Role of adrenal stress hormones in forming lasting memories in the brain

James L McGaugh and Benno Roozendaal

Recent experiments investigating the effects of adrenal stress hormones on memory provide extensive evidence that epinephrine and glucocorticoids modulate long-term memory consolidation in animals and human subjects. Release of norepinephrine and activation of β-adrenoceptors within the basolateral amygdala is critical in mediating adrenal stress hormone regulation of memory consolidation.

Address
Center for the Neurobiology of Learning and Memory and Department of Neurobiology and Behavior, University of California, Irvine, California 92697-3800, USA

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Abbreviations

BLA	basolateral amygdala
cAMP	adenosine 3′,5′-cyclic monophosphate
CREB	cAMP-response element-binding protein
ERK2	extracellular regulated kinase
GRs	glucocorticoid receptors
LTP	long-term potentiation
NCAMs	neural cell adhesion molecules
NMDA	*N*-methyl-D-aspartate
NTS	nucleus of the solitary tract
PKA	cAMP-dependent protein kinase, protein kinase A

Introduction

Emotionally arousing experiences tend to be well and long remembered. Evidence from many different types of experiments indicates that adrenal stress hormones, released during or after emotionally arousing experiences, play a critical role in consolidating lasting memories. Although the adrenomedullary hormone epinephrine (adrenaline) and the adrenocortical hormone corticosterone (in the rat; cortisol in humans) affect brain function through different specific mechanisms and pathways, they converge in regulating memory consolidation by influencing central noradrenergic mechanisms. The amygdala is a critical site of the converging modulatory influences of adrenal stress hormones on memory consolidation [1,2]. This review summarizes evidence from recent studies investigating brain processes underlying adrenergic and glucocorticoid influences on memory consolidation.

Adrenergic influences on memory consolidation

Pathways of activation

Gold and van Buskirk [3] provided the first evidence suggesting that an endogenous hormone regulates memory consolidation. They showed that systemic injections of epinephrine administered after training produced dose-dependent enhancement of long-term retention of inhibitory avoidance training. Recent studies have advanced our understanding of how epinephrine influences memory consolidation. Gold *et al.* suggested that epinephrine may influence memory via the release of hepatic glucose ([4] but also see [5]). Other findings have revealed a peripheral–central neuronal pathway mediating the effects of epinephrine on memory consolidation. Several findings suggest that epinephrine activates β-adrenoceptors on vagal afferents terminating on brainstem noradrenergic cell groups in the nucleus of the solitary tract (NTS). Post-training electrical stimulation of the ascending vagus nerve induces memory enhancement similar to that produced by epinephrine [6]. Noradrenergic projections originating in the NTS innervate forebrain structures involved in learning and memory, including the amygdala, and may also influence norepinephrine release via descending projections to the nucleus paragigantocellularis in the lower medulla, which projects to the locus coeruleus [7]. Noradrenergic neurons in the locus coeruleus project to many forebrain regions, including the hippocampus and the amygdala. Temporary inactivation of the NTS with a local infusion of lidocaine blocks epinephrine effects on memory consolidation [8] and post-training infusions of epinephrine or the β-adrenoceptor agonist clenbuterol into the NTS induce dose-dependent memory enhancement [9]. The NTS thus appears to act as an interface between the peripheral endocrine/autonomic milieu and the neural mechanisms regulating memory consolidation.

Noradrenergic activation in the amygdala is involved in epinephrine influences on memory

Extensive evidence indicates that epinephrine affects memory consolidation by involving noradrenergic activation in the amygdala. Antagonism of β-adrenoceptors in the amygdala blocks epinephrine effects on memory consolidation, and infusions of norepinephrine or β-adrenoceptor agonists into the amygdala after training enhance memory consolidation [10–12]. Activation of both β- and α-adrenoceptors in the basolateral nucleus of the amygdala (BLA) is critical for mediating these noradrenergic influences on memory consolidation [13–15].

In vivo microdialysis and high-performance liquid chromatography studies indicate that epinephrine released by emotionally arousing training experiences induces the release of norepinephrine in the amygdala. Footshock stimulation, such as that used in inhibitory avoidance training, induces the release of norepinephrine in the amygdala. The amount of release varies directly with stimulus intensity [16,17]. Systemic injections of epinephrine also enhance norepinephrine release in the amygdala, an

effect that is blocked by temporary inactivation of the NTS [18]. Infusions of epinephrine into the NTS potentiate training-induced norepinephrine release in the amygdala and enhance retention performance [19••]. Moreover, inhibitory avoidance training increases norepinephrine levels in the amygdala after training, and the levels assessed in individual animals correlate highly with later retention performance [20]. These findings, together with those of studies of drug effects on norepinephrine release [21], provide strong support for the hypothesis that norepinephrine release in the amygdala plays an important, possibly critical, role in mediating emotional arousal effects on memory consolidation.

Noradrenergic activation may activate glutamatergic mechanisms in the BLA [22] and facilitate *N*-methyl-D-aspartate (NMDA)-dependent neuroplasticity in BLA pyramidal neurons [23,24]. The finding that epinephrine does not reverse memory impairments induced by NMDA antagonists also suggests that the effects of epinephrine on memory consolidation involve NMDA-dependent mechanisms [25]. Noradrenergic activation involves β-adrenoceptor influences on adenosine 3′,5′-cyclic monophosphate (cAMP) and cAMP-dependent protein kinase (PKA) formation. Auditory fear conditioning is attenuated by administration of a PKA inhibitor directly into the BLA [26], and consolidation of fear memories is impaired in transgenic mice that overexpress an inhibitory isoform of PKA [27], suggesting a crucial role for PKA in memory consolidation. The finding that blockade of PKA prevents late-phase long-term potentiation (LTP) in the lateral amygdala [28] implies the involvement of neuroplasticity in this nucleus. PKA activation results in phosphorylation of the transcription factor cAMP-response element-binding protein (CREB) [29], and manipulation of CREB levels in the amygdala influences long-term memory formation for aversive conditioning [30,31•]. Such activation-induced changes in plasticity mediated by epinephrine may regulate BLA effects on memory consolidation in other brain regions [1,32].

Glucocorticoid influences on memory consolidation

Emotional arousal also activates the hypothalamic–pituitary–adrenocortical axis, resulting in elevated plasma levels of corticosterone. Extensive evidence indicates that glucocorticoids influence long-term memory consolidation [2,33]. Acute post-training administration of low doses of glucocorticoids enhances memory consolidation, in a manner highly similar to that seen with epinephrine [34–37]. Blockade of the corticosterone stress response with the corticosterone synthesis inhibitor metyrapone prevents inhibitory avoidance retention enhancement induced by post-training epinephrine injections or exposure to psychological stress [38,39]. This suggests that these major hormonal systems — adrenergic and glucocorticoid — appear to interact to influence memory consolidation.

Glucocorticoid effects on memory are not restricted to influences on consolidation. When administered shortly before retention testing, glucocorticoids impair retrieval of memory for spatial/contextual information [40], an effect that is temporary and dissipates within several hours after stress exposure or hormone injection. The effects of chronic glucocorticoid administration on memory function and the brain were recently reviewed elsewhere [41•].

Glucocorticoid influences on memory involve the amygdala

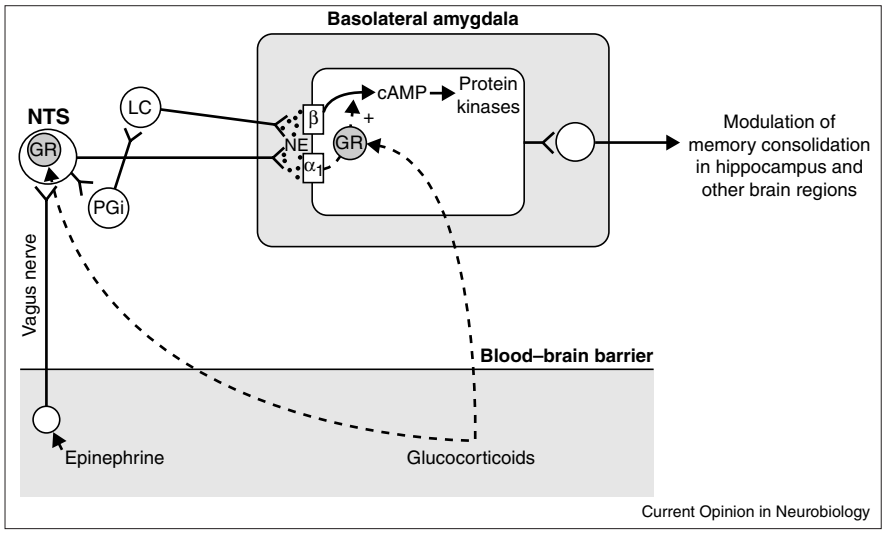
Glucocorticoid hormones freely enter the brain and bind to two intracellular types of adrenal steroid receptors [42]. Extensive evidence indicates that the low-affinity glucocorticoid receptors (GRs), and not the high-affinity mineralocorticoid receptors, are involved in mediating glucocorticoid effects on memory consolidation [43–47]. The hippocampus has a high density of GRs [42]. Post-training infusions of corticosterone, or specific agonists or antagonists of GRs into the hippocampus, affect memory consolidation for both aversive and appetitive tasks [48,49]. Glucocorticoid effects on memory consolidation also require activation of the amygdala [2,50]. Infusions of the specific GR agonist RU 28362 into the BLA, immediately after inhibitory avoidance training, enhance retention performance [51]. Intra-BLA infusions of the GR antagonist RU 38486 impair retention performance in a watermaze spatial task [51]. Furthermore, selective lesions of the BLA block inhibitory avoidance retention enhancement induced by post-training systemic injections of the synthetic glucocorticoid dexamethasone [52]. These recent findings indicate that glucocorticoid effects on memory consolidation depend critically on the BLA and that the BLA is also a locus of action of glucocorticoids in modulating memory consolidation.

Lesions of the BLA also block retention enhancement induced by intra-hippocampal infusions of a GR agonist [49]. These findings indicate that an intact BLA is required for enabling memory enhancement induced by local GR activation in the hippocampus. More generally, the findings suggest that training-induced activation of the BLA is needed for regulating stress hormone effects on memory consolidation processes in other brain regions [2,53••]. BLA lesions also block stress-induced impairment of LTP in the hippocampus [54•]. Projections from the BLA to the nucleus accumbens may be critically involved in mediating these BLA influences on memory consolidation [55,56].

Molecular mechanisms of glucocorticoid effects

Many recent studies have focused on the putative molecular mechanisms underlying glucocorticoid effects on memory consolidation. Aversive training and post-training injections of glucocorticoids affect expression of neural cell adhesion molecules (NCAMs) in the hippocampus and the prefrontal cortex [57•,58], and may cause long-term synaptic structural changes. Glucocorticoids act through intracellular and intranuclear receptors and can affect gene transcription by direct binding of receptor homodimers to DNA [59,60]. Consistent with a role of this pathway in memory consolidation, a recent study has reported that a point mutation in

Figure 1



Interactions of adrenal stress hormones with the noradrenergic system in the BLA in modulating memory consolidation. Adrenal stress hormones are released during training in aversively motivated tasks and are known to enhance memory consolidation. Epinephrine, which does not cross the blood–brain barrier, induces the release of norepinephrine (NE) in the BLA by activating vagal afferents to the NTS. Noradrenergic neurons in the NTS project directly to the BLA, and indirectly via the locus coeruleus (LC). Norepinephrine binds to both β-adrenoceptors (β) and α_1-adrenoceptors (α_1) at postsynaptic sites and activates cAMP and protein kinase formation. Glucocorticoids freely enter the brain and bind to GRs in noradrenergic cell bodies in the NTS to potentiate norepinephrine release in the BLA, as well as postsynaptically in BLA neurons to facilitate the norepinephrine signal cascade. These stress hormone effects on noradrenergic activation in the BLA are required for regulating memory consolidation in other brain regions. PGi, nucleus paragigantocellularis.

the mouse GR, which selectively prevents dimerization and DNA-binding of the GR, impairs spatial memory performance [61••]. Glucocorticoids may also affect memory consolidation through transactivation or protein–protein interactions with other transcription factors or effector systems. Training on a watermaze spatial task increases phosphorylation of extracellular regulated kinase (ERK2), a subtype of the mitogen-activated protein kinases [62•]. Phosphorylation of ERK2 in the amygdala was found only in rats that were trained under high stress conditions (i.e. cold water). The training conditions were accompanied by high plasma levels of training-induced corticosterone. ERK2 is considered critical for memory consolidation and long-term neuronal plasticity in both the amygdala and the hippocampus [63,64] and can be activated by noradrenergic stimulation and cAMP formation [65,66].

Noradrenergic activation in the amygdala is involved in glucocorticoid influences on memory

Brainstem noradrenergic cell groups, including the NTS and the locus coeruleus, express high densities of GRs [67]. Post-training activation of GRs on noradrenergic cell groups in the NTS induces dose-dependent memory enhancement [37]. As noted above, the NTS projects directly to the amygdala and infusion of a β-adrenoceptor antagonist into the BLA blocks this glucocorticoid-induced memory enhancement [37]. Moreover, infusion of a β-adrenoceptor antagonist into the BLA blocks the retention enhancement induced by post-training systemic injections of dexamethasone or by direct intra-hippocampal infusions of a GR agonist [68,69••]. Other findings suggest that the BLA may be a critical locus of interaction between glucocorticoids and the noradrenergic system in modulating memory consolidation. Retention enhancement induced by a GR agonist infused into the BLA after training is blocked by concurrent infusions of a β-adrenoceptor antagonist or RP-cAMPs, a drug that blocks the norepinephrine signal cascade by inhibiting PKA activity [68,70]. The findings of this study also indicate that GR activation in the BLA may facilitate memory consolidation by potentiating the efficacy of the norepinephrine signal cascade, via an interaction with G-protein-mediated actions [70].

Adrenal stress hormone effects on memory consolidation in human subjects

Findings of studies of stress hormone effects on memory in human subjects are generally consistent with those of the animal studies discussed above. Blockade of β-adrenoceptors prevents the enhancing effects of emotional arousal on memory consolidation [71,72]. Glucocorticoid-induced impairment of declarative memory retrieval has also been observed in human subjects [73,74]. A brief social stress exposure was reported to impair memory processing in male but not female volunteers [75•]. The report that, in human subjects, glucocorticoid effects on memory consolidation enhancement depend on the emotionally arousing content of the material [76•], is consistent with extensive evidence from animal studies indicating that noradrenergic activation in the amygdala is involved in mediating glucocorticoid effects on memory consolidation.

Conclusions and future directions

Recent findings have provided new insights into the brain processes mediating adrenal stress hormone influences on memory consolidation. As summarized in Figure 1, the BLA is a critical locus mediating epinephrine and glucocorticoid

influences on memory consolidation. In addition, noradrenergic activation within the BLA is essential for the memory modulating influences of systemically administered epinephrine and glucocorticoids, as well as for the effects of glucocorticoids infused directly into the hippocampus. Thus, epinephrine and glucocorticoid effects on the consolidation of memory for emotional experiences are intimately linked to noradrenergic activation in the BLA. A major goal of future studies will be to understand how noradrenergic activation in the amygdala enables long-term memory consolidation in other brain regions.

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