Nonlinearity in Biology, Toxicology, and Medicine, 3: 57–78, 2005

ISSN: 1540-1421
DOI: 10.2201/nonlin.003.01.004

International Hormesis Society

THE RELATIONSHIP BETWEEN ACUTE GLUCOCORTICOID LEVELS AND HIPPOCAMPAL FUNCTION DEPENDS UPON TASK AVERSIVENESS AND MEMORY PROCESSING STAGE

Cheryl D. Conrad □ Arizona State University, Department of Psychology

□ *This review evaluates the effects of glucocorticoids (GCs), the adrenal steroids released in response to stress, on memory functions requiring the hippocampus in animals and humans. The data support the hypothesis that the learning function between GCs and hippocampal-dependent memory is modulated by 1) the aversive nature of the learning paradigm and 2) stage of memory processing (acquisition, consolidation, retrieval). When tasks are minimally aversive, the glucocorticoid receptor (GR) mediates an inverted U-shaped relationship between GC levels and hippocampal function, while the mineralocorticoid receptor (MR) mediates attentional processes and/or reaction to novelty. This inverted U-shaped relationship during minimally aversive training paradigms describes GC-mediated memory processing at both acquisition and consolidation. In contrast, highly aversive paradigms activate the amygdala and elevate GCs as part of the training procedure, revealing a nonlinear inverted U-shaped relationship during acquisition and a positive linear function during consolidation. Thus, highly aversive tasks that activate the amygdala shift the memory function from an inverted U-shaped curve to a linear representation between GC levels and memory consolidation.*

Keywords. stress, amygdala, mineralocorticoid, learning, spatial memory, passive avoidance, Pavlovian conditioning

Abbreviations. ACTH, adrenocorticotropin hormone; CRH, corticotrophin releasing hormone; GC, glucocorticoid; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; LTP, long-term potentiation; LTD, long-term depression; MR, mineralocorticoid receptor; PBP, primed burst potentiation

INTRODUCTION

This review examines how memory mediated by the hippocampus is influenced by stress hormones called glucocorticoids (GCs), steroids such as corticosterone in rats and mice and cortisol in human and non-human primates. The literature reveals that GCs demonstrate a non-linear function with hippocampal-dependent memory during the acquisition and consolidation from minimally aversive tasks: optimal performance occurs at low to moderate GC levels and impaired memory occurs at very low or high GC levels. This non-linear relationship between GC levels and hippocam-

Address correspondence to Dr. Cheryl D. Conrad, Department of Psychology, Arizona State University, Box 871104, Tempe, AZ 85287-1104. TEL: (480) 965-7761. FAX: (480) 965-8544. E-mail: conradc@asu.edu

pal-dependent memory has been previously described (Lupien and Lepage 2001; Kim and Diamond 2002). In this review, however, the relationship between GC levels and hippocampal-dependent memory is proposed to shift from an inverted U-shaped function to a positive linear function when GC manipulations occur during memory consolidation and the task is sufficiently aversive to activate the amygdala. Amygdalar activation is proposed to be a critical determinant in the facilitation of memory consolidation by high levels of GCs.

The current review emphasizes the acute actions of GCs in the adult male, and not long-term GC actions and/or developmental influences. These "activational actions" of GCs refer to reversible events occurring after a single exposure to GCs in the adult. Brief exposures to GCs are thought to be beneficial for adaptation to the environment. In contrast, prolonged exposure to GCs can be detrimental, leading to long-lasting changes that predispose organisms to disease (McEwen *et al.*, 1997). Thus, mechanisms that underlie the response to acute and chronic GC exposure are different (for review, see McEwen 2000), and this critique focuses on acute GC exposure.

THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS

The HPA axis represents the anatomical regions involved in the hormonal cascade that eventually triggers the release of GCs in response to a stressor (for review, see Dallman *et al.*, 1987; de Kloet 1991). When a stressor is initially detected, the hypothalamus releases corticotrophin releasing hormone (CRH) into the local hypophyseal portal blood system. CRH triggers the anterior pituitary to secrete adrenocorticotropin hormone (ACTH), which then stimulates the adrenal cortex, located near the kidneys, to release GCs into the bloodstream. Due to this multi-step hormonal cascade, the rise of GC levels in response to a stressor occurs relatively slowly over many minutes. GC release is regulated by potent negative-feedback at the anterior pituitary, hypothalamus, and hippocampus, a limbic structure involved in learning and memory. The hippocampus contains one of the highest concentrations of receptors for GCs in the brain (McEwen *et al.*, 1968, 1969), which suggests that the hippocampus is sensitive to changes in GC levels and that GCs may significantly impact hippocampal function.

Two receptors mediate GC actions on brain function: the mineralocorticoid receptor (MR or Type I) and the glucocorticoid receptor (GR or Type II). Within the hippocampus, the binding affinity of GCs to MRs is nearly ten-fold higher than to GRs (Veldhuis *et al.*, 1982). The GC occupancy of hippocampal MR is consistently high even during nonstress (approximately 70% to 90%), whereas the occupancy of hippocampal GRs fluctuates between 10% and 90% as a function of stress or the circadian

rhythm (Reul and de Kloet 1985; Reul *et al.*, 1987; de Kloet *et al.*, 1993a). The ability of hippocampal GR to detect large differences in GC levels has led to the hypothesis that hippocampal GR mediates the GC signal for stress responses (de Kloet and Reul 1987).

PARADIGMS USED TO INVESTIGATE GC INFLUENCE ON HIPPOCAMPAL FUNCTION

The hippocampus is an integral part of spatial memory processing, whereby multiple cues are used to navigate within an environment. How the hippocampus represents the environment is debatable with several prominent theories that include: cognitive mapping (O'Keefe and Nadel 1978), configural versus elemental associations (Rudy and Sutherland 1995), and flexible relations of multiple versus individual representations (Eichenbaum *et al.*, 1990). Regardless of how the information is represented, spatial mazes are very sensitive to hippocampal system disruptions. Examples of spatial mazes include the radial arm maze (Olton *et al.*, 1978), Morris water maze (Morris *et al.*, 1982), radial arm water maze (Diamond *et al.*, 1999), and Y-maze (Conrad *et al.*, 1996). Spatial abilities require rodents (typically rats and mice) to locate a goal by using extra-maze (distal) cues. Rats with hippocampal lesions fail to remember the goal location when extra-maze cues are essential for navigation. In contrast, rats with hippocampal lesions readily locate the goal when it is visible or when the start and goal locations are held constant. These studies show that hippocampal damage impairs place learning (complex representations), but spares response learning (simple representations).

Declarative (explicit) memory is proposed to be a broader domain of hippocampal-dependent memory that encompasses spatial memory (Cohen and Eichenbaum 1991; Squire 1992) in humans (Zola-Morgan *et al.*, 1986) and non-human primates (Zola *et al.*, 2000). Declarative memory refers to the conscious recall of everyday facts and events (Cohen and Eichenbaum 1991) and involves a temporal component (Eichenbaum *et al.*, 1994). As suggested by Eichenbaum, the hippocampus is required during the intermediate period when the relationship between events is processed, but is not necessary for short- or long-term storage of this information. For instance, hippocampal damage does not disrupt immediate recall of declarative memory, nor the long-term storage and recollection of facts learned before (retrograde) hippocampal damage. However, hippocampal damage impairs the long-term storage of newly-learned facts (anterograde amnesia). Hippocampal damage also disrupts working memory, which is the short-term representation of information required for only the current trial, while sparing reference memory, the long-term representation of information required over many trials. Hippocampal lesions impair working memory when complex representations of the environment are required to nav-

igate (place learning), but not when simple representations are used (response learning). Immediate recall in humans parallels response learning in rodents, whereby information lacks complex representations and hence is hippocampal-independent.

Hippocampal integrity is also necessary when animals must recognize environments that were previously paired with an aversive event. For instance, a previously neutral environment can be paired with footshock to produce an association between the environment and the aversive stimulus. The training environment acts as a conditioned stimulus in both passive avoidance (Sahgal 1993; Lorenzini *et al.*, 1996) and contextual fear conditioning (Kim and Fanselow 1992; Phillips and LeDoux 1992; Maren and Holt 2000). For passive avoidance, rodents are given a brief footshock upon entering the preferred dark side of a two-compartment chamber. After a delay, memory for the aversive event is determined by reluctance (increased latency) to enter the dark compartment. For contextual fear conditioning, rodents are exposed to brief footshocks without the opportunity to escape. After a delay, memory for the aversive event is determined by enhanced freezing in the previously aversive environment. A potential problem is that memory for the aversive environment can be supported by both hippocampal and non-hippocampal systems (Penick and Solomon 1991; Kim and Fanselow 1992; Phillips and LeDoux 1994; Young *et al.*, 1994; Gale *et al.*, 1996; Hall *et al.*, 1996; Logue *et al.*, 1997; Maren *et al.*, 1997). Specifically, the hippocampus is involved when processing of the environment uses complex representations (place learning), but not when a single cue representation (response) is used. The difficulty is determining when the hippocampus contributes to performance because both strategies (place and response) have the same behavioral outcome: enhanced latency (passive avoidance) and freezing (contextual conditioning). Thus, findings from multiple paradigms are helpful in interpreting the literature.

Hippocampal function is also necessary for trace conditioning, when a temporal gap occurs between a neutral and an aversive stimulus (Moyer Jr. *et al.*, 1990; Weiss *et al.*, 1999). The trace conditioning studies in this review presented rats with white noise (250 ms) as the conditioned stimulus, followed 500 ms later by periorbital eyeshock (100 ms) as the unconditioned stimulus (Beylin and Shors 1998; Beylin and Shors 2003). Hippocampal function is required when the delay between the conditioned and unconditioned stimulus is 250–500 ms, but not when the delay is removed.

Hippocampal function can be investigated at the cellular level using long-term potentiation (LTP), long-term depression (LTD), and primed burst potentiation (PBP). LTP, PBP and LTD exhibit long-lasting changes in synaptic activity after high frequency stimulation of neuronal afferents. These paradigms are believed to model some aspects of learning and memory (Teyler and DiScenna 1987; Bliss and Collingridge 1993) because they are rapidly induced, correlate with behavioral learning (Berger 1984; Mor-

ris *et al.*, 1986), and share some common cellular mechanisms with spatial learning (Garcia 2001). This model can be studied *in vivo* and *in vitro* within the hippocampus, allowing the influence of GCs to be observed in the whole system (e.g. anesthetized or behaving animals) and in isolation (e.g. hippocampal slices).

THE DUAL ROLE OF GCS IN MEMORY FUNCTION: THE INVOLVEMENT OF THE AMYGDALA IN HIGHLY AVERSIVE TASKS

As reviewed by de Kloet and colleagues (1999), the manner in which GCs influence memory depends upon the context during information processing. GCs tend to facilitate memory on highly aversive paradigms, including passive avoidance, trace conditioning, and fear conditioning, while they impair memory on less aversive tasks, such as spatial mazes and nonemotional declarative memory. In specific examples, rats that were chronically stressed or exposed to stress levels of GCs showed facilitated performance on highly aversive fear conditioning (Conrad *et al.*, 1999b; Conrad *et al.*, 2004), and impaired spatial memory on the less aversive Y-maze (Conrad *et al.*, 1996). Facilitated performance in highly aversive or emotionally arousing tasks has been observed across many paradigms using a single exposure to stress levels of GCs, including passive avoidance (Flood *et al.*, 1978; Gibbs and Ng 1984), trace conditioning (Beylin and Shors 1998; Beylin and Shors 2003), and cued recall of emotionally arousing pictures in humans (Buchanan and Lovallo 2001). In contrast, stress levels of GCs impaired Y-maze spatial memory in rats (Conrad *et al.*, 1999a) and emotionally neutral declarative memory in humans (Newcomer *et al.*, 1994; Kirschbaum *et al.*, 1996; Newcomer *et al.*, 1999; Plihal and Born 1999; Wolf *et al.*, 2001; Monk and Nelson 2002). As described earlier, hippocampal function is required for successful performance in these highly aversive tasks. However, the neural network underlying successful performance in highly aversive and less aversive tasks is not identical. Thus, the contribution of unique neural substrates under these two distinct conditions is a factor in GC modulation of hippocampal function.

The amygdala may play a greater role under highly aversive conditions than under less aversive conditions and is thought to be an underlying component in emotional responses (LeDoux 1992; Cahill and McGaugh 1996). In one study, performance in stressful (cold water) and nonstressful (warm water) conditions of the Morris water maze was compared to determine the contribution of the hippocampus and amygdala (Akirav *et al.*, 2001). The joint activation of the amygdala and hippocampus occurred when rats performed well in the maze under the stressful condition. In contrast, only the hippocampus was activated in rats that did not learn the maze under the stressful condition, and in rats that learned the maze during the nonstressful condition. Another study found that rats tested in the cold water con-

dition on the water maze had higher GC levels and performed better relative to rats tested in the warm water condition that exhibited lower GC levels (Sandi *et al.*, 1997). Moreover, administering post-training GCs to rats tested in the warm water condition improved spatial memory (Sandi *et al.*, 1997). These findings may also help to explain potential inconsistencies in the literature. For instance, passive avoidance tasks typically use footshock as an aversive stimulus, which is interpreted as being equally aversive across passive avoidance tasks. However, a study by Bohus and colleagues (1970) showed that rats exhibited impaired passive avoidance when injected with 2 mg/100 gm of GCs prior to 0.5 mA footshock, but showed functional passive avoidance when the same amount of GCs were given prior to 1.0 mA footshock. The lower footshock intensity may not have been sufficiently aversive under these testing conditions. Thus, potentially anomalous findings may be explained by how subjects perceive a given task, with tasks perceived as highly aversive causing more amygdala activation.

In another elegant series of studies, hippocampal LTP was examined after exposure to electrical stimulation of the amygdala or swim stress (Akirav and Richter-Levin 1999). Amygdala stimulation 30 seconds before testing facilitated hippocampal LTP, while amygdala stimulation 1 hour before testing impaired hippocampal LTP. Additionally, stress exposure modified the influence of the amygdala by blocking the facilitatory action of amygdala stimulation and impairing hippocampal LTP. These data show that: 1) the activation of the amygdala facilitates or inhibits hippocampal function depending upon when activation occurs, and 2) stressors modulate this process. In summary, all of these studies illustrate that animals perform well when GCs and the amygdala are activated as a consequence of the training conditions. Reviews have described these emotionally arousing conditions as "training conditions that consequently result in enhanced GC levels during the post-training period" (Sandi 1998), which contrasts with "distracting" stressors that are out of context of the original learning task (de Kloet *et al.*, 1999) or unrelated to the task (Wolf 2003). Thus, the beneficial effects of GCs may arise under sufficiently stressful or emotionally arousing conditions during the training procedure.

Many reviews have discussed the role of the amygdala in modulating the storage of memory (Cahill and McGaugh 1996; McGaugh and Roozendaal 2002), including memory mediated by the hippocampus (Roozendaal *et al.*, 1997; Ferry and McGaugh 2000; Richter-Levin and Akirav 2000; Roozendaal 2000; McGaugh 2002). GCs can directly influence amygdala function because the amygdala contains GRs and MRs (Warembourg 1975; Sarrieau *et al.*, 1985; Reul and de Kloet 1986). Intra-amygdala infusions of GR agonists dose-dependently enhanced passive avoidance (Roozendaal and McGaugh 1997a; Roozendaal *et al.*, 2002), and lesions of the basolateral amygdaloid (BLA) subnucleus or its efferents blocked the GR agonist-induced facilitation in passive avoidance (Roozendaal and McGaugh 1996; Roozendaal *et*

al., 2001) and in the Morris water maze (Roozendaal *et al.*, 2003). Additionally, many studies have demonstrated a reciprocal relationship between GCs and neuromodulatory factors. In passive avoidance, for example, GCs reduced or blocked the facilitatory actions of adrenaline (Borrell *et al.*, 1984) and nootropics/cholinomimetics (Mondadori *et al.*, 1992). Moreover, intra-amygdala infusion of β-adrenoceptor antagonists (Quirarte *et al.*, 1997; Roozendaal *et al.*, 2002), cholinergic antagonists (Power *et al.*, 2000), and protein kinase A inhibitors (Roozendaal *et al.*, 2002) blocked the facilitation of passive avoidance from post-training GC administration. Therefore, highly aversive tasks such as passive avoidance and classical conditioning have the added complexity that the training procedure enhances emotionality, amygdala contribution (Cahill 2000), and GC release (Sandi 1998), thereby facilitating hippocampal-dependent memory.

STAGE OF MEMORY PROCESSING

The influence of GCs on memory also depends upon the specific phases of memory processing, including acquisition, consolidation, and retrieval (for review, see Lupien and McEwen 1997; Roozendaal 2002). Acquisition refers to the accumulation and integration of information. Consolidation involves strengthening of the learned information and assumes that processes underlying information storage are initiated at training and continue for some time following the completion of training (for review, see McGaugh 1989). Finally, retrieval is the recollection of previously learned information. The presence of GCs during each phase of memory processing determines whether GCs enhance, impair or have no effect on memory.

Stress levels of GCs prior to acquisition impair memory on all hippocampal-dependent tasks, regardless of task aversiveness. Adrenalectomized rats injected with the GR agonist RU362 before training showed impaired spatial memory on the Y-maze (Conrad *et al.*, 1997). The highest dose or stress levels of GCs prior to training impaired passive avoidance in rats (Bohus *et al.*, 1970; Kóvacs *et al.*, 1977) and chicks (Sandi and Rose 1994). A problem with administering GCs prior to acquisition is that separating the effects of GCs on acquisition and consolidation becomes difficult: GCs remain elevated during acquisition and for some time afterward. Consequently, some effects of GCs on acquisition may carry over to influence consolidation. The process of elimination can be used by comparing pre- and post-training effects of GCs on hippocampal function.

In contrast to acquisition, the effects of stress levels of GCs on memory consolidation are dependent upon the aversiveness of the task. On minimally aversive tasks, immediate post-training injections of GC agonists in adrenalectomized rats impaired Y-maze performance (Conrad *et al.*, 1997). GR antagonists given to intact rats before or after training impaired water

maze performance (Oitzl and de Kloet 1992). In humans, post-training infusions (i.v.) of cortisol impaired declarative memory for information learned before GC administration (retrograde impairment, Wolf *et al.*, 2001). Conversely, in highly aversive passive avoidance, the majority of studies find that post-training stress levels of GCs improve memory. Post-training intra-hippocampal infusions of GC agonists facilitated passive avoidance in rats (Roozendaal and McGaugh 1997b). GC injections up to one hour post-training enhanced passive avoidance in chicks (Sandi and Rose 1994) and rats (Flood *et al.*, 1978). Stimulating GC secretion by injecting ACTH also enhanced passive avoidance in rats immediately following training (Gold and Van Buskirk 1976). In humans, elevating GCs by immersing the forearm into cold water enhanced declarative memory for emotionally arousing facts, but not declarative memory for neutral facts (Cahill *et al.*, 2003). The opposing actions of GCs on spatial mazes and highly arousing tasks may be due to the recruitment of the amygdala as described earlier. For instance, BLA lesions blocked the facilitatory actions of intra-hippocampal-infusion of GC agonists on passive avoidance (Roozendaal and McGaugh 1997b). Thus, GCs impair memory consolidation on minimally aversive tasks and facilitate memory consolidation on highly aversive tasks.

Additionally, memory retrieval is impaired by stress levels of GCs. Stress levels of GCs or metyrapone administration impaired retrieval in the water maze in intact rats (Roozendaal *et al.*, 1996a; de Quervain *et al.*, 1998) and declarative memory in humans (de Quervain *et al.*, 2000). The impairment of memory retrieval by GCs appears to be time-dependent (de Quervain *et al.*, 1998) and selective for hippocampal systems because GCs do not disrupt immediate recall or recognition memory in humans (de Quervain *et al.*, 2000). Adrenalectomized rats injected with selective MR and GR agonists prior to retrieval exhibited enhanced retrieval in the Y-maze (Conrad *et al.*, 1997). However, adrenalectomized rats injected with vehicle also performed well, suggesting that the injection procedure was arousing and benefited performance regardless of treatment condition. Another study discovered that administration of MR but not GR antagonists before retrieval altered water maze search strategies (Oitzl and de Kloet 1992). Impaired memory retrieval occurs when GCs are elevated approximately 30 to 90 minutes prior to retrieval assessment. Comparisons between low and highly aversive tasks are not yet available for memory retrieval as the influence of GCs on retrieval is a relatively recent discovery.

Overall, the literature reveals an interesting pattern for how stress levels of GCs influence hippocampal-dependent memory. The majority of the findings indicate that stress levels of GCs impair memory at acquisition regardless of task aversiveness and at retrieval, at least for less aversive tasks. Unfortunately, there is no data regarding the effects of GCs on retrieval for highly aversive tasks. However, stress levels of GCs have opposing actions during memory consolidation with GCs impairing consolidation on less

aversive tasks and facilitating consolidation on highly aversive tasks. The emphasis of the studies described so far has been on a single dose of stress levels of GCs. However, the amounts of GCs released by stressful experiences do not always reach maximum levels. Thus, stress levels of GCs are just one component from a continuum of GC levels that can influence hippocampal-dependent memory.

Influence of Memory Processing Stage and Task Aversiveness on GC Dose-Response Function and Memory

The dose-response function that represents GC levels and hippocampal-dependent memory depends upon the stage of memory processing and the aversive nature of the task. During acquisition, the effects of GCs on hippocampal function are described by an *inverted U-shaped* relationship, which is independent of task aversiveness. In contrast to acquisition, the function representing the effects of GCs on hippocampal ability during memory consolidation depends upon task aversiveness: during minimally aversive tasks, the inverted U-shaped curve continues to represent GC levels and memory, whereas during highly aversive tasks, GCs and memory exhibit a *positive linear* relationship. Because less aversive tasks demonstrate an inverted U-shaped function at every stage of memory processing, separating the effects of GCs on each stage of memory processing is not necessary. However, the presence of GCs at each stage of memory processing is critical for interpretation only for highly aversive tasks.

Many studies support the hypothesis that GCs have nonlinear effects on hippocampal function on tasks that are minimally aversive. For spatial tasks, low to moderate levels of GCs can benefit memory. Long-term adrenalectomized rats replaced acutely with moderate levels of GCs in the drinking water during water maze training showed improved or restored performance (Conrad and Roy 1995; McCormick *et al.*, 1997). Another study found that low levels of GCs given continuously via drinking water enhanced performance in the Morris water maze early in training, despite serum GC levels that were indistinguishable from controls (3.7 µg/dl, Bennett *et al.*, 1996). Perhaps the continual presence of GCs provided a strong negative feedback signal that prevented a stress-induced GC surge, allowing for optimum performance. In contrast, the impairing effects of GCs occur when GCs reach extremely high or low levels, such as those achieved by high stress, adrenalectomy, or pharmaceutical manipulation. In adrenalectomized rats replaced with stress levels of corticosterone, spatial memory was impaired on the water maze (Roozendaal *et al.*, 1996b) and Y-maze (Conrad *et al.*, 1999a). Adrenalectomy or metyrapone administration without GC replacement impaired spatial memory on the radial arm maze (Vaher *et al.*, 1994), water maze (Oitzl and de Kloet 1992; Roozendaal *et al.*, 1996a; Roozendaal *et al.*, 1996b), and Y-maze (Conrad *et al.*, 1997). More-

over, pre-training intra-hippocampal infusions of GR antagonists impaired spatial memory on the water maze (Roozendaal and McGaugh 1997b). In young human adults, metyrapone increased the rate of forgetting on a declarative memory task (Lupien *et al.*, 2002). Altogether, these reports show an inverted U-shaped function between GCs and hippocampal-dependent memory on minimally aversive tasks.

Yau and colleagues (1995) published the first behavioral findings showing a non-linear relationship between corticosterone and spatial memory in young and aged rats. For young rats, morning serum corticosterone levels had a tendency to be positively related to spatial memory performance, whereas evening levels were unrelated to performance. In contrast to the findings with young rats, aged rats showed a negative correlation between morning corticosterone levels and spatial memory. The investigators found that aged rats had greater diversity in serum corticosterone levels and spatial memory ability. Furthermore, aged rats that demonstrated the best spatial memory had lower serum corticosterone levels that more closely resembled a young rat profile, and aged rats with the highest corticosterone levels exhibited the worst spatial ability. The average morning peak of serum corticosterone levels for the aged rats was 6 μg/dL, which was significantly higher than for the young rats (2 μg/dL). Thus, nonstress levels of corticosterone (2 μg/dL) and very mild stress levels of corticosterone (up to 6 μg/dL) allowed for functional spatial memory.

Models of hippocampal synaptic plasticity that are believed to parallel hippocampal learning show an inverted U-shaped function similar to that described for GC levels and spatial memory. In a seminal study by Diamond and colleagues (1992), adrenalectomized rats replaced with corticosterone showed maximum PBP induction when serum corticosterone levels were between 11 and 20 μg/dL. In contrast, a positive correlation between PBP and serum corticosterone was observed with low levels of corticosterone (0–10 μg/dL), and a negative correlation between PBP and serum corticosterone occurred with high levels of corticosterone (20 μg/dL or greater). In a complementary study, intact rats received stress levels of corticosterone or the corticosterone synthesis inhibitor metyrapone, and induction of LTP was investigated (Kerr *et al.*, 1994). Rats with moderate levels of serum corticosterone (15 μg/dL) exhibited the most robust LTP induction compared to rats with serum corticosterone levels that were very low (7 μg/dL) or high (25 μg/dL). Thus, different techniques (replacement versus chemical blocking) to manipulate serum corticosterone levels found that moderate levels (11–20 μg/dL) enhanced PBP/LTP, while lower or higher levels impaired PBP/LTP.

During acquisition in highly aversive tasks, GC levels and hippocampal function exhibit an inverted U-shaped function as well. The possibility that footshock intensity has an inverted U-shaped relationship with learning was shown nearly 100 years ago (Yerkes and Dodson 1908). Only one mouse

learned to discriminate between two chambers after 15 trials when one chamber was paired a mild footshock, whereas all mice learned in less than 10 trials following a higher footshock intensity. The highest footshock intensity, however, delayed learning in all mice. One-trial learning paradigms that have been used since then show an inverted U-shaped relationship with GC levels and memory. Pre-training injections of GCs at 1 and 5 mg/kg enhanced passive avoidance, while high doses (10 and 25 mg/kg) impaired performance (Kóvacs *et al.*, 1977). A dose-response function of GCs given before passive avoidance training in chicks found moderate doses of GCs facilitated performance, whereas the highest and lowest doses did not (Sandi and Rose 1994). In contextual fear conditioning, adrenalectomy impaired performance and GC replacement in the drinking water restored performance (Pugh *et al.*, 1997b). Thus, intermediate levels benefit and very low or high levels of GC impair memory acquisition on highly aversive tasks.

The influence of GCs during memory consolidation on highly aversive tasks appears to be characterized by a positive linear function. In one study, a positive correlation was observed among footshock intensity, GC levels, and contextual fear conditioning (Cordero *et al.*, 1998). The higher the footshock intensity, the more GCs were secreted, which facilitated contextual fear conditioning. Other studies found that post-training GR agonists (s.c.) facilitated passive avoidance in sham-operated rats (Roozendaal and McGaugh 1996) or post-training intra-amygdala or hippocampal GR agonist infusions dose-dependently facilitated passive avoidance (Roozendaal and McGaugh 1997a, b). However, not all reports show a linear function between GC levels and memory consolidation. As early as 1976, Gold and Van Buskirk found that post-training injections of ACTH, the hormone that signals GC release, enhanced passive avoidance at moderate doses and impaired it at high doses. Contextual fear conditioning showed a nonlinear function with dose of GCs injected (Pugh *et al.*, 1997b): adrenalectomized rats given moderate doses of GCs (0.25 mg/kg or 1 mg/kg) post-training showed the best contextual conditioning, while the lowest and highest dose of GCs (0 and 2.5 mg/kg, respectively) impaired contextual conditioning. Serum levels of GC within 30 minutes after injection were 15 μg/dL, 40 μg/dL, and 80 μg/dL for the rats injected with 0.25 mg/kg, 1 mg/kg, and 2.5 mg/kg, respectively. A possible explanation for these contradictory results may be the perceived aversiveness of the task. First, higher footshock intensity produces better retention, which correlates with high GCs (Cordero *et al.*, 1998). These data show that better retention occurs when the task is sufficiently aversive, but presenting a shock does not guarantee that the task will be perceived as aversive. In the passive avoidance study by Gold and Van Buskirk, the footshock was high (.7mA), but was presented for only .35 s, which may be an insufficient duration to be perceived as highly aversive. Second, the contribution of the amygdala may help to de-

termine the aversiveness of a task. BLA lesions blocked the memory-enhancing effects of GCs on passive avoidance (Roozendaal and McGaugh 1997b). Thus, for conditions in which passive avoidance was perceived as aversive, GCs demonstrate a linear relationship with memory consolidation.

In conclusion, GCs have a complex relationship with hippocampal-dependent memory, and this function depends upon the stage of memory processing and the aversive nature of the task. Under minimally aversive conditions, GCs have an inverted U-shaped relationship with hippocampal-dependent memory at all stages. For highly aversive tasks, GCs exhibit an inverted U-shaped function with hippocampal-dependent memory during acquisition and a positive linear function during consolidation. Potential inconsistencies may arise when subjects do not perceive the task as aversive or when the amygdala is not sufficiently involved. Thus, GC levels exhibit an inverted U-shaped relationship with memory during minimally aversive tasks when the amygdala is not activated. When the task is sufficiently aversive to activate the amygdala during memory consolidation, the relationship between GCs and memory becomes a positive linear function.

INVOLVEMENT OF THE GR AND MR IN MEDIATING THE NON-LINEAR RELATIONSHIP BETWEEN GCS AND HIPPOCAMPAL FUNCTION ON MINIMALLY AVERSIVE TASKS

Both GR and MR have the potential to mediate the inverted U-shaped relationship between GCs and hippocampal function in minimally aversive tasks and in models of hippocampal plasticity and learning. The GR is critical for the impairing effects of GCs on hippocampal function, which are represented by the negative slope of the inverted U-shaped curve. Several studies have demonstrated that GRs negatively regulate hippocampal excitability, LTP, and PBP. Direct intra-hippocampal application of dexamethasone, a GR agonist, decreased neuronal activity (Michal 1974). Stress and the GR agonist RU362 enhanced LTD (Pavlides *et al.*, 1995a; Coussens *et al.*, 1997; Xu *et al.*, 1998), while the GR antagonist RU486 blocked LTD (Coussens *et al.*, 1997; Xu *et al.*, 1998). Injections of the GR agonist RU362 in adrenalectomized rats suppressed LTP *in vivo* (Pavlides *et al.*, 1995b) and *in vitro* (Pavlides *et al.*, 1996), an effect that was prevented by pre-treatment with the GR antagonist RU486 (Pavlides *et al.*, 1995b). These studies demonstrate that GRs within the hippocampus mediate the actions of GCs on hippocampal LTP. Behavioral studies support these electrophysiological findings: injections of the GR agonist RU362 impaired spatial memory performance on the Y-maze in adrenalectomized rats (Conrad *et al.*, 1997; Conrad *et al.*, 1999a). Thus, hippocampal function is reduced when GRs are highly occupied by stress levels of GCs.

Conversely, activation of the MR facilitates hippocampal function. Injections of the MR agonist aldosterone in anesthetized, adrenalectomized

rats enhanced LTP *in vitro* (Pavlides *et al.*, 1996), *in vivo* (Pavlides *et al.*, 1995b), and in freely moving animals (Pavlides *et al.*, 1994). The aldosterone enhancement in LTP was abolished by pre-injections of the MR antagonist RU318 (Pavlides *et al.*, 1995b). Again, behavioral studies support the electrophysiological findings: adrenalectomized rats injected with the MR agonist aldosterone, showed functional spatial memory on the Y-maze (Conrad *et al.*, 1997).

The GR and MR have been proposed to have opposing, yet complementary effects that mediate the biphasic actions of GCs on hippocampal function (de Kloet and Reul 1987; de Kloet 1991; Joëls and de Kloet 1992; Conrad *et al.*, 1997). Originally, MR activation was hypothesized to regulate the positive slope of the inverted U-shaped relationship between GC levels and hippocampal function. However, studies have recently indicated a different role for MRs. The GC occupation of GR and MR in the absence of stress should be approximately 10% and 90%, respectively (Reul and de Kloet 1985). It follows that if MR mediates the positive slope of hippocampal function, then blocking GR during non-stress should be insufficient to alter hippocampal function. This hypothesis predicts that adrenalectomized rats given MR agonists will perform similarly to intact rats given GR antagonists, as both conditions exhibit high MR activity. In contrast to this prediction, adrenalectomized rats given the MR agonist aldosterone performed well on the Y-maze, while intact rats injected with the GR antagonist RU555 performed poorly (Conrad *et al.*, 1999a). Furthermore, acute injections of GR antagonists impaired performance on the water maze (Oitzl and de Kloet 1992; Roozendaal and McGaugh 1997b; Oitzl *et al.*, 1998), context conditioning after moderate foot shock (Cordero and Sandi 1998), and passive avoidance (Johnston and Rose 1998). These data show that preventing GR activation, *even in the presence of functional MRs,* impairs hippocampal function. Therefore, the high activation or blockade of GRs determines spatial memory ability; MR activation alone is not sufficient. A review by Lupien and colleagues (in this issue) proposes that the ratio of MR to GR determines memory ability in humans with high ratios facilitating and low ratios impairing memory function. Thus, blocking GR function would reduce the MR/GR ratio and impair hippocampal function, which supports these experimental observations.

One study using a rewarded spatial maze demonstrated results contradictory to those described above (Douma *et al.*, 1998). Intact rats injected repeatedly with MR antagonist, but not GR antagonist, showed impaired spatial reference memory. According to the hypothesis, intact rats injected with MR antagonist should exhibit intact spatial memory because GRs are functional. Compensatory changes in brain function seem unlikely to account for these findings because antagonists were administered every other day. Moreover, reference memory was altered early in training, which emphasizes the acute actions of the MR antagonist, as opposed to long-term

compensatory changes. A major difference in this study was that the rats were rewarded with palatable food, which can increase arousal and motivation. Thus, the possibility that the amygdala altered the dynamics of hippocampal function cannot be discounted and may explain these contradictory results.

What role do MRs have on hippocampal function assessed by spatial memory performance? Previous investigators have suggested a modulatory role through altering attentional processing (for review, see Lupien and McEwen 1997) or reactivity to the environment (de Kloet *et al.*, 1993a; de Kloet *et al.*, 1993b). Such functions would be supportive, but not necessary, to spatial processing and corroborate the behavioral profile (Conrad *et al.*, 1999a). Indeed, the MR antagonist spironolactone did not alter consolidation of spatial memory, but changed search patterns (Oitzl and de Kloet 1992; Yau *et al.*, 1999). In fear conditioning, the MR antagonist RU318 did not affect performance (Cordero and Sandi 1998). In another study, an inverted U-shaped function was demonstrated among exploration in the open field, circulating levels of corticosterone, and MR occupation levels (de Kloet *et al.*, 1993b). This study indicates that MRs regulate exploration in a biphasic fashion, with moderate corticosterone levels corresponding to the most interest in the environment. Thus, MR-induced enhancements in attention may benefit performance. Consequently, blocking MRs does not necessarily impair performance, indicating that the role of the MR in hippocampal function is supportive but not necessary.

One question that remains is how GR and MR regulate hippocampal function. The GR and MR could work independently to benefit hippocampal function by concurrently activating separate systems. For example, GR activation could enhance memory consolidation, while MR activation could enhance attention; the combined activation of both GR and MR may be additive. In another scenario, GR and MR activation could work synergistically to benefit memory. Support for a GR/MR synergism leading to enhancement of hippocampal function has not been demonstrated behaviorally, but is suggested by electrophysiological studies. The GR- and MR-induced excitability of hippocampal potassium or calcium channels was greater when both GR and MR were activated together than the sum of either GR or MR activation alone (Karst *et al.*, 1994; Hesen and Joëls 1995). The GR and MR are highly concentrated and co-localized within the hippocampus (Reul and de Kloet 1986; Van Eekelen *et al.*, 1988), which suggests that they have the potential to act synergistically within the same neurons or in adjacent cells. Whether GR and MR synergism occurs through separate systems or within the same cell or region (e.g. hippocampus) is not clear and requires investigation.

Several other important concepts are revealed by the electrophysiological studies and behavioral paradigms. First, electrophysiological studies demonstrate that synaptic excitability occurs locally within the hippocam-

pus in response to MR and GR manipulation. Some preparations involve the addition of steroids to hippocampal slices, showing that the actions of steroids occur within the hippocampus and not at other targets that modulate the hippocampus. Moreover, studies have shown that behaviors relying upon hippocampal function are altered by direct infusion of GR antagonists or agonists into the hippocampus (Michal 1974; Cottrell and Nakajima 1977). Second, comparing performance on hippocampal-dependent and independent tasks complements the hypothesis that GCs act locally within the hippocampal system. For instance, GR antagonists impair contextual conditioning, a form of learning that requires hippocampal function, without disturbing auditory cue conditioning, which does not require the hippocampus (Pugh *et al.*, 1997a). Finally, several strains of transgenic mice have been developed with impaired GR activity (Pepin *et al.*, 1992; Cole *et al.*, 1995). These mice showed performance deficits on tasks requiring hippocampal function (allocentric or spatial strategy), with no impairment when navigation could be performed without the hippocampus (egocentric or response strategy; Oitzl *et al.*, 1997; Rousse *et al.*, 1997; Steckler *et al.*, 1999; Oitzl *et al.*, 2001). Thus, the influence of GR and MR on hippocampal function under these conditions may involve local actions within the hippocampal system.

SIGNIFICANCE AND CONCLUSION

Stress levels of GCs facilitate hippocampal-dependent memory under highly aversive conditions while impairing memory under less aversive conditions. Under highly aversive conditions that activate the amygdala, the information remembered at this time may have important life-saving repercussions. For example, a rat may have located food near a predator habitat. Remembering the environmental cues surrounding the predator will minimize future exposure to this potentially life-threatening event. Recognition of the predator should activate the amygdala to identify the situation as potentially threatening, and the degree of GC secretion should determine how well the encounter is remembered. If the predator was indifferent to the rat, moderate GC levels may moderately facilitate memory. However, if the predator pursued the rat, then high GC levels may maximize memory retention. A caveat is that remembering and avoiding all scenarios of predator exposure may be counter-productive, because the rat may never eat when constantly avoiding predators. Thus, selecting the appropriate situations to remember better (predator pursuit) than others (predator presence only) will be most cost-effective for the rat. The degree of GC secretion during a highly aversive event may help determine how well information surrounding the event is remembered.

For minimally aversive conditions that do not require amygdala involvement, stress levels of GCs impair memory. By definition, the event is

not life-threatening when the amygdala is not activated, and stress levels of GCs may impair spatial memory under these conditions as a cost-effective strategy. For example, a rat foraging for food will explore many environments and may encounter a predator in one of them. The potentially life-threatening predator stimulates a stress response and GC release in the rat. The spatial representation of the previous, safe environments in the process of consolidation are susceptible to perturbations and the cost of maintaining consolidation for these environments is hypothesized to be an inefficient use of resources after encountering the predator in one area. In this scenario, the rat would benefit most by maintaining a representation of the predator habitat at the expense of hindering representation of the safe areas. Thus, stress levels of GCs will impair spatial memory of the safe environments while facilitating memory of the life-threatening predator habitat.

The purpose of this review was to evaluate the complex effects of acute GC exposure on hippocampal function. A pattern observed in the literature is that GCs have a non-linear relationship with hippocampal function, and amygdala contribution modifies this relationship. GCs facilitate memory consolidation under highly aversive conditions when GC secretion is intrinsic to the training procedure. Amygdala involvement during highly aversive conditions is hypothesized to be a critical factor in determining whether memory is facilitated by GCs. Under highly aversive conditions, GCs have a positive linear function with memory ability, which plateaus at maximum memory retention (see Fig. 2B from Sandi, 1998). In contrast, minimally aversive conditions that do not involve the amygdala demonstrate an inverted U-shaped relationship with serum GC levels, spatial memory, and synaptic plasticity models using LTP/PBP. During minimally aversive conditions, low to moderate levels of GCs (2–20 μg/dL serum blood) are beneficial, whereas extremely low or high levels are detrimental. The GRs appear to mediate the influence of GCs on hippocampal function through memory consolidation and may act locally within the hippocampus. In contrast, the MRs may benefit hippocampal function through indirect processes that influence attention or environmental reactivity. Electrophysiological data suggest that the MR and GR work synergistically to influence hippocampal function, but behavioral studies investigating this hypothesis have not yet been conducted.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Mental Health MH64727. My sincere appreciation to the following individuals for providing feedback on this manuscript: Ryan Wright, Rudy Bellani, Katie McLaughlin, Sarah Baran, Jonathan Kleen, Melanie Paquette, Elizabeth Lightner, Cainan Foltz, Joseph Nguyen, Lindsay Wieczorek, Sergey Tsekha-

nov and, James Harman. Finally, the anonymous reviewers' comments were much appreciated.

REFERENCES

Akirav I, and Richter-Levin G. 1999. Biphasic modulation of hippocampal plasticity by behavioral stress and basolateral amygdala stimulation in the rat. J Neurosci 19(23): 10530–10535

Akirav I, Sandi C, and Richter-Levin G. 2001. Differential activation of hippocampus and amygdala following spatial learning under stress. Eur J Neurosci 14: 719–725

Bennett MC, Mlady GW, Fleshner M, and Rose GM. 1996. Synergy between chronic corticosterone and sodium azide treatments in producing a spatial learning deficit and inhibiting cytochrome oxidase activity. PNAS 93: 1330–1334

Berger TW. 1984. Long-term potentiation of hippocampal synaptic transmission affects rate of behavioral learning. Science 224: 627–630

Beylin AV, and Shors TJ. 1998. Stress enhances excitatory trace eyeblink conditioning and opposes acquisition of inhibitory conditioning. Behav Neurosci 112(6): 1327–1338

Beylin AV, and Shors TJ. 2003. Glucocorticoids are necessary for enhancing the acquisition of associative memories after acute stressful experience. Horm Behav 43: 124–131

Bliss TVP, and Collingridge GL. 1993. A synaptic model of memory: Long-term potentiation in the hippocampus. Nature 361: 31–39

Bohus B, Grubits J, Kovács G, and Lissák K. 1970. Effect of corticosteroids on passive avoidance behaviour of rats. Acta Physiol Acad Scient Hung Tom 38: 381–391

Borrell J, de Kloet ER, and Bohus B. 1984. Corticosterone decreases the efficacy of adrenaline to affect passive avoidance retention of adrenalectomized rats. Life Sci 34: 99–105

Buchanan TW, and Lovallo WR. 2001. Enhanced memory for emotional material following stress-level cortisol treatment in humans. Psychoneuroendocrinology 26: 307–317

Cahill L, and McGaugh JL. 1996. The neurobiology of memory for emotional events: Adrenergic activation of the amygdala. Proc West Pharmacol Soc 39: 81–84

Cahill L. 2000. Modulation of long-term memory storage in humans by emotional arousal: Adrenergic activation and the amygdala. The Amygdala: A functional Analysis. Aggleton J. Oxford, England, Oxford University Press: 425–445

Cahill L, Gorski L, and Le K. 2003. Enhanced human memory consolidation with post-learning stress: Interaction with the degree of arousal at encoding. Learn Mem 10: 270–274

Cohen NJ, and Eichenbaum H. 1991. The theory that wouldn't die: A critical look at the spatial mapping theory of hippocampal function. Hippocampus 1: 265–268

Cole TJ, Blendy JA, Monaghan AP, Krieglstein K, Schmid W, Aguzzi A, Fantuzzi G, Hummler E, Unsicker K, and Schütz G. 1995. Targeted disruption of the glucocorticoid receptor gene blocks adrenergic chromaffin cell development and severely retards lung maturation. Genes Dev 9: 1608–1621

Conrad CD, and Roy EJ. 1995. Dentate gyrus destruction and spatial learning impairment after corticosteroid removal in young and middle-aged rats. Hippocampus 5: 1–15

Conrad CD, Galea LAM, Kuroda Y, and McEwen BS. 1996. Chronic stress impairs rat spatial memory on the Y-Maze, and this effect is blocked by tianeptine pretreatment. Behav Neurosci 110(6): 1321–1334

Conrad CD, Lupien SJ, Thanasoulis LC, and McEwen BS. 1997. The effects of Type I and Type II corticosteroid receptor agonists on exploratory behavior and spatial memory in the Y-Maze. Brain Res 759: 76–83

Conrad CD, Lupien SJ, and McEwen BS. 1999a. Support for a bimodal role for Type II adrenal steroid receptors in spatial memory. Neurobiol Learn Mem 72(1): 39–46

Conrad CD, Magariños AM, LeDoux JE, and McEwen BS. 1999b. Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. Behav Neurosci 113(5): 902–913

Conrad CD, MacMillan II DD, Tsekhanov S, Wright RL, Baran SE, and Fuchs RE. 2004. Influence of chronic corticosterone and glucocorticoid receptor antagonism in the amygdala on fear conditioning. Neurobiol Learn Mem 81: 186200

Cordero MI, Merino JJ, and Sandi C. 1998. Correlational relationship between shock intensity and corticosterone secretion on the establishment and subsequent expression of contextual fear conditioning. Behav Neurosci 112(4): 885–891

Cordero MI, and Sandi C. 1998. A role for brain glucocorticoid receptors in contextual fear conditioning: Dependence upon training intensity. Brain Res 786: 11–17

Cottrell GA, and Nakajima S. 1977. Effect of corticosteroids in the hippocampus on passive avoidance behavior in the rat. Pharm Biochem Behav 7: 277–280

Coussens CM, Kerr DS, and Abraham WC. 1997. Glucocorticoid receptor activation lowers the threshold for NMDA-receptor-dependent homosynaptic long-term depression in the hippocampus through activation of voltage-dependent calcium channels. J Neurophysiol 78: 1–9

Dallman MF, Akana SF, Cascio CS, Darlington DN, Jacobson L, and Levin N. 1987. Regulation of ACTH secretion: Variations on a theme of B. Rec Prog Horm Res 43: 113–173

de Kloet ER, and Reul JMHM. 1987. Feedback action and tonic influence of corticosteroids on brain function: A concept arising from the heterogeneity of brain receptor systems. Psychoneuroendocrinology 12(2): 83–105

de Kloet ER. 1991. Brain corticosteroid receptor balance and homeostatic control. Front Neuroendocrinol 12(2): 95–164

de Kloet ER, Oitzl MS, and Joëls M. 1993a. Functional implications of brain corticosteroid receptor diversity. Cell Mol Neurobiol 13(4): 433–455

de Kloet ER, Sutanto W, Van Den Berg DTWM, Carey MP, Van Haarst AD, Hornsby CD, Meijer OC, Rots NY, and Oitzl MS. 1993b. Brain mineralocorticoid receptor diversity: Functional implications. J Steroid Biochem Molec Biol 47: 183–190

de Kloet ER, Oitzl MS, and Joels M. 1999. Stress and cognition: Are corticosteroids good or bad guys? TINS 22(10): 422–426

de Quervain DJ-F, Roosendaal B, and McGaugh JL. 1998. Stress and glucocorticoids impair retrieval of long-term spatial memory. Nature 394: 787–790

de Quervain DJ-F, Roozendaal B, Nitsch RM, McGaugh JL, and Hock C. 2000. Acute cortisone administration impairs retrieval of long-term declarative memory in humans. Nat Neurosci 3: 313–314

Diamond DM, Bennett MC, Fleshner M, and Rose GM. 1992. Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. Hippocampus 2(4): 421–430

Diamond DM, Park CR, Heman KL, and Rose GM. 1999. Exposing rats to a predator impairs spatial working memory in the radial arm water maze. Hippocampus 9: 542–552

Douma BRK, Korte SM, Buwalda B, la Fleur SE, Bohus B, and Luiten PGM. 1998. Repeated blockade of mineralocorticoid receptors, but not of glucocortoicoid receptors impairs food rewarded spatial learning. Psychoneuroendocrinology 23(1): 33–44

Eichenbaum H, Stewart C, and Morris RGM. 1990. Hippocampal representation in place learning. J Neurosci 10(11): 3531–3542

Eichenbaum H, Otto T, and Cohen NJ. 1994. Two functional components of the hippocampal memory system. Behav Brain Sci 17: 449–518

Ferry B, and McGaugh JL. 2000. Role of amygdala norepinephrine in mediating stress hormone regulation of memory storage. Acta Physiolog Acad Scient Hung 21(6): 481–493

Flood JF, Vidal D, Bennett EL, Orme AE, Vasquez S, and Jarvik ME. 1978. Memory facilitating and antiamnestic effects of corticosteroids. Pharm Biochem Behav 8: 81–87

Gale GD, Anagnostaras SG, and Fanselow MS. 1996. Fornix lesions and olfactory feature positive and feature negative conditional discriminations in pavlovian contextual fear conditioning. Soc Neurosci Abst 22: 545.7

Garcia R. 2001. Stress, hippocampal plasticity, and spatial learning. Synapse 40: 180–183

Gibbs ME, and NG KT. 1984. Hormonal influence on the duration of short-term and intermediate stages of memory. Behav Brain Res 11: 109–116

Gold PE, and Van Buskirk R. 1976. Effects of posttrial hormone injections on memory processes. Horm Behav 7: 509–517

Hall G, Purves D, and Bonardi C. 1996. Contextual control of conditioned responding in rats with dorsal hippocampal lesions. Behav Neurosci 110(5): 933–945

Hesen W, and Joëls M. 1995. Corticosteroid-mediated modulation of carbachol responsiveness in CA1 pyramidal neurons: A voltage clamp analysis. Synapse 20: 299–304

Joëls M, and de Kloet ER. 1992. Control of neuronal excitability by corticosteroid hormones. TINS 15(1): 25–30

Johnston ANB, and Rose SPR. 1998. Isolation-stress-induced facilitation of passive avoidance memory in the day-old chick. Behav Neurosci 112(4): 929–936

Karst H, Wadman WJ, and Joëls M. 1994. Corticosteroid receptor-dependent modulation of calcium currents in rat hippocampal CA1 neurons. Brain Res 649: 234–242

Kerr DS, Huggett AM, and Abraham WC. 1994. Modulation of hippocampal long-term potentiation and long-term depression by corticosteroid receptor activation. Psychobiology 22(2): 123–133

Kim JJ, and Fanselow MS. 1992. Modality-specific retrograde amnesia of fear. Science 256: 675–677

Kim JJ, and Diamond DM. 2002. The stressed hippocampus, synaptic plasticity and lost memories. Nat Neurosci 3: 453–462

Kirschbaum C, Wolf OT, May M, Wippich W, and Hellhammer DH. 1996. Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. Life Sci 58: 1475–1483

Kóvacs GL, Telegdy G, and Lissák K. 1977. Dose-dependent action of corticosteroids on brain serotonin content and passive avoidance behavior. Horm Behav 8: 155–165

LeDoux JE. 1992. Brain mechanisms of emotion and emotional learning. Curr Opin Neurobiol 2: 191–197

Logue SF, Paylor R, and Wehner JM. 1997. Hippocampal lesions cause learning deficits in inbred mice in the Morris water maze and conditioned-fear task. Behav Neurosci 111(1): 104–113

Lorenzini CA, Baldi E, Bucherelli C, Sacchetti B, and Tassoni G. 1996. Role of dorsal hippocampus in acquisition, consolidation and retrieval of rat's passive avoidance response: A tetrodotoxin functional inactivation study. Brain Res 730: 32–39

Lupien SJ, and McEwen BS. 1997. The acute effects of corticosteroids on cognition: Integration of animal and human model studies. Brain Res Rev 24: 1–27

Lupien SJ, and Lepage M. 2001. Stress, memory, and the hippcampus: Can't live with it, can't live without it. Behav Brain Res 127: 137–158

Lupien SJ, Wilkinson CW, Briére S, Ménard C, Ng Ying Kin NMK, and Nair NPV. 2002. The modulatory effects of corticosteroids on cognition: Studies in young human population. Psychoneuroendocrinology 27: 401–416

Maren S, Aharonov G, and Fanselow MS. 1997. Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. Behav Brain Res 88: 261–274

Maren S, and Holt W. 2000. The hippocampus and contextual memory retrieval in Pavlovian conditioning. Behav Brain Res 110: 97–108

McCormick CM, McNamara M, Mukhopadhyay S, and Kelsey JE. 1997. Acute corticosterone replacement reinstates performance on spatial and nonspatial memory tasks 3 months after adrenalectomy despite degeneration in the dentate gyrus. Behav Neurosci 111(3): 518–531

McEwen BS, Weiss JM, and Schwartz LS. 1968. Selective retention of corticosterone by limbic structures in rat brain. Nature 220: 911–912

McEwen BS, Weiss JM, and Schwartz LS. 1969. Uptake of corticosterone by rat brain and its concentration by certain limbic structures. Brain Res 16: 227–241

McEwen BS, Conrad CD, Kuroda Y, Frankfurt M, Magariños AM, and McKittrick C. 1997. Prevention of stress-induced morphological and cognitive consequences. Eur Neuropsychopharm 7: S323–S328

McEwen BS. 2000. The neurobiology of stress: From serendipity to clinical relevance. Brain Res 886: 172–189

McGaugh JL. 1989. Dissociating learning and performance: Drug and hormone enhancement of memory storage. Brain Res Bull 23: 339–345

McGaugh JL. 2002. Memory consolidation and the amygdala: A systems perspective. TINS 25(9): 456–461

McGaugh JL, and Roozendaal B. 2002. Role of adrenal stress hormones in forming lasting memories in the brain. Curr Opin Neurobiol 12: 205–210

Michal EK. 1974. Dexamethasone inhibits multi-unit activity in the rat hippocampus. Brain Res 65: 180–183

Mondadori C, Ducret T, and Häusler A. 1992. Elevated corticosteroid levels block the memory-improving effects of nootropics and cholinomimetics. Psychopharmacology 108: 11–15

Monk CS, and Nelson CA. 2002. The effects of hydrocortisone on cognitive and neural function: A behavioral and event-related potential investigation. Neuropsychopharmacology 26: 505–519

Morris RGM, Garrud P, Rawlins JNP, and O'Keefe J. 1982. Place navigation impaired in rats with hippocampal lesions. Nature 297: 681–683

Morris RGM, Anderson E, Lynch GS, and Baudry M. 1986. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 319: 774–776

Moyer Jr. JR, Deyo RA, and Disterhof JF. 1990. Hippocampectomy disrupts trace eye-blink conditioning in rabbits. Behav Neurosci 104: 243–252

Newcomer JW, Craft S, Hershey T, Askins K, and Bardgett ME. 1994. Glucocorticoid-induced impairment in declarative memory performance in adult humans. J Neurosci 14(4): 2047–2053

Newcomer JW, Selke G, Melson AK, Hershey T, Craft S, Richards K, and Alderson AL. 1999. Decreased memory performance in healthy humans induced by stress-level cortisol treatment. Arch Gen Psychiat 56: 527–533

O'Keefe J, and Nadel L. 1978. The Hippocampus as a Cognitive Map. Clarendon Press, Oxford, England

Oitzl MS, and de Kloet ER. 1992. Selective corticosteroid antagonists modulate specific aspects of spatial orientation learning. Behav Neurosci 106(1): 62–71

Oitzl MS, de Kloet ER, Joëls M, Schmid W, and Cole TJ. 1997. Spatial learning deficits in mice with a targeted glucocorticoid receptor gene disruption. Eur J Neurosci 9: 2284–2296

Oitzl MS, Fluttert M, Sutanto W, and de Kloet ER. 1998. Continuous blockade of brain glucocorticoid receptors facilitates spatial learning and memory in rats. Eur J Neurosci 10: 3759–3766

Oitzl MS, Reichardt HM, Joëls M, and de Kloet ER. 2001. Point mutation in the mouse glucocorticoid receptor preventing DNA binding impairs spatial memory. PNAS 98(22): 12790–12795

Olton DS, Walker JA, and Gage FH. 1978. Hippocampal connections and spatial discrimination. Brain Res 139: 295–308

Pavlides C, Kimura A, Magariños AM, and McEwen BS. 1994. Type 1 adrenal steroid receptors prolong hippocampal long-term potentiation. NeuroReport 5: 2673–2677

Pavlides C, Kimura A, Magariños AM, and McEwen BS. 1995a. Hippocampal homosynaptic long-term depression / depotentiation induced by adrenal steroids. Neuroscience 68(2): 379–385

Pavlides C, Watanabe Y, Magariños AM, and McEwen BS. 1995b. Opposing roles of Type I and Type II adrenal steroid receptors in hippocampal long-term potentiation. Neuroscience 68(2): 387–394

Pavlides C, Ogawa S, Kimura A, and McEwen BS. 1996. Role of adrenal steroid mineralocorticoid and glucocorticoid receptors in long-term potentiation in the CA1 field of hippocampal slices. Brain Res 738: 229–235

Penick S, and Solomon PR. 1991. Hippocampus, context and conditioning. Behav Neurosci 105(5): 611–617

Pepin M-C, Pothier F, and Barden N. 1992. Impaired type II glucocorticoid-receptor function in mice bearing antisense RNA transgene. Nature 355: 725–728

Phillips RG, and LeDoux JE. 1992. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 106(2): 274–285

Phillips RG, and LeDoux JE. 1994. Lesions of the dorsal hippocampal formation interfere with background but not foreground contextual fear conditioning. Learn Mem 1: 34–44

Plihal W, and Born J. 1999. Memory consolidation in human sleep depends on inhibition of glucocorticoid release. NeuroReport 10: 2741–2747

Power AE, Roozendaal B, and McGaugh JL. 2000. Glucocorticoid enhancement of memory consolidation in the rat is blocked by muscarinic receptor antagonism in the basolateral amygdala. Eur J Neurosci 12: 3481–3487

Pugh CR, Fleshner M, and Rudy JW. 1997a. Type II glucocorticoid receptor antagonists impair contextual but not auditory-cue fear conditioning in juvenile rats. Neurobiol Learn Mem 67: 75–79

Pugh CR, Tremblay D, Fleshner M, and Rudy JW. 1997b. A selective role for corticosterone in contextual-fear conditioning. Behav Neurosci 111(3): 503–511

Quirarte GL, Roozendaal B, and McGaugh JL. 1997. Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala. PNAS 94(25): 14048–14053

Reul JMHM, and de Kloet ER. 1985. Two receptor systems for corticosterone in rat brain: Microdistribution and differential occupation. Endocrinology 117(6): 2505–2511

Reul JMHM, and de Kloet ER. 1986. Anatomical resolution of two types of corticosterone receptor sites in rat brain with *in vitro* autoradiography and computerized image analysis. J Steroid Biochem 24: 269–272

Reul JMHM, van den Bosch FR, and de Kloet ER. 1987. Differential response of type I and type II corticosteroid receptors to changes in plasma steroid level and circadian rhythmicity. Neuroendocrinology 45: 407–412

Richter-Levin G, and Akirav I. 2000. Amygdala-hippocampus dynamic interaction in relation to memory. Mol Neurobiol 22: 11–20

Roozendaal B, Bohus B, and McGaugh JL. 1996a. Dose-dependent suppression of adrenocortical activity with metyrapone: Effects on emotion and memory. Psychoneuroendocrinology 21(8): 681–693

Roozendaal B, and McGaugh JL. 1996. Amygdaloid nuclei lesions differentially affect glucocorticoid-induced memory enhancement in an inhibitory avoidance task. Neurobiol Learn Mem 65: 1–8

Roozendaal B, Portillo-Marquez G, and McGaugh JL. 1996b. Basolateral amygdala lesions block glucocorticoid-induced modulation of memory for spatial learning. Behav Neurosci 110(5): 1074–1083

Roozendaal B, and McGaugh JL. 1997a. Glucocorticoid receptor agonist and antagonist administration into the basolateral but not central amygdala modulates memory storage. Neurobiol Learn Mem 67: 176–179

Roozendaal B, and McGaugh JL. 1997b. Basolateral amygdala lesions block the memory-enhancing effect of glucocorticoid administration in the dorsal hippocampus of rats. Eur J Neurosci 9: 76–83

Roozendaal B, Quirarte GL, and McGaugh JL. 1997. Stress-activated hormonal systems and the regulation of memory storage. Ann NY Acad Sci 821: 247–258

Roozendaal B. 2000. Glucocorticoids and the regulation of memory consolidation. Psychoneuroendocrinology 25: 213–238

Roozendaal B, de Quervain DJ-F, Ferry B, Setlow B, and McGaugh JL. 2001. Basolateral amygdala-nucleus accumbens interactions in mediating glucocorticoid enhancement of memory consolidation. J Neurosci 21(7): 2518–2525

Roozendaal B. 2002. Stress and memory: Opposing effects of glucocorticoids on memory consolidation and memory retrieval. Neurobiol Learn Mem 78: 578–595

Roozendaal B, Quirarte GL, and McGaugh JL. 2002. Glucocorticoids interact with the basolateral amygdala b-adrenoceptor-cAMP / PKA system in influencing memory consolidation. Eur J Neurosci 15: 553–560

Roozendaal B, Griffith QK, Buranday J, de Quervain DJ-F, and McGaugh JL. 2003. The hippocampus mediates glucocorticoid-induced impairment of spatial memory retrieval: Dependence on the basolateral amygdala. PNAS 100: 1328–1333

Rousse I, Beaulieu S, Rowe W, Meaney MJ, Barden N, and Rochford J. 1997. Spatial memory in transgenic mice with impaired glucocorticoid receptor function. NeuroReport 8: 841–845

Rudy JW, and Sutherland RJ. 1995. Configural assocaition theory and the hippocampal formation: an appraisal and reconfiguration. Hippocampus 5: 375–389

Sahgal A. 1993. Passive avoidance procedures. Behavioral Neuroscience: A Practical Approach. Sahgal A. New York, Oxford University Press. Vol 1: 49–56

Sandi C, and Rose SPR. 1994. Corticosterone enhances long-term retention in one-day-old chicks trained in a weak passive avoidance learning paradigm. Brain Res 647: 106–112

Sandi C, Loscertales M, and Guaza C. 1997. Experience-dependent facilitating effect of corticosterone on spatial memory formation in the water maze. Eur J Neurosci 9: 637–642

Sandi C. 1998. The role and mechanisms of action of glucocorticoid involvement in memory storage. Neural Plast 6: 41–52

Sarrieau A, Dussaillant M, Agid F, Philibert D, Agid Y, and Rostene W. 1985. Autoradiographic localization of glucocorticoid and progesterone binding sites in the human post-mortem brain. J Steroid Biochem 25: 717–721

Squire LR. 1992. Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. Psychol Rev 99(2): 195–231

Steckler T, Weis C, Sauvage M, Mederer A, and Holsboer F. 1999. Disrupted allocentric but preserved egocentric spatial learning in transgenic mice with impaired glucocorticoid receptor function. Behav Brain Res 100: 77–89

Teyler TJ, and DiScenna P. 1987. Long-term potentiation. Ann Rev Neurosci 10: 131–161

Vaher P, Luine V, Gould E, and McEwen BS. 1994. Adrenalectomy impairs spatial memory in rats. Ann NY Acad Sci 746: 405–407

Van Eekelen JAM, Jiang W, de Kloet ER, and Bohn MC. 1988. Distribution of the mineralocorticoid and the glucocorticoid receptor mRNAs in the rat hippocampus. J Neurosci Res 21: 88–94

Veldhuis HD, Van Koppen C, Van Ittersum M, and de Kloet ER. 1982. Specificity of the adrenal steroid receptor system in rat hippocampus. Endocrinology 110: 2044–2051

Warembourg M. 1975. Radioautographic study of the rat brain after injection of (1,2–^{3}H)corticosterone. Brain Research 89: 61–70

Weiss C, Bouwmeester H, Power JM, and Disterhoft JF. 1999. Hippocampal lesions prevent trace eyeblink conditioning in the freely moving rat. Behav Brain Res 99: 123–132

Wolf OT, Convit A, McHugh PF, Kandil E, Thorn EL, De Santi S, McEwen BS, and de Leon MJ. 2001. Cortisol differentially affects memory in young and elderly men. Behav Neurosci 115: 1002–1011

Wolf OT. 2003. HPA axis and memory. Best Pract Res Clin Endocrinol Metab 17(2): 287–299

Xu L, Holscher C, Anwyl R, and Rowan MJ. 1998. Glucocorticoid receptor and protein/RNA synthesis-dependent mechanisms underlie the control of synaptic plasticity by stress. PNAS 95: 3204–3208

Yau JLW, Olsson T, Morris RGM, Meaney MJ, and Seckl JR. 1995. Glucocorticoids, hippocampal corticosteroid receptor gene expression and antidepressant treatment: Relationship with spatial learning in young and aged rats. Neuroscience 66(3): 571–581

Yau JLW, Noble J, and Seckl JR. 1999. Continuous blockade of brain mineralocorticoid receptors impairs spatial learning in rats. Neurosci Lett 277: 45–48

Yerkes RM, and Dodson JD. 1908. The relation of strength of stimulus to rapidity of habit-formation. J Comp Neurol Psychol 18: 459–482

Young SL, Bohenek DI, and Fanselow MS. 1994. NMDA processes mediate anterograde amnesia of contextual fear conditioning induced by hippocampal damage: immunization against amnesia by context preexposure. Behav Neurosci 108(1): 19–29

Zola SM, Squire LR, Teng E, Stefanacci L, Buffalo EA, and Clark RE. 2000. Impaired recognition memory in monkeys after damage limited to the hippocampal region. J Neurosci 20: 451–463

Zola-Morgan S, Squire LR, and Amaral DG. 1986. Human amnesia and the medial temporal region: Enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci 6: 2950–2967