hours after training, indicates that the treatments selectively affect the consolidation of long-term memory (Barros et al. 2002, Bianchin et al. 1999, Schafe & LeDoux 2000). Moreover, as discussed below, the findings of many recent studies indicate that the BLA is selectively involved in the memory-modulatory influences. The adjacent central nucleus does not appear to play a significant, if any, role in modulating memory consolidation (DaCunha et al. 1999, McGaugh et al. 2000, Parent & McGaugh 1994, Tomaz et al. 1992). Thus, the effects of relatively large intra-amygdala drug infusions (i.e., >0.2 μl) that may spread to several amygdala regions, including the infusion volumes (e.g., 1.0 μl) typically used in many early studies, are most likely due to selective influences on the BLA.

Although many of the experiments investigating BLA involvement in memory consolidation have used inhibitory avoidance training and testing (Izquierdo et al. 1997, McGaugh et al. 2000, McGaugh & Izquierdo 2000, Parent & McGaugh 1994, Wilensky et al. 2000), comparable effects of posttraining amygdala treatments have been obtained in experiments using a wide variety of training tasks, including contextual fear conditioning (LaLumiere et al. 2003, Sacchetti et al. 1999, Vazdarjanova & McGaugh 1999), cued fear conditioning (Sacchetti et al. 1999, Schafe & LeDoux 2000), Y-maze discrimination training (McGaugh et al. 1988), change in reward magnitude (Salinas et al. 1997), conditioned place preference (Hsu et al. 2002, Schroeder & Packard 2000), radial maze appetitive training (Packard & Chen 1999), water-maze spatial and cued training (Packard et al. 1994), conditioned taste aversion (Miranda et al. 2003), olfactory training (Kilpatrick & Cahill 2003a), and extinction of conditioned reward (Schroeder & Packard 2003). Additionally, Walker et al. (2002) reported that intra-amygdala drug infusions (D-cycloserine) administered before extinction training enhance the extinction of conditioned fear. Studies to date have not examined the effects of amygdala infusions administered after fear extinction trials. Although there is abundant evidence that the BLA is involved in modulating memory of aversively motivated training, such as footshock training used in inhibitory avoidance and Pavlovian fear conditioning, the evidence also clearly indicates that the BLA is quite promiscuous in influencing the consolidation of memory for many different kinds of motivationally arousing training experiences (McGaugh 2002b, Packard & Cahill 2001).

As memory for different types of training is known to involve different brain regions (Eichenbaum & Cohen 2001, Packard & Knowlton 2002, Poldrack & Packard 2003), the extensive evidence that posttraining intra-amygdala drug infusions affect memory for many kinds of training is consistent with the hypothesis that the amygdala regulates memory consolidation occurring at other brain sites. In view of the evidence suggesting that the amygdala may be a locus of plasticity mediating fear-based learning (Davis 2000, LeDoux 2000, Shumyatsky et al. 2002, Stork & Pape 2002), posttraining intra-amygdala infusions may also directly influence consolidation occurring within the amygdala (Schafe et al. 2001). This hypothesis is supported by considerable evidence that intra-amygdala infusions of the NMDA receptor antagonist AP-5 typically impair memory for fear-based learning (Fanselow & Kim 1994, Kim & McGaugh 1992, Maren et al. 1996, Stork & Pape 2002, Walker & Davis 2000). However, the evidence that posttraining intra-BLA infusions of AP-5 can either enhance or impair memory consolidation, depending on the training conditions (LaLumiere et al. 2004), suggests that AP-5 effects on memory are not solely due to blocking of neuroplasticity within the BLA. Moreover, memory consolidation is modulated by activating or blocking either NMDA receptors or non-NMDA glutamate receptors in the BLA posttraining (Bonini et al. 2003, Rubin et al. 2001). Additionally, there is considerable evidence that an intact and functioning amygdala is not required for many types of fear-based learning, including inhibitory avoidance and contextual fear conditioning (Amorapanth et al. 2000; Berlau & McGaugh 2003; Cahill et al. 2000; Killcross et al. 1997; Lehmann et al. 2000, 2003; Vazdarjanova & McGaugh 1998). There is also much evidence that memory for these kinds of training is modulated by posttraining drug infusions administered to many other brain regions (e.g., Sacchetti et al. 1999, 2002; Walz et al. 2000). Such evidence clearly suggests that if the BLA is a locus of fear-based memory it is not a unique locus; brain regions other than the amygdala are involved in the consolidation of memory of fear-based training.

STRESS HORMONES INFLUENCE MEMORY CONSOLIDATION VIA NEUROMODULATORY INTERACTIONS WITHIN THE BASOLATERAL AMYGDALA

The early evidence that drugs administered systemically after training can enhance memory consolidation in rats (McGaugh & Petrinovich 1965) suggested the possibility that adrenal stress hormones, epinephrine and corticosterone, released by the emotionally arousing training typically used in such studies may play a role in aiding the consolidation of memory of the training experiences (Gold & McGaugh 1975). There is now extensive evidence supporting this hypothesis. Posttraining systemic injections of epinephrine or corticosterone, as well as drugs affecting adrenergic and glucocorticoid receptors, produce dose-dependent and time-dependent enhancement of memory (Bohus 1994, de Kloet 1991, Gold &

van Buskirk 1975, Izquierdo & Diaz 1983, Lupien & McEwen 1997, McEwen & Sapolsky 1995, Sandi & Rose 1994). Furthermore, these two hormones interact in influencing memory consolidation (Borrell et al. 1983). Administration of metyrapone, a drug that attenuates the increase in corticosterone induced by aversive stimulation, blocks the memory-enhancing effects of posttraining systemic injections of epinephrine (Roozendaal et al. 1996). Moreover, there is considerable evidence that the BLA is critically involved in mediating the memory-modulating effects of epinephrine and corticosterone (McGaugh et al. 2000; McGaugh & Roozendaal 2002; Roozendaal 2000, 2002).

Noradrenergic Influences

The finding that *stria terminalis* lesions block the memory-enhancing effects of systemically administered epinephrine (Liang & McGaugh 1983) was the first to suggest that epinephrine effects on memory might involve the amygdala (see also Torras-Garcia et al. 1998). Additional evidence supporting this possibility was provided by the finding that epinephrine effects on memory are also blocked by lesions of the amygdala (Cahill & McGaugh 1991) as well as by intra-amygdala infusions of the β-adrenoceptor antagonist propranolol (Liang et al. 1986). An important implication of these findings, as well as the earlier findings of Gallagher et al. (1981), was that memory consolidation is influenced by NE release in the amygdala. In strong support of this implication, many subsequent studies have reported that posttraining intra-amygdala (or intra-BLA) infusions of NE or the β-adrenoceptor agonist clenbuterol enhance memory in rats (e.g., Ferry & McGaugh 1999; Hatfield & McGaugh 1999; Introini-Collison et al. 1991, 1996; Izquierdo et al. 1992; Liang et al. 1990, 1995). Moreover, intra-amygdala infusions of the noradrenergic toxin DSP-4 impair inhibitory avoidance memory, and posttraining intra-amygdala infusions of NE block the impairment (Liang 1998). The finding of Liang et al. (1990) that *stria terminalis* lesions block the memory-enhancing effects of posttraining intra-amygdala infusions of NE is consistent with the hypothesis that the effects involve projections to other brain regions mediated, at least in part, by that pathway.

In addition to β-adrenoceptor influences, α-adrenoceptor influences in the BLA also modulate memory consolidation. Posttraining intra-BLA infusions of the α_1-adrenoceptor antagonist prazosin impair inhibitory avoidance memory, whereas infusions of the α_1 agonist phenylephrine, together with yohimbine, a presynaptic α_2-adrenoceptor antagonist, enhance retention (Ferry et al. 1999b). The α_1-induced enhancement is likely due to an interaction involving β-adrenoceptors because posttraining intra-BLA infusions of the β-adrenoceptor antagonist atenolol block the memory enhancement produced by activation of α_1 receptors. The evidence that retention is enhanced by posttraining intra-amygdala infusions of the synthetic cAMP analog 8-bromo-cAMP (Liang et al. 1995) suggests that activation of β-adrenoceptors modulates memory via a direct coupling to adenylate cyclase. Thus, the finding that blocking α_1-adrenoceptors with intra-amygdala

infusions of prazosin does not prevent the memory enhancement induced by concurrently infused 8-bromo-cAMP is consistent with the hypothesis that the memory-enhancing effects of α-adrenoceptor activation are mediated by an interaction with β-adrenoceptors (Ferry et al. 1999a).

There is also considerable evidence that the amygdala is involved in mediating the memory-modulating effects of systemically administered stress hormones and drugs. As noted above, *stria terminalis* or amygdala lesions or infusions of β-adrenoceptor antagonists block the memory-enhancing effects of epinephrine. Findings of several studies suggest that epinephrine effects involve activation of β-adrenoreceptors on the ascending vagus projecting to the nucleus of the solitary tract (NTS), which provides direct NE activation of the amygdala as well as indirect activation via projections to the locus coeruleus (Liang 2001, Williams & Clayton 2001). The finding that intra-NTS infusions of the β-adrenoceptor antagonist propranolol (Clayton & Williams 2000b) or inactivation of the NTS with lidocaine (Williams & McGaugh 1992) prevent epinephrine enhancement of memory provides evidence that the NTS is part of a brain stem system that, together with the locus coeruleus, enables epinephrine-induced memory enhancement. Amygdala or *stria terminalis* lesions also block the effects of systemically administered drugs affecting GABAergic, opioid peptidergic, and muscarinic cholinergic receptors (Ammassari-Teule et al. 1991, Introini-Collison et al. 1989, McGaugh et al. 1986, Tomaz et al. 1992). Moreover, the evidence that β-adrenoceptor antagonists infused into the amygdala (and, more specifically, the BLA) block the memory-modulating effects of these systemically administered drugs affecting GABAergic and opiate peptidergic receptors indicates that their effects, like those produced by intra-amygdala infusions, involve a common action on NE activation within the amygdala (McGaugh et al. 1988, 2000). Ragozzino & Gold (1994) reported that posttraining intra-amygdala infusions of glucose block the memory-impairing effects of the opiate drug morphine. However, as such glucose infusions do not attenuate the memory impairment induced by propranolol (Lennartz et al. 1996, McNay & Gold 1998), glucose effects appear to act prior to adrenergic activation within the amygdala, consistent with evidence that intra-amygdala propranolol infusions block opiate effects on memory consolidation (McGaugh et al. 1988). The finding that glutamate infused concurrently with propranolol prevented propranolol-induced memory impairment (Lennartz et al. 1996) suggests that glutamate influences in the amygdala occur at a step beyond noradrenergic activation.

Evidence from studies using in vivo microdialysis and high-performance liquid chromatography (HPLC) to assess NE release in the amygdala supports the view that NE release in the amygdala plays an important, perhaps even critical, role in amygdala influences on memory. Footshock stimulation like that used in inhibitory avoidance training induces NE release in the amygdala; the NE levels vary directly with the footshock intensity (Galvez et al. 1996, Quirarte et al. 1998). Systemic administration of memory-enhancing doses of picrotoxin or naloxone (GABA and opioid receptor antagonists, respectively) increases NE release, whereas injections

of memory-impairing doses of muscimol or β-endorphin (GABA and opioid receptor agonists, respectively) decrease NE release (Hatfield et al. 1999, Quirarte et al. 1998). Moreover, systemic administration of memory-enhancing doses of epinephrine, electrical stimulation of the vagus nerve projecting to the NTS, or infusions of glutamate or the β-adrenoceptor clenbuterol into the NTS also increase NE release and enhance memory (Clayton & Williams 2000a, Hassert 2004, Miyashita & Williams 2002, Williams et al. 1998).

Recent experiments also examined the effects of inhibitory avoidance training on amygdala NE release (McIntyre et al. 2003). As is shown in Figure 1*A*, the training induced an increase in NE release that was sustained for at least 2 h. Additionally, the NE release induced by the single footshock training trial was greater than that induced in animals given a similar footshock in a holding cage (Galvez et al. 1996, Quirarte et al. 1998). Figure 1*B* shows the NE levels of the individual rats given inhibitory avoidance training as well as the retention score (latency to reenter the shock compartment) on a 24-h test. Animals with higher NE levels after training displayed better retention performance than those with lower levels. The NE levels during the first five sample periods following the training correlated highly with subsequent retention performance. These in vivo microdialysis findings fit well with the evidence from pharmacological studies suggesting that noradrenergic activation of the amygdala plays an important role in amygdala modulation of memory consolidation.

Cholinergic Influences

The finding that ST lesions block the memory-enhancing effect of systemically administered cholinergic drugs (Introini-Collison et al. 1989) was the first to suggest that cholinergic drugs may affect memory consolidation, at least in part, through an influence involving the amygdala. Subsequent studies provided extensive evidence that, in rats, posttraining intra-amygdala infusions of muscarinic cholinergic agonists and antagonists enhance and impair, respectively, memory for many kinds of training, including inhibitory avoidance, Pavlovian fear conditioning, conditioned place preference, and change in reward magnitude (Introini-Collison et al. 1996, Passani et al. 2001, Power et al. 2003, Power & McGaugh 2002, Salinas et al. 1997, Schroeder & Packard 2002, Vazdarjanova & McGaugh 1999). Findings of experiments using posttraining infusions of the muscarinic cholinergic agonist oxotremorine administered together with selective M1 and M2 antagonists indicate that both receptor types are involved in the memory-enhancing effects of cholinergic activation (Power et al. 2003). Lesions of the nucleus basalis, the major source of cholinergic activation of the BLA, impair the learning and retention of inhibitory avoidance, and posttraining intra-BLA infusions of either oxotremorine or the acetylcholinesterase inhibitor physostigmine attenuate the memory impairment (Power & McGaugh 2002). In contrast to the effects of GABAergic and opioid peptidergic drugs, cholinergic effects are not mediated by adrenergic activation. Intra-amygdala infusions of β-adrenoceptor antagonists do not block the

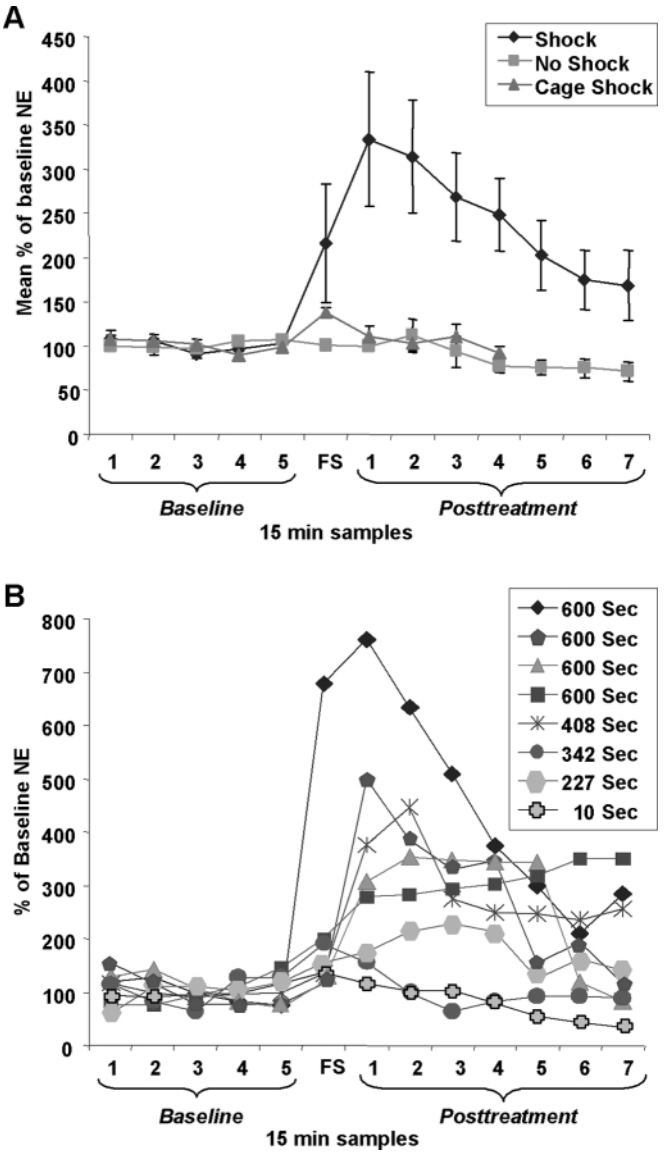

Figure 1 (*A*) Inhibitory avoidance training increases amygdala NE levels as assessed by in vivo microdialysis and high-performance liquid chromatography (HPLC). The No Shock animals were treated as the Shock (i.e., trained) animals but received no footshock. The Cage Shock animals received footshock in a different apparatus. (*B*) Amygdala NE release assessed by in vivo microdialysis and HPLC and inhibitory avoidance retention latencies of individual rats given footshock training. The correlation between NE levels assessed on the first 5 posttraining samples and 24-h retention latencies varied from +0.75 to +0.92. From McIntyre et al. 2002.

memory-enhancing effects of concurrently infused oxotremorine. Moreover, the muscarinic cholinergic antagonist atropine, at a subeffective dose when infused alone, blocks the memory-enhancing effects of intra-amygdala infusions of clenbuterol (Dalmaz et al. 1993, Salinas et al. 1997). Thus, cholinergic activation in the BLA, like that of glutamate effects discussed above, appears to provide modulatory influences on memory storage downstream from adrenergic activation.

Studies of the effects of histamine antagonists and agonists infused into the BLA provide additional evidence of a role of acetylcholine in the BLA in modulating consolidation (Cangioli et al. 2002, Passani et al. 2001). H_3 antagonists (ciproxifan, clobenprobit, or thioperamide) infused into the BLA decreased acetylcholine release, as assessed by in vivo microdialysis, and concurrent infusions of the H_2 agonist cimetidine blocked the decreased acetylcholine release. Moreover, posttraining intra-BLA infusions of H_3 antagonists, administered in doses found to decrease acetylcholine release, impaired memory for contextual fear conditioning (Passani et al. 2001). There is also evidence that acetylcholine is released within the amygdala during training. Studies using in vivo microdialysis have shown that acetylcholine levels in the amygdala increase while rats perform a spontaneous alternation task and that the increase is correlated with good performance on the task (Gold 2003, McIntyre et al. 2003). Because an intact amygdala is not required for the learning or retention of this task it is highly unlikely that the acetylcholine affects performance by influencing neuroplasticity within the amygdala. Rather, because this task is known to involve hippocampal functioning, these findings are consistent with other evidence, discussed below, suggesting that the amygdala influences memory processing that involves the hippocampus.

Glucocorticoid Influences

The glucocorticoid corticosterone (cortisol in humans) secreted from the adrenal cortex following arousing or stressful stimulation readily enters the brain. As noted above, extensive evidence indicates that posttraining systemically administered corticosterone and the synthetic glucocorticoid dexamethasone enhance memory consolidation and that the enhancement is due to selective activation of glucocorticoid receptors (Bohus 1994; Cordero & Sandi 1998; de Kloet 1991; Hui et al. 2004; Lupien & McEwen 1997; McGaugh & Roozendaal 2002; Oitzl & de Kloet 1992; Pugh et al. 1997; Roozendaal 2000, 2002; Sandi et al. 1997; Sandi & Rose 1994; Zorawski & Killcross 2002). Furthermore, the effects of corticosterone, like those of epinephrine, are mediated by the BLA. Selective lesions of the BLA block the memory-enhancing effects of dexamethasone (Roozendaal & McGaugh 1996a), and selective posttraining intra-BLA infusions of the glucocorticoid receptor agonist RU28362 enhance memory for inhibitory avoidance training (Roozendaal & McGaugh 1997b).

Additionally, glucocorticoid influences on memory, like that of epinephrine, involve β-adrenoceptor and cholinergic activation within the BLA. Intra-BLA infusions of a β-adrenoceptor antagonist block the memory-enhancing effects of

systemic injections of dexamethasone as well as the effects of the glucocorticoid receptor agonist RU28362 infused into the BLA concurrently (Quirarte et al. 1997). The enhancement of memory for inhibitory avoidance training induced by intra-BLA infusions of RU28362 is also blocked by concurrent infusion of Rp-cAMPS, a drug that inhibits PKA activity and thus blocks the norepinephrine signal cascade. Moreover, intra-BLA infusions of the glucocorticoid receptor antagonist RU38486 attenuate the memory-enhancing effects of clenbuterol infused concurrently such that a much higher dose of the β-adrenoceptor agonist clenbuterol (100 ng versus 1 ng) is required to induce memory enhancement (Roozendaal et al. 2002a). Such findings suggest that activation of glucocorticoid receptors in the BLA may facilitate memory consolidation by potentiating the norepinephrine signal cascade through an interaction with G protein–mediated effects.

Glucocorticoid effects on memory also appear to involve activation of brain stem nuclei, including the NTS, that send noradrenergic projections to the amygdala. The finding that infusions of RU28362 into the NTS enhance inhibitory avoidance retention and that intra-BLA infusions of a β-adrenoceptor antagonist block the enhancement (Roozendaal et al. 1999a) provides additional evidence that the NTS influences on memory consolidation involve noradrenergic influences within the amygdala (Clayton & Williams 2000a,b; Miyashita & Williams 2002; Williams et al. 1998, 2001). Other findings indicate that cholinergic activation within the BLA is also critical for enabling glucocorticoid enhancement of memory consolidation. Atropine infused into the BLA blocks the memory-enhancing effects of RU28362 infused concurrently posttraining, as well as the effects of systemically administered dexamethasone (Power et al. 2000). Finally, memory-modulating effects like those found with glucocorticoids are also found with corticotropin-releasing hormone (CRH). Posttraining intra-amygdala infusions of CRH enhance inhibitory avoidance retention (Liang & Lee 1988), and posttraining intra-BLA infusions of a specific CRH receptor antagonist impair retention (Roozendaal et al. 2002b).

Neuromodulatory Interactions Within the Amygdala Modulate Memory Consolidation

Figure 2 summarizes schematically the interactions of posttraining neuromodulatory influences within the amygdala affecting memory consolidation, as discussed in the preceding sections. The influences of epinephrine, opioid peptides, and GABA (gamma amino butyric acid) converge in regulating norepinephrine release in the amygdala. The effects of activation of α-adrenoceptors involve an interaction with β-adrenoceptor activation. Acetylcholine and glutamate influences occur at steps beyond the activation of β-adrenoceptors. Glucocorticoid effects on memory consolidation involve activation of brain stem nuclei (NTS and locus coeruleus) that send noradrenergic projections to the amygdala as well as potentiating the noradrenergic signal cascade within the amygdala. As discussed below, extensive evidence suggests that projections from the amygdala mediated by the ST, as

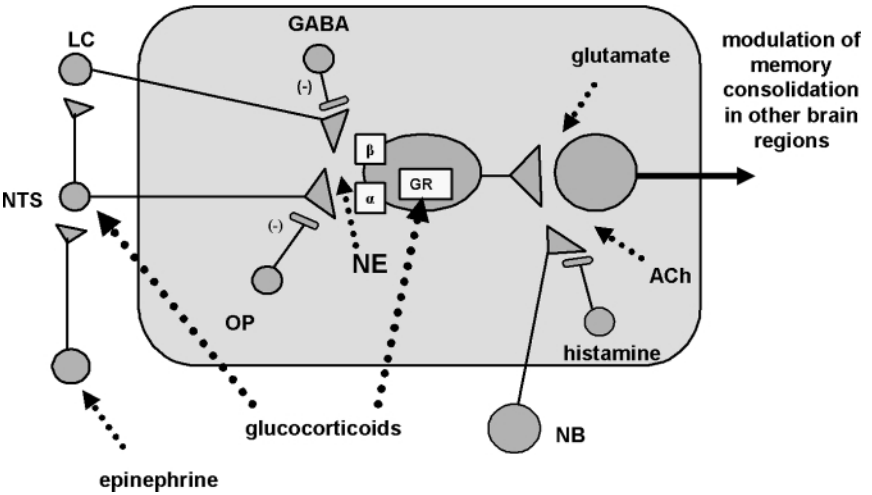

Figure 2 Schematic representation of neuromodulatory interactions within the basolateral amygdala affecting memory consolidation suggested by the experimental findings. NE release within the amygdala is critical for memory-modulatory influences. Epinephrine released from the adrenal medulla activates receptors on the ascending vagus projecting to the nucleus of the solitary tract (NTS), which sends noradrenergic projections to the amygdala, as well as the locus coeruleus (LC), which also sends noradrenergic projections to the amygdala. Opioid peptides (OP) and GABA inhibit norepinephrine (NE) release. Corticosterone released from the adrenal cortex activates glucocorticoid receptors (GR) in the NTS and BLA and elsewhere in the brain. In the BLA, corticosterone interacts with β-adrenergic activation. Glutamatergic and cholinergic activation (ACh) from the nucleus basalis (NB) occur at a step beyond noradrenergic activation. Activation of histamine receptors regulates ACh release. These modulatory influences converge in activating amygdala projections to other brain regions involved in memory consolidation.

well as other pathways, modulate memory consolidation occurring in other brain regions.

THE BASOLATERAL AMYGDALA INTERACTS WITH OTHER BRAIN SYSTEMS IN MODULATING MEMORY CONSOLIDATION

There is now abundant evidence that neuromodulatory interactions occurring within the amygdala influence memory consolidation. Although it remains possible that such influences may be due, at least in part, to influences on neuroplasticity within the amygdala, several kinds of evidence suggest that alterations in

amygdala functioning affect memory consolidation through amygdala influences on other brain regions involved in memory consolidation. First, the BLA sends projections to many other brain regions (Petrovich et al. 2001, Pitkänen 2000, Price 2003, Sah et al. 2003, Young 1993). Some of these projections are mediated by the ST. Thus, the evidence, discussed above, that ST lesions block the memory-modulating effects of electrical stimulation and intra-amygdala drug infusions strongly suggests that modulation within the amygdala is not sufficient to affect memory; efferent projections seem required. Second, posttraining treatments affect memory for many kinds of training. Although many (perhaps most) of the studies have used fear-based training (i.e., footshock), the evidence summarized above clearly indicates that amygdala modulation of memory consolidation is not restricted to findings of studies using fear-based learning tasks. Third, there is evidence that training known to involve the amygdala (Pavlovian fear conditioning) induces the expression of several transcriptionally regulated genes implicated in synaptic plasticity in many brain areas, including the hippocampus, striatum, and cortex, as well as the amygdala (Ressler et al. 2002). As these effects were seen only when the stimuli used in the training induced behavioral learning, they were not simply due to nonspecific effects of stress or arousal but appeared to be involved in memory consolidation. Fourth, as discussed below, extensive evidence from many types of studies indicates that the amygdala interacts with other brain regions in modulating the consolidation of memory for different kinds of training (McGaugh 2002a).

Caudate Nucleus, Hippocampus, and Nucleus Accumbens

The amygdala sends direct projections to the caudate nucleus (via the ST) and both direct and indirect projections to the hippocampus (Petrovich et al. 2001, Pitkänen 2000). The finding that ST lesions block the memory-enhancing effects of oxotremorine infused posttraining into the caudate nucleus suggests that efferents from the amygdala influence memory processing involving the caudate nucleus (Packard et al. 1996). Much evidence indicates that the caudate and hippocampus are involved in different kinds of learning (e.g., McDonald & White 1993, Packard & McGaugh 1992). In a study of rats given water-maze training (swimming to a platform submerged below the water surface), Packard and colleagues (Packard & Teather 1998, Packard et al. 1994) found that amphetamine infused posttraining into the caudate selectively enhanced memory of visually cued training, whereas infusions administered into the dorsal hippocampus selectively enhanced memory of spatial training. In contrast, amphetamine infused into the amygdala posttraining enhanced memory for both types of training. Additional findings indicated that inactivation of the hippocampus (with lidocaine) prior to testing blocked retention of spatial training and inactivation of the caudate blocked retention of visually cued training. However, inactivation of the amygdala prior to retention testing did not block memory of either kind of training. These findings provide strong evidence that the amygdala modulates the consolidation of both caudate-dependent

and hippocampus-dependent tasks and is not a locus of memory for either type of training. In other experiments, Packard and his colleagues found that glutamate infused into the caudate or hippocampus posttraining enhanced response learning or spatial learning, respectively (Packard 1999). Additionally, in rats trained in a radial-maze task, lidocaine infused into the amygdala blocked the memory enhancement induced by posttraining intrahippocampal infusions of glutamate (Packard & Chen 1999).

Other recent findings of studies of the effects of posttraining intra-amygdala infusions of a glucocorticoid agonist provide additional evidence of amygdala-hippocampus interactions in memory consolidation. Unilateral posttraining intrahippocampal infusions of RU28362 enhanced rats' retention of inhibitory avoidance training. The glucocorticoid-induced retention enhancement was blocked selectively by ipsilateral infusions of a β-adrenoceptor antagonist into the BLA or by lesions of the BLA (Roozendaal & McGaugh 1997a; Roozendaal et al. 1999b). These findings indicate that the hippocampus is involved in memory for inhibitory avoidance and that glucocorticoids influence memory by activating hippocampal glucocorticoid receptors as well as receptors located in the NTS and BLA, as discussed above. Other evidence indicates that glucocorticoids affect memory by activating the nucleus accumbens. The BLA projects to the nucleus accumbens primarily via the ST (Kelley et al. 1982, Wright et al. 1996). The possible importance of the BLA-ST-nucleus accumbens pathway in memory consolidation is suggested by the finding that lesions of the nucleus accumbens, like lesions of the BLA, block the memory-enhancing effects of systemically administered dexamethasone (Roozendaal & McGaugh 1996b, Setlow et al. 2000). Furthermore, the finding that unilateral lesions of the BLA combined with contralateral (unilateral) lesions of the nucleus accumbens also blocked dexamethasone effects strongly indicates that these two structures interact via the ST in influencing memory consolidation (Setlow et al. 2000).

Hippocampal and BLA glucocorticoid influences on memory for inhibitory avoidance training also involve the nucleus accumbens as well as the ST. As is shown in Figures 3*A* and 3*B*, bilateral lesions of either the ST or nucleus accumbens block the memory-enhancing effects of posttraining intra-BLA or intrahippocampal infusions of RU28362 (Roozendaal et al. 2001). Because the BLA does not project to the hippocampus via the ST, indirect projections to the hippocampus via the entorhinal cortex seem likely to enable the BLA-hippocampus interaction in memory modulation. Because the hippocampus is known to project to the nucleus accumbens, that region may be a critical locus of converging BLA and hippocampal modulatory influences on memory consolidation. The finding that inactivation of the nucleus accumbens with infusions of bupivacaine prior to training blocks the acquisition of contextual fear conditioning provides evidence consistent with this hypothesis (Haralambous & Westbrook 1999). Understanding the roles of the BLA-nucleus accumbens and hippocampus-nucleus accumbens pathways in modulating glucocorticoid effects on memory consolidation will require further investigation. It also remains to be determined whether these pathways are

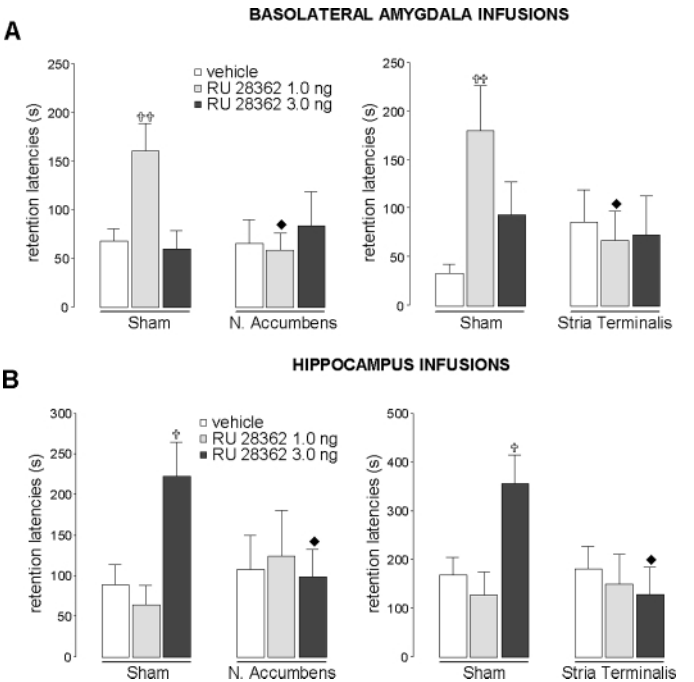

Figure 3 (*A*) Bilateral lesions of the nucleus accumbens or *stria terminalis* block the enhancement of inhibitory avoidance retention induced by posttraining intra-BLA infusions of the glucocorticoid receptor agonist RU28362. (*B*) Bilateral lesions of the nucleus accumbens or *stria terminalis* block the enhancement of inhibitory avoidance retention induced by posttraining intrahippocampal infusions of the glucocorticoid receptor agonist RU28362. From Roozendaal et al. 2001.

also involved in mediating other BLA neuromodulatory influences on memory consolidation.

In most of the studies summarized above, the animals given footshocks during fear-based training received only a few footshocks; only one footshock was given for inhibitory avoidance training. Other studies have reported that more extensive stressful experiences, such as those induced by prolonged restraint, many footshocks, or confinement on an elevated platform prior to training can either enhance or impair acquisition, depending on the type of training task used (Kim et al. 2001, Shors 2001). Additionally, consistent with findings discussed above, amygdala lesions block the stress-induced modulation of learning (Kim et al. 2001) as well as stress-induced enhancement of conditioning (trace conditioning) that is known to depend on the hippocampus and to involve the actions of glucocorticoids (Beylin & Shors 2003). The evidence that stress induced in rats shortly after the induction of long-term potentiation in the dentate gyrus of the hippocampus disrupts

the maintenance of LTP (long-term potentiation) (Korz & Frey 2003) is consistent with the evidence suggesting that stress effects on memory involve influences on hippocampal functioning.

Studies of BLA influences on hippocampal neuroplasticity provide additional important evidence of amygdala-hippocampal interactions (Abe 2001). Electrical stimulation of the BLA enhances the induction of LTP in the dentate gyrus of the hippocampus (Akirav & Richter-Levin 1999, Frey et al. 2001, Ikegaya et al. 1995a). Also, selective lesions of the BLA or infusions of a β-adrenoceptor antagonist into the BLA block the induction of LTP in the dentate gyrus (Ikegaya et al. 1994, 1995b, 1997). Also, consistent with the findings of BLA modulation of memory, NE and corticosterone both influence the effects of BLA stimulation on dentate gyrus LTP (Akirav & Richter-Levin 2002). Thus, although it is not known what specific pathway(s) connect the BLA with the hippocampus, it is clear from these findings that alterations in BLA functioning regulate hippocampal neuroplasticity. It is also not yet known whether the BLA influences the induction of LTP in other regions of the hippocampus or in other areas of the brain. The recent findings that Pavlovian fear conditioning induces an increase in synchronization of theta-frequency activity in the lateral amygdala and CA1 region of the hippocampus strongly suggest that activation of an amygdala-hippocampus circuit is involved in fear-based learning (Seidenbecher et al. 2003). More generally, studies of synchronized oscillatory activity within the BLA suggest that such activity may facilitate the temporal lobe as well as neocortical processes involved in consolidating explicit or declarative memory (Paré 2003, Pelletier & Paré 2004).

BLA-Cortical Interactions in Memory Consolidation

It is now well established that various regions of the cortex are involved in memory consolidation. Posttraining infusions of drugs into cortical regions can impair or enhance the consolidation of memory for several kinds of training (Ardenghi et al. 1997, Baldi et al. 1999, Izquierdo et al. 1997, Sacchetti et al. 1999). Moreover, the findings of several recent studies indicate that the BLA modulates cortical functioning involved in memory consolidation (Paré 2003). Neurons within the BLA project directly to the entorhinal cortex (Paré & Gaudreau 1996, Paré et al. 1995, Petrovich et al. 2001, Pikkarainen et al. 1999). Posttraining drug infusions administered into the entorhinal cortex modulate consolidation of memory for inhibitory avoidance training (Izquierdo & Medina 1997). Recent findings have shown that such modulation requires a functioning BLA (Roesler et al. 2002). As is shown in Figure 4*A*, unilateral posttraining infusions of 8-Bromo-cAMP produce dose-dependent memory enhancement. The enhancement is blocked in animals with ipsilateral lesions of the BLA. Further, as is shown in Figure 4*B*, lesions of the BLA contralateral to the entorhinal cortex infusions do not block the memory enhancement induced by 8-Bromo-cAMP. These findings clearly suggest that the BLA influence is mediated by direct connections with the ipsilateral entorhinal cortex and is not due to other possible effects of a BLA lesion. Other recent

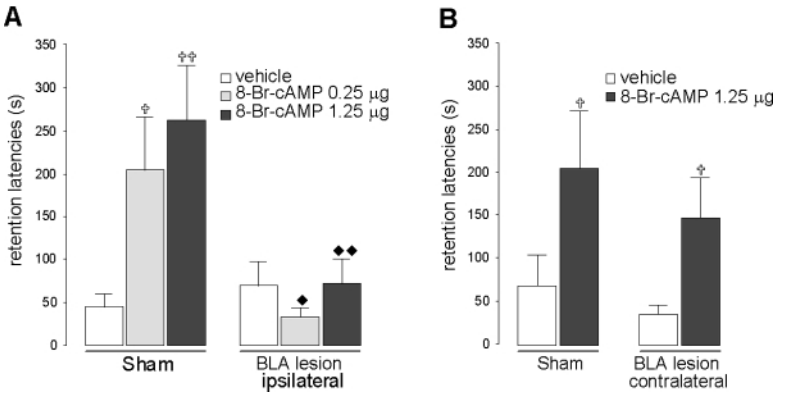

Figure 4 (*A*) Unilateral BLA lesions block the enhancement of inhibitory avoidance retention induced by posttraining ipsilateral infusions of 8-Bromo-cAMP administered into the entorhinal cortex. (*B*) Unilateral BLA lesions do not block the memory-enhancing effects of 8-Bromo-cAMP infused posttraining into the contralateral entorhinal cortex. From Roesler et al. 2002.

studies have reported that BLA lesions also block the memory-enhancing effects of oxotremorine infused posttraining into the anterior cingulate cortex (Malin & McGaugh 2003) and that a β-adrenoceptor antagonist infused into the BLA blocks the memory enhancement induced by 8-Br-cAMP infused into the insular cortex posttraining (M.I. Miranda and J.L. McGaugh, submitted manuscript).

It is likely that the BLA also influences cortical functioning via its projection, largely through the ST (Price 1981), to the nucleus basalis (NB), which provides cholinergic activation of the cortex. The NB-cortical projections are essential for learning-induced cortical plasticity (Miasnikov et al. 2001). Stimulation of the BLA activates the cortex, as indicated by EEG desynchronization, and potentiates NB influences on cortical activation. Moreover, inactivation of the NB with lidocaine blocks the BLA effects on cortical activation (Dringenberg & Vanderwolf 1996, Dringenberg et al. 2001). These findings suggest that the BLA may influence cortical functioning in memory consolidation, at least in part, through its effects on the NB and consequent cholinergic activation of the cortex. Recent findings support this suggestion (Power et al. 2002). Selective lesions of cortical NB corticopetal cholinergic projections induced by 192-IgG saporin blocked the dose-dependent enhancement of inhibitory avoidance induced by posttraining intra-BLA infusions of NE. Although these findings indicate that memory-modulatory influences within the BLA require cholinergic activation of the cortex, it is not clear from these findings whether BLA-induced cholinergic activation is required for such modulation or, alternatively, whether cortical cholinergic activity is required for BLA influences on memory consolidation. In any case, it is clear that a functioning cortex is required for BLA influences on memory consolidation.

EMOTIONAL AROUSAL, STRESS HORMONES, AND AMYGDALA ACTIVATION MODULATE HUMAN MEMORY CONSOLIDATION

The extensive findings of animal experiments discussed above provide considerable evidence that stress hormones released by emotional experiences influence memory consolidation and that the influence is mediated by activation of the amygdala. The findings of many studies of effects of emotional arousal, stress hormones, and amygdala activation on human memory are consistent with those of animal studies (Buchanan & Adolphs 2003, Cahill 2000, Cahill & McGaugh 1998, Dolan 2000, McGaugh 2000). The stress hormone cortisol administered prior to presentations of words or pictures enhanced subsequent recall (Abercrombie et al. 2003, Buchanan & Lovallo 2001). Amphetamine administered to human subjects, either before or after they learned lists of words, also enhanced long-term memory (Soetens et al. 1993, 1995). Administration of the β-adrenoceptor antagonist propranolol to subjects prior to their viewing an emotionally arousing slide presentation blocked the enhancing effects of emotional arousal on long-term memory (Cahill et al. 1994). Epinephrine or cold pressor stress (known to induce the release of epinephrine) administered after subjects viewed emotionally arousing slides enhanced the subjects' long-term memory of the slides (Cahill & Alkire 2003, Cahill et al. 2003). Similar effects were produced by administration of the α_2 adrenoceptor antagonist yohimbine, which acts to stimulate NE release (O'Carroll et al. 1999, Southwick et al. 2002). The findings of these human studies are consistent with those of animal experiments in indicating a critical role of emotional activation and stress hormones in memory consolidation.

There is also considerable evidence from human studies indicating that the amygdala is involved in enabling the enhanced memory induced by emotional arousal. In human subjects with selective bilateral lesions of the amygdala, memory for emotionally arousing material is not enhanced, as it is in normal subjects (Adolphs et al. 1997, Cahill et al. 1995). Unilateral lesions, involving the temporal lobe, that damage the amygdala produce similar effects (Frank & Tomaz 2003, LaBar & Phelps 1998). Studies using positron emission tomography (PET) and fMRI brain imaging have provided additional evidence that the influence of emotional arousal on memory involves activation of the amygdala. Cahill et al. (1996) reported that amygdala activity assessed by PET imaging of subjects as they viewed emotionally arousing films correlated highly (+0.93) with subjects' recall of the films three weeks later. The valence of the emotional influence appears not to be critical for activation of the amygdala (Anderson et al. 2003, Small et al. 2003). In subsequent studies using PET imaging Hamann et al. (1999, 2002) reported that amygdala activity induced by viewing either pleasant or unpleasant slides correlated highly with memory for the slides assessed one month later. Studies using fMRI have obtained highly similar findings. Canli et al. (2000) found that subjects' memory for a series of scenes tested three weeks after brain scanning correlated highly with amygdala activity induced by viewing the scenes. Furthermore, and

importantly, the relationship between amygdala activity during encoding and memory was greatest for the scenes rated as most emotionally intense. An additional finding of these studies was that, with both PET and fMRI experiments, activity of the right amygdala was related to enhanced memory in men, whereas activity of the left amygdala correlated with enhanced memory in women (Cahill et al. 2001, Canli et al. 2002). Such findings indicate that it will be essential to consider possible sex differences in future studies of emotionally influenced memory and that understanding the bases of such differences will provide further insight into mechanisms of emotional arousal underlying influences on memory consolidation. There is evidence from human imaging studies that the amygdala is also activated during the retrieval of previously learned emotionally arousing material and that the effect is independent of the valence of the emotional material (Dolan 2000).

Other findings based on an analysis of PET scans provide evidence, consistent with that from many animal studies, indicating that amygdala activation influences memory processing in other brain regions. Hamann et al. (1999) and Dolcos et al. (2003) found that the activity levels of amygdala and hippocampal/parahippocampal regions were correlated during the encoding of emotionally arousing material. The findings of a "path analysis" (structural equation modeling) study (Kilpatrick & Cahill 2003b) of amygdala activity scanned while subjects viewed neutral or emotionally arousing films (Cahill et al. 1996) suggest that emotional arousal increased amygdala influences on activity of the ipsilateral parahippocampal gyrus and ventrolateral prefrontal cortex. These findings provide additional evidence that amygdala influences on other brain regions are critical in creating lasting memories.

CONCLUSIONS

It has long been known, or at least commonly believed, that emotionally arousing experiences tend to be well remembered. The findings of animal and human studies reviewed here provide extensive evidence that supports this conclusion. Additionally, the findings have revealed some of the neurobiological processes that enable emotional experiences to create strong, long-lasting memories. Emotionally significant experiences, whether pleasant or unpleasant, activate hormonal and brain systems that regulate the consolidation of newly acquired memories. Many neuromodulatory systems play a role, and critical interactions among them occur in the basolateral region of the amygdala. These effects are integrated through common actions on noradrenergic and cholinergic activation within the basolateral amygdala, which, in turn, regulate memory consolidation through the amygdala's projections to many other brain regions involved in processing memories of different kinds. Through the activation of these interacting systems, our emotionally exciting experiences become well remembered.

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