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Glucocorticoids and the regulation of memory consolidation

Benno Roozendaal *

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

Abstract

This paper summarizes recent findings on the amygdala's role in mediating acute effects of glucocorticoids on memory consolidation in rats. Posttraining activation of glucocorticoid-sensitive pathways involving glucocorticoid receptors (GRs or type II) enhances memory consolidation in a dose-dependent inverted-U fashion. Selective lesions of the basolateral nucleus of the amygdala (BLA) or infusions of β-adrenoceptor antagonists into the BLA block the memory-modulatory effects of systemic injections of glucocorticoids. Additionally, posttraining infusions of a specific GR agonist administered directly into the BLA enhance memory consolidation, whereas those of a GR antagonist impair. These findings indicate that glucocorticoid effects on memory consolidation are mediated, in part, by an activation of GRs in the BLA and that the effects require β-adrenergic activity in the BLA. Other findings indicate that the BLA interacts with the hippocampus in mediating glucocorticoid-induced modulatory influences on memory consolidation. Lesions of the BLA or inactivation of β-adrenoceptors within the BLA also block the memory-modulatory effects of intra-hippocampal administration of a GR agonist or antagonist. These findings are in agreement with the general hypothesis that the BLA integrates hormonal and neuromodulatory influences on memory consolidation. However, the BLA is not a permanent locus of storage for this information, but modulates consolidation processes for explicit/associative memories in other brain regions, including the hippocampus.

Keywords: Amygdala; Basolateral nucleus; Corticosterone; Dexamethasone; Glucocorticoid receptor; Hippocampus; Norepinephrine; β-adrenoceptor; Memory consolidation

* Tel.: + 1-949-824-5250; fax: + 1-949-824-2952.
E-mail address: broozend@uci.edu (B. Roozendaal)

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1. Introduction

Stressful events induce the release of adrenal stress hormones, including catecholamines and glucocorticoids (Smith, 1973; McCarty and Gold, 1981; de Boer et al., 1990; Roozendaal et al., 1991, 1996a). Findings from both animal and human studies have shown that these hormones have profound effects on cognition (Bohus, 1994; McEwen and Sapolsky, 1995; McGaugh et al., 1996; Lupien and McEwen, 1997; Cahill and McGaugh, 1998). Sustained stressors or pathophysiological conditions such as affective disorders have detrimental effects on cognition (McEwen and Sapolsky, 1995). These impairing effects have been attributed mainly to glucocorticoids that are released from the adrenal cortex (Dachir et al., 1993; Arbel et al., 1994; Bodnoff et al., 1995; Conrad et al., 1996). In contrast, brief periods of stress usually enhance the formation of new memories (Shors et al., 1992). The role of peripheral catecholamines in memory consolidation was established several decades ago (Gold and van Buskirk, 1975). More recent findings indicate that glucocorticoids are also implicated in regulating memory consolidation processes (Oitzl and de Kloet, 1992; Sandi and Rose, 1994a; Roozendaal and McGaugh, 1996b; de Kloet et al., 1998).

This paper summarizes recent findings concerning acute or phasic effects of glucocorticoids on memory consolidation in rats. Studies of the effects of epinephrine as well as those of other neuromodulatory systems have shown that the amygdala is critically involved in integrating the modulatory effects of acute stress on memory consolidation (McGaugh et al., 1996; Roozendaal et al., 1996b). The focus of this paper is on studies examining the amygdala's role in mediating glucocorticoid effects on memory consolidation. Other recent findings indicate that the amygdala interacts with other brain structures in modulating memory consolidation. In the context that the hippocampus is considered a 'classical' brain structure implicated in glucocorticoid action (McEwen and Sapolsky, 1995), this paper will review evidence that the amygdala interacts with the hippocampus in mediating glucocorticoid effects on memory consolidation. Finally, the relationship between the acute and chronic effects of glucocorticoids on memory consolidation will be discussed.

2. Regulation of memory consolidation

For several decades experiments have examined the effects of drugs and hormones on selective processes of memory consolidation (McGaugh, 1989; McGaugh et al., 1992, 1996; Cahill and McGaugh, 1998). The general hypothesis guiding this research was proposed originally by Mueller and Pilzecker one century ago. Their 'perseveration–consolidation' hypothesis proposed that memory traces are initially fragile after learning and become consolidated over time (Mueller and Pilzecker, 1900). Almost half a century later this theory was investigated in laboratory animals for the first time (Duncan, 1949; Gerard, 1949). As Mueller and Pilzecker would have predicted, electroconvulsive shock given to rats shortly after learning

markedly impaired later retention whereas the treatment given several hours after training did not impair retention. Later, McGaugh (1966) found that stimulant drugs such as strychnine and amphetamine given to rats shortly after training could induce retrograde hypermnesia. Thus, with the use of electrical brain stimulation or drug injections administered during a critical time window shortly after training it is possible to influence selectively the consolidation of lasting memories without directly affecting the animal's performance during acquisition or retention testing (McGaugh, 1966; McGaugh and Herz, 1972). Consistent with this 'memory modulation' hypothesis, a familiar pattern of posttraining injection treatments is both its time- and dose-dependency. Drug effects are greatest when administered immediately after training and are generally ineffective when administered several hours later (McGaugh, 1966, 1989). Moreover, drug effects on memory consolidation are not linear with the dose, but typically follow a so-called Yerkes–Dodson or inverted-U shape dose-response relationship. Optimal enhancing effects on memory are seen at midrange doses whereas high doses are less effective or may even impair memory.

The observation that some experiences are remembered vividly, whereas others are not remembered at all, or at best very remotely, led to the suggestion that there may be an endogenous mechanism that serves to regulate the strength of the memories (Gold and McGaugh, 1975). Strong memories are often based on experiences that are meaningful or emotionally arousing and may need to be remembered well. The association between enhanced memory and the emotionally arousing characteristics of such an event suggested that the degree to which memories are lasting may be influenced by hormonal systems activated by experience (Gold and van Buskirk, 1975). Thus, it was proposed that the physiology of memory consolidation may involve stress hormones as endogenous modulators of the neurobiological processes underlying memory consolidation. A corollary of this view is that with peripheral posttraining injections of stress hormones it should be possible to mimic the animal's endogenous response to an emotionally arousing experience and thus induce a strong memory for that event.

3. Glucocorticoid effects on memory consolidation

The earliest experiments to suggest that hormones of the hypothalamic pituitary-adrenocortical axis affect learning processes used pretraining manipulations of pituitary-adrenal hormones. For example, Mirsky et al. (1953) studied the effects of pretraining injections of adrenocorticotropin (ACTH) on learned behavioral responses to stressful situations in monkeys and found that the injections profoundly altered extinction behavior. Subsequently, de Wied and his associates found effects of ACTH and corticosteroids on extinction of avoidance behavior in rats (de Wied, 1966; Bohus and de Wied, 1980). However, the discovery that adrenocortical hormones given after a training experience can act in a retrograde fashion to affect memory raised the possibility that these hormones released after an acute stressful event may affect memory for that event (Kovacs et al., 1977; Flood et al., 1978). In

order to provide a basis for considering the relationship between glucocorticoids and the amygdala in memory consolidation, a brief description of the main characteristics of glucocorticoids on memory consolidation will be presented here.

Single injections of moderate doses of corticosterone or the synthetic glucocorticoid dexamethasone enhance memory for inhibitory avoidance training when administered immediately after training (Kovacs et al., 1977; Flood et al., 1978; Roozendaal and McGaugh, 1996a,b; Roozendaal et al., 1999b). Glucocorticoid effects on memory enhancement for inhibitory avoidance training follow an inverted-U shape dose-response relationship. Similar biphasic effects of posttraining corticosteroids in rats have been observed in a contextual-cue fear conditioning paradigm (Pugh et al., 1997; Cordero and Sandi, 1998), a spatial water-maze task (Sandi et al., 1997) as well as in an avoidance task in 1 day-old chicks (Sandi and Rose, 1994a, 1997). Moreover, Sandi and Rose (1994a) have shown that corticosterone injections are effective in enhancing consolidation processes for avoidance learning in chicks when given up to 60 min after training. Dexamethasone enhanced memory for avoidance learning in mice when injected up to 150 min after training (Flood et al., 1978). Although the time courses differ slightly between these studies, which were done in different species, they both illustrate the time-dependent characteristics of glucocorticoids in influencing memory consolidation processes.

It should be noted that, inherent to an inverted-U shaped relationship of glucocorticoids on memory consolidation, the effects depend not only on the dose, but also on the relative aversiveness of the task and the memory performance of the control animals. For example, posttraining injections of moderate doses of dexamethasone can induce memory impairment in a spatial version of the water maze, a task which is much more stressful for rats than is inhibitory avoidance training and consequently results in high circulating levels of endogenous glucocorticoids (Roozendaal et al., 1996a). However, if the training conditions are made less stressful (e.g. by increasing the water temperature of the maze), posttraining glucocorticoid injections can enhance consolidation processes (Sandi et al., 1997). Removal of endogenous corticosterone by adrenalectomy (ADX) also impairs memory in a spatial water-maze task (Oitzl and de Kloet, 1992; Roozendaal et al., 1996d). Selective removal of the adrenal medulla, thus sparing glucocorticoids, does not impair memory in the water maze (Oitzl and de Kloet, 1992). This ADX-induced memory impairment is reversed by posttraining injections of dexamethasone in doses comparable to those known to enhance memory in the inhibitory avoidance task (Roozendaal et al., 1996d). Such findings suggest that the impairment is caused by the lack of glucocorticoids and that memory consolidation processes for spatial water-maze training, like those for inhibitory avoidance training, depend on posttraining dose-dependent activation of glucocorticoid-sensitive pathways. These findings also support the hypothesis that endogenously released glucocorticoids are involved in regulating memory consolidation.

The issue of whether dexamethasone enters the brain is a subject of current debate (e.g. Lupien and McEwen, 1997; de Kloet et al., 1998). Studies reporting no active uptake of dexamethasone into the brain (e.g. de Kloet et al., 1975; Coutard et al., 1978) have suggested that the facilitating effects of dexamethasone on

memory consolidation might be due to suppressed plasma concentrations of endogenous corticosterone resulting from a dexamethasone-induced inhibition of hypothalamic–pituitary–adrenocortical axis activity. In this way, dexamethasone injections deplete endogenous corticosterone from the brain and the effects show resemblance with a state of ADX. This hypothesis is supported by some recent findings showing that mice with a genetic disruption of the multiple drug resistance (mdr1a) gene showed increased labeling of [^{3}H]-dexamethasone in the forebrain (Meijer et al., 1998). This drug-transporting P-glycoprotein may, in intact animals, act at the level of the blood-brain barrier to induce resistance for penetration of dexamethasone into the brain. However, the findings that: (i) the effects of dexamethasone and ADX on memory consolidation are opposite; (ii) injections of the endogenous ligand corticosterone induce memory-enhancing effects comparable to those induced by dexamethasone; (iii) the dose-response effects of dexamethasone follow an inverted-U curve; (iv) dexamethasone also enhances memory for spatial training in ADX rats; (v) intra-cerebral infusions of glucocorticoids induce effects similar to those observed with dexamethasone; and (vi) the effects of systemic dexamethasone on memory are blocked by intra-cerebral infusions of the specific GR antagonist RU 38486, strongly suggest that the effects of peripheral dexamethasone administration on memory consolidation are due, at least in experiments using rats, to an activation of central adrenal steroid receptors.

3.1. Glucocorticoid versus mineralocorticoid receptors

Dexamethasone has a high affinity for glucocorticoid receptors (GRs or type II) (Reul and de Kloet, 1985; de Kloet, 1991). Therefore, an activation of GRs, and not mineralocorticoid receptors (MRs or type I), may be involved in modulation of memory consolidation. GRs have a low affinity for corticosterone and become occupied only during stress and at the circadian peak, when levels of glucocorticoids are high. In contrast, MRs have a high affinity for corticosterone and are almost saturated under basal conditions (Reul and de Kloet, 1985). Therefore, it is likely that stress-activated GRs, and not the tonically activated MRs, mediate stress effects on memory consolidation (de Kloet, 1991). To examine explicitly whether these effects depend on GR activation, intact rats were given intra-cerebroventricular (ICV) infusions of specific antagonists for either GRs or MRs. Consistent with the hypothesis, pretraining or immediate posttraining infusions of a GR, but not an MR, antagonist impaired spatial memory in a water maze (Oitzl and de Kloet, 1992; Roozendaal et al., 1996d). Additionally, posttraining infusions of the GR antagonist impaired memory for an avoidance task in chicks (Sandi and Rose, 1994b) and blocked the enhancing effects of posttraining corticosterone (Sandi and Rose, 1994a). Administration of a GR antagonist or GR antisense oligonucleotide (i.e. interfering with GR gene expression) directly into the hippocampus shortly before learning impaired retention behavior in a Porsolt swimming task (de Kloet et al., 1988; Korte et al., 1996). Moreover, GR-knockout mice show impaired memory consolidation (Oitzl et al., 1998a). These findings clearly suggest that GRs, and not MRs, are involved in regulating glucocorticoid effects on memory consol-

idation. This conclusion is also consistent with that of a recent study examining the effects of systemic administration of different doses of corticosterone to ADX rats on spatial memory in a Y-maze discrimination task (Conrad et al., 1999). It was found that the level of GR occupancy, as measured by a binding assay, was significantly correlated with spatial memory performance following an inverted-U shape curve, whereas the level of MR occupancy was not. In contrast, Oitzl and colleagues have shown in an elegant series of studies that MRs are implicated in the interpretation of environmental stimuli and the selection of behavioral strategies (Oitzl and de Kloet, 1992; Oitzl et al., 1994).

4. Role of the amygdala in glucocorticoid effects on memory consolidation

The amygdala is a temporal lobe structure implicated in the expression of emotional stress responses (Roozendaal et al., 1990, 1991, 1992; LeDoux, 1995) and in memory for particularly emotionally arousing events (McGaugh et al., 1992, 1996). Lesions of the amygdala have been shown to block the enhancing effects of emotional arousal on memory consolidation. Lesions of the amygdala also block the memory-modulatory effects of systemic administration of epinephrine and other neuromodulators (McGaugh et al., 1992, 1996; Roozendaal et al., 1996b). This section summarizes findings of experiments investigating the involvement of the amygdala in mediating glucocorticoid effects on memory consolidation.

4.1. Lesion and infusion studies

Emerging evidence indicates that glucocorticoid effects on memory consolidation are mediated by influences involving the amygdala. In an initial study examining this issue, immediate posttraining systemic injections of dexamethasone were administered to rats with bilateral excitotoxic lesions of selective amygdala nuclei, induced 1 week earlier. If the amygdala is critically involved in mediating glucocorticoid influences on memory consolidation, then lesions of the amygdala should block these modulatory effects. As is shown in Fig. 1A, although lesions of the amygdala restricted to the basolateral nucleus (BLA) alone did not impair memory for inhibitory avoidance training, the BLA lesions did block the memory-enhancing effects of posttraining systemic injections of dexamethasone (Roozendaal and McGaugh, 1996a). In contrast, lesions of the adjacent central nucleus (CEA) impaired inhibitory avoidance performance, but did not block the dexamethasone-induced memory enhancement. These findings indicate that an intact BLA is necessary for systemically administered glucocorticoids to modulate memory formation. This view is supported further by the finding that bilateral lesions of the stria terminalis, a major afferent-efferent pathway of the amygdala, block the memory-enhancing effects of posttraining systemic injections of dexamethasone (Roozendaal and McGaugh, 1996b). Lesions of the BLA or stria terminalis not only block the *enhancing* effects of glucocorticoids or GR agonists, but they also completely block the *impairing* effects of ADX or ICV administration of the GR antagonist RU 38486 (Roozendaal and McGaugh, 1996b; Roozendaal et al., 1996d).

Although these findings clearly illustrate the critical involvement of the BLA in mediating the modulatory effects of glucocorticoids on memory consolidation, they do not reveal whether the effects are caused by binding of glucocorticoids to GRs in the BLA. The BLA contains a moderate density of GRs (Honkaniemi et al.,

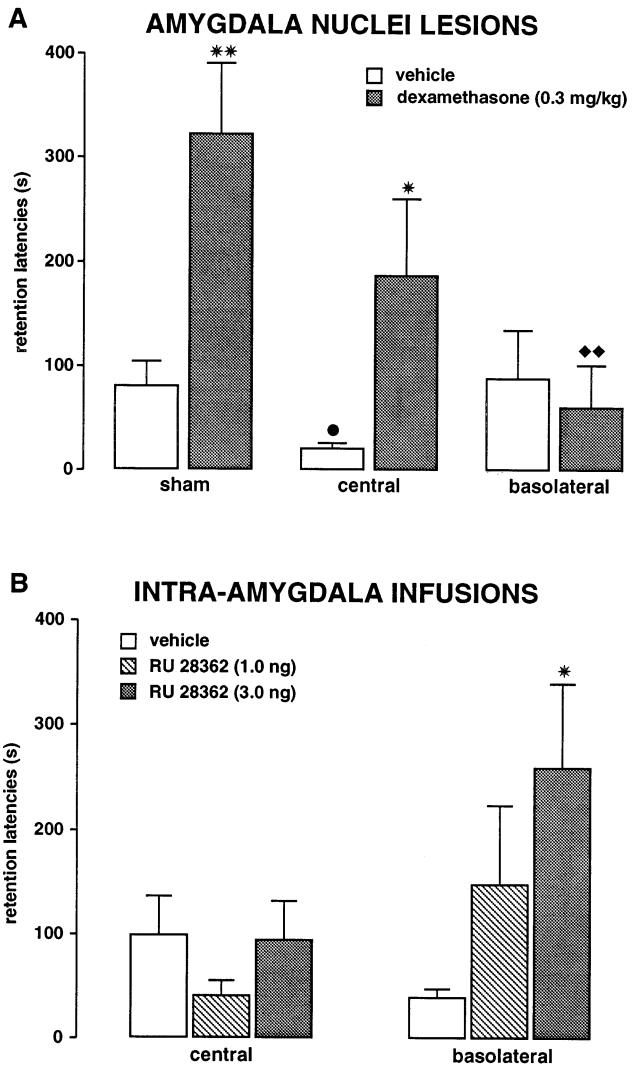

Fig. 1. Step-through latencies (mean ± S.E.M.) for a 48-h inhibitory avoidance test. (A) Rats with sham, or lesions of either the central or basolateral nucleus of the amygdala had been treated with dexamethasone (0.3 mg/kg, SC) or vehicle immediately after training. (B) Rats received posttraining microinfusions of the glucocorticoid receptor agonist RU 28362 (1.0 or 3.0 ng) in the central or basolateral nucleus. *$P < .05$; **$P < .01$ as compared with the corresponding vehicle group; ●$P < .05$ as compared with the corresponding sham lesion-vehicle group; ◆◆$P < .01$ as compared with the corresponding sham lesion-dexamethasone group (from Roozendaal and McGaugh 1996a, 1997b).

1992; Morimoto et al., 1996). To examine whether glucocorticoid effects on memory consolidation involve binding to GRs in the BLA, microinfusions of the specific GR agonist RU 28362 were given directly into either the BLA or CEA immediately after inhibitory avoidance training. As is shown in Fig. 1B, posttraining infusions of the GR agonist administered into the BLA enhanced retention in a dose-dependent fashion, but the GR agonist infusions were ineffective when administered into the CEA (Roozendaal and McGaugh, 1997b). Moreover, administration of the GR antagonist RU 38486 selectively into the BLA impaired memory for a spatial water-maze task (Roozendaal and McGaugh, 1997b). These findings strongly suggest that the modulatory effects of glucocorticoids on memory consolidation are mediated, in part, by direct binding to GRs in the BLA. The CEA has a high density of GRs (as well as MRs) that surpasses that of the BLA (Honkaniemi et al., 1992; Morimoto et al., 1996). However, these receptors seem not to be involved in regulating memory consolidation. In contrast, it has been reported that adrenal steroid receptors in the CEA are involved in allostatic load (Schulkin et al., 1994), the expression of conditioned fear (Corodimas et al., 1994), and corticotropin-releasing hormone-induced enhancement of acoustic startle (Lee et al., 1994).

4.2. Involvement of noradrenergic mechanisms within the basolateral amygdala

Evidence summarized in the previous section suggests that glucocorticoids can enhance memory consolidation by a direct activation of GRs in the BLA. Strikingly similar findings of the involvement of the amygdala have been observed previously with epinephrine as well as many other hormones and drugs (McGaugh et al., 1996). Unlike glucocorticoids, epinephrine does not readily enter the brain (Weil-Malherbe et al., 1959) and its effects thus appear to be initiated by an activation of peripheral β-adrenergic mechanisms (Introini-Collison et al., 1992). However, epinephrine effects also involve central noradrenergic mechanisms, as epinephrine is known to enhance locus coeruleus neuronal activity (Holdefer and Jensen, 1987) and increase norepinephrine release in the brain (Gold and van Buskirk, 1978). Other studies have shown that the effects of epinephrine on memory consolidation depend on the integrity of the noradrenergic system in the amygdala. Infusions of β-adrenoceptor antagonists into the amygdala block the memory-modulatory effects of systemically administered epinephrine (Liang et al., 1986, 1990, 1995). Moreover, systemic injections of epinephrine induce the release of norepinephrine within the amygdala (Williams et al., 1998).

Recent findings suggest that the enhancing effects of glucocorticoids on memory consolidation also depend on the integrity of the amygdala β-adrenergic system. Microinfusions of β-adrenoceptor antagonists administered into the BLA block the enhancing effects of posttraining systemic dexamethasone on memory for inhibitory avoidance training (Quirarte et al., 1997a) (Fig. 2). We have also found that the β-adrenoceptor antagonist atenolol infused into the BLA blocks the memory enhancement induced by a GR agonist infused concurrently (Quirarte et al., 1997a). Furthermore, the finding that higher doses of the GR agonist are ineffective in

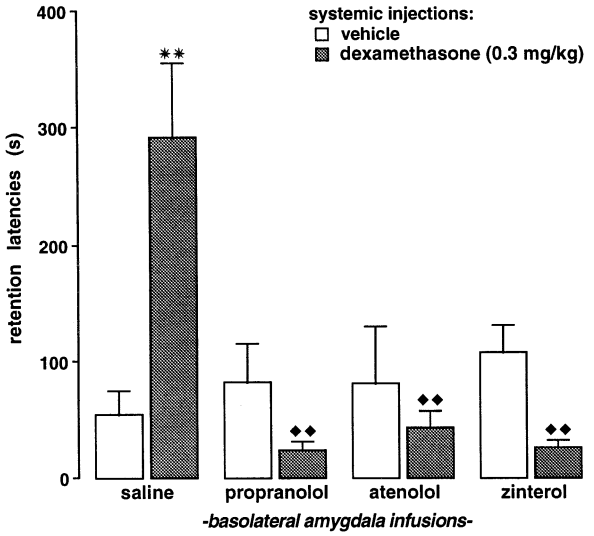

Fig. 2. Step-through latencies (mean ± S.E.M.) for a 48-h inhibitory avoidance test. Effects of pretraining infusions of either the non-specific β-adrenoceptor antagonist propranolol (0.5 μg in 0.2 μl), the β_1-adrenoceptor antagonist atenolol (0.5 μg in 0.2 μl), or the β_2-adrenoceptor zinterol (0.5 μg in 0.2 μl) into the basolateral amygdala and immediate posttraining systemic injections of dexamethasone (0.3 mg/kg, SC). $^{**}P < .01$ as compared with the corresponding vehicle group; ◆◆ $P < .01$ as compared with the corresponding saline-dexamethasone group (from Quirarte et al., 1997a).

enhancing memory in animals given atenolol concurrently suggests that atenolol does not simply induce a shift in the dose-response effects of glucocorticoids. Because adrenal steroid receptors are intracellular and intranuclear (Joëls and de Kloet, 1994), the latter findings suggest that one locus of glucocorticoid–noradrenergic interaction is postsynaptically in BLA neurons.

4.2.1. Interaction with postsynaptic noradrenergic mechanisms

Norepinephrine or β-adrenoceptor agonists such as clenbuterol and isoproterenol administered into the amygdala dose-dependently enhance memory for several tasks, including inhibitory avoidance, a probe burying paradigm and the spatial water-maze task (Liang et al., 1990; Introini-Collison et al., 1991; Roozendaal et al., 1993; Liang et al., 1995; Ferry et al., 1999; Hatfield and McGaugh, 1999). As is shown in Fig. 3, pretraining infusions of the GR antagonist RU 38486 into the BLA shift the dose-response curve of clenbuterol to the right (Quirarte et al., 1997b), indicating that a blockade of GRs makes the BLA less sensitive to the memory-facilitating action of clenbuterol. These findings are consistent with the view that glucocorticoids may exert a permissive action on the efficacy of the noradrenergic system (de Kloet, 1991).

The molecular or cellular mechanisms underlying glucocorticoid actions on the noradrenergic system in the BLA in regulating memory consolidation have not yet been studied. Moreover, the results obtained from examining glucocorticoid–nora-

drenergic interactions in other brain regions seem far from clear. It has been reported that GR activation can change the excitability of hippocampal neurons induced by noradrenergic stimulation (Joëls and de Kloet, 1989). Pharmacological studies suggest that glucocorticoids may interfere with β-adrenoceptor activation-induced signal transduction involving cAMP production (Stone et al., 1987). Those findings also suggest that the effects may involve a coupling of GRs with postsynaptic α_1-adrenergic mechanisms possibly affecting G-protein expression via a genomic action (Stone et al., 1987; Duman et al., 1989). Consistent with this view, a recent in situ hybridization study has reported colocalization of the mRNAs for GRs and α_1-adrenoceptors in hippocampal neurons (Williams et al., 1997). However, because of the rapid and transient noradrenergic response after training (Quirarte et al., 1998), it seems unlikely that the linkage between glucocorticoids and the noradrenergic system within the BLA in influencing memory consolidation is based entirely on genomic actions by intracellular receptors. Non-genomic membrane actions of glucocortioids may exist and there may even be a membrane form of GR that acts more directly on second messengers, but there is little evidence for this. Orchinik et al. (1991) showed rapid glucocorticoid actions on a G-protein mediated event in the newt, but the membrane receptor has low affinity for dexamethasone and thus GRs are probably not involved here. Another important issue that needs further clarification is that in most electrophysiological and pharmacological studies glucocorticoids decrease the efficacy of the noradrenergic

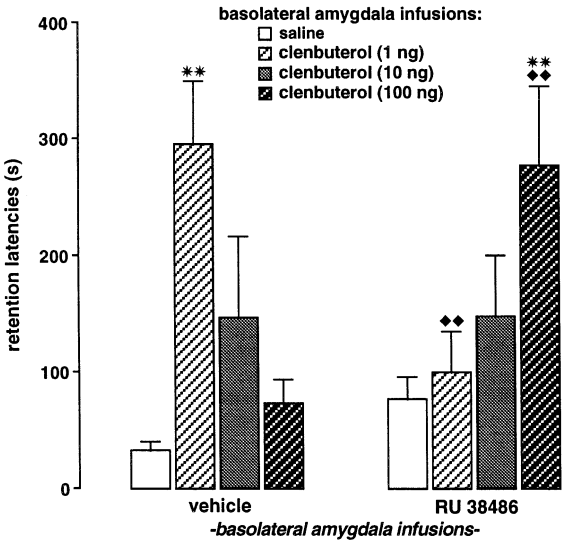

Fig. 3. Step-through latencies (mean ± S.E.M.) for a 48-h inhibitory avoidance test. Effects of pretraining infusions of the glucocorticoid receptor antagonist RU 38486 (1.0 ng in 0.2 μl) into the basolateral amygdala and immediate posttraining infusions of the β-adrenoceptor agonist clenbuterol (1, 10 or 100 ng in 0.2 μl) into the basolateral amygdala. $^{**}P < .01$ as compared with the corresponding saline group; ◆◆$P < .01$ as compared with the corresponding vehicle-clenbuterol group.

system whereas our behavioral data indicate facilitating effects. Thus, these effects may be site-specific. Moreover, it is possible that the time of administration of glucocorticoids in relation to the noradrenergic agent (i.e. allowing genomic versus non-genomic effects to occur) may be important in determining the direction of the effect. In support of the view that glucocorticoids in the BLA may interfere with β-adrenoceptor activation-induced cAMP production via α_1-adrenoceptors, we recently found that an inactivation of α_1-adrenoceptors in the BLA with the selective antagonist prazosin induced a shift in the dose-response effects of clenbuterol similar to that observed with the GR antagonist (Ferry et al., 1999). The memory-enhancing effects induced by intra-BLA infusions of a synthetic cAMP analog were not shifted by prazosin (Ferry et al., 1999), indicating that the interaction of α_1-adrenergic mechanisms (and possibly glucocorticoids) with the β-adrenoceptor–cAMP system must occur somewhere between the membrane-bound β-adrenoceptor and the intracellular cAMP production site.

4.2.2. Interaction with presynaptic noradrenergic mechanisms

The findings suggesting that glucocorticoids interact postsynaptically with the noradrenergic system in BLA pyramidal neurons in regulating memory consolidation do not rule out the possibility that interactions between glucocorticoids and the noradrenergic system may also occur at the level of noradrenergic soma in the brainstem that send projections to the BLA. The BLA receives noradrenergic innervation from cell groups in the nucleus of the solitary tract (NTS) as well as from the locus coeruleus (Fallon and Ciofi, 1992; Fallon, personal communication). The cell bodies of the noradrenergic neurons in the brainstem that project to the BLA contain among the highest densities of GRs in the mammalian brain (Härfstrand et al., 1987; Morimoto et al., 1996). Interestingly, those cell bodies appear to be devoid of MRs. Glucocorticoid influences on noradrenergic neurons have been examined extensively in catecholaminergic neurons in the locus coeruleus. Glucocorticoids activate noradrenergic neurons in the locus coeruleus during emotionally arousing situations (McEwen, 1987), but they do not seem to affect levels of tyrosine hydroxylase (Markey et al., 1982) or norepinephrine synthesis rate in the locus coeruleus of non-stressed rodents (McEwen, 1987; Lachuer et al., 1992). Glucocorticoids may affect the release of norepinephrine from its terminalis via a genomic action on the activity or density of presynaptic α_2-adrenoceptors (Jhanwar-Uniyal and Leibowitz, 1986; Pacák et al., 1992). However, presynaptic influences on the release of norepinephrine appear not to be exclusively genomic as a recent microdialysis study found evidence for enhanced release of norepinephrine in the prefrontal cortex within 15 min after systemic administration of corticosterone (Thomas et al., 1994). Our recent study examining the memory-modulatory effects of infusions of the GR agonist RU 28362 administered into the NTS provides further evidence that glucocorticoids may activate the noradrenergic system at the brainstem level. Posttraining administration of the GR agonist into the NTS dose-dependently enhances memory for inhibitory avoidance training (Roozendaal et al., 1999b). As is shown in Fig. 4, inactivation of β-adrenoceptors in the BLA with atenolol blocks the memory enhancement induced by intra-NTS infusions of

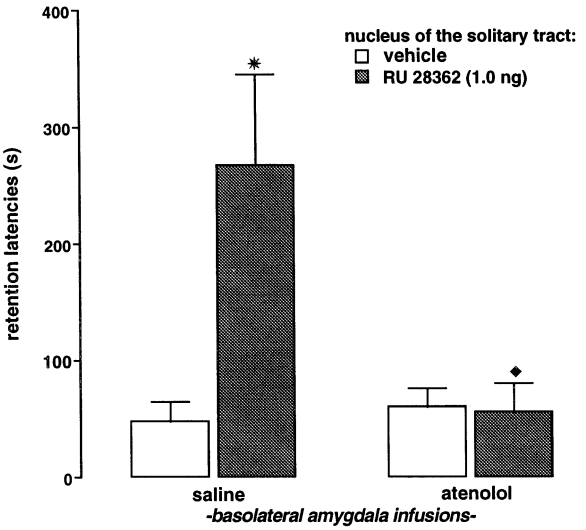

Fig. 4. Step-through latencies (mean ± S.E.M.) for a 48-h inhibitory avoidance test. Effects of pretraining infusions of the β_1-adrenoceptor antagonist atenolol (0.5 μg in 0.2 μl) into the basolateral amygdala and immediate posttraining infusions of the specific glucocorticoid receptor agonist RU 28362 (1.0 ng in 0.5 μl) into the nucleus of the solitary tract. $^*P < .05$ as compared with the corresponding vehicle group; ◆$P < .05$ as compared with the saline group RU 28362 (from Roozendaal et al., 1999b).

the GR agonist. Therefore, acute posttraining GR activation of noradrenergic soma in the NTS may increase the release of norepinephrine in the amygdala. These findings are in general agreement with the view that glucocorticoids may exert a permissive, facilitating action on stress-induced activation of the noradrenergic system at both presynaptic sites in the brainstem projecting to the BLA as well as postsynaptically in the BLA. These findings are summarized schematically in Fig. 5. In this context it is important to note that a suppression of corticosterone stress responses with the 11β-hydroxylase inhibitor metyrapone blocks the memory-enhancing effects of posttraining systemic injections of epinephrine, a major activator of the amygdala noradrenergic system (Roozendaal et al., 1996c).

5. Interactions of the basolateral amygdala with the hippocampus in mediating glucocorticoid effects on memory consolidation

Clearly, systemically administered or released glucocorticoids not only occupy GRs in the BLA but, as well, bind to adrenal steroid receptors throughout the brain. The hippocampal formation (both the dentate gyrus and Ammon's horn) has a high density of both GRs and MRs (Reul and de Kloet, 1985) and is considered to regulate some aspects of memory processes (Olton et al., 1979; Morris et al., 1982; Eichenbaum and Otto, 1992; Moser et al., 1993). Administration of corticosterone or the GR agonist RU 28362 directly into the hippocampus has been shown

to enhance memory consolidation in a dose-dependent manner (Cottrell and Nakajima, 1977; Micheau et al., 1985; Roozendaal and McGaugh, 1997a). Moreover, intra-hippocampal infusions of the GR antagonist RU 38486 impair memory in the spatial water-maze and Porsolt swimming task (de Kloet et al., 1988; Roozendaal and McGaugh, 1997a).

Based on these findings, it may appear surprising that BLA lesions completely block the effects of systemic or ICV administration of glucocorticoids and the GR antagonist (Roozendaal and McGaugh, 1996a; Roozendaal et al., 1996d). Such findings suggested that lesions of the BLA might also block the memory-modulatory effects induced by a direct manipulation of GR activity in the hippocampus. To examine this issue, rats with bilateral lesions of either the BLA or the CEA were trained in an inhibitory avoidance task and immediately after training given infusions of the GR agonist RU 28362 into the dorsal hippocampus (Roozendaal and McGaugh, 1997a). As is shown in Fig. 6, BLA lesions blocked the memory-enhancing effect of RU 28362. As expected, lesions of the CEA were ineffective in blocking the glucocorticoid effect. These findings show that, although glucocorticoids can bind directly to hippocampal GRs, some additional influence from the BLA is required in order for these hormones to influence memory consolidation. These findings are of interest in relation to evidence indicating that lesions of the BLA or temporary inactivation of the BLA with tetracaine or the β-adrenoceptor

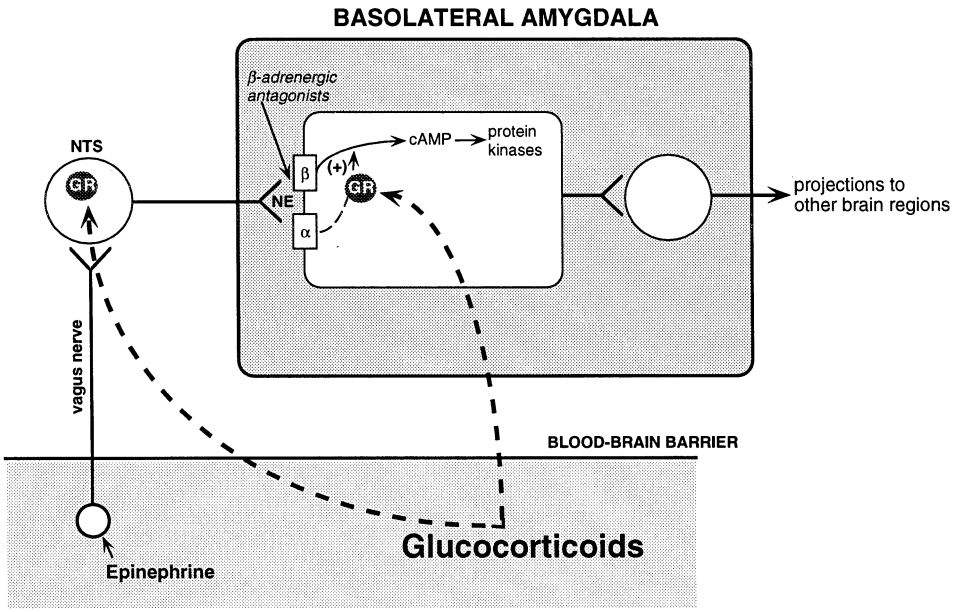

Fig. 5. Schematic summarizing the interactions of glucocorticoids with the noradrenergic system of the basolateral amygdala at both presynaptic and postsynaptic sites as suggested by the findings of our experiments; α, α-adrenoceptor; β, β-adrenoceptor; GR, glucocorticoid receptor; NTS, nucleus of the solitary tract.

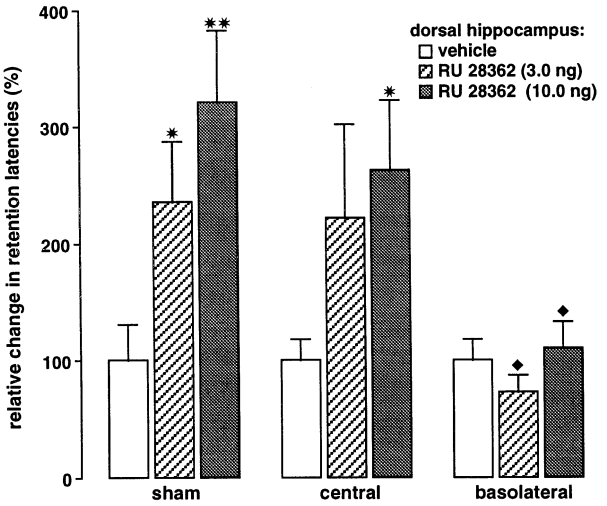

Fig. 6. Relative change in step-through latencies (mean ± SEM) for a 48-h inhibitory avoidance test. Effects of immediate posttraining infusions of the specific glucocorticoid receptor agonist RU 28362 (3.0 or 10.0 ng in 0.5 μl) into the dorsal hippocampus in rats with lesions of the basolateral or central nuclei of the amygdala. $*P < .05$; $**P < .01$ as compared with the corresponding vehicle group; ◆$P < .05$ as compared with the sham lesion group (from Roozendaal and McGaugh, 1997a).

antagonist propranolol attenuate the induction of long-term potentiation (LTP) in perforant path-granule cell synapses in the dentate gyrus (Ikegaya et al., 1994, 1995, 1997). Moreover, the facilitating effects of stress on learning of a hippocampal-dependent variant of eyeblink conditioning are blocked by either inactivation of the BLA or by ADX (Beylin and Shors, 1997; Shors and Mathew, 1998).

BLA lesions also block the impairing effects of a GR antagonist administered into the hippocampus (Roozendaal and McGaugh, 1997a), indicating that this enabling influence of the BLA on memory consolidation processes in or involving the hippocampus is not restricted to facilitating effects. In a study exploring this issue more extensively, we used rats whose adrenal glands were removed three months prior to the start of the experiment. Bilateral lesions of the BLA (or sham lesions) were induced at the same time. ADX induced severe damage to the granule cell layer in the dentate gyrus consistent with that reported by Sloviter et al. (1989, 1993, 1995) and others (Sapolsky et al., 1991; Conrad and Roy, 1993, 1995). In agreement with other findings (Conrad and Roy, 1993, 1995), ADX rats showed impaired memory for the spatial version of the water-maze task. However, the critical finding was that the BLA lesions completely blocked the impairing effects of long-term ADX on water-maze performance without affecting the ADX-induced neurodegenerative changes in the dentate gyrus (Roozendaal et al., 1998).

Such an enabling influence of the BLA on glucocorticoid-induced memory consolidation processes involving the hippocampus is consistent with our general hypothesis of BLA function in memory modulation. A detailed description of this role goes beyond the scope of this paper and has been recently reviewed elsewhere

(McGaugh et al., 1996; Cahill and McGaugh, 1998). The critical hypothesis, however, is that the BLA integrates hormonal and neuromodulatory influences on memory consolidation, but is not a locus for permanent storage of this information. Rather, BLA activation may modulate consolidation processes for explicit/associative memories in other brain structures, including the hippocampus. It has been reported that noradrenergic stimulation of the BLA induces temporary neuroplasticity in pyramidal neurons of the BLA in vitro (Huang et al., 1994; Wang et al., 1996). Therefore, it is possible that this norepinephrine-induced neuroplasticity in the BLA is essential in order for glucocorticoids to modulate memory processes in the hippocampus as well as other brain structures.

5.1. In search of a neural pathway underlying basolateral amygdala-hippocampus interactions

There are at least two ways in which this influence from the BLA may reach the hippocampus. First, it is known that aversively motivated training experiences induce activation of the amygdala and augment autonomic and humoral stress responses (Roozendaal et al., 1990, 1991, 1992). It is possible that some aspects of these evoked peripheral stress responses feed back to the hippocampus and enable glucocorticoids to enhance memory consolidation. Alternatively, it is possible that BLA activity affects hippocampal memory consolidation processes through either direct or indirect neural connections, independent of autonomic or neuroendocrine stress activation. To examine this issue, unilateral infusions of the GR agonist RU 28362 were given into the dorsal hippocampus of rats immediately after they were trained in an inhibitory avoidance task (Roozendaal et al., 1999a). The GR agonist was administered alone or in combination with the β-adrenoceptor antagonist atenolol infused 10 min before training into either the ipsilateral or contralateral BLA. If the influence of the BLA on glucocorticoid-induced effects on hippocampal memory processes is mediated by peripheral stress responses resulting from BLA activation, then either ipsilateral or contralateral inactivation of the BLA should have similar effects. On the other hand, if the effects are mediated through largely unilaterally organized neural connections between the BLA and the hippocampus, inactivation of the ipsilateral, but not the contralateral, BLA should block the effects of the GR agonist in the hippocampus. As is shown in Fig. 7, only infusions of atenolol into the ipsilateral, and not the contralateral, BLA blocked these unilateral hippocampal glucocorticoid effects. These results very strongly suggest that the BLA influence on glucocorticoid-induced memory consolidation modulation involving the hippocampus was mediated through neural connections, and not through activation of peripheral stress responses. This hypothesis is also supported by two findings discussed above. First, the permissive influence of the BLA on glucocorticoid-induced memory processes involving the hippocampus is not restricted to enhancing effects, but includes impairing effects as well (Roozendaal et al., 1996d; Roozendaal and McGaugh, 1997a; Roozendaal et al., 1998). Second, lesions of the CEA are *ineffective* in blocking the memory-modulatory effects of systemically or intra-hippocampally administered glucocorticoids (Roozendaal and

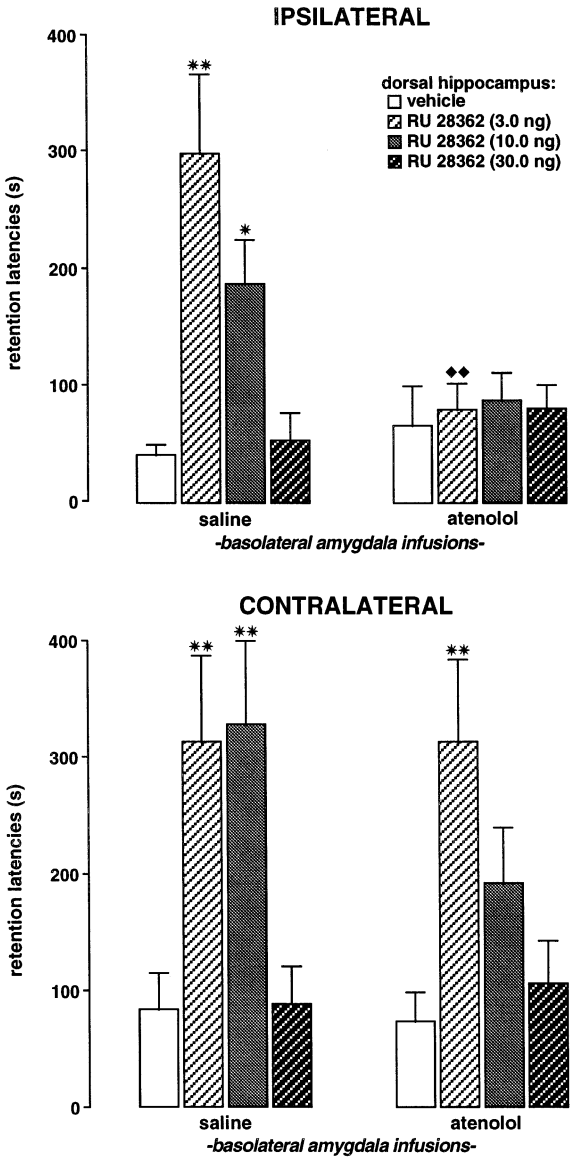

Fig. 7. Step-through latencies (mean ± S.E.M.) for a 48-h inhibitory avoidance test. Effects of immediate posttraining unilateral infusions of the glucocorticoid receptor agonist RU 28362 (3.0, 10.0 or 30.0 ng in 0.5 μl) into the dorsal hippocampus and pretraining unilateral infusions of either saline or the β-adrenoceptor antagonist atenolol (0.5 μg in 0.2 μl) into either the ipsilateral or contralateral basolateral amygdala. $^{*}P < .05$; $^{**}P < .01$ as compared with the corresponding intra-hippocampal vehicle group; ◆◆$P < .01$ as compared with the corresponding intra-basolateral amygdala saline group (from Roozendaal et al., 1999a).

McGaugh, 1996a, 1997a). The CEA is a major output nucleus of the amygdala with direct connections to brainstem and hypothalamic regulatory centers (Krettek and Price, 1978; Luiten and Room, 1980). Therefore, if the BLA influence on the hippocampus were mediated through activation of peripheral stress responses, such an influence would presumably involve descending projections via the CEA.

The BLA projects directly to the dentate gyrus and Ammon's horn, as well as indirectly via the entorhinal cortex (Racine et al., 1983; Thomas et al., 1984). A recent study reported that different nuclear divisions of the amygdala project to hippocampal areas in segregated terminal fields (Pikkarainen et al., 1999). However, most of these projections reach the ventral hippocampus, which may have only limited involvement in learning and memory (Moser et al., 1993). Climbing fibers from the ventral to the dorsal hippocampus may be involved. Recent experiments suggest that the BLA may influence hippocampal memory processes in an indirect way via projections to the nucleus accumbens. The nucleus accumbens receives input from various limbic structures, including the BLA (Krettek and Price, 1978; Yim and Mogenson, 1982) and the hippocampal formation (DeFrance et al., 1980; Lopes da Silva et al., 1984; Yang and Mogenson, 1984; Groenewegen et al., 1987). Convergence of these projections may take place in the core subdivision of the nucleus accumbens (Finch, 1996; Mulder et al., 1998). We found that bilateral lesions of the nucleus accumbens core, but not shell, blocked the memory-enhancing effects of systemic dexamethasone (Setlow et al., in press). As is shown in Fig. 8, also unilateral, contralateral lesions of the nucleus accumbens and the BLA, i.e. induced at opposite sides of the brain, blocked the memory-enhancing effects of

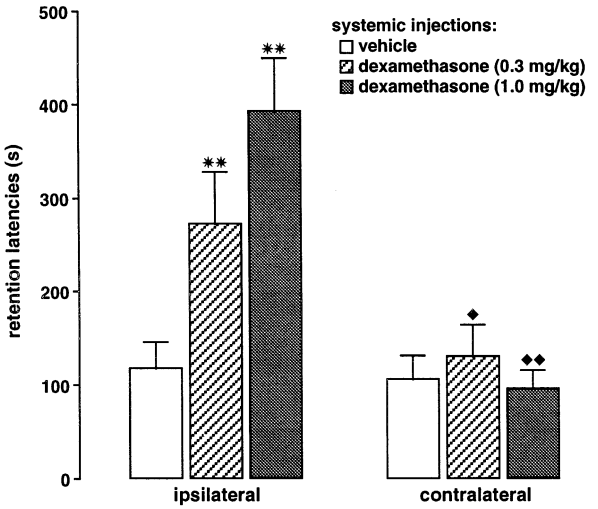

Fig. 8. Step-through latencies (mean ± S.E.M.) for a 48-h inhibitory avoidance test. Effects of immediate posttraining systemic injections of dexamethasone (0.3 or 1.0 mg/kg, SC) to rats with either ipsilateral or contralateral unilateral lesions of the basolateral amygdala and nucleus accumbens. $^{**}P < .01$ as compared with the corresponding vehicle group; ◆ $P < .05$; ◆◆ $P < .01$ as compared with the corresponding ipisilateral lesion group (from Setlow et al., in press).

posttraining systemic dexamethasone injections. In contrast, unilateral, ipsilateral lesions of the nucleus accumbens and the BLA, i.e. induced both at the same side of the brain, were ineffective in blocking the memory-enhancing effects of sytemically administered dexamethasone. Thus, bilateral damage to the BLA-accumbens pathway, irrespective of at what level this may occur, blocks the memory-modulatory effects of glucocorticoids. Interestingly, preliminary unpublished findings indicate that posttraining infusions of the GR agonist into the nucleus accumbens also enhance memory for inhibitory avoidance training, an effect that is blocked by BLA lesions (Roozendaal et al., unpublished findings). An influence of the BLA on hippocampal memory processes via the nucleus accumbens is supported further by evidence indicating that lesions of the stria terminalis, which carries projections from the BLA to the nucleus accumbens (Kelley et al., 1982), block the memory-enhancing effects of systemic injections of dexamethasone (Roozendaal and McGaugh, 1996b), as well as those induced by intra-BLA or intra-hippocampal administration of the GR agonist RU 28362 (de Quervain et al., 1998a). It is not known whether BLA-nucleus accumbens projections may underlie the influence of the BLA on hippocampal neuroplasticity. However, it has been reported that preactivation of the BLA increases the potential for fimbria-fornix stimulation to induce spike activity in the nucleus accumbens (Mulder et al., 1998). The exact role of the nucleus accumbens in integrating information derived from the BLA and the hippocampus remains to be elucidated, but such integration is not unique for memory consolidation and has been described previously for several learned and unlearned behaviors (Mogenson et al., 1988; Everitt and Robbins, 1992; Roozendaal and Cools, 1994). As hippocampal-nucleus accumbens connections are unidirectional (Kelley and Domesick, 1982), this implies that there must exist pathways which feed back to the hippocampus or cortical areas to ensure permanent storage of the information. Such pathways exist in the forms of both striato-pallido-thalamo-cortical loops (Alexander et al., 1990) and nucleus accumbens projections to dopaminergic midbrain neurons which, in turn, project to the hippocampus (Fallon and Loughlin, 1995; Gasbarri et al., 1997).

6. Conclusion: integrating the acute and chronic effects of glucocorticoids on memory consolidation

The sections above summarized recent findings indicating that acute posttraining administration of glucocorticoids has dose-dependent enhancing effects on specific processes of memory consolidation and that these effects are mediated by influences involving the BLA. A last question addressed here is that of how the effects of such selective manipulations of memory consolidation are to be integrated with those of studies examining the effects of chronic stress or repeated exposure to glucocorticoids. As noted in the introduction, those studies generally reported impaired cognitive performance (Luine et al., 1993; Arbel et al., 1994; Luine et al., 1994; Bodnoff et al., 1995). Several hypotheses have been proposed previously to explain this discrepancy (for a review see: McEwen and Sapolsky, 1995). For example,

chronic exposure to stress or glucocorticoids induces changes in adrenal steroid receptor density and/or affinity that may account for some of the cognitive effects (Lorens et al., 1990; Barbazanges et al., 1996). Prolonged exposure to glucocorticoids is also associated with several adverse effects on brain morphology, particularly in the hippocampus. The exposure may 'endanger' neuronal integrity (Sapolsky, 1992), and cause atrophy of apical dendrites in the Ammon's horn (AusDerMuhlen and Ockenfels, 1969; Sapolsky et al., 1985; Woolley et al., 1991; Magarinos and McEwen, 1995). It has been proposed that also these neurodegenerative changes may induce some of the deleterious behavioral effects. Moreover, possible differential effects of genomic and non-genomic actions of glucocorticoids on second messenger systems have been discussed above. However, in the context of this paper it is important to note that because of the nature of these chronic or repeated treatments it is often impossible to dissociate glucocorticoid effects on memory consolidation from those on other cognitive or non-cognitive aspects of the task (also see Lupien and McEwen, 1997). The importance of such a distinction was shown recently in a study demonstrating that acute administration of doses of glucocorticoids comparable to those that enhance memory consolidation have profound impairing effects on memory retrieval (de Quervain et al., 1998b). Rats were trained in a water maze to find a submerged platform in a fixed location. One day later, memory for the location of the platform during training was tested using a probe trial, i.e. in the absence of the platform. Control rats spent most time in the vicinity of the 'platform location', however, rats that were given systemic injections of corticosterone shortly before retention testing failed to remember the platform location. Based on these findings, together with the fact that also in many of the chronic experiments rats are tested while under the influence of glucocorticoids, it seems likely that some of the effects of chronic stress and glucocorticoids on cognitive performance may be due to influences on memory retrieval. Also the finding that the impairing effects of prolonged glucocorticoid exposure are not blocked by the noradrenergic reuptake inhibitor desipramine (McEwen et al., 1995) suggests that the effects are independent of central noradrenergic mechanisms and, thus, that different cognitive stages may be affected. Moreover, changed receptor densities induced by prolonged glucocorticoid exposure may alter autonomic, neuroendocrine and behavioral responsiveness during learning, which may influence memory consolidation in an indirect way (see Oitzl et al., 1998b). Thus, the complex and often opposing actions of glucocorticoids on different cognitive stages make it essential that in order to examine their effects on processes of memory consolidation, the effects must be dissociated from those on other cognitive and non-cognitive aspects.

In conclusion, stress-induced or acute exogenously administered glucocorticoids have dose-dependent enhancing effects on selective processes of memory consolidation in rats. These effects are exerted via an activation of GRs in multiple brain sites. This paper focused on the amygdala as part of a modulatory brain system in mediating glucocorticoid effects on memory consolidation. Our findings indicate that glucocorticoids can directly activate GRs in the BLA to enhance memory consolidation. These effects involve a facilitating action on stress-induced noradren-

ergic neurotransmission in the BLA. Furthermore, evidence was presented that BLA activity is required in order for glucocorticoids administered directly into the hippocampus to enhance memory consolidation. Thus, stress- and glucocorticoid-induced activation of noradrenergic mechanisms in the BLA appear to be crucial in coordinating memory consolidation processes in other brain regions, including the hippocampus.

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