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GLUCOCORTICOIDS INTERACT WITH EMOTION-INDUCED NORADRENERGIC ACTIVATION IN INFLUENCING DIFFERENT MEMORY FUNCTIONS

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Abstract—Extensive evidence from rat and human studies indicates that glucocorticoid hormones influence cognitive performance. Posttraining activation of glucocorticoid-sensitive pathways dose-dependently enhances the consolidation of long-term memory. Glucocorticoid effects on memory consolidation rely on noradrenergic activation of the basolateral amygdala and interactions of the basolateral amygdala with other brain regions. Glucocorticoids interact with the noradrenergic system both at a postsynaptic level, increasing the efficacy of the β-adrenoceptor-cyclic AMP/protein kinase A system, as well as presynaptically in brainstem noradrenergic cell groups that project to the basolateral amygdala. In contrast, memory retrieval and working memory performance are impaired with high circulating levels of glucocorticoids. Glucocorticoid-induced impairment of these two memory functions also requires the integrity of the basolateral amygdala and the noradrenergic system. Such critical interactions between glucocorticoids and noradrenergic activation of the basolateral amygdala have important consequences for the role of emotional arousal in enabling glucocorticoid effects on these different memory functions. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: amygdala, corticosterone, emotional arousal, memory consolidation, memory retrieval, working memory.

Adrenal hormones (i.e. catecholamines and glucocorticoids) are secreted during emotionally arousing events and influence, together with other components of the stress system, the organism's ability to cope with stress. There is extensive evidence that these hormones have also profound effects on cognitive functioning (McGaugh and Roozendaal, 2002). Immediate posttraining systemic injections of epinephrine or norepinephrine to rats enhance the consolidation and/or storage of novel information (Gold and van Buskirk, 1975). Recent evidence indicates that epinephrine also enhances memory consolidation for emotionally arousing material in human subjects (Cahill and Alkire, 2003). It is now also well established that glucocorticoid hormones dose-dependently enhance memory consolidation in animal and human subjects (de Kloet et al., 1999; Roozendaal, 2000). Blockade of glucocorticoid production with the synthesis inhibitor metyrapone impairs memory consolidation (Roozendaal et al., 1996b; Maheu et al., 2004) and prevents stress- and epinephrine-induced memory enhancement (Roozendaal et al., 1996a; Liu et al., 1999), whereas acute systemic administration of glucocorticoids enhances memory when given either before or immediately after a training experience (Flood et al., 1978; Roozendaal and McGaugh, 1996; Sandi and Rose, 1997; Roozendaal et al., 1999b; Buchanan and Lovallo, 2001; Abercrombie et al., 2003). In addition to such enhancing effects of acutely administered glucocorticoids on memory consolidation, elevated levels of glucocorticoids at the time of retention testing impair the retrieval of previously acquired information (de Quervain et al., 1998, 2000; Wolf et al., 2001; Roozendaal et al., 2003, 2004a,b). High levels of glucocorticoids also impair working memory performance (Lupien et al., 1999; Wolf et al., 2001; Roozendaal et al., 2004c).

Research in our laboratory has focused primarily on the brain systems mediating such stress hormone effects on memory. Extensive evidence indicates that the amygdala plays a key role in mediating epinephrine effects on memory consolidation. However, as epinephrine does not readily cross the blood–brain barrier, a peripheral–central pathway is involved in mediating epinephrine effects on amygdala activity in modulating memory consolidation (McGaugh et al., 1996; Williams and Clayton, 2001). Systemic epinephrine can activate peripheral β-adrenoceptors located on vagal afferents terminating in the nucleus of the solitary tract (NTS). In turn, noradrenergic cell groups in the NTS send direct projections to the amygdala (Fallon and Ciofi, 1992), or indirectly via the locus coeruleus (Williams and Clayton, 2001). The evidence that a blockade of β-adrenoceptors in the amygdala prevents memory enhancement induced by systemic injections of epinephrine (Liang et al., 1986) indicates that epinephrine effects on memory consolidation depend critically on noradrenergic activity of the amygdala. There is now extensive evidence that several neuromodulatory and neurotransmitter systems interact with the noradrenergic system of the amygdala in influencing memory consolidation (McGaugh et al., 1996; McGaugh, 2000, 2004). As discussed below the neurobiological mechanisms underlying the acute effects

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Abbreviations: BLA, basolateral complex of the amygdala; cAMP, cyclic AMP; CEA, central nucleus of the amygdala; GR, glucocorticoid receptor; mPFC, medial prefrontal cortex; MR, mineralocorticoid receptor; NTS, nucleus of the solitary tract; PKA, protein kinase A; RU 38486, mifepristone.

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of glucocorticoids on memory consolidation are highly similar to those of epinephrine in that they require noradrenergic activation within the amygdala that influences memory consolidation via interactions with other brain regions. The findings suggest also that the impairing effects of glucocorticoids on memory retrieval and working memory depend on noradrenergic activation within the amygdala. Such critical interactions between glucocorticoids and noradrenergic activation of the amygdala have important consequences for the role of emotional arousal in enabling glucocorticoid effects on these different memory functions.

Glucocorticoid effects on memory consolidation: involvement of the amygdala

Unlike catecholamines, glucocorticoid hormones readily enter the brain and bind directly to two intracellular types of adrenal steroid receptors (Reul and de Kloet, 1985; de Kloet, 1991). Glucocorticoid receptors (GRs) have a low affinity for corticosterone and become occupied only during stress and at the circadian peak, when circulating levels of glucocorticoids are high. In contrast, mineralocorticoid receptors (MRs) have a 10-fold higher affinity for corticosterone and are almost saturated under basal conditions (Reul and de Kloet, 1985). Extensive evidence indicates that glucocorticoid effects on memory consolidation involve a selective activation of GRs. For example, immediate posttraining i.c.v. or local infusions of a GR antagonist, but not an MR antagonist, impair memory consolidation (Oitzl and de Kloet, 1992; Roozendaal et al., 1996c; 1999a; Roozendaal and McGaugh, 1997a,b). Furthermore, genetic disruption of GR functioning interferes with memory consolidation processes (Oitzl et al., 2001).

Both MRs and GRs are expressed in the brain. In contrast to MRs, which are most densely expressed in limbic areas, GRs are ubiquitous and are found both in neurons and in glial cells (de Kloet, 1991). Recent findings suggest that glucocorticoids may act in many different, though interacting, brain regions to enhance memory consolidation. Our studies have focused primarily on the amygdala, and interactions of the amygdala with other brain regions, as there is extensive evidence that the amygdala is a critical component of the neural circuitry regulating the effects, on memory consolidation, of drugs and hormones affecting several receptor systems (McGaugh et al., 1996; McGaugh, 2000, 2004). Furthermore, as noted above, the amygdala mediates epinephrine as well as glucocorticoid effects on memory consolidation. Selective NMDA-induced lesions of the amygdala restricted to the basolateral complex (BLA; consisting of the lateral, basal and accessory basal nuclei) block 48-h inhibitory avoidance retention enhancement induced by posttraining systemic injections of the synthetic glucocorticoid dexamethasone (Roozendaal and McGaugh, 1996). In contrast, lesions of the adjacent central nucleus (CEA), made with ibotenic acid, do not block the dexamethasone-induced memory enhancement. Selective BLA lesions also block memory impairment induced by an i.c.v. administration of a GR antagonist (Roozendaal et al., 1996c). Posttraining infusions of the specific GR agonist RU 28362 administered into the BLA enhance retention in a dose-dependent fashion, but are ineffective when administered into the CEA (Roozendaal and McGaugh, 1997a), whereas intra-BLA, but not intra-CEA, infusions of the GR antagonist RU 38486 (mifepristone) impair retention in a water-maze spatial task (Roozendaal and McGaugh, 1997a). Moreover, intra-BLA infusions of RU 38486 attenuate the facilitating effects of chronic corticosterone administration on contextual fear conditioning (Conrad et al., 2004). These findings indicate that the modulatory effects of glucocorticoids on memory consolidation are mediated, in part, by direct binding to GRs in the BLA. Such a selective involvement of the BLA in regulating glucocorticoid effects on memory consolidation is consistent with the evidence that the BLA is also the critical subdivision of the amygdala mediating the modulatory effects of drugs affecting several other neurotransmitter systems (McGaugh, 2004).

Many findings from our laboratory indicate that BLA activity enhances memory by influencing consolidation processes occurring in other brain regions, including the hippocampus (McGaugh, 2002, 2004). It is well established that the hippocampus has a high density of adrenal steroid receptors (Reul and de Kloet, 1985) and that the hippocampus is involved in spatial/contextual learning and memory (Morris et al., 1982; Eichenbaum and Otto, 1992). Furthermore, cumulative evidence indicates that hippocampal adrenal steroid receptors are involved in neuroplasticity (Foy et al., 1987; Diamond et al., 1992; Pavlides et al., 1993; Korz and Frey, 2003) and memory consolidation (de Kloet, 1991). We found that posttraining infusions of the GR agonist RU 28362 into the dorsal hippocampus enhance rat's retention of inhibitory avoidance and that pretraining infusions of the antagonist RU 38486 impair retention of water-maze spatial training (Roozendaal and McGaugh, 1997b). Additionally, and most importantly, selective BLA lesions block the memory-modulatory effects of the intra-hippocampal infusions of drugs affecting GRs. These findings parallel those of electrophysiological studies reporting that the BLA modulates long-term potentiation in the hippocampus (Ikegaya et al., 1994, 1997; Akirav and Richter-Levin, 1999, 2002; Frey et al., 2001; Nakao et al., 2004) and that BLA lesions block stress effects on hippocampal long-term potentiation (Kim et al., 2001).

Other recent findings indicate similar interactions of the BLA with other brain regions. Posttraining infusions of RU 28362 into either the medial prefrontal cortex or nucleus accumbens enhance memory consolidation for inhibitory avoidance training; effects that are blocked by lesions of the BLA (B. Roozendaal, J. R. McReynolds, C. K. McIntyre and J. L. McGaugh, unpublished observations). Thus, these findings indicate that although glucocorticoids may act in many different brain regions to enhance memory consolidation, the modulatory effects of such local glucocorticoid administrations on memory consolidation depend on BLA activity. That is, influences from the BLA appear to be essential in enabling glucocorticoid effects on memory consolidation involving other brain regions.

Glucocorticoid effects on memory consolidation: interactions with noradrenergic mechanisms in the amygdala

The enhancing effects of glucocorticoids on memory consolidation depend on the integrity of the amygdala noradrenergic system. As shown in Fig. 1, microinfusions of antagonists for either β_1- or β_2-adrenoceptors administered into the BLA shortly before inhibitory avoidance training block the memory-enhancing effects of posttraining systemic dexamethasone (Quirarte et al., 1997). Studies using *in vivo* microdialysis and HPLC have shown that footshock stimulation of the same intensity and duration as used for inhibitory avoidance training induces the release of norepinephrine in the amygdala and that this increase in norepinephrine levels varies directly with stimulus intensity (Galvez et al., 1996; Quirarte et al., 1998). Furthermore, amygdala norepinephrine levels assessed following inhibitory avoidance training correlate with retention latencies tested 24 h later (McIntyre et al., 2002), whereas posttraining infusions of norepinephrine or β-adrenoceptor agonists administered into the BLA enhance memory consolidation (Ferry et al., 1999; Hatfield and McGaugh, 1999). Other experiments using inhibitory avoidance training found that noradrenergic activity within the BLA is also critical for the memory-modulatory effects of GR activation in the hippocampus (Roozendaal et al., 1999a). Unilateral infusions of the β_1-adrenoceptor antagonist atenolol into the BLA block the memory-enhancing effect of posttraining infusions of the GR agonist RU 28362 administered into the ipsilateral hippocampus but do not block the memory enhancement produced by posttraining infusions of RU 28362 into the contralateral hippocampus. These findings provide further evidence that β-adrenoceptor activity within the BLA is critical in enabling glucocorticoid effects on memory consolidation and that this is the case even if the glucocorticoids are administered in other brain regions. In accord with this evidence, electrophysiological studies have shown that a β-adrenoceptor antagonist infused into the BLA blocks the effect of electrical stimulation of the perforant path on dentate gyrus population-spike long-term potentiation (Ikegaya et al., 1997). Furthermore, destruction of noradrenergic terminals in the brain produced by the neurotoxin *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine (DSP-4) prevents the effect of electrical stimulation of the BLA on hippocampal neuroplasticity (Akirav and Richter-Levin, 2002).

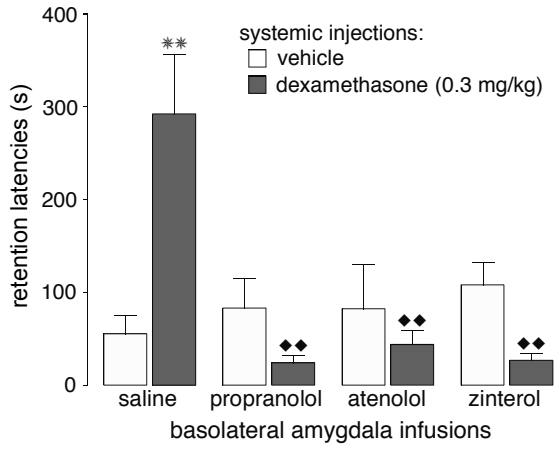

Fig. 1. Step-through latencies (mean+S.E.M.) in seconds on a 48-h inhibitory avoidance retention test. Pretraining infusions of the nonspecific β-adrenoceptor antagonist propranolol (0.5 μg in 0.2 μl), the β_1-adrenoceptor antagonist atenolol (0.5 μg in 0.2 μl), or the β_2-adrenoceptor antagonist zinterol (0.5 μg in 0.2 μl) into the BLA blocked the enhancing effect of immediate posttraining systemic injections of dexamethasone (0.3 mg/kg, s.c.) on memory consolidation. ** $P<0.01$ compared with the corresponding vehicle group; ◆◆ $P<0.01$ compared with the saline-dexamethasone group. Reprinted from Quirarte et al., 1997.

Glucocorticoids also interact directly with noradrenergic mechanisms within the BLA. Atenolol or the cyclic AMP (cAMP)-dependent protein kinase (PKA) inhibitor Rp-cAMPS administered into the BLA blocks the memory enhancement induced by infusions of a GR agonist into the BLA (Roozendaal et al., 2002). In contrast, inactivation of α_1-adrenoceptors in the BLA does not block GR agonist effects on memory consolidation. These findings suggest that glucocorticoid effects on memory consolidation require activation of the β-adrenoceptor-cAMP/PKA pathway in the BLA. Other recent findings indicate that glucocorticoids enhance memory consolidation by potentiating the efficacy of this signaling pathway in the BLA. Posttraining intra-BLA infusions of the β-adrenoceptor agonist clenbuterol or the cAMP analog 8-Br-cAMP enhance memory consolidation in a dose-dependent fashion (Liang et al., 1995; Ferry et al., 1999). As shown in Fig. 2, the GR antagonist RU 38486 infused into the BLA shortly before training shifted the dose-response effects of clenbuterol such that a much higher dose of clenbuterol was required to induce comparable memory enhancement (Roozendaal et al., 2002). In contrast, the GR antagonist did not modify the dose-response effects of 8-Br-cAMP, indicating that cAMP acts in the BLA downstream from the locus of interaction of glucocorticoids with the β-adrenoceptor-cAMP/PKA pathway. Glucocorticoids may interact with postsynaptic α_1-adrenoceptors to potentiate β-adrenoceptor-cAMP/PKA efficacy. This conclusion is consistent with evidence from studies investigating glucocorticoid–norepinephrine interactions on cAMP accumulation in cortical areas (Stone et al., 1987; Duman et al., 1989).

In addition to interacting with the noradrenergic signaling cascade at a postsynaptic level, glucocorticoids may influence noradrenergic function by altering the synthesis of norepinephrine (McEwen, 1987). Brainstem noradrenergic cell groups express high levels of GRs (Härfstrand et al., 1987). Posttraining activation of GRs within noradrenergic cell groups of the NTS induces dose-dependent memory enhancement for inhibitory avoidance training and the β-adrenoceptor antagonist atenolol infused into the BLA concurrently blocks the enhancement (Roozendaal et al., 1999b), suggesting that glucocorticoids increase the synthesis and subsequent release of norepinephrine in the BLA. In support of this view, in experiments using *in vivo* microdialysis and HPLC, we recently found that systemic administration of corticosterone after inhibitory avoidance training increased training-induced norepinephrine levels

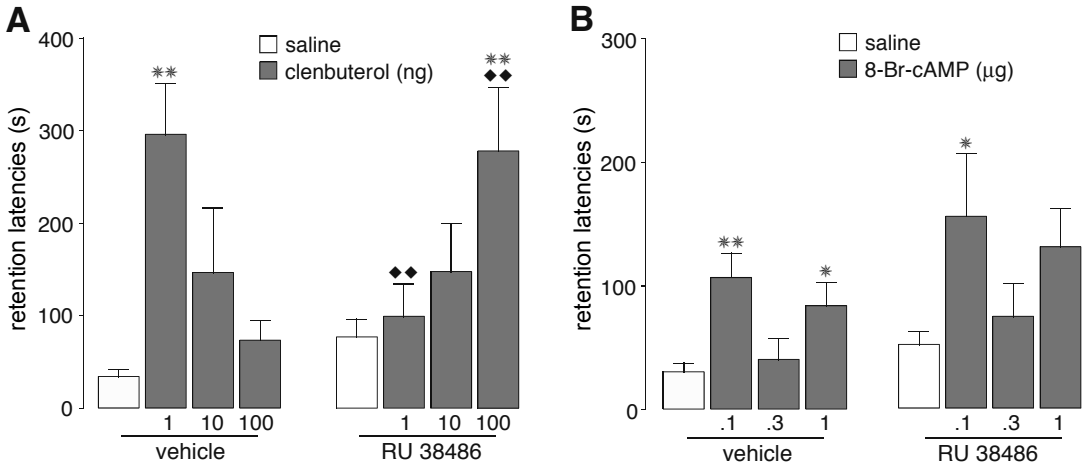

Fig. 2. Step-through latencies (mean+S.E.M.) in seconds on a 48-h inhibitory avoidance retention test. (A) Pretraining infusions of the GR antagonist RU 38486 (1 ng in 0.2 μl) into the BLA shifted the dose-response effects of immediate posttraining infusions of the β-adrenoceptor agonist clenbuterol (1, 10 or 100 ng in 0.2 μl) on memory consolidation. (B) Pretraining intra-BLA infusions of RU 38486 did not modify the dose-response effects of immediate posttraining infusions of the synthetic cAMP analog 8-Br-cAMP (0.1, 0.3 or 1.0 μg in 0.2 μl). ✶ $P<0.05$; ✶✶ $P<0.01$ compared with the corresponding saline group; ◆◆ $P<0.01$ compared with the corresponding vehicle group. Reprinted from Roozendaal et al., 2002.

in the amygdala and that norepinephrine levels correlated with later retention performance (McIntyre et al., 2004). The additional finding that corticosterone did not increase amygdala norepinephrine levels of rats that did not receive inhibitory avoidance training is consistent with the hypothesis that glucocorticoids interact with emotional arousal in influencing norepinephrine levels. Lastly, glucocorticoids may increase brain norepinephrine levels via an extraneuronal mechanism. Norepinephrine is rapidly taken up by glial cells after its release through a specific catecholamine-transporter protein. Corticosterone is a potent inhibitor of this catecholamine uptake through a rapid, nongenomic action (Grundemann et al., 1998). Thus, this evidence indicates that glucocorticoids are intimately linked with noradrenergic mechanisms and *permissively* increase noradrenergic neurotransmission in the brain during emotional arousal. The interaction of glucocorticoids with the noradrenergic system in the BLA in modulating memory consolidation is summarized in Fig. 3. Such interactions of glucocorticoids with the noradrenergic system of the BLA may be necessary for regulating memory consolidation in other brain regions.

Glucocorticoid effects on other memory functions

Memory retrieval. Although most studies investigating the effects of acutely administered glucocorticoids on memory have focused on consolidation, other findings indicate that glucocorticoids are also involved in stress effects on other memory functions. Stress exposure or glucocorticoids administered immediately after learning impair retention performance tested 30–60 min after training (Diamond et al., 1999; Woodson et al., 2003; Okuda et al., 2004a), i.e. at a time when the memory trace has not yet been consolidated into long-term memory. These findings strongly suggest that glucocorticoids can directly influence retention performance. We have found that glucocorticoids can affect retention performance by influencing the retrieval of previously acquired information. Stress exposure or glucocorticoids administered systemically shortly before testing on spatial/contextual tasks, 24 h after training, induce temporary retention performance impairment (de Quervain et al., 1998; Roozendaal et al., 2003, 2004a). As the same treatments administered shortly before training do not affect either acquisition or retention performance assessed immediately after acquisition, the findings strongly suggest that glucocorticoids impair retrieval of long-term memory. Likewise, stress-level glucocorticoid administration to human subjects impairs delayed, but not immediate, recall on episodic tasks (de Quervain et al., 2000; Wolf et al., 2001).

Extensive cognitive and neurobiological research indicates that the hippocampus is an important brain region implicated in memory retrieval (Hirsch, 1974; Squire et al., 2001). Glucocorticoid-induced memory retrieval impairment depends, in part, on GR activation in the hippocampus. The GR agonist RU 28362 administered into the hippocampus shortly before probe-trial testing in a water maze impairs retrieval of spatial memory (Roozendaal et al., 2003). Additionally, recent findings from an $H_2{}^{15}O$-positron-emission tomography study in human subjects indicate that a stress-level dose of cortisone reduces regional blood flow in the right parahippocampal gyrus, an effect that correlates with memory retrieval impairment on episodic tasks (de Quervain et al., 2003).

The β-adrenoceptor antagonist propranolol administered systemically 30 min before inhibitory avoidance retention testing blocks memory retrieval impairment induced by concurrent injections of corticosterone (Roozendaal et al., 2004a). Our finding that a β-adrenoceptor antagonist infused into the hippocampus prevents the impairing effect of concurrent intra-hippocampal administration of a GR agonist on memory retrieval indicates that glucocorticoids interact with noradrenergic mechanisms of the hippocampus in regulating memory retrieval (Roozendaal et al.,

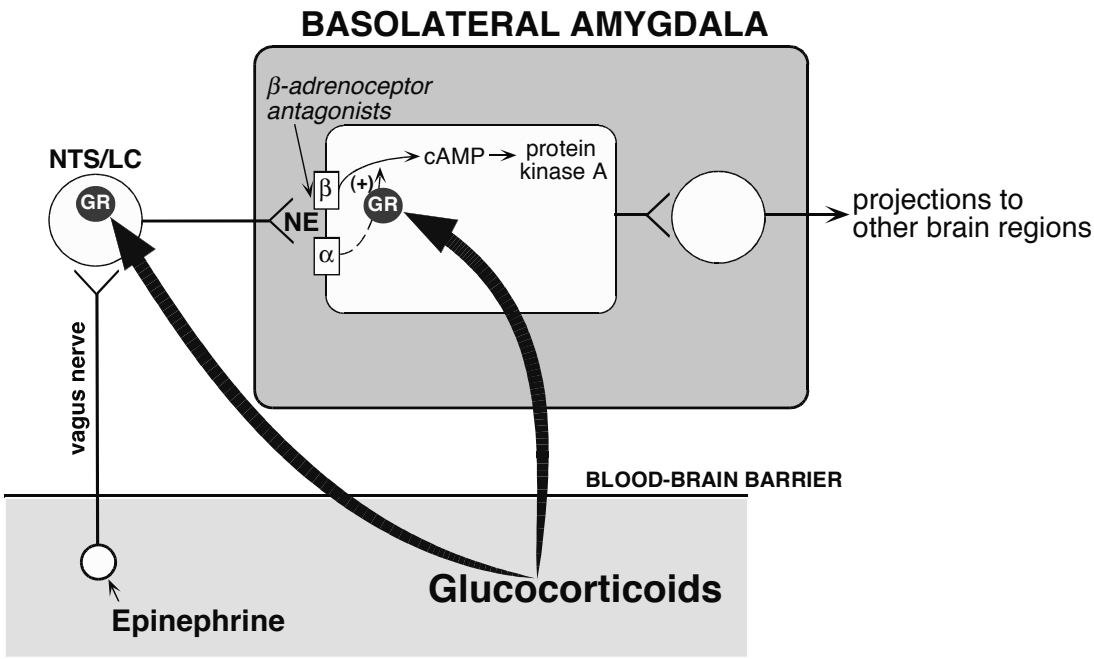

Fig. 3. Schematic summarizing the interactions of glucocorticoids with the noradrenergic system of the BLA at both presynaptic and postsynaptic sites as suggested by the findings of our experiments. Norepinephrine (NE) is released following training in aversively motivated tasks and binds to both β-adrenoceptors and α_1-adrenoceptors at postsynaptic sites. The β-adrenoceptor is coupled directly to adenylate cyclase to stimulate cAMP formation. The α_1-adrenoceptor modulates the response induced by β-adrenoceptor stimulation. Glucocorticoids may influence the β-adrenoceptor-cAMP system via a coupling with α_1-adrenoceptors. In addition, glucocorticoids may activate the noradrenergic system by activation of GRs in brainstem noradrenergic cell groups. α_1, α_1-adrenoceptor; β, β-adrenoceptor; LC, locus coeruleus. Reprinted from Roozendaal, 2000.

2004b). As stimulation of β_1-adrenoceptors before retention testing with systemic injections of the selective agonist xamoterol induces retention impairment comparable to that seen after GR activation (Roozendaal et al., 2004b), the findings provide additional evidence that glucocorticoid effects on memory retrieval impairment involve a facilitation of noradrenergic mechanisms in the hippocampus. However, the recent findings that infusion of noradrenergic agents (as well as drugs affecting several other classes of neurotransmitters) into a variety of brain regions influences memory retrieval (Barros et al., 2001) indicate that the hippocampus does not act in isolation in retrieval. Highly comparable to our findings on memory consolidation, BLA lesions block hippocampal glucocorticoid effects on memory retrieval (Roozendaal et al., 2003). Moreover, our finding that a β-adrenoceptor antagonist infused into the BLA before retention testing blocks memory retrieval impairment induced by concurrent intra-hippocampal infusions of a GR agonist (Roozendaal et al., 2004b) strongly suggests that noradrenergic activation of the BLA is essential for enabling hippocampal glucocorticoid impairment of memory retrieval. Such findings indicating that the role of BLA noradrenergic activity in regulating emotional arousal effects on hippocampus-dependent cognitive processes is not restricted to modulating memory consolidation but extends to memory retrieval suggest that a common neurobiological substrate may be involved and that stress effects on these two cognitive phases may be regulated in a coordinated, albeit opposite, fashion (Roozendaal, 2002).

Working memory. Stress exposure or glucocorticoid administration also profoundly impairs working memory (Arnsten and Goldman-Rakic, 1998; Wolf et al., 2001), which is known to rely on the integrity of the medial prefrontal cortex (mPFC) (Fuster, 1991). Mild uncontrollable stress impairs performance of rats on a delayed alternation task, a task commonly used to assess working memory in rodents (Murphy et al., 1996). Such stress also increases norepinephrine (and dopamine) turnover in the mPFC (Finlay et al., 1995; Morrow et al., 2000). Excessive levels of norepinephrine or an activation of the cAMP/PKA pathway in the mPFC is known to induce working memory impairment (Taylor et al., 1999; Arnsten, 2000). Like stress, glucocorticoid administration impairs working memory. The mPFC expresses high mRNA and protein levels for GRs (Meaney and Aitken, 1985). We recently reported that systemic injections of stress doses of corticosterone or intra-mPFC administration of the GR agonist RU 28362 impair delayed alternation performance (Roozendaal et al., 2004c). In addition, cortisol administration impairs working memory performance in human subjects (Lupien et al., 1999; Young et al., 1999; Wolf et al., 2001). Glucocorticoids appear to interact with noradrenergic mechanisms in inducing working memory impairment as systemic administration of the β-adrenoceptor antagonist propranolol blocks the impairing effect of corticosterone on working memory (Roozendaal et al., 2004c). Furthermore, as systemic administration of corticosterone increases levels of norepinephrine in the mPFC (Thomas et al., 1994), such

findings suggest that corticosterone effects on working memory impairment may involve a facilitation of noradrenergic mechanisms in the mPFC.

Glucocorticoid-induced working memory impairment also depends on interactions of the mPFC with the BLA. We reported that BLA lesions block working memory impairment induced by either systemic injections of corticosterone or intra-mPFC infusions of RU 28362 (Roozendaal et al., 2004c). Based on the evidence summarized above indicating that norepinephrine is critically involved in regulating BLA activity, it seems likely that the effect of systemically administered propranolol in preventing corticosterone-induced working memory impairment may also be mediated, in part, by a blockade of β-adrenoceptor activity within the BLA. The finding that BLA lesions alone do not affect working memory is in accord with previous evidence (Aggleton et al., 1989), and suggests that BLA activity is involved in modulating stress or emotional arousal effects on working memory involving other brain regions.

Role of emotional arousal in enabling glucocorticoid effects on memory functions

In the previous sections we summarized recent findings indicating that although glucocorticoids may exert opposing effects on different aspects of memory and act in many different brain regions to induce these complex effects, all of these modulatory actions depend on noradrenergic activity within the BLA. Lesions of the BLA or a β-adrenoceptor antagonist administered either systemically or into the BLA blocks glucocorticoid-induced enhancement of memory consolidation (Roozendaal and McGaugh, 1996, 1997b; Quirarte et al., 1997; Roozendaal et al., 1999a, 2002 as well as the impairment of memory retrieval and working memory (Roozendaal et al., 2003, 2004a,b,c). A corollary of this view is that glucocorticoids should affect memory only under experimental conditions that induce noradrenergic activation of the BLA. Extensive evidence indicates that the amygdala is activated during emotionally arousing experiences (Campeau et al., 1991; Cahill et al., 1996; Adolphs and Tranel, 2000; Dolan, 2000; Pelletier et al., 2005) and that emotional arousal induces norepinephrine release in the BLA (Quirarte et al., 1998; McIntyre et al., 2002; van Stegeren et al., 2005). Thus, emotional arousal-induced BLA activation may be a critical step in enabling glucocorticoid effects in modulating memory processes. Alternatively, it is possible that basal noradrenergic activity of the BLA is sufficiently high to enable glucocorticoid effects on these memory functions. We recently investigated this issue in rats trained on an object recognition task. Although no rewarding or aversive stimulation is used during object recognition training (Ennaceur and Delacour, 1988), we previously found that such training induces modest novelty-induced stress or arousal (Okuda et al., 2004a). Thus, rats habituated extensively to the training apparatus (in the absence of any objects) would be expected to be less aroused by object recognition training than rats not given prior habituation training. As shown in Fig. 4, in rats that were not previously habituated to the experimental context, corticosterone administered systemically immediately after training enhanced 24-h retention performance. In contrast, corticosterone did not affect 24-h retention for the same training experience of rats that received extensive prior habituation to the experimental context and, thus, had decreased novelty-induced emotional arousal during training (Okuda et al., 2004a). The findings of that study further indicated that glucocorticoid effects on impairment of memory retrieval also depend on the level of emotional arousal. Immediate posttraining administration of corticosterone to non-habituated rats, in doses that enhanced 24-h retention, impaired object recognition performance tested at a 1-h retention interval, whereas corticosterone administered after training to well-habituated rats did not impair 1-h retention.

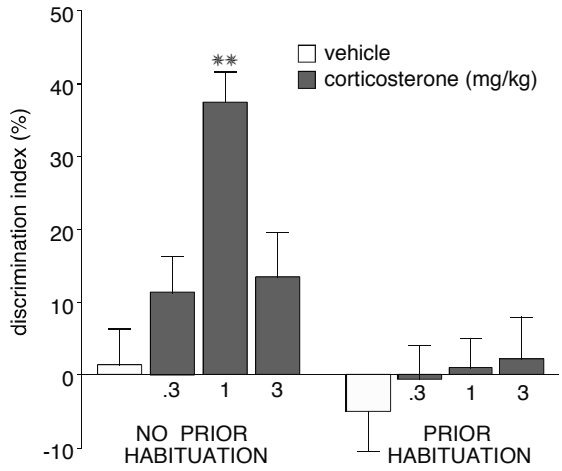

Fig. 4. Posttraining administration of corticosterone (0.3, 1.0 or 3.0 mg/kg, s.c.) enhanced 24-h object recognition performance of rats that were not previously habituated to the experimental context, but not of rats that received extensive prior habituation. The discrimination index (mean+S.E.M.) was calculated as the difference in time exploring the novel and familiar object, expressed as the ratio of the total time spent exploring both objects. ✶✶ $P<0.01$ compared with the corresponding vehicle group. Reprinted from Okuda et al., 2004a.

To test whether training-induced noradrenergic activation is the critical component of emotional arousal in enabling glucocorticoid effects on memory consolidation, the β-adrenoceptor antagonist propranolol was co-administered with the systemic corticosterone injection immediately after object recognition training to non-habituated animals. As expected on the basis of our findings using other types of emotionally arousing training, propranolol administered in a low and otherwise ineffective dose blocked the corticosterone-induced memory enhancement (Okuda et al., 2004b). Furthermore, propranolol administered directly into the BLA blocked the enhancing effects of corticosterone on memory consolidation. However, it is more interesting to determine whether the failure of corticosterone to enhance memory consolidation under low-arousing conditions is due to insufficient training-induced noradrenergic activation and, thus, whether pharmacological augmentation of noradrenergic activity would mimic

the effects of emotional arousal and enable glucocorticoid effects on memory consolidation during such low-arousing conditions. To examine this implication, low doses of the α_2-adrenoceptor antagonist yohimbine, which increases norepinephrine levels in the brain, were administered systemically to well-habituated rats immediately after object recognition training. Posttraining injections of this dose of yohimbine alone did not enhance memory consolidation but, importantly, simultaneously administered corticosterone induced dose-dependent enhancement of memory consolidation (Okuda et al., 2004b). Such observations strongly suggest that because glucocorticoid effects on memory consolidation and other cognitive processes depend critically on interactions with noradrenergic mechanisms of the BLA (and possibly other brain regions), they only modulate memory processes under emotionally arousing conditions that induce the release of norepinephrine.

Some recent findings in human subjects are consistent with the view that glucocorticoid effects on memory consolidation depend on the level of training-associated emotional arousal. Buchanan and Lovallo (2001) reported that cortisol administered shortly before training enhanced long-term memory of emotionally arousing, but not emotionally neutral, pictures. Studies investigating the effects on memory consolidation of posttraining administration of epinephrine (Cahill and Alkire, 2003) or cold pressor stress exposure, causing endogenous stress hormone activation (Cahill et al., 2003), obtained similar results. Furthermore, it has been reported that enhanced human memory for emotionally arousing material depends on amygdala–hippocampus interactions (Kilpatrick and Cahill, 2004; Kensinger and Corkin, 2004; Richardson et al., 2004) and is blocked by amygdala lesions or the administration of β-adrenoceptor antagonists (Cahill et al., 1994, 1995 van Stegeren et al., 2005). Other recent findings in human subjects indicate that glucocorticoids or psychosocial stress exposure may selectively impair retrieval of emotionally arousing, but not emotionally neutral, information (Kuhlmann et al., 2005a,b) and that successful retrieval of emotionally arousing information induces greater activity in both the amygdala and hippocampus than does retrieval of emotionally neutral information (Dolcos et al., 2005). Furthermore, it has been reported that the effects of psychosocial stress exposure on impairment of working memory require concurrent activation of glucocorticoids and the sympathetic nervous system (Elzinga and Roelofs, 2005).

CONCLUSIONS

The evidence summarized in this paper indicates that adrenal stress hormones influence memory processes in various animal and human memory tasks. Acutely administered or released glucocorticoids dose-dependently enhance the consolidation of long-term memory, but impair processes of memory retrieval and working memory. Although glucocorticoids may act in many different brain regions to modulate these memory processes, the effects appear to depend critically on training-induced BLA activation and noradrenergic neurotransmission within the BLA. These findings may help to explain why glucocorticoids do not uniformly modulate memory for all kinds of information but, rather, preferentially influence the consolidation and retrieval of emotionally arousing information.

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