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Stress and Memory: Opposing Effects of Glucocorticoids on Memory Consolidation and Memory Retrieval

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It is well established that glucocorticoid hormones, secreted by the adrenal cortex after a stressful event, influence cognitive performance. Some studies have found glucocorticoid-induced memory enhancement. However, many studies have reported impairing effects of glucocorticoids on memory function. This paper reviews recent findings from this laboratory on the acute effects of glucocorticoids in rats on specific memory phases, i.e., memory consolidation and memory retrieval. The evidence suggests that the consequences of glucocorticoid activation on cognition depend largely on the different memory phases investigated. Posttraining activation of glucocorticoid-sensitive pathways involving glucocorticoid receptors enhances memory consolidation in a pattern highly similar to that previously described for adrenal catecholamines. Also, similar to catecholamine effects on memory consolidation, glucocorticoid influences on memory consolidation depend on noradrenergic activation of the basolateral complex of the amygdala and interactions with other brain regions. By contrast, memory retrieval processes are usually impaired with high circulating levels of glucocorticoids or following infusions of glucocorticoid receptor agonists into the hippocampus. The hypothesis is proposed that these apparently dual effects of glucocorticoids on memory consolidation and memory retrieval might be related and that the basolateral complex of the amygdala is a key structure in a memory-modulatory system that regulates, in concert with other brain regions, stress and glucocorticoid effects on both memory consolidation and memory retrieval.

Key Words: amygdala; corticosterone; dexamethasone; emotional arousal; hippocampus; memory storage; norepinephrine.

This paper is dedicated to the memory of my mentor and friend, Dr. Béla Bohus.

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INTRODUCTION

Adrenal hormones (i.e., catecholamines and glucocorticoids) are secreted during stressful events and influence, together with other components of the stress system, the organism's ability to cope with stress. These hormones also affect memory function by influences on limbic brain structures. It is well established that adrenal catecholamines promote consolidation and/or storage of novel information (Bohus, 1994; McGaugh, Cahill, & Roozendaal, 1996; McGaugh & Roozendaal, 2002). Immediate posttraining systemic injections of epinephrine or norepinephrine to rats enhance memory of aversively motivated inhibitory avoidance training (Gold & van Buskirk, 1975; Borrell, de Kloet, Versteeg, & Bohus, 1983; Liang, Juler, & McGaugh, 1986; Cahill & McGaugh, 1991; Roozendaal, Carmi, & McGaugh, 1996a). These findings, which have been confirmed by experiments using many different types of training tasks, support the hypothesis that endogenously released epinephrine modulates memory consolidation (Izquierdo & Diaz, 1985; Sternberg, Isaacs, Gold, & McGaugh, 1985; McGaugh, Ferry, Vazdarjanova, & Roozendaal, 2000; Liang, 2001). In contrast, there are conflicting findings concerning glucocorticoid effects on cognition (Lupien & McEwen, 1997; de Kloet, Oitzl, & Joëls, 1999; Roozendaal, 2000). Although some studies have found glucocorticoid-induced memory enhancement (Cottrell & Nakajima, 1977; Sandi & Rose, 1994a; Sandi, Loscertales, & Guanza, 1997; Buchanan & Lovallo, 2001), the potentially disruptive effects of glucocorticoids on memory have recently received much attention (Newcomer, Craft, Hershey, Askins, & Bardgett, 1994; Kirschbaum, Wolf, May, Wippick, & Hellhammer, 1996; Lupien et al., 1997; Diamond, Park, Heman, & Rose 1999). Such evidence raises the question whether glucocorticoids differ fundamentally from catecholamines in their effects on memory function.

The evidence reviewed in this paper suggests that the consequences of glucocorticoid activation on cognition depend largely on the different memory phases investigated. In recent studies, we have examined the acute effects of glucocorticoids on different memory phases, i.e., memory consolidation and memory retrieval. Glucocorticoids, or their specific receptor agonists or antagonists, were administered to rats either immediately after training on several tasks to examine their effects on memory consolidation or shortly before retention testing to examine effects on memory retrieval. The findings indicate that memory consolidation is enhanced by posttraining activation of glucocorticoid-sensitive pathways in a manner similar to that described for catecholamines. As epinephrine effects on memory consolidation require activation of the amygdala (McGaugh et al., 1996), this paper will also give an overview of the amygdala's role in mediating glucocorticoid effects on memory consolidation. The evidence strongly suggests that epinephrine and glucocorticoids influence memory consolidation through activation of similar neural systems. Memory retrieval is usually impaired when glucocorticoids are administered shortly before retention testing. I will address the issue of whether these apparently dual effects of glucocorticoids on memory consolidation and memory retrieval might be related and serve to enable appropriate cognitive responses.

GLUCOCORTICOID EFFECTS ON MEMORY CONSOLIDATION

Extensive evidence from both animal and human studies indicates that memory traces are initially fragile after training and become consolidated only over time (McGaugh,

2000). Memory formation can be influenced during this critical time window by many kinds of manipulations, including electrical brain stimulation and injections of protein-synthesis inhibitors (Duncan, 1949; McGaugh, 1966; Flood, Bennett, Orme, & Rosenzweig, 1975; Davis & Squire, 1984). An early study has demonstrated that systemic injections of glucocorticoids given after a training experience reverse the amnestic effects of protein-synthesis inhibitor administration on inhibitory avoidance retention in mice (Flood, Vidal, Bennett, Orme, Vasquez, & Jarvik, 1978). Subsequent studies have shown that systemic injections of moderate doses of corticosterone or the synthetic glucocorticoid dexamethasone enhance long-term memory for inhibitory avoidance training when administered shortly, but not several hours, after a training experience (Kovacs, Telegdy, & Lissak, 1977; Flood et al., 1978; Roozendaal & McGaugh, 1996; Roozendaal, Williams, & McGaugh, 1999b). Glucocorticoid effects on memory enhancement for inhibitory avoidance training follow an inverted-U-shape dose–response relationship. Similar biphasic effects of posttraining glucocorticoids in rats have been observed in a contextual-cue fear conditioning task (Pugh, Tremblay, Fleshner, & Rudy, 1997; Cordero & Sandi, 1998) and a water-maze spatial task (Sandi, Loscertales, & Guanza, 1997) as well as with training of 1-day-old chicks in an avoidance task (Sandi & Rose, 1994a, 1997). The evidence that adrenocortical hormones administered after a training experience enhance memory consolidation suggests that these hormones released after an acute stressful event may affect memory for that event. This view is supported by the finding that removal of endogenous corticosterone by adrenalectomy impairs memory in a water-maze spatial task (Oitzl & de Kloet, 1992; Roozendaal, Portillo-Marquez, & McGaugh, 1996b). The adrenalectomy-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., 1996b). Such findings strongly suggest that the memory impairment is caused by the lack of glucocorticoids and support the view that memory consolidation processes depend on posttraining activation of glucocorticoid-sensitive pathways.

Glucocorticoid hormones can enter the brain and bind to two intracellular types of adrenal steroid receptors (Reul & 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 & de Kloet, 1985). Thus, it is likely that glucocorticoid effects on memory consolidation are due to activation of GRs. Immediate posttraining intracerebroventricular infusions of a GR antagonist, but not an MR antagonist, impair spatial memory in a water maze (Oitzl & de Kloet, 1992; Roozendaal et al., 1996b). Additionally, posttraining infusions of a GR antagonist impair memory for an avoidance task in chicks (Sandi & Rose, 1994b) and block the enhancing effects of posttraining corticosterone (Sandi & Rose, 1994a). Also, administration of a GR antagonist or GR antisense oligonucleotide directly into the hippocampus shortly before learning impairs retention behavior in a Porsolt swimming task (de Kloet et al., 1988; Korte et al., 1996). These findings clearly support the view that GRs are selectively involved in regulating glucocorticoid effects on memory consolidation. This conclusion is further supported by the findings of a study examining the effects of systemic administration of different doses of corticosterone to adrenalectomized rats tested on spatial memory in a Y-maze

discrimination task (Conrad, Lupien, & McEwen, 1999). 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.

Involvement of the basolateral amygdala. 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). Most studies investigating glucocorticoid effects on learning and memory have implicated the hippocampus as the major target structure. However, our studies have focused primarily on the role of the amygdala, which expresses a moderate density of GRs (Honkaniemi et al., 1992), as this brain structure is activated by emotionally arousing experiences and modulates memory consolidation processes in other brain regions (McGaugh et al., 1996, 2000). Furthermore, as noted above, extensive evidence from this laboratory indicates that the amygdala mediates adrenal catecholamine effects on memory consolidation. Epinephrine effects on memory consolidation are blocked by lesions of the amygdala (Cahill & McGaugh, 1991). Additionally, infusions of adrenoceptor agonists enhance memory when administered directly into the amygdala (Introini-Collison, Miyazaki, & McGaugh, 1991; Liang, Chen, & Huang, 1995; Ferry, Roozendaal, & McGaugh, 1999). Glucocorticoid effects on memory consolidation also require activation of the amygdala (Roozendaal, 2000). As shown in Fig. 1A, selective NMDA-induced lesions of the basolateral complex of the amygdala (BLA) block 48-h inhibitory avoidance retention enhancement induced by posttraining systemic injections of dexamethasone (Roozendaal & McGaugh, 1996). In contrast, lesions of the adjacent central nucleus of the amygdala (CEA), made with ibotenic acid, do not block dexamethasone-induced retention enhancement. Selective BLA lesions also block memory impairment induced by an intracerebroventricular administration of a GR antagonist (Roozendaal et al., 1996b) or after either short- or long-term adrenalectomy (Roozendaal et al., 1996b; Roozendaal, Sapolsky, & McGaugh, 1998). Figure 1B shows that infusions of the specific GR agonist RU 28362 administered into the BLA immediately after inhibitory avoidance training enhance retention performance in a dose-dependent way, whereas infusions into the CEA are ineffective (Roozendaal & McGaugh, 1997a). Furthermore, intra-BLA, but not intra-CEA, infusions of the GR antagonist RU 38486 impair retention performance in a water-maze spatial task. These findings indicate, therefore, that glucocorticoid effects on memory consolidation depend critically on the BLA and that the BLA is a locus of action of glucocorticoids in modulating memory consolidation.

Extensive evidence indicates that the BLA does not serve as a permanent locus for the memory trace, but, instead, that BLA activation facilitates consolidation processes in other brain regions, including the hippocampus (McGaugh et al., 1996, 2000). We have examined BLA–hippocampus interactions in mediating glucocorticoid effects on memory consolidation for inhibitory avoidance and water-maze spatial training. The hippocampus has a high density of GRs (Reul & de Kloet, 1985) and posttraining infusions of corticosterone or the GR agonist RU 28362 into the hippocampus enhance memory consolidation for both appetitive and aversive tasks (Cottrell & Nakajima, 1977; Kovacs et al., 1977; Micheau, Destrade, & Soumireu-Mourat, 1985; Roozendaal & McGaugh, 1997b). However, lesions of the BLA, but not the CEA, block this hippocampal GR activation-induced retention enhancement (Roozendaal & McGaugh, 1997b). These findings indicate that an

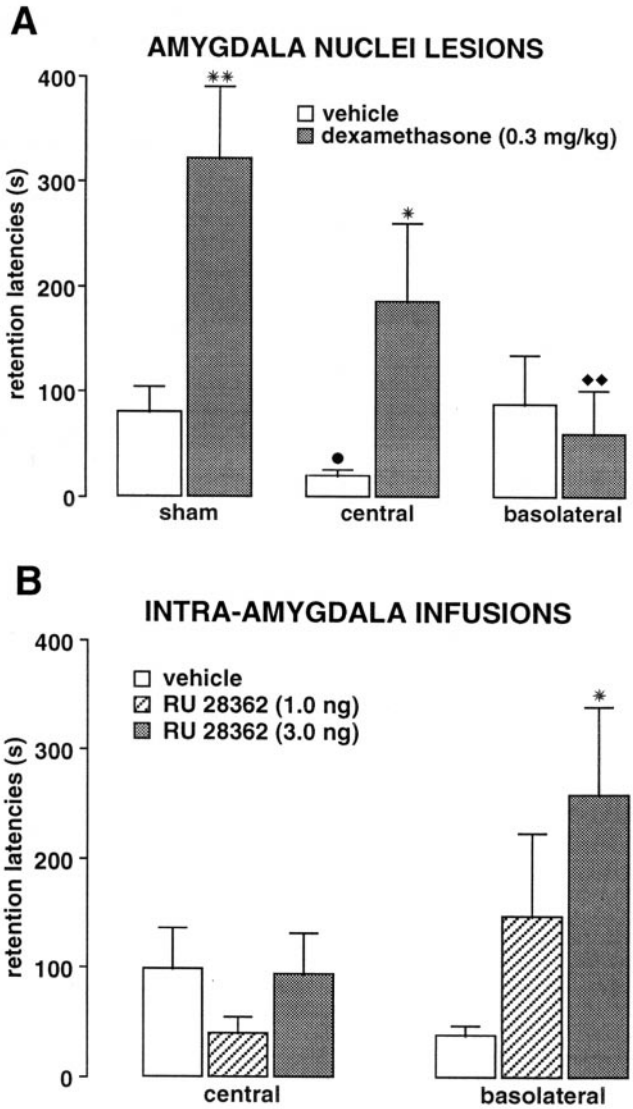

FIG. 1. Step-through latencies (means + SEM) in seconds for a 48-h inhibitory avoidance test. (A) Rats with sham lesions or lesions of either the central or the basolateral amygdala had been treated with dexamethasone (0.3 mg/kg, sc) or vehicle immediately after training. (B) Rats received posttraining infusions of the glucocorticoid receptor agonist RU 28362 (1.0 or 3.0 ng in 0.2 μl) into the central or basolateral amygdala. *$p < .05$; **$p < .01$ compared with the corresponding vehicle group; ●$p < .05$ compared with the corresponding sham lesion-vehicle group; ◆◆$p < .01$ compared with the corresponding sham lesion–dexamethasone group. (Reproduced, with permission, from Roozendaal & McGaugh, 1996, 1997a.)

intact BLA enables memory enhancement induced by local GR activation in the hippocampus and are consistent with the view that the BLA regulates memory consolidation processes in other brain regions. These findings are also in agreement with electrophysiological evidence indicating that BLA lesions or pharmacological blockade of the BLA prevents the effects of perforant path electrical stimulation on dentate gyrus long-term potentiation and on stress-induced impairment of long-term potentiation (Ikegaya, Saito, &

Abe, 1995, 1997; Kim, Lee, Han, & Packard, 2001). Although the BLA projects to many different hippocampal fields and also indirectly via the entorhinal cortex (Pikkarainen, Rönkkö, Savander, Insausti, & Pitkänen, 1999), our findings suggest that the BLA affects memory consolidation processes in—or involving—the hippocampus primarily through converging influences onto the nucleus accumbens. Lesions of the nucleus accumbens block inhibitory avoidance memory enhancement induced by systemic injections of dexamethasone (Setlow, Roozendaal, & McGaugh, 2000). Furthermore, nucleus accumbens lesions block memory enhancement induced by either intraBLA or intrahippocampal infusions of the GR agonist RU 28362 (Roozendaal, de Quervain, Ferry, Setlow, & McGaugh, 2001a).

Involvement of noradrenergic mechanisms in the basolateral amygdala. As discussed above, the amygdala also mediates the memory-modulatory effects of epinephrine (Liang et al., 1986; Cahill & McGaugh, 1991). However, unlike glucocorticoids, epinephrine does not readily cross the blood–brain barrier. Many experiments have revealed a peripheral–central pathway mediating epinephrine influences on the amygdala in modulating memory consolidation (McGaugh et al., 1996). In brief, systemic epinephrine can activate β-adrenoceptors on vagal afferents terminating in the nucleus of the solitary tract (NTS). In turn, noradrenergic cell groups in the NTS project directly to the amygdala or indirectly via the locus coeruleus (Fallon & Ciofi, 1992). Systemic injections of epinephrine then induce the release of norepinephrine in the amygdala (Williams, Men, Clayton, & Gold, 1998). Moreover, a blockade of β-adrenoceptors in the amygdala prevents memory enhancement induced by systemic injections of epinephrine (Liang et al., 1986), indicating that epinephrine effects on memory consolidation depend critically on noradrenergic activation of the amygdala.

Glucocorticoid effects on memory consolidation also depend on emotional arousal-induced noradrenergic activation in the BLA. As shown in Fig. 2, pretraining infusions of β-adrenoceptor antagonists into the BLA block inhibitory avoidance retention enhancement induced by systemic injections of dexamethasone (Quirarte, Roozendaal, & McGaugh, 1997). Furthermore, infusions of a β-adrenoceptor antagonist into the BLA block retention enhancement induced by posttraining intrahippocampal infusions of the GR agonist RU 28362 (Roozendaal, Nguyen, Power, & McGaugh, 1999a). A β-adrenoceptor antagonist administered into the BLA also blocks retention enhancement induced by a GR agonist infused concurrently (Quirarte et al., 1997), indicating that the BLA is a locus of interaction of glucocorticoids with the noradrenergic system in modulating memory consolidation. The β-adrenoceptor is coupled to adenylate cyclase to directly stimulate adenosine 3′,5′-cyclic monophosphate (cAMP) and cAMP-dependent protein kinase (PKA) (Daly, Padgett, Creveling, Cantacuzene, & Kirk, 1981). GRs interact with the noradrenergic response affecting memory consolidation by interfering with the β-adrenoceptor–cAMP/PKA system at a postsynaptic site (Roozendaal, Quirarte, & McGaugh, 2002). 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 (Introini-Collison et al., 1991; Liang et al., 1995; Ferry et al., 1999). The GR antagonist RU 38486 infused into the BLA shifted the dose–response effects of clenbuterol such that a much higher dose of clenbuterol was required to induce memory enhancement. In contrast, the GR antagonist did not modify the dose–response effects of 8-Br cAMP,

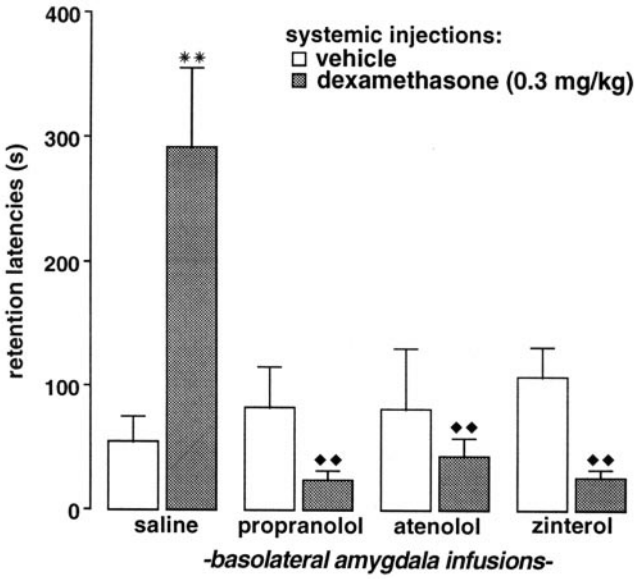

FIG. 2. Step-through latencies (means + SEM) in seconds for a 48-h inhibitory avoidance test. Effects of pretraining infusions of the nonspecific β-adrenoceptor antagonist propranolol (0.5 μg in 0.2 μl), the β_1-adrenoceptor antagonist atenolol (0.5 μg in 0.2 μl), or the β_2-adrenoceptor antagonist zinterol (0.5 μg in 0.2 μl) into the basolateral amygdala and immediate posttraining injections of dexamethasone (0.3 mg/kg, sc). $^{**}p < .01$ compared with the corresponding vehicle group; ◆◆$p < .01$ compared with the corresponding saline–dexamethasone group. (Reproduced, with permission, from Quirarte et al., 1997.)

indicating that cAMP acts in the BLA downstream of the locus of interaction of glucocorticoids with the β-adrenoceptor–cAMP/PKA pathway. These findings strongly suggest that glucocorticoids can enhance memory consolidation, in a permissive fashion, by potentiating β-adrenoceptor–cAMP efficacy in the BLA, at a locus between the membrane-bound β-adrenoceptor and the intracellular cAMP formation site. GRs may influence β-adrenoceptor–cAMP efficacy in the BLA via a coupling with α_1-adrenoceptors (Roozendaal et al., 2002).

In addition to interacting with the noradrenergic signaling cascade at a postsynaptic level, glucocorticoids influence amygdala noradrenergic function by altering levels of available norepinephrine (Markey, Towle, & Sze, 1982; McEwen, 1987). Brain-stem noradrenergic cell groups express high densities of GRs (Harfstrand et al., 1987), and posttraining activation of GRs within noradrenergic cell groups in the NTS induces dose-dependent memory enhancement. The β-adrenoceptor antagonist atenolol infused into the BLA blocks this memory enhancement (Roozendaal et al., 1999b), suggesting that glucocorticoids can act presynaptic to the β-adrenoceptor–cAMP/PKA pathway to increase synthesis and subsequent release of norepinephrine in the BLA. Although glucocorticoids also influence memory consolidation through interactions with other systems, including direct influences on DNA, such a linkage of glucocorticoids with emotional arousal-influenced noradrenergic mechanisms may explain, at least in part, why glucocorticoids relatively selectively enhance memory for emotionally arousing experiences (Lupien & McEwen, 1997; de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Buchanan & Lovallo, 2001). The interaction of glucocorticoids with the noradrenergic system in the BLA in modulating memory consolidation is summarized in Fig. 3.

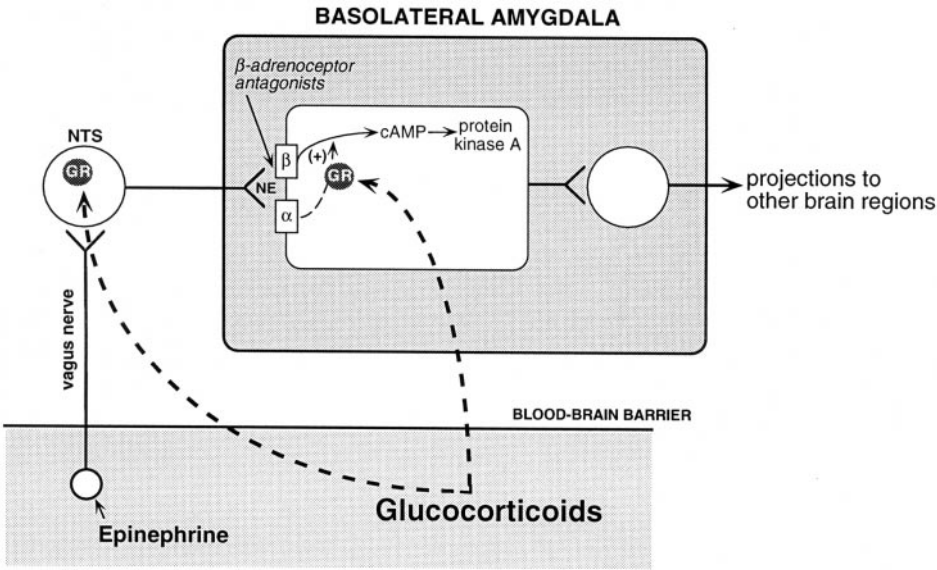

FIG. 3. Schematic summarizing the interactions of glucocorticoids with the noradrenergic system of the basolateral amygdala at both presynaptic and postsynaptic sites as suggested by the findings of our experiments. Norepinephrine (NE) is released following training in aversively motivated tasks and 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 brain-stem noradrenergic cell groups. α, α-adrenoceptor; β, β-adrenoceptor; cAMP, adenosine 3′,5′-cyclic monophosphate; GR, glucocorticoid receptor; NTS, nucleus of the solitary tract. Reprinted from *Psychoneuroendocinology,* 25, B. Roozendaal, "Glucocorticoids and the regulation of memory consolidation", 213–238. Coopyright 2000 with permission from Elsevier Science.

GLUCOCORTICOID EFFECTS ON MEMORY RETRIEVAL

As reviewed in the preceding section, posttraining administration of glucocorticoids enhances memory consolidation processes in a dose-dependent fashion. However, to observe glucocorticoid effects on memory consolidation, it is important to maintain a long interval (i.e., 24 or 48 h) between training (and drug treatment) and retention testing to allow for memory consolidation as well as clearance of the drug. The necessity of such a long interval becomes evident when considering studies that examined the effects of pretraining or immediate posttraining stress exposure or glucocorticoid administration with retention testing shortly after training. The finding that glucocorticoids impair retention performance when rats or human subjects are tested shortly after training, while glucocorticoid levels are still elevated (e.g., Kirschbaum et al., 1996; Diamond et al., 1999), led to the hypothesis that circulating glucocorticoids may not only affect long-lasting memory formation, but also directly affect retention performance. Studies from this laboratory examining this hypothesis have found that glucocorticoids can affect retention performance of long-term memory by influencing memory retrieval processes. In one study, 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. As shown in Fig. 4, control rats spent more time in

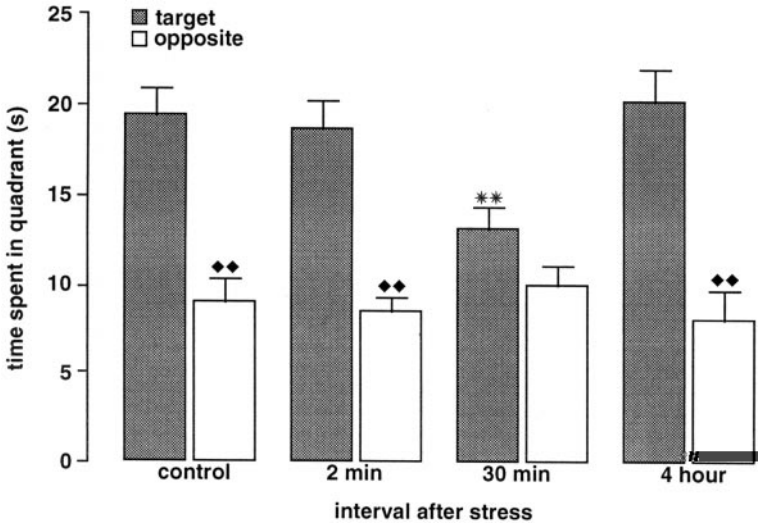

FIG. 4. Time (means + SEM) in seconds spent in target quadrant and opposite quadrant during a 60-s probe trial retention test in a water maze. Effect of stress of foot-shock exposure at 2 or 30 min or 4 h before retention testing on water-maze spatial performance. $^{**}p < .01$ compared with nonstressed controls; ♦♦ $p < .01$ compared with time in target quadrant. Reprinted by permission from *Nature*, D. J.-F. de Quervain, B. Roozendaal, and J. L. McGaugh, "Stress and glucocorticoids impair retrieval of long-term spatial memory", Copyright 1998, MacMillan Publishers, Ltd.

the vicinity of the "platform location" (i.e., target quadrant) than in the opposite quadrant. However, rats that were given an aversive experience of foot-shock exposure 30 min before retention testing failed to indicate memory of the platform location as indicated by equal swim times in both quadrants (de Quervain, Roozendaal, & McGaugh, 1998). Stress effects on memory retrieval are time-dependent in that they do not permanently block the memory. Retention performance was not impaired when rats were tested either 2 min or 4 h after foot-shock exposure. This time course on retention impairment correlated with plasma corticosterone levels, which peak 30 min after stress exposure and return to baseline within 4 h. Blockade of this stress-induced elevation in corticosterone levels with the synthesis-inhibitor metyrapone prevented stress-induced memory retrieval impairment. Furthermore, injections of stress doses of corticosterone given 30 min before retention testing impaired memory retrieval in a pattern highly reminiscent of that found after stress exposure (de Quervain et al., 1998). These findings demonstrate that once memories are consolidated, the efficacy or accuracy of the information retrieved remains vulnerable to glucocorticoids at the time of recall. Similar glucocorticoid effects on memory retrieval were recently reported with human subjects. Oral administration of stress doses of cortisone (a precursor of the endogenous human glucocorticoid cortisol) 1 h before retention testing impaired hippocampal-dependent free recall of previously learned words (de Quervain et al., 2000). It remains, however, possible that under different training conditions, as with memory consolidation, glucocorticoids may facilitate memory retrieval.

Subsequent studies have shown that this glucocorticoid-induced memory retrieval impairment depends, in part, on GR activation in the hippocampus. Infusion of the GR agonist RU 28362 administered into the hippocampus of rats 1 h before retention testing induces similar selective memory retrieval impairment in the water maze. In contrast, GR

agonist infusions into the BLA do not impair memory retrieval (Roozendaal, Griffith, & McGaugh, manuscript in preparation). These findings suggest that glucocorticoids block hippocampal-dependent influences on memory retrieval. Cellular actions of glucocorticoids on hippocampus neurons are consistent with this view and indicate that peripheral injections of stress doses of corticosterone reduce hippocampal firing rate with a delay of approximately 30–60 min (Pfaff, Silva, & Weiss, 1971; Joëls, 2001) An involvement of the hippocampus in memory retrieval is also supported by the findings of several recent studies by Izquierdo and colleagues indicating participation of hippocampal metabotropic glutamate receptors, PKA, and mitogen-activated protein kinases in memory retrieval in an inhibitory avoidance task (Izquierdo, Barros, Ardenghi, Pereira, Rodrigues, Choi, Medina, & Izquierdo, 2000; Szapiro, Izquierdo, Alonso, Barros, Paratcha, Ardenghi, Pereira, Medina, & Izquierdo, 2000). It should be noted that stress levels of glucocorticoids may impair short-term memory retrieval (i.e., working memory) by influences on the prefrontal cortex (Lupien, Gillin, & Hauger, 1999; Arnsten, 2000).

It has been suggested that the effects of glucocorticoid administration shortly before retention testing may not be caused by influences on memory retrieval but, instead, may be interpreted as behavioral performance deficits that are due to impaired MR function (de Kloet et al., 1999). Blockade of MRs shortly before retention testing impairs performance in a water-maze spatial task by altering search pattern and behavioral response to novelty (Oitzl & de Kloet, 1992). Yet, glucocorticoid effects on memory retrieval impairment appear to differ in several critical ways from the effects observed after MR blockade. First, glucocorticoid elevations selectively impair retention performance, whereas infusions of an MR antagonist, consistent with a role in behavioral exploration, alter both retention and acquisition performance. Second, infusion of a specific GR agonist induces a pattern of effects on memory retrieval similar to that found after corticosterone injection, an effect that seems difficult to reconcile with impaired MR function. Third, glucocorticoids also impair free recall of previously learned words in human subjects, a function for which execution does not depend on a locomotor response or behavioral exploration. Taking this evidence into consideration, these findings clearly suggest that glucocorticoid impairment of memory retrieval of spatial/contextual (in rats) and declarative information (in humans) is due to enhanced GR function at the time of the retention test.

Possible consequences of long-term glucocorticoid exposure. Such acute effects of glucocorticoids on memory retrieval may also explain, in part, the detrimental effects of long-term glucocorticoid treatment on cognitive performance. Long-term exposure to stress or glucocorticoids impairs memory function in both animals and human subjects (Dachir, Kadar, Robinzon, & Levy, 1993; Luine, Spencer, & McEwen, 1993; Arbel, Kadar, Silbermann, & Levy, 1994; Luine, Villegas, Martinez, & McEwen, 1994; Bodnoff, Humphrey, Lehman, Diamond, Rose, & Meaney, 1995; Conrad, Galea, Kuroda, & McEwen, 1996; Krugers, Douma, Andringa, Bohus, Korf, & Luiten, 1997; Belanoff, Gross, Yager, & Schatzberg, 2001). These impairments seem also to be restricted to memory for spatial/contextual or declarative information. Furthermore, continuous excessive circulating levels of glucocorticoids are frequently associated with declarative memory impairment in patients with Cushing's syndrome, major depression, schizophrenia, and Alzheimer's disease (Whelan, Schteingart, Starkman, & Smith, 1980; Reus, 1984; Wolkowitz & Weingartner, 1988; Belanoff et al., 2001). Due to the chronic nature of those

treatments or pathophysiological conditions, it cannot be determined whether these effects are due to influences on memory consolidation or to influences on memory retrieval, or both. Prolonged exposure to stress or glucocorticoids induces changes in adrenal steroid receptor density and/or affinity (Barbazanges, Vincenzo, Le Moal, & Maccari, 1996) and may alter responsiveness of neurotransmitter action (Karten, Slagter, & Joëls, 1999). Such changes may potentially affect glucocorticoid effects on memory function. Furthermore, morphological findings indicate that prolonged glucocorticoid exposure is associated with atrophy of apical dendrites in the CA3 subfield of Ammon's horn and may contribute to the precipitation of this pathology (Sapolsky, Krey, & McEwen, 1985). It has been proposed that these neurodegenerative changes are also, in part, responsible for the deleterious behavioral effects. However, a recent study from this laboratory examining the cognitive consequences of CA3 lesions has challenged this view (Roozendaal, Phillips, Power, Brooke, Sapolsky, & McGaugh, 2001b). The findings of that study strongly suggest that memory retrieval impairments induced by excitotoxic CA3 neuronal injury are not caused by the neuronal damage per se, but that the effects are mediated by CA3 lesion-induced effects on glucocorticoid feedback. As shown in Fig. 5, kainic acid-induced lesions of the CA3 subfield of Ammon's horn selectively impaired probe-trial retention performance, as indicated by less time spent in the quadrant that contained the platform during training and increased latencies to cross that platform location. However, the CA3 lesions also inhibited glucocorticoid feedback mechanisms, resulting in chronically elevated plasma corticosterone levels. Systemic injections of the corticosterone-synthesis inhibitor metyrapone administered 90 min before retention testing blocked the lesion-induced elevation of corticosterone levels and, most importantly, also blocked the retention impairment induced by CA3 lesions. Metyrapone did not block CA3 lesion-induced memory retrieval impairment in rats given corticosterone (2 mg/kg, sc) supplementation 30 min before retention testing, indicating that the metyrapone effect is due to the blockade of corticosterone synthesis. These findings strongly suggest that CA3 damage-induced retention deficits are mediated indirectly through glucocorticoid dysregulation. As the findings indicate that CA3 neuronal damage alone is not sufficient to induce cognitive impairments, it seems unlikely that glucocorticoid-induced CA3 atrophy accounts for chronic stress effects on cognitive impairment. It is more likely that elevated glucocorticoid levels directly impair memory function in concert with changes in other neurotransmitter systems. Based on these findings, considered together with the fact that in chronic glucocorticoid treatment experiments subjects are usually tested while under the influence of glucocorticoids, it seems likely that, at least, some of the detrimental effects of long-term stress on cognitive performance may be attributed to glucocorticoid influences on memory retrieval.

AN INTEGRATED HYPOTHESIS OF GLUCOCORTICOID EFFECTS ON MEMORY CONSOLIDATION AND MEMORY RETRIEVAL

The findings summarized above indicate that acute glucocorticoid administration influences memory consolidation as well as memory retrieval processes. In the experiments discussed earlier, glucocorticoid effects on memory consolidation and memory retrieval were examined separately in different experiments. However, it is important to note that in "normal" cognition, memory consolidation and retrieval processes occur continuously and simultaneously. Thus, a single glucocorticoid rush can enhance consolidation of novel

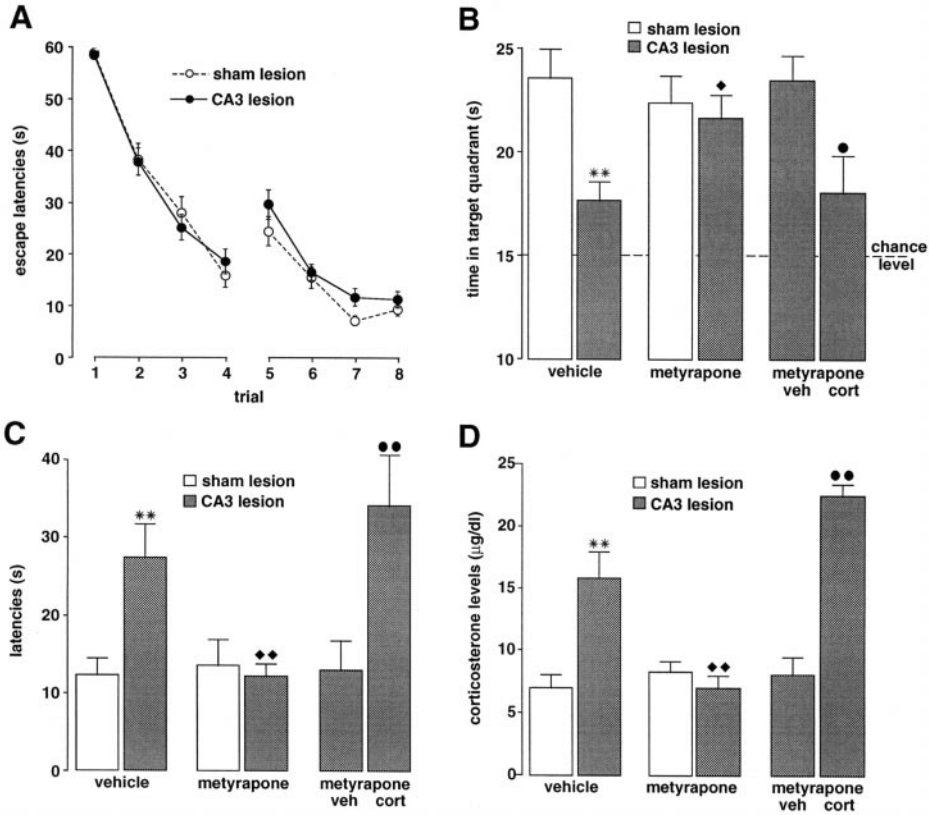

FIG. 5. Effect of the corticosterone-synthesis inhibitor metyrapone (35 mg/kg, sc) injected 90 min before the 24-h probe-trial retention test on the effects of kainic acid-induced lesions of CA3 on water-maze spatial performance and plasma corticosterone. (A) Training escape latencies (means + SEM) of sham- and CA3-lesioned rats during two sessions of four daily trials on a water-maze spatial task. (B) Time spent in the target quadrant (means + SEM) in seconds on the 60-s probe trial in sham- and CA3-lesioned rats treated with either vehicle or metyrapone. Other CA3-lesioned, metyrapone-treated rats received additional injections of vehicle or corticosterone (2 mg/kg, sc) 30 min before retention testing. (C) Latencies (means + SEM) in seconds to cross the platform location on the probe trial in sham- or CA3-lesioned rats. (D) Plasma corticosterone levels (means ± SEM) in μg/dl as assessed immediately after the probe trial. $^{**}p < .01$ CA3 lesion compared to sham lesion; ♦$p < .05$, ♦♦$p < .01$ metyrapone compared to vehicle; ●$p < .05$, ●●$p < .01$ corticosterone compared to vehicle. veh, vehicle; cort, corticosterone. Reproduced, with permission, from Roozendaal et al., 2001, *Nature Neuroscience*, 4.

information, while simultaneously impairing retrieval of previously stored information. Thus, for example, memory retrieval may be temporarily disrupted during a stressful experience such as a job interview or academic examination. However, strong and vivid memories of this event will probably endure a lifetime due to simultaneous stress hormone actions on memory consolidation. It is plausible that a temporary disruption of memory retrieval during stressful conditions may diminish retroactive interference, thereby facilitating memory consolidation of such arousing experiences. In this view, glucocorticoid-induced downregulation of memory retrieval is thus not simply detrimental but serves an important adaptive value. An important question that arises is that of whether glucocorticoid effects on memory consolidation and memory retrieval involve two totally independent processes or whether they are regulated simultaneously in an orchestrated fashion.

If the latter is the case, the neurobiological mechanisms underlying glucocorticoid influences on memory retrieval must be similar or, at least, linked to those underlying memory consolidation.

Is there, in addition to anecdotal evidence, any experimental evidence to support the view that the neural mechanisms underlying glucocorticoid effects on memory consolidation and memory retrieval are related? As discussed in the preceding sections, glucocorticoid effects on memory consolidation depend on noradrenergic activation of the BLA. The blockade of noradrenergic activity in the BLA or lesions of the BLA prevent glucocorticoid effects on memory consolidation. Recent findings indicate that glucocorticoid effects on memory retrieval also require noradrenergic activation and BLA activation. Systemic injections of the β-adrenoceptor antagonist propranolol block the impairing effects of corticosterone injections administered shortly before retention testing on memory retrieval in an inhibitory avoidance task (Roozendaal & McGaugh, manuscript in preparation). Although this study did not examine whether noradrenergic activation of the BLA is required, it was also found that excitotoxic lesions of the BLA prevent memory retrieval impairment in a water-maze spatial task induced by intrahippocampal infusions of the GR agonist RU 28362 (Roozendaal, Griffith, & McGaugh, manuscript in preparation). These findings indicate that BLA lesions and noradrenergic blockade prevent glucocorticoid-induced memory consolidation enhancement as well as glucocorticoid effects on memory retrieval impairment. Thus, the findings suggest that the BLA is a key structure in a memory-modulatory system that regulates stress and glucocorticoid effects on both memory consolidation and memory retrieval. These findings support the hypothesis that glucocorticoid effects on memory consolidation and memory retrieval are not two independent processes, but that they are linked in terms of function and neurobiological substrate. Accordingly, it can be hypothesized that during low-arousing conditions (with low circulating levels of stress hormones, including glucocorticoids), the brain is in a state that allows for recall of information, but that does not allow for strong memory consolidation. During a stressful experience, the release of stress hormones and neurotransmitters may activate the BLA, switching the brain into a "memory consolidation state," allowing for strong consolidation of this event, but as a consequence, simultaneously compromising memory retrieval. However, the modulatory effects do not depend solely on BLA activation as glucocorticoid infusions into the BLA enhance memory consolidation, but appear to be insufficient to impair memory retrieval. Therefore, it is likely that a dynamic interplay between the BLA and other brain regions, including the hippocampus and the prefrontal cortex, coordinates the antagonizing stress effects on memory consolidation and memory retrieval. Findings of several animal experiments agree with such a hypothesis. For example, activation of noradrenergic mechanisms in the prefrontal cortex, which is known to impair short-term memory retrieval (i.e., working memory) (Mao, Arnsten, & Li, 1999; Arnsten, 2000), enhances long-term memory consolidation (Liang, 2001). Furthermore, the prefrontal cortex tonically suppresses BLA activity (Rosenkranz & Grace, 2001), whereas inhibition of the prefrontal cortex (thus impairing short-term memory retrieval) increases the effect of BLA stimulation on dopamine release in the nucleus accumbens (NAc) (enhancing memory consolidation) (Jackson & Moghaddam, 2001). Evidence also indicates that hippocampal-evoked activity in the NAc suppresses BLA-evoked activity in the same NAc neurons (Floresco, Blaha, Yang, & Phillips, 2001). Thus it is possible that ultimately

the NAc integrates and gates information from the BLA, hippocampus, and prefrontal cortex on memory consolidation and memory retrieval.

In conclusion, glucocorticoids appear to influence different cognitive phases. Immediate posttraining injections of glucocorticoids enhance memory consolidation. These effects depend on noradrenergic activation of the BLA and interactions of the BLA with other brain regions. In contrast, memory retrieval processes are impaired with high circulating levels of glucocorticoids. Although such effects on memory retrieval may appear detrimental, it has been suggested that this may favor memory consolidation, allowing a more appropriate response. A challenge for future research will be to explore how the neurobiological mechanisms underlying these processes are related.

REFERENCES

Arbel, I., Kadar, T., Silbermann, M., & Levy, A. (1994). The effects of long-term corticosterone administration on hippocampal morphology and cognitive performance of middle-aged rats. *Brain Research,* **657,** 227–235.

Arnsten, A. F. (2000). Stress impairs prefrontal cortical function in rats and monkeys: Role of dopamine D1 and norepinephrine alpha-1 receptor mechanisms. *Progress in Brain Research,* **126,** 183–192.

Barbazanges, A., Vincenzo, P., Le Moal, M., & Maccari, S. (1996). Maternal glucocorticoid secretion mediates long-term effects of prenatal stress. *Journal of Neuroscience,* **16,** 3943–3949.

Belanoff, J. K., Gross, K., Yager, A., & Schatzberg, A. F. (2001). Corticosteroids and cognition. *Journal of Psychiatric Research,* **35,** 127–145.

Bodnoff, S. R., Humphreyz, A. G., Lehman, J. C., Diamond, D. M., Rose, G. M., & Meaney, M. J. (1995). Enduring effects of chronic corticosterone treatment on spatial learning, synaptic plasticity, and hippocampal neuropathology in young and mid-aged rats. *Journal of Neuroscience,* **15,** 61–69.

Bohus, B. (1994). Humoral modulation of learning and memory processes: Physiological significance of brain and peripheral mechanisms. In J. Delacour (Ed.), *The memory system of the brain* (pp. 337–364). Singapore: World Scientific.

Borrell, J., de Kloet, E. R., Versteeg, D. H. G., & Bohus, B. (1983). Inhibitory avoidance deficit following short-term adrenalectomy in the rat: The role of adrenal catecholamines. *Behavioral and Neural Biology,* **39,** 241–258.

Buchanan, T. W., & Lovallo, W. R. (2001). Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology,* **26,** 307–317.

Cahill, L., & McGaugh, J. L. (1991). NMDA-induced lesions of the amygdaloid complex block the retention enhancing effect of posttraining epinephrine. *Psychobiology,* **19,** 206–210.

Conrad, C. D., Galea, L. A. M., Kuroda, Y., & McEwen, B. S. (1996). Chronic stress impairs rat spatial memory on the Y-maze, and this effect is blocked by tianeptine pretreatment. *Behavioral Neuroscience,* **110,** 1321–1334.

Conrad, C. D., Lupien, S. J., & McEwen, B. S. (1999). Support for a bimodal role for Type II adrenal steroid receptors in spatial memory. *Neurobiology of Learning and Memory,* **72,** 39–46, doi:10.1006/nlme.1998.3898.

Cordero, M. I., & Sandi, C. (1998). A role for brain glucocorticoid receptors in contextual fear conditioning: Dependence upon training intensity. *Brain Research,* **786,** 11–17.

Cottrell, G. A., & Nakajima, S. (1977). Effects of corticosteroids in the hippocampus on passive avoidance behavior in the rat. *Pharmacology, Biochemistry & Behavior,* **7,** 277–280.

Dachir, S., Kadar, T., Robinzon, B., & Levy, A. (1993). Cognitive deficits induced in young rats by long-term corticosterone administration. *Behavioral and Neural Biology,* **60,** 103–109.

Daly, J. W., Padgett, Y., Creveling, D., Cantacuzene, D., & Kirk, K. L. (1981). Cyclic AMP-generating systems: Regional differences in activation by adrenergic receptors in rat brain. *Journal of Neuroscience,* **1,** 49–59.

Davis, H. P., & Squire, L. R. (1984). Protein synthesis and memory: A review. *Psychological Bulletin,* **96,** 518–559.

de Kloet, E. R. (1991). Brain corticosteroid receptor balance and homeostatic control. *Frontiers in Neuroendocrinology,* **12,** 95–164.

de Kloet, E. R., de Kock, S., Schild, V., & Veldhuis, H. D. (1988). Antiglucocorticoid RU 38486 attenuates retention of a behavior and disinhibits the hypothalamic–pituitary–adrenal axis at different sites. *Neuroendocrinology,* **47,** 109–115.

de Kloet, E. R., Oitzl, M. S., & Joëls, M. (1999). Stress and cognition: Are corticosteroids good or bad guys? *Trends in Neuroscience,* **22,** 422–426.

de Quervain, D. J.-F., Roozendaal, B., & McGaugh, J. L. (1998). Stress and glucocorticoids impair retrieval of long-term spatial memory. *Nature,* **394,** 787–790.

de Quervain, D. J.-F., Roozendaal, B., Nitsch, R. M., McGaugh, J. L., & Hock, C. (2000). Acute cortisone administration impairs retrieval of long-term declarative memory in humans. *Nature Neuroscience,* **3,** 313–314.

Diamond, D. M., Park, C. R., Heman, K. L., & Rose, G. M. (1999). Exposing rats to a predator impairs spatial working memory in the radial arm water maze. *Hippocampus,* **9,** 542–552.

Duncan, C. P. (1949). The retroactive effect of electroshock on learning. *Journal of Comparative and Physiological Psychology,* **42,** 32–44.

Fallon, J. H., & Ciofi, P. (1992). Distribution of monoamines within the amygdala. In J. Aggleton (Ed.), *The amygdala: Neurobiological aspects of emotion, memory, and mental dysfunction* (pp. 94–114). New York: Wiley–Liss.

Ferry, B., Roozendaal, B., & McGaugh, J. L. (1999). Basolateral amygdala noradrenergic influences on memory storage are mediated by an interaction between β- and α_1-adrenoceptors. *Journal of Neuroscience,* **19,** 5119–5123.

Flood, J. F., Bennett, E. L., Orme, A. E., & Rosenzweig, M. R. (1975). Relation of memory formation to controlled amounts of brain protein synthesis. *Physiology and Behavior,* **15,** 97–102.

Flood, J. F., Vidal, D., Bennett, E. L., Orme, A. E., Vasquez, S., & Jarvik, M. E. (1978). Memory facilitating and anti-amnestic effects of corticosteroids. *Pharmacology, Biochemistry & Behavior,* **8,** 81–87.

Floresco, S. B., Blaha, C. D., Yang, C. R., & Phillips, A. G. (2001). Modulation of hippocampal and amygdalar-evoked activity of nucleus accumbens neurons by dopamine: Cellular mechanisms of input selection. *Journal of Neuroscience,* **21,** 2851–2860.

Gold, P. E., & van Buskirk, R. B. (1975). Facilitation of time-dependent memory processes with posttrial epinephrine injections. *Behavioral Biology,* **13,** 145–153.

Härfstrand, A., Fuxe, K., Cintra, A., Agnati, L. F., Zini, I., Wikström, A. C., Okret, S., Yu, Z. Y., Goldstein, M., Steinbusch, H., Verhofstad, A., & Gustafsson, J. Å (1987). Glucocorticoid receptor immunoreactivity in monoaminergic neurons of rat brain. *Proceedings of the National Academy of Sciences of the United States of America,* **83,** 9779–9783.

Honkaniemi, J., Pelto-Huikko, M., Rechardt, L., Isola, J., Lammi, A., Fuxe, K., Gustafsson, J. Å., Wikström, A. C., & Hökfelt, T. (1992). Colocalization of peptide and glucocorticoid receptor immunoreactivities in the rat central amygdaloid nucleus. *Neuroendocrinology,* **55,** 451–459.

Ikegaya, Y., Saito, H., & Abe, K. (1995). Requirement of basolateral amygdala neuron activity for the induction of long-term potentiation in the dentate gyrus in vivo. *Brain Research,* **671,** 351–354.

Ikegaya, Y., Nakanishi, K., Saito, H., & Abe, K. (1997). Amygdala β-noradrenergic influence on hippocampal long-term potentiation in vivo. *NeuroReport,* **8,** 3143–3146.

Introini-Collison, I. B., Miyazaki, B., & McGaugh, J. L. (1991). Involvement of the amygdala in the memory-enhancing effects of clenbuterol. *Psychopharmacology,* **104,** 541–544.

Izquierdo, L. A., Barros, D. M., Ardenghi, P. G., Pereira, P., Rodrigues, C., Choi, H., Medina, J. H., & Izquierdo, I. (2000). Different hippocampal molecular requirements for short- and long-term retrieval of one-trial avoidance learning. *Behavioural Brain Research,* **111,** 93–98.

Izquierdo, I., & Diaz, R. D. (1985). Influences on memory of posttraining or pre-test injections of ACTH, vasopressin, epinephrine, or β-endorphin and their interaction with naloxone. *Psychoneuroendocrinology,* **10,** 165–172.

Jackson, M. E., & Moghaddam, B. (2001). Amygdala regulation of nucleus accumbens dopamine output is governed by the prefrontal cortex. *Journal of Neuroscience,* **21,** 676–681.

Joëls, M. (2001). Corticosteroid actions in the hippocampus. *Journal of Neuroendocrinology,* **13,** 657–669.

Karten, Y. J. G., Slagter, E., & Joëls, M. (1999). Effects of long-term elevated corticosteroid levels on synaptically evoked population spikes in the rat CA1 hippocampal area. *Neuroscience Letters,* **265,** 41–44.

Kim, J. J., Lee, H. J., Han, J. S., & Packard, M. G. (2001). Amygdala is critical for stress-induced modulation of hippocampal long-term potentiation and learning. *Journal of Neuroscience,* **21,** 5222–5228.

Kirschbaum, C., Wolf, O. T., May, M., Wippich, W., & Hellhammer, D. H. (1996). Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sciences,* **58,** 1475–1483.

Korte, S. M., de Kloet, E. R., Buwalda, B., Bouman, S. D., & Bohus, B. (1996). Antisense to the glucocorticoid receptor in hippocampal dentate gyrus reduces immobility in forced swim test. *European Journal of Pharmacology,* **301,** 19–25.

Kovacs, G. L., Telegdy, G., & Lissak, K. (1977). Dose-dependent action of corticosteroids on brain serotonin content and passive avoidance behavior. *Hormones & Behavior,* **8,** 155–165.

Krugers, H. J., Douma, B. R. K., Andringa, G., Bohus, B., Korf, J., & Luiten, P. G. M. (1997). Exposure to chronic psychological stress and corticosterone in the rat: Effects on spatial discrimination learning and hippocampal protein kinase C_{γ}-immunoreactivity. *Hippocampus,* **7,** 427–436.

Liang, K. C. (2001). Epinephrine modulation of memory: Amygdala activation and regulation of long-term memory storage. In P. E. Gold & W. T. Greenough (Eds.), *Memory consolidation: Essays in honor of James L. McGaugh* (pp. 165–183). Washington, DC: Am. Psychol. Assoc.

Liang, K. C., Chen, L. L., & Huang, T. E. (1995). The role of amygdala norepinephrine in memory formation: Involvement of memory enhancing effect of peripheral epinephrine. *Chinese Journal of Physiology,* **38,** 81–91.

Liang, K. C., Juler, R., & McGaugh, J. L. (1986). Modulating effects of posttraining epinephrine on memory: Involvement of the amygdala noradrenergic system. *Brain Research,* **368,** 125–133.

Luine, V. N., Spencer, R. L., & McEwen, B. S. (1993). Effects of chronic corticosterone ingestion on spatial memory performance and hippocampal serotonergic function. *Brain Research,* **616,** 65–70.

Luine, V., Villegas, M., Martinez, C., & McEwen, B. S. (1994). Repeated stress causes reversible impairments of spatial memory performance. *Brain Research,* **639,** 167–170.

Lupien, S. J., Gaudreau, S., Tchiteya, B. M., Maheu, F., Sharma, S., Nair, N. P. V., Hauger, R. L., McEwen, B. S., & Meaney, M. J. (1997). Stress-induced declarative memory impairment in healthy elderly subjects: Relationship to cortisol reactivity. *Journal of Clinical Endocrinology and Metabolism,* **82,** 2070–2075.

Lupien, S. J., Gillin, C. J., & Hauger, R. L. (1999). Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: A dose–response study in humans. *Behavioral Neuroscience,* **113,** 420–430.

Lupien, S. J., & McEwen, B. S. (1997). The acute effects of corticosteroids on cognition: Integration of animal and human model studies. *Brain Research Reviews,* **24,** 1–27.

Mao, Z. M., Arnsten, A. F., & Li, B. M. (1999). Local infusion of an alpha-1 adrenergic agonist into the prefrontal cortex impairs spatial working memory performance in monkeys. *Biological Psychiatry,* **46,** 1259–1265.

Markey, K. A., Towle, A. C., & Sze, P. Y. (1982). Glucocorticoid influence on tyrosine hydroxylase in mouse locus coeruleus during postnatal development. *Endocrinology,* **111,** 1519–1523.

McEwen, B. S. (1987). Glucocorticoid–biogenic amine interaction in relation to mood and behavior. *Biochemical Pharmacology,* **36,** 1755–1763.

McGaugh, J. L. (1966). Time-dependent processes in memory storage. *Science,* **153,** 1351–1358.

McGaugh, J. L. (2000). Memory—A century of consolidation. *Science,* **287,** 248–251.

McGaugh, J. L., Cahill, L., & Roozendaal, B. (1996). Involvement of the amygdala in memory storage: Interaction with other brain systems. *Proceedings of the National Academy of Sciences of the United States of America,* **93,** 13508–13514.

McGaugh, J. L., Ferry, B., Vazdarjanova, A., & Roozendaal, B. (2000). Amygdala: Role in modulation of memory storage. In J. P. Aggleton (Ed.), *The amygdala: A functional analysis* (pp. 391–423). Oxford: Oxford Univ. Press.

McGaugh, J. L., & Roozendaal, B. (2002). Role of adrenal stress hormones in forming lasting memories in the brain. *Current Opinion in Neurobiology,* **12,** 205–210.

Micheau, J., Destrade, C., & Soumireu-Mourat, B. (1985). Time-dependent effects of posttraining intrahippocampal injections of corticosterone on retention of appetitive learning tasks in mice. *European Journal of Pharmacology,* **106,** 39–46.

Newcomer, J. W., Craft, S., Hershey, T., Askins, K., & Bardgett, M. E. (1994). Glucocorticoid-induced impairment in declarative memory performance in adult humans. *Journal of Neuroscience,* **14,** 2047–2053.

Oitzl, M. S., & de Kloet, E. R. (1992). Selective corticosteroid antagonists modulate specific aspects of spatial orientation learning. *Behavioral Neuroscience,* **106,** 62–71.

Pfaff, D. W., Silva, M. T. A., & Weiss, J. M. (1971). Telemetred recording of hormone effects on hippocampal neurons. *Science,* **171,** 394–395.

Pikkarainen, M., Rönkkö, S., Savander, V., Insausti, R., & Pitkänen, A. (1999). Projections from the lateral, basal, and accessory basal nuclei of the amygdala to the hippocampal formation in rat. *Journal of Comparative Neurology,* **403,** 229–260.

Pugh, C. R., Tremblay, D., Fleshner, M., & Rudy, J. W. (1997). A selective role for corticosterone in contextual-fear conditioning. *Behavioral Neuroscience,* **111,** 503–511.

Quirarte, G. L., Roozendaal, B., & McGaugh, J. L. (1997). Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala. *Proceedings of the National Academy of Sciences of the United States of America,* **94,** 14048–14053.

Reul, J. M. H. M., & de Kloet, E. R. (1985). Two receptor systems for corticosterone in the rat brain: Microdistribution and differential occupation. *Endocrinology,* **117,** 2505–2512.

Reus, Y. (1984). Hormonal mediation of the memory disorder in depression. *Drug Level Research,* **4,** 489–500.

Roozendaal, B. (2000). Glucocorticoids and the regulation of memory consolidation. *Psychoneuroendocrinology,* **25,** 213–238.

Roozendaal, B., Carmi, O., & McGaugh, J. L. (1996a). Adrenocortical suppression blocks the memory-enhancing effects of amphetamine and epinephrine. *Proceedings of the National Academy of Sciences of the United States of America,* **93,** 1429–1433.

Roozendaal, B., de Quervain, D. J.-F., Ferry, B., Setlow, B., & McGaugh, J. L. (2001a). Basolateral amygdala-nucleus accumbens interactions in mediating glucocorticoid enhancement of memory consolidation. *Journal of Neuroscience,* **21,** 2518–2525.

Roozendaal, B., & McGaugh, J. L. (1996). Amygdala nuclei lesions differentially affect glucocorticoid-induced memory enhancement in an inhibitory avoidance task. *Neurobiology of Learning and Memory,* **65,** 1–8, doi:10.1006/nlme.1996.0001.

Roozendaal, B., & McGaugh, J. L. (1997a). Glucocorticoid receptor agonist and antagonist administration into the basolateral but not central amygdala modulates memory storage. *Neurobiology of Learning and Memory,* **67,** 176–179, doi:10:1006/nlme.1996.3765.

Roozendaal, B., & McGaugh J. L. (1997b). Basolateral amygdala lesions block the memory-enhancing effect of glucocorticoid administration in the dorsal hippocampus of rats. *European Journal of Neuroscience,* **9,** 76–83.

Roozendaal, B., Nguyen, B. T., Power, A. E., & McGaugh, J. L. (1999a). Basolateral amygdala noradrenergic influence enables enhancement of memory consolidation induced by hippocampal glucocorticoid receptor activation. *Proceedings of the National Academy of Sciences of the United States of America,* **96,** 11642–11647.

Roozendaal, B., Phillips, R. G., Power, A. E., Brooke, S. M., Sapolsky, R. M., & McGaugh, J. L. (2001b). Memory retrieval impairment induced by hippocampal CA3 lesions is blocked by adrenocortical suppression. *Nature Neuroscience,* **4,** 1169–1171.

Roozendaal, B., Portillo-Marquez, G., & McGaugh, J. L. (1996b). Basolateral amygdala lesions block glucocorticoid-induced modulation of memory for spatial learning. *Behavioral Neuroscience,* **110,** 1074–1083.

Roozendaal, B., Quirarte, G. L., & McGaugh, J. L. (2002). Glucocorticoids interact with the basolateral amygdala β-adrenoceptor–cAMP/PKA system in influencing memory consolidation. *European Journal of Neuroscience,* **15,** 553–560.

Roozendaal, B., Sapolsky, R. M., & McGaugh, J. L. (1998). Basolateral amygdala lesions block the disruptive effects of long-term adrenalectomy on spatial memory. *Neuroscience,* **84,** 453–465.

Roozendaal, B., Williams, C. L., & McGaugh, J. L. (1999b). Glucocorticoid receptor activation in the rat nucleus of the solitary tract facilitates memory consolidation: Involvement of the basolateral amygdala. *European Journal of Neuroscience,* **11,** 1317–1323.

Rosenkranz, J. A., & Grace, A. A. (2001). Dopamine attenuates prefrontal cortical suppression of sensory inputs to the basolateral amygdala of rats. *Journal of Neuroscience,* **21,** 4090–4103.

Sandi, C., Loscertales, M., & Guanza, C. (1997). Experience-dependent facilitating effect of corticosterone on spatial memory formation in the water maze. *European Journal of Neuroscience,* **9,** 637–642.

Sandi, C., & Rose, S. P. R. (1994a). Corticosterone enhances long-term memory in one day-old chicks trained in a weak passive avoidance learning paradigm. *Brain Research,* **647,** 106–112.

Sandi, C., & Rose, S. P. R. (1994b). Corticosteroid receptor antagonists are amnestic for passive avoidance learning in day-old chicks. *European Journal of Neuroscience,* **6,** 1292–1297.

Sandi, C., & Rose, S. P. R. (1997). Training-dependent biphasic effects of corticosterone in memory formation for a passive avoidance task in chicks. *Psychopharmacology,* **133,** 152–160.

Sapolsky, R., Krey, L., & McEwen, B. S. (1985). Prolonged glucocorticoid exposure reduces hippocampal neuron number: Implications for aging. *Journal of Neuroscience,* **5,** 1222–1227.

Setlow, B., Roozendaal, B., & McGaugh, J. L. (2000). Involvement of a basolateral amygdala complex–nucleus accumbens pathway in glucocorticoid-induced modulation of memory consolidation. *European Journal of Neuroscience,* **12,** 367–375.

Sternberg, D. B., Isaacs, K. R., Gold, P. E., & McGaugh, J. L. (1985). Epinephrine facilitation of appetitive learning: Attenuation with adrenergic receptor antagonists. *Behavioral and Neural Biology,* **44,** 447–453.

Szapiro, G., Izquierdo, L. A., Alonso, M., Barros, D., Paratcha, G., Ardenghi, P., Pereira, P., Medina, J. H., & Izquierdo, I. (2000). Participation of hippocampal metabotropic glutamate receptors, protein kinase A and mitogen-activated protein kinases in memory retrieval. *Neuroscience,* **99,** 1–5.

Whelan, T. B., Schteingart, D. E., Starkman, M. N., & Smith, A. (1980). Neuropsychological deficits in Cushing's syndrome. *Journal of Nervous and Mental Disease,* **168,** 753–757.

Williams, C. L., Men, D., Clayton, E. C., & Gold, P. E. (1998). Norepinephrine release in the amygdala following systemic injection of epinephrine or escapable footshock: Contribution of the nucleus of the solitary tract. *Behavioral Neuroscience,* **112,** 1414–1422.

Wolkowitz, O. M., & Weingartner, H. (1988). Defining cognitive changes in depression and anxiety: A psychobiological analysis. *Psychiatrical Psychobiology,* **3,** 1315–1385.