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Review

Role of amygdala norepinephrine in mediating stress hormone regulation of memory storage

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KEY WORDS norepinephrine; amygdalaloid body; learning; memory; adrenal cortex hormones; stress; alpha adrenergic receptors; beta adrenergic receptors

ABSTRACT

There is extensive evidence indicating that the noradrenergic system of the amygdala, particularly the basolateral nucleus of the amygdala (BLA), is involved in memory consolidation. This article reviews the central hypothesis that stress hormones released during emotionally arousing experiences activate noradrenergic mechanisms in the BLA, resulting in enhanced memory for those events. Findings from experiments using rats have shown that the memory-modulatory effects of the adrenocortical stress hormones epinephrine and glucocorticoids involve activation of β-adrenoceptors in the BLA. In addition, both behavioral and microdialysis studies have shown that the noradrenergic system of the BLA also mediates the influences of other neuromodulatory systems such as opioid peptidergic and GABAergic systems on memory storage. Other findings indicate that this stress hormone-induced activation of noradrenergic mechanisms in the BLA regulates memory storage in other brain regions.

INTRODUCTION

Mueller and Pilzecker[1] were the first to propose that memory traces are fragile in the beginning and become consolidated over time. Guided by this view, numerous studies have shown that treatments such as electrical brain stimulation or drug injections given during a critical time shortly after training can alter the consolidation of lasting memory traces. The neuropharmacological analysis of memory processes is complicated by the fact that drugs administered before training can indirectly influence learning and memory by affecting sensory-motor, arousal or attentional processes. Thus, administration of drugs immediately after training, at a time when memory storage processes are assumed to be susceptible to modulation, has been used extensively to examine the direct influence of a drug on memory storage[2-4]. Posttraining treatments obviously avoid the non-specific drug effects on performance during training and subsequent testing. Studies using posttraining drug administration have provided extensive evidence supporting the hypothesis that the strength of long-term memories is influenced by hormonal systems activated by experience[5,6]. The hypothesis that norepinephrine plays a role in learning and memory emerged several decades ago when Kety[6] suggested that brain processes associated with affective states, including the release of biogenic amines, may modulate synaptic processes in ways that selectively strengthen recently activated neuronal circuits. Considerable evidence now indicates that stress-released adrenergic catecholamine systems are involved in regulating long-term memory storage. The first experiments investigating this general hypothesis examined the effects of a large variety of sympathomimetics and anti-adrenergic agents on learning and memory. Depletion of norepinephrine by tyrosine hydroxylase inhibition with α-MPT, 6-hydroxydopamine, or dopamine hydroxylase inhibition with diethyldithiocarbamate (DDC) usually im-

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paired learning performance. Similar impairing effects were found with a disruption of vesicular storage by reserpine (see 7 and 8 for review). In contrast, numerous studies have shown that amphetamine, known to influence the release of catecholamines from peripheral storage sites[9], enhances memory when administered systemically either shortly before or shortly after training[10-13]. Moreover, the fact that amphetamine enhances memory when administered posttraining supports the view that it enhances retention by influencing memory storage processes. Although the use of amphetamine (that passes the blood-brain barrier) or non-specific antiadrenergic agents clearly implicate norepinephrine in learning and memory, it remains unclear whether the effects involve peripheral or central mechanisms.

Recent research in our laboratory has been focused on the hormonal and brain systems that mediate the effects of emotional arousal on memory storage. This article reviews the role of norepinephrine in mediating the effects of stress-released hormones on memory storage. Our recent findings suggest that peripheral stress hormones influence memory storage by activating noradrenergic mechanisms in the amygdala. Furthermore, our data suggests that this noradrenergic activation of the amygdala, and more precisely the basolateral nucleus of the amygdala, serves to modulate memory storage in other brain regions.

ADRENERGIC CATECHOLAMINES AND MEMORY STORAGE FROM THE PERIPHERY TO THE BRAIN

The findings from the late 70s were the first to suggest the involvement of central norepinephrine in memory. Haycock *et al*[14] reported that intra-ventricular infusions of norepinephrine facilitated retention, whereas DDC, a drug that depletes catecholamines, impaired inhibitory avoidance retention when administered posttraining[15]. Furthermore, concurrent infusions of norepinephrine into the ventricles or systemic injections of norepinephrine or epinephrine blocked the retention impairment produced by peripheral administration of DDC[16-18]. Providing further evidence for the view that central norepinephrine function modulates memory, Gold and van Buskirk[19] showed that inhibitory avoidance training decreased brain norepinephrine levels under conditions that result in good retention, suggesting an enhanced release of this neuromodulator during training.

Although these results suggest the involvement of central norepinephrine in regulating memory storage, series of experiments have shown that this process is initiated in the periphery, by the release of epinephrine from the adrenal medulla. Systemic administration of epinephrine (that does not pass the blood brain barrier) enhances retention in different tasks, including inhibitory avoidance[20], multitrial avoidance[21], a one-trial appetitive task[22] and an aversively motivated discrimination task[23]. Epinephrine is effective when given immediately after training and moderate doses produce greatest enhancement whereas larger doses are less effective or even impair retention. Doses of epinephrine found to enhance retention produce plasma epinephrine levels comparable to those found after inhibitory avoidance training[24]. Moreover, retention enhancement induced by epinephrine is blocked by the β-adrenoceptor antagonist propranolol, a drug that readily enters the brain[22,25] as well as by sotalol, an adrenoceptor antagonist that does not enter the brain[26]. Posttraining administration of β-adrenoceptor agonists that enter the brain, including dipivefrin and clenbuterol, also enhance memory consolidation, which can be blocked by propranolol, but not by sotalol[26]. Moreover, the memory-enhancing effect of clenbuterol is selectively blocked by centrally, but not peripherally, acting adrenoceptor antagonists[27]. Such findings indicate that the effects of epinephrine on memory storage are initiated by activation of peripheral β-adrenoceptors but also involve activation of central β-adrenoceptors.

Other findings have indicated that posttraining systemic injections of 4-OH amphetamine (a derivative of amphetamine that does not pass the blood-brain barrier) enhances inhibitory avoidance retention, whereas central injections of amphetamine are ineffective[28]. The effects of systemic administration of amphetamine and 4-OH amphetamine do not seem to involve peripheral sympathetic neurons, the primary source of peripheral norepinephrine, as sympathetic denervation induced 24 h prior to training by 6-OHDA did not attenuate the memory-enhancing effects of either drug[28]. In contrast, adrenal demedullation, ie, elimination of peripheral epinephrine, attenuates the effects of both amphetamine and 4-OH amphetamine on memory for active avoidance as well as inhibitory avoidance training[28]. More recently, Williams *et al*[29] have shown that the peripherally acting β-adrenoceptor antagonist sotalol blocks the memory-enhancing effects of systemically administered 4-OH amphetamine. These findings provide strong support for the view that central effects of epinephrine on memory storage are mediated by the release of peripheral epinephrine from the adrenal medulla.

A large number of studies have suggested that the vagus nerve might be playing a critical role in mediating the peripheral effects of epinephrine on brain systems involved in memory storage. The vagus nerve influences pontine and limbic structures by relaying input regarding peripheral states to the central nervous system. Peripheral vagal afferents project to the nucleus of the solitary tract (NTS), a brainstem structure with a high population of noradrenergic neurons[30]. The fact that the NTS receives peripheral input and conveys information to forebrain structures involved in learning and memory suggests that central noradrenergic neurons arising in the NTS mediate the effects of peripheral physiological influences on memory consolidation. This implication is supported by evidence that infusions of the local anesthetic lidocaine into the NTS posttraining impair inhibitory avoidance retention[31]. Moreover, injections of lidocaine into the NTS block the memory-enhancing effects of systemic posttraining injections of epinephrine[32]. Additionally, posttraining stimulation of the ascending vagus nerve enhances memory[33].

INVOLVEMENT OF THE NORADRENERGIC SYSTEM OF THE AMYGDALA IN MEMORY STORAGE

A large number of studies have investigated influence of peripheral signals on memory storage in the brain. Earlier findings suggest that the effects of peripheral epinephrine on memory involve central release of norepinephrine. As noted above, Gold & van Burskirk[19] report that epinephrine produces dose-dependent effects on brain norepinephrine levels shortly after administration. Moreover, doses of epinephrine that produce optimal memory-enhancing effects moderately reduce levels of brain norepinephrine, presumably by a release of this hormone, while doses that impair memory greatly reduce brain norepinephrine levels.

Extensive evidence indicates that effects of peripheral epinephrine on memory involve amygdala. Reversible inactivation of the NTS or the parabrachial nucleus (that projects to the amygdala) impairs inhibitory avoidance retention[31]. A similar impairment has been observed with posttraining bilateral inactivation of the amygdala[34]. Amygdala stimulation induces retrograde amnesia[21,35] and this memory deficit is attenuated by the depletion of endogenous peripheral epinephrine by adrenodemedullation or adrenodenervation[21,36] and restored by systemic administration of epinephrine posttraining[21]. These data are consistent with the hypothesis that the memory-modulating effects of epinephrine are mediated by the activation of the NTS-amygdala pathway.

Studies investigating the interaction between central and peripheral adrenergic mechanisms suggest that effects of peripheral epinephrine on memory involve the noradrenergic system of the amygdala. Studies using *in vivo* microdialysis and high performance liquid chromatography have reported that footshock stimulation induces norepinephrine release within the amygdala depending on the stimulation intensity[37,38]. Furthermore, norepinephrine release in the amygdala has been potentiated by peripheral administration of epinephrine, the opiate antagonist naloxone or the indirect catecholamine agonist amphetamine[29,38,39]. These findings are consistent with the evidence that intra-amygdala infusions of β-adrenergic antagonists block the effect of naloxone on memory storage[40,41] and that opiate agonists inhibit the release of norepinephrine in the brain[42]. Second, posttraining infusions on norepinephrine or the β-adrenergic agonist clenbuterol into the amygdala induce a dose-dependent enhancement of retention[43-47]. Posttraining intra-amygdala infusions of norepinephrine attenuate the retention deficits induced by adrenal demedullation[45]. In addition, posttraining intra-amygdala injections of the β-adrenoceptor antagonist propranolol block the memory-enhancing effects of systemic epinephrine[45,47] and retention deficits induced by posttraining infusions of the β-adrenergic antagonist propranolol into the amygdala are attenuated by concurrent infusions of norepinephrine[48]. Taken together, these findings strongly suggest that the effects of norepinephrine on memory storage are mediated by the amygdala and that the effects involve activation of β-adrenergic mechanisms.

Involvement of the basolateral nucleus of the amygdala Findings from our laboratory indicate that the memory-modulating effects of norepinephrine are selectively mediated by the basolateral nucleus of the amygdala (BLA) and not any other nuclei. Lesions of the BLA but not the central nucleus of the amygdala block the impairment of memory induced by benzodiazepines[49]. Further, intra-BLA but not intra-central nucleus infusions of benzodiazepine impair retention[50] whereas infusion of a benzodiazepine antagonist into the BLA but not into the central nucleus enhances memory[51]. Extensive evidence has since implicated the BLA in the modulation of memory storage[52]. Recent findings indicate that the BLA is involved in mediating the amygdala noradrenergic influences on memory storage.

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Intra-BLA infusion of epinephrine enhances memory for spatial learning whereas intra-BLA infusion of the β-adrenoceptor antagonist propranolol impairs it[53]. In another study, we have found that infusion of the β-adrenoceptor agonist clenbuterol enhances inhibitory avoidance retention. These findings suggest that β-adrenoceptors in the BLA play an important role in the regulation of memory storage.

Role of the alpha-adrenoceptors As abovementioned, norepinephrine is released in the amygdala by stressful or arousing stimulation used in inhibitory avoidance training[37,38]. The amygdala contains a high density of β- as well as α-adrenoceptor subtypes[54,55]. Posttraining infusion of the non-selective α-adrenergic antagonist phentolamine into the amygdala has been reported to induce a dose-dependent enhancement of inhibitory avoidance retention[56] whereas administration of the selective α_1-adrenergic antagonist prazosin did not induce significant effects[41], although the data obtained by Liang *et al*[47] shows a tendency towards impairment of retention.

Recent results obtained in our laboratory suggest that both types of α-adrenoceptors (α_1 and α_2) in the BLA are involved in modulating memory[57,58]. Posttraining activation of BLA α-adrenoceptors with the non-selective agonist phenylephrine induces a complex pattern of effects (Fig 1a, b). Although none of the doses induced significant effects, low doses of phenylephrine tended to impair whereas the highest dose did not. These results are consistent with previous findings indicating a lack of significant effect induced by posttraining infusion of phenylephrine into the amygdala[47]. Although phenylephrine has been described as a selective α_1-adrenoceptor agonist[59], there is evidence that it also stimulates prejunctional α_2-adrenoceptos likely due to a combined activation of α_1- and α_2-adrenoceptors, which may have opposite effects on memory storage. Anatomical findings have reported a higher density of α_2-adrenoceptors as compared to α_1-adrenoceptors in the amygdala[54,55]. Additionally, activation of pre-synaptic α_2-adrenoceptors blocks norepinephrine release[63,64]. Such findings suggest that lower doses of phenylephrine predominantly activate α_2 adrenoceptors, resulting in retention impairment, whereas at higher doses phenylephrine also activates α_1-adrenoceptors, counterbalancing the α_2-adrenergic inhibitory effect on retention. In support of this hypothesis , we found that phenylephrine co-administered together with yohimbine, which blocks α_2-adrenoceptors, significantly enhanced the retention performance (Fig 1b). A differentiated role of the α_1- and α_2-adrenoceptors in the BLA in regulating memory storage is also supported by our recent findings that immediate posttraining inactivation of α_1-adrenoceptors with prazosin dose-dependently impaired (Fig 2), whereas blokade of α_2-adrenoceptors with yohimbine dose-dependently increased later retention performance (Fig 3).

Interaction between alpha- and beta-adrenoceptors Earlier studies found that α_1- and α_2-adrenoceptors interact in modulating catecholamine-induced physiological responses in the rat brain[65-67]. Recent behavioral findings obtained in our laboratory suggest that norepinephrine in the amygdala regulates memory storage through an interaction between α_1- and β-adrenoceptors. Posttraining infusions of the β-adrenoceptor antagonist atenolol into the BLA block the memory enhancement induced by selective α_1-adrenoceptor activation (Fig 1b, c).

Additionally, posttraining infusions of the α_1-adrenergic antagonist prazosin shifted the dose-response effects of the β-adrenergic agonist clenbuterol when both drugs were infused together into the BLA (Fig 4). Interestingly, the memory-enhancing effects of the opioid peptidergic antagonist naloxone (among other drugs) are blocked by administration of β-adrenergic, but not α_1-adrenergic, antagonists in the amygdala[41]. The above findings are consistent with the view that β-adrenergic receptor is the primary noradrenergic receptor involved in modulating memory storage and α-adrenoceptor manipulation acts by modulating β-adrenergic activity. Thus, our results indicate that α_1- and β-adrenoceptors interact in regulating memory storage and that α_1-adrenergic activity in the BLA facilitates the effects of β-adrenoceptor activation.

Second messengers such as cAMP permit the distribution of cell-surface regulatory input within the cell interior, amplification of the initial signal and enable synergistic or antagonistic regulation of other signaling pathways. Norepinephrine increases cAMP levels in brain tissue[68], an effect involving an interaction between β- and α_1-adrenoceptors[67-70]. The β-adrenoceptor is coupled directly to adenylate cyclase via the guanine-nucleotide-binding regulatory G_s protein[71,72], whereas the α_1-adrenoceptor site appears to be indirectly coupled to the cAMP-generating system via potentiating the β-adrenoceptor activation[65,73]. In view of these findings, recent experiments in our laboratory addressed the locus of interaction between the β- and α_1-adrenoceptors in the

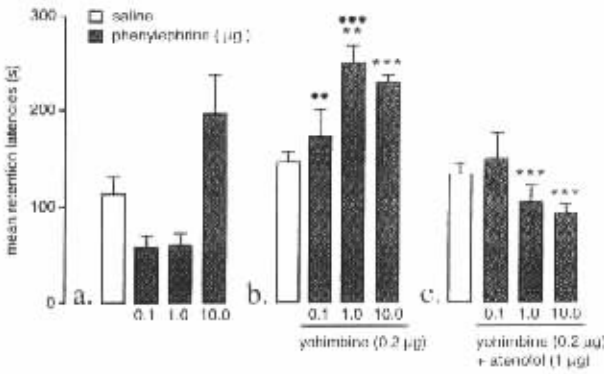

Fig 1. The effects of immediate posttraining infusions of various adrenergic agents into the basolateral amygdala on the mean latency (± SEM) to enter the dark compartment on the retention test. Phenylephrine (an α-adrenoceptor agonist) was injected alone (a), or in combination with 0.2 μg of yohimbine (b) (a selective α_2-adrenoceptor antagonist) or 1.0 μg of atenolol (c) (a β-adrenoceptor antagonist). $^{**}P < 0.01$, $^{***}P < 0.001$ as compared with each corresponding control groups; ●●$P < 0.01$, ●●●$P < 0.001$ as compared with the corresponding groups injected with phenylephrine alone. ($n = 8-12$/group). (From Ref 57).

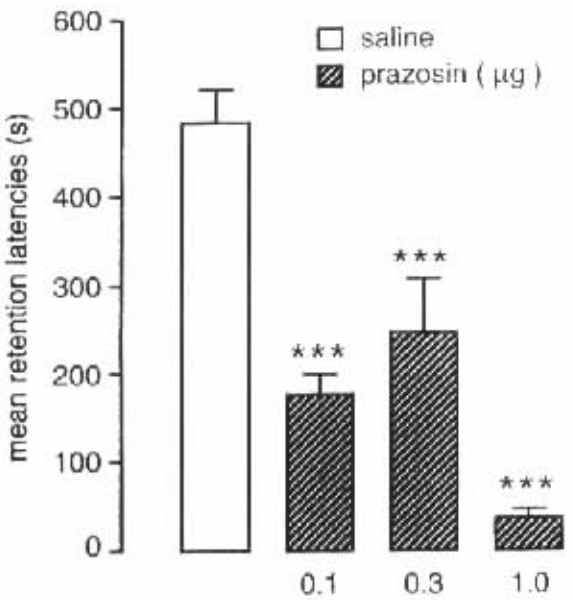

Fig 2. The effects of immediate posttraining infusions of various doses of prazosin (a selective α_1-adrenoceptor antagonist) into the basolateral amygdala on the mean latency (± SEM) to enter the dark compartment on the retention test. $^{***}P < 0.001$ as compared with vehicle-infused group. ($n = 7-9$/group). (From Ref 57).

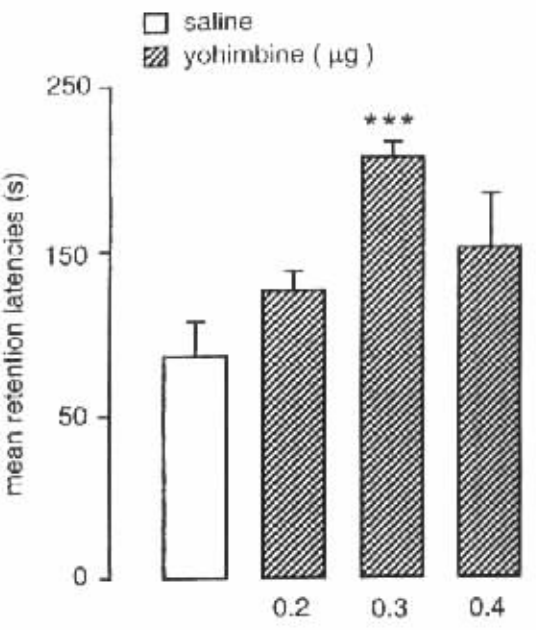

Fig 3. The effects of pretraining infusions of various doses of yohimbine (an α_2-adrenoceptor antagonist) into the basolateral amygdala on the mean latency (± SEM) to enter the dark compartment on the retention test. $^{***}P < 0.001$ as compared with vehicle-infused group. ($n = 8-10$/group).

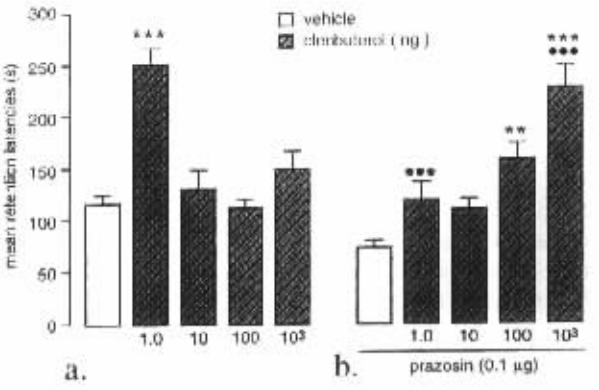

Fig 4. The effects of immediate post-training infusion of several doses of the selective β-adrenoceptor agonist clenbuterol alone (a) or in combination with the selective α_1-adrenoceptor antagonist prazosin (b) into the basolateral amygdala on the mean retention latencies (± SEM) to enter the dark compartment on the retention test. $^{**}P < 0.01$; $^{***}P < 0.001$ as compared with vehicle-infused group; ●●●$P < 0.001$ as compared with the corresponding groups infused with clenbuterol alone. ($n = 9-12$/group). (From Ref 131).

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BLA[58]. Posttraining infusions of 8-bromo-cAMP (a cAMP analog that readily enters the cell) into the BLA dose-dependently enhanced memory retention, suggesting that cAMP in the BLA is involved in inhibitory avoidance memory storage (Fig 5a). In addition, concurrent administration of prazosin did not alter the memory-enhancing effect of 8-bromo-cAMP (Fig 5b). These findings are in agreement with studies showing that posttraining infusions of 8-bromo-cAMP into the hippocampus or the amygdala enhance memory retention in the inhibitory avoidance task[47,74,75]. Moreover, they provide evidence concerning the interaction between β- and α_1-adrenoceptors and rule out the possibility that the α_1-adrenoceptor modulates memory storage by acting downstream from cAMP synthesis in the BLA. If that were the case, infusions of prazosin should have attenuated the dose-response effects of 8-bromo-cAMP. The lack of effect induced by prazosin clearly suggests that α_1-adrenoceptors influence β-adrenoceptor-mediated effects on memory by acting upstream from cAMP formation.

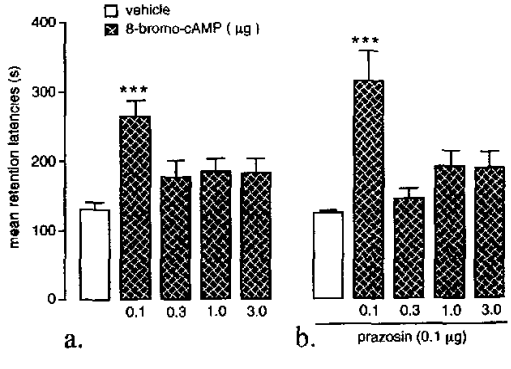

Fig 5. The effects of immediate post-training infusion of several doses of 8-bromo-cAMP, an analog of cAMP that passes the cell membrane, alone (a) or in combination with the selective α_1-adrenoceptor antagonist prazosin (b) into the BLA on the mean retention latencies (± SEM) to enter the dark compartment on the retention test. ***$P < 0.001$ compared with vehicle-infused group. ($n = 10 - 13$/group). (From Ref 58).

Although these findings are consistent with pharmacological evidence indicating a direct interaction between postsynaptic α_1- and β-adrenoceptors in cAMP synthesis, the finding that prazosin did not alter the dose-response effects of 8-bromo-cAMP on memory might also reflect an indirect participation of the α_1-adrenoceptors in the β-mediated memory storage modulation. It is possible that the role of the α_1-adrenoceptors in memory storage is independent of the β-mediated cAMP generation and might interact with β-adrenoceptors via another intracellular route[59]. Furthermore, although several findings have reported co-localization of β- and α_1-adrenoceptors in brain neurons[76], our observations can not exclude the possibility that the effects induced by clenbuterol and prazosin are mediated by an interaction between β- and α_1-adrenoceptors located on different cells in the BLA.

In summary, these findings have provided some new insights into the involvement of adrenergic mechanisms in the BLA in mediating effects of norepinephrine on memory storage. Memory enhancement induced by β-receptor activation in the BLA is mediated by cAMP generation, and this process is modulated by α_1-adrenoceptor stimulation.

INTERACTION BETWEEN THE NORADRENERGIC SYSTEM OF THE AMYGDALA AND OTHER NEUROMODULATORY SYSTEMS

Glucocorticoids Considerable evidence indicates that acute effects of glucocorticoid on memory storage, like those of drugs affecting the adrenergic systems, are mediated by the BLA. Lesions of the BLA, but not the central nucleus, block the memory enhancing effects of posttraining administration of the synthetic glucocorticoid dexamethasone on inhibitory avoidance learning[77]. Lesions of the stria terminalis (a major afferent/efferent amygdala pathway) also block the memory-enhancing effects of posttraining infusions of dexamethasone[78]. Moreover, lesions of either the BLA or stria terminalis block the impairing effects of adrenalectomy (which eliminates circulating glucocorticoids) on spatial memory in a water maze task[78,79]. The memory-modulatory effects of glucocorticoids in the BLA depend on the integrity of the β-adrenergic system. Pretraining infusions of β-adrenoceptor antagonists into the BLA block the memory-enhancing effect of posttraining systemic injections of dexamethasone[80]. Additionally, the β-adrenoceptor antagonist atenolol blocks the memory-enhancing effects of glucocorticoids when both were infused concurrently immediately after training into the BLA[80]. The finding that higher doses of glucocorticoids were ineffective in enhancing memory in animals given atenolol concurrently suggests that β-adrenergic activation in the BLA is required in order for glucocorticoids to modulate memory storage processes. Moreover, these findings suggest that glucocorticoids and the noradrenergic systems interact postsynaptically in BLA neurons. In support of this view, we found that pretraining infusions of a glucocorticoid receptor antagonist into the BLA shifted the dose-response effects of posttraining infusions of clenbuterol to the right[81].

Previous ligand binding studies have also suggested

that effects of glucocorticoids on memory are mediated through an interaction with adrenoceptors in the brain[82-84]. Glucocorticoid and α_1-adrenoceptors are co-localized in the hippocampus[85], and may directly interact in stress-induced learning situations. α_1-Adrenoceptor activation down-regulates corticosteroid binding[86], which suggests that catecholamine release can modulate corticosteroid receptor-mediated negative feedback, possibly via activation of α_1-adrenoceptors. Recent results from our laboratory indicate that α_1-adrenoceptor and glucocorticoid receptors in the BLA interact in modulating memory storage[87]. Pretraining infusion of the α_1-adrenoceptor antagonist prazosin into the BLA blocks the memory enhancing effects induced by posttraining infusion of the glucocorticoid agonist GR 28362. The fact that higher doses of the glucocorticoid agonist were ineffective in enhancing memory in animals given prazosin concurrently suggests that α_1-adrenergic activation in the BLA is required by glucocorticoids to modulate memory storage process. Pretraining administration of the glucocorticoid receptor antagonist GR 38486 blocks the memory-enhancing effects induced by posttraining α_1-adrenoceptor activation when both drugs were infused into the BLA. In addition, the fact that glucocorticoid antagonist attenuated the dose-response effects induced by α_1-adrenoceptor activation support the view that glucocorticoid receptors influence, but are not critical for the effect of α_1-adrenoceptor activation.

Thus the memory-modulatory effects of α_1-adrenoceptors are mediated through an interaction with the glucocorticoid receptors. Moreover, the interaction between the α_1- and β-adrenoceptors in the BLA may be under the influence of the glucocorticoid receptors.

Other neuromodulatory systems Opioid peptidergic and GABAergic influences on memory also involve β-adrenergic activation in the amygdala. Extensive evidence indicates that these systems play a role in modulation of memory storage. Memory retention is reportedly enhanced by posttraining administration of an opioid receptor antagonist, naloxone[88-91]. In contrast, opioid receptor agonists induce impairment of memory that is blocked by naloxone[92-95]. Extensive evidence also indicates that GABAergic antagonists enhance, and that GABAergic agonists impair memory retention[96,97].

The memory-enhancing effects of intra-amygdala infusions of naloxone are blocked by lesions of the noradrenergic bundle[98] and the memory-enhancing effects of systemic administration of naloxone are blocked by posttraining intra-amygdala infusions of β-adrenoceptor antagonists[41]. Furthermore, propranolol also blocks the memory-enhancing effect of naloxone when both drugs are infused into the amygdala posttraining[40]. Intra-amygdala infusions of propranolol block the modulatory effects of GABAergic agonists and antagonists on memory[99,100]. Using microdialysis to examine norepinephrine release we recently found that β-endorphin attenuates the release of norepinephrine in the amygdala when injected systemically after a footshock administration[38]. In contrast, naloxone potentiated this footshock-induced release of norepinephrine. Other recent findings[101] indicate that systemic administration of the GABAergic antagonist picrotoxin induce norepinephrine release in the amygdala. These findings are consistent with the hypothesis that the influence of the opioid peptidergic and the GABAergic systems on memory storage, as well as that of epinephrine, are mediated by the release of norepinephrine in the amygdala.

INTERACTION BETWEEN THE AMYGDALA AND OTHER BRAIN SYSTEMS IN MEMORY STORAGE

As has been summarized above, the studies of the effects of hormones and drugs affecting several neurotransmitter systems provide strong support for the hypothesis that the amygdala, more precisely the BLA, is a critical site for integrating the interactions of these systems in regulating memory storage. However, our findings also suggest that BLA is not the actual site of memory storage, but, rather influences retention by modulating these processes occurring in other brain regions. Lesions of the amygdala or the BLA, induced between one week and one month after aversive training do not block inhibitory avoidance performance[34,102-104]. Intra-BLA injection of the GABAergic antagonist bicuculline or the agonist muscimol respectively enhances and impairs short-term olfactory memory traces during conditioned learning, whereas lesion of the BLA does not block the acquisition[105-107]. Additionally, large lesions of the amygdaloid complex induced before training typically attenuate but do not block inhibitory avoidance retention performance[108]. Further, although amygdala lesions typically impair the expression of conditioned fear as assessed by fear-potentiated startle[109] or "freezing" behavior[110], overtraining of fear conditioning attenuates the freezing deficit and enables reacquisition of fear-potentiated startle[111,112]. Additionally, recent findings from our laboratory indicate that lesions of the BLA attenuate "freezing" but do not block the memory of contextual fear conditioning[113]. Other recent findings indicate that memo-

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ry for Pavlovian fear conditioning is impaired by post-training intra-BLA infusions of lidocaine and enhanced by infusions of oxotremorine[114].

The stria terminalis is a major amygdala pathway that carries both afferent and efferent projections. Lesions of the stria terminalis block the effect, on memory, of posttraining electrical amygdala stimulation[115]. In addition, stria terminalis lesions block the memory enhancement induced by posttraining systemic administration of the adrenergic agonist clenbuterol which readily enters the brain, as well as by posttraining intra-amygdala infusions of norepinephrine[43,46]. These results suggest that modulatory influences on memory involving the amygdala are not based on alteration of memory storage processes within the amygdala, but, rather, appear to be due to influences mediated by amygdala efferents. The amygdala sends efferent projections to many brain regions including the striatum, via the stria terminalis. Further, the finding that *N*-methyl-*D*-aspartate infused into the amygdala induces c-*fos* expression in the dentate gyrus of the dorsal hippocampus and the caudate nucleus indicates that the amygdala is functionally connected with these brain regions[116].

There is considerable evidence based on "double dissociation" studies indicating that the caudate nucleus and hippocampus are involved in mediating different forms of memory[117,118]. Hippocampal lesions selectively impair water-maze spatial learning[119,120] whereas caudate lesions selectively impair water-maze visually cued learning[117]. Recent findings indicate that the amygdala modulates memory storage for both hippocampal-and caudate nucleus-dependent tasks[121,122]. Unilateral post-training infusions of amphetamine administered into the dorsal hippocampus immediately after a single training session enhanced memory storage for the spatial but not the cued version of the water maze, while amphetamine infused into the caudate nucleus after training enhanced memory for the cued but not the spatial version of the task. However, amphetamine infused into the amygdala enhanced both. Inactivation of the amygdala prior to the retention tests did not block the enhanced retention induced by posttraining infusions of amphetamine into the amygdala[121] which clearly indicates that the amygdala modulates memory storage processes involving other brain regions. Moreover, it is evident that the learning is not mediated by lasting neural changes located within the amygdala.

Recent findings indicate that BLA plays a role in processing of hippocampal-dependent memory consolidation. Posttraining intra-hippocampal administration of a glucocorticoid receptor agonist enhances retention of inhibitory avoidance training. However, the memory-enhancement is completely blocked in animals with BLA lesions[123]. Intra-BLA infusion of the β-adrenergic antagonist atenolol also blocks the memory-enhancement induced by intra-hippocampal infusion of glucocorticoids[124]. These findings are of interest in reference to the BLA influences on hippocampal long-term potentiation phenomenon. Selective lesioning of the BLA or intra-BLA infusion of β-adrenergic antagonist respectively attenuated and blocked the induction of long-term potentiation in the dentate gyrus *in vivo*[125-127]. Moreover, high-frequency stimulation of the BLA facilitates the induction of long-term potentiation in the dentate gyrus[128]. These physiological results are consistent with those of behavioral studies indicating that modulation of memory storage involves noradrenergic influences in the BLA and that the BLA influences memory by modulating memory storage in other brain structures.

Although the pathway which affects hippocampal memory and neuroplasticity is not known, some evidence indicates an involvement of the BLA-nucleus accumbens pathway. The nucleus accumbens receives projections from both the BLA and hippocampus[129]. As discussed earlier, lesions of the stria terminalis, that carries the projections from the BLA to the nucleus accumbens, as well as lesions of the amygdala block the effects of glucocorticoids and epinephrine on memory consolidation. The findings that lesions of the nucleus accumbens also block the memory-modulating effects of posttraining systemic injections of a glucocorticoid agonist[130] supports the view that the BLA-nucleus accumbens pathway may mediate BLA influences on memory which involves the hippocampus.

CONCLUSION

Taken collectively, these studies indicate that adrenal stress hormones and the amygdala are involved in regulating memory consolidation. In particular, our findings consistently indicate that β- and α-adrenergic activation in the amygdala, and especially the BLA, are critically involved in regulating the formation of long-term memory regarding emotional events. Also, our findings indicate that the amygdala is not required for the expression of memory and regulates neural plasticity in other brain regions. The findings provide strong support for the hypothesis that the BLA is part of a neuromodulatory system that regulates the strength of memories in relation to their emotional significance.

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杏仁核内去甲肾上腺素在应激激素调控记忆保持过程中的作用

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关键词 去甲肾上腺素; 杏仁核; 学习; 记忆; 肾上腺皮质激素; 应激; α肾上腺素受体类; β肾上腺素受体

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