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Memory enhancement of classical fear conditioning by post-training injections of corticosterone in rats

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Abstract

There is extensive evidence that post-training administration of the adrenocortical hormone corticosterone facilitates memory consolidation processes in a variety of contextual and spatial-dependent learning situations. The present experiments examine whether corticosterone can modulate memory of auditory-cue classical fear conditioning, a learning task that is not contingent on contextual or spatial representations. Male Sprague–Dawley rats received three pairings of a single-frequency auditory stimulus and footshock, followed immediately by a post-training subcutaneous injection of either corticosterone (1.0 or 3.0 mg/kg) or vehicle. Retention was tested 24 h later in a novel test chamber and suppression of ongoing motor behavior served as the measure of conditioned fear. Corticosterone dose-dependently facilitated suppression of motor activity during the 10-s presentation of the auditory cue. As corticosterone administration did not alter responding after unpaired presentations of tone and shock, tone alone, shock alone or absence of tone/shock, the findings indicated that corticosterone selectively facilitated memory of the tone–shock association. Furthermore, injections of corticosterone given 3 h after training did not alter motor activity during retention testing, demonstrating that corticosterone enhanced time-dependent memory consolidation processes. These findings provide evidence that corticosterone modulates the consolidation of memory for auditory-cue classical fear conditioning and are consistent with a wealth of data indicating that glucocorticoids can modulate a wide variety of emotionally influenced memories.

Keywords: Auditory fear conditioning; Emotion; Glucocorticoids; Learning; Memory consolidation; Stress hormone

1. Introduction

Considerable evidence supports a role of adrenocortical hormones in facilitating the consolidation of long-term memories of emotionally arousing experiences (for reviews: de Kloet, Oitzl, & Joëls, 1999; McGaugh & Roozendaal, 2002; Roozendaal, 2000, 2002). Most studies have examined glucocorticoid effects on memory consolidation in relation to hippocampal function in experiments using tasks that have a strong spatial and/or contextual component. Such a focus on the hippocampus as a primary target structure for glucocorticoid actions seems relevant, as the hippocampus contains a high density of adrenal steroid receptors (McEwen, Weiss, & Schwartz, 1969; Reul & de Kloet, 1985) and glucocorticoids are known to influence several forms of neuroplasticity in hippocampal neurons (Diamond, Bennett, Fleshner, & Rose, 1992; Pavlides, Watanabe, & McEwen, 1993; Xu, Anwyl, & Rowan, 1997). Removal of the adrenal glands has been reported to impair rats' performance in a spatial version of the water maze, an effect due to the loss of glucocorticoids rather than adrenal medullary hormones (Oitzl & de Kloet, 1992; Roozendaal, Portillo-Marquez, & McGaugh, 1996b). Furthermore, administration of a specific glucocorticoid receptor (GR) antagonist to rats immediately after water-maze spatial training produces retention impairment. In contrast, immediate post-training systemic or intra-hippocampal administration of glucocorticoids or a GR agonist dose-dependently enhances long-term memory consolidation of spatial/contextual learning in a

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variety of appetitively or aversively motivated tasks, including conditioned place preference, inhibitory avoidance and contextual fear conditioning (Conrad, Lupien, & McEwen, 1999b; Cordero & Sandi, 1998; Cottrell & Nakajima, 1977; Micheau, Destrade, & Soumireu-Mourat, 1984; Roozendaal & McGaugh, 1997a; Sandi & Rose, 1997).

Findings from our laboratory indicate that the basolateral complex of the amygdala (BLA), which has a moderate density of GRs, also participates in the influence of glucocorticoids on memory consolidation. Lesions or functional inactivation of the BLA block memory enhancement induced by post-training systemic injections of glucocorticoids (Quirarte, Roozendaal, & McGaugh, 1997; Roozendaal & McGaugh, 1996; Roozendaal et al., 1996b) and infusions of glucocorticoids or GR antagonists into the BLA modulate memory consolidation (Roozendaal & McGaugh, 1997b; Roozendaal, Quirarte, & McGaugh, 2002). Other findings indicate that the BLA interacts with the hippocampus in mediating stress and stress hormone effects on memory (Roozendaal, de Quervain, Ferry, Setlow, & McGaugh, 2001; Roozendaal & McGaugh, 1997a; Roozendaal, Nguyen, Power, & McGaugh, 1999) and neuroplasticity (Akirav & Richter-Levin, 1999; Ikegaya, Saito, & Abe, 1995; Kim, Lee, Han, & Packard, 2001). Therefore, it is not known whether glucocorticoids infused into the BLA strengthen only memory processes involving the hippocampus or whether glucocorticoid-induced activation of the BLA can also facilitate memory consolidation processes that are independent of the hippocampus.

Extensive evidence indicates that auditory fear conditioning critically depends on BLA activity and does not involve the hippocampus, or involves it only minimally (Davis, Rainnie, & Cassell, 1994; Kim, Rison, & Fanselow, 1993; Maren, Aharonov, & Fanselow, 1997; Phillips & LeDoux, 1992, 1994). In classical or Pavlovian fear conditioning, a neutral conditioning stimulus (e.g., a tone) acquires the capacity to elicit defensive responses after an association with a noxious unconditioned stimulus (e.g., a footshock). The role of glucocorticoids in modulating memory consolidation for auditory fear conditioning is unclear. Pretraining injections of the synthetic glucocorticoid dexamethasone have been reported to facilitate an aversively motivated version of classical fear conditioning in pigs, but to impair conditioning in an appetitively motivated task (Mormede & Dantzer, 1977). In other experiments, adrenalectomy or administration of a GR antagonist immediately after training failed to impair retention of auditory fear conditioning (Pugh, Fleshner, & Rudy, 1997a, 1997b). These studies suggest that glucocorticoid effects on memory consolidation may be limited to selectively strengthening the consolidation of hippocampus-dependent context representations. According to this view, auditory fear conditioning, unlike inhibitory avoidance or contextual fear conditioning, should not be susceptible to post-training intra-amygdala drug manipulations (Wilensky, Schafe, & LeDoux, 1999, 2000). However, recent findings indicate that dexamethasone, given to rats immediately after training, enhances conditioned responses obtained with either appetitive or aversive discrete-cue tasks, which clearly brings this view into question (Zorawski & Killcross, 2002).

To address this issue further, we investigated the effects of post-training glucocorticoid administration in modulating consolidation of memory for auditory-cue classical fear conditioning. Facilitation of memory would be consistent with involvement of the amygdala. Rats were given systemic injections of corticosterone immediately after auditory fear conditioning. Suppression of motor activity during an auditory stimulus was examined 24 h later in a novel test chamber and used as the measure of conditioned fear. To assess whether corticosterone selectively facilitated the association of the auditory stimulus and footshock, other groups of rats received corticosterone injections after unpaired presentations of tone and shock, tone alone, shock alone or absence of tone/shock. Furthermore, as it has been reported that corticosterone potentiates the conditioned fear response to acoustic stimuli when levels are elevated during retention testing (Corodimas, LeDoux, Gold, & Schulkin, 1994), one group of rats received delayed injections of corticosterone administered 3 h after auditory fear conditioning to examine possible residual effects of the post-training drug treatment on conditioned performance.

2. Materials and methods

2.1. Subjects

Adult male Sprague–Dawley rats ($n = 187$; weighing 305 ± 18 g at time of training) from Charles River Laboratories (Wilmington, MA) were individually housed in a temperature-controlled (22 °C) vivarium on a standard 12/12-h light/dark cycle (lights on at 7:00 h) and given food and water ad libitum. Rats were adapted to the vivarium for at least 1 week after arrival and were handled 3 min for two consecutive days before training. Training and testing were performed between 10:00 and 15:00 h at the rat's nadir of diurnal rhythm for corticosterone. All experimental procedures were performed in compliance with NIH guidelines and were approved by the University of California, Irvine's Institutional Animal Care and Use Committee.

2.2. Auditory-cue fear conditioning and testing

Rats were trained in a darkened room within a bare conditioning chamber equipped with two transparent Plexiglas walls along its length (Coulbourn Instruments,

Allentown, PA; Model #E10-16SC modified into a $51 \times 29 \times 25.5$ cm single chamber with no ceiling). A small houselight, turned away from the subject, provided ambient light. The floor of the chamber consisted of 4.8 mm diameter steel rods spaced 18.0 mm apart, wired to a precision-regulated bipolar shock generator (Coulbourn Model #E13-14) for the delivery of footshock. A calibrated open-field speaker and tone generator (Coulbourn Model #E69-20) delivered the auditory stimulus.

On the conditioning day, the rats were transported to the laboratory and placed within the conditioning chamber for an acclimation period of 5 min. For paired training, the subjects were given three trials consisting of a tone (6 kHz, 70 dB, 5 s) as the conditioning stimulus coterminating with a mild footshock (0.5 mA, 1 s, 40 Hz bipolar pulse) as the unconditioned stimulus (i.e., the interval between tone onset and shock onset was 4 s). The intertrial interval between tone–shock pairings was approximately 4 min. The animals were removed from the conditioning chamber immediately after the last tone–shock pairing and, after injection of corticosterone or vehicle, returned to their home cages. For unpaired training, the subjects were given a pseudorandom presentation of either a tone or shock (neither three consecutive tones nor three consecutive shocks) approximately every 2 min, receiving a total of three tones and three shocks of the same intensity and duration in the same total amount of time as the paired groups. For the other control groups (tone alone, shock alone and no tone/shock groups), the tone and/or shock generators were turned off. For the delayed-injection groups, all of the procedures for fear conditioning were identical to those described above for the paired training group, except that the injections were given 3 h after training.

After 24 h, retention was tested in a novel chamber that had different dimensions than the conditioning chamber ($29 \times 29 \times 24$ cm, Coulbourn Model #E10-10; the floor of the chamber consisted of 6.4 mm diameter steel rods spaced 17.4 mm apart) placed within a small soundproof isolation cabinet in a different experimental room to reduce contextual cues. The chamber contained small objects and toys (e.g., wooden blocks, rubber and fuzzy balls, plastic tubing, etc.) to facilitate the rat's natural tendency to explore and to further differentiate it from the conditioning chamber. The testing chamber was equipped with an infrared activity monitor (Coulbourn Model #E24-61), tone generator (Coulbourn Model #E69-20), calibrated open-field speaker, and a small houselight (turned away from the subject to provide ambient light). Approximately 3 min after the subject was placed in the test chamber, the rat was given a 10-s presentation of the conditioned tone (6 kHz, 70 dB). The Coulbourn *WinLinc* program recorded and quantified movement detection units (as defined by Coulbourn) in 1-s bins during the testing phase. Subjects that ceased their exploration of the chamber prior to the time of the tone presentation were eliminated from further analysis.

2.3. Drug and injection procedure

The adrenocortical hormone corticosterone (Sigma Chemicals, St. Louis, MO) was injected subcutaneously in the nape of the neck immediately after the last of the three tone–shock pairings at concentrations of 1.0 or 3.0 mg/kg in a volume of 2.0 ml/kg body weight. For all other groups (i.e., unpaired tone–shock, tone alone, shock alone, no tone/shock, and delayed injection), the rats were injected with only the higher dose of corticosterone (3.0 mg/kg, 1.0 mg/kg) or vehicle. The corticosterone solution was prepared by first dissolving it in 100% ethanol, then diluting in 0.9% saline to reach its appropriate concentration. The final concentration of ethanol was 5%. The vehicle solution contained 5% ethanol in saline only. These doses were selected on the basis of previous experiments (de Quervain, Roozendaal, & McGaugh, 1998). For each squad of subjects (which always consisted of six rats), individuals were randomly assigned to the experimental corticosterone or vehicle control group. Drug solutions were freshly prepared before each experiment.

2.4. Statistical analysis

The motion during the testing phase was quantified for time periods immediately before and during the tone presentation. For each subject, the mean movement for the 10 s immediately prior to the tone and the 10 s during the tone presentation was determined. To ascertain whether learning had occurred, paired t tests were used to compare the two time periods for each group. The rats were always trained in groups of 6, of which 3 were injected with vehicle and 3 with corticosterone (either 1.0 or 3.0 mg/kg). Therefore, each of the two doses of corticosterone used for the paired training experiment had a separate vehicle group. As these vehicle-injected groups did not differ in movement either before ($p = .78$, unpaired t test) or during tone presentation ($p = .68$), these two groups were collapsed for final analysis. One-way ANOVAs were used to determine differences between the three experimental groups both before and during the tone. Post hoc analysis with Fisher's PLSD was used to determine the significances between individual groups. Retention data for all other experimental groups were analyzed with unpaired t tests. A probability level of less than 0.05 was accepted as statistically significant.

3. Results

Fig. 1 illustrates the effects of immediate post-training administration of corticosterone on conditioned

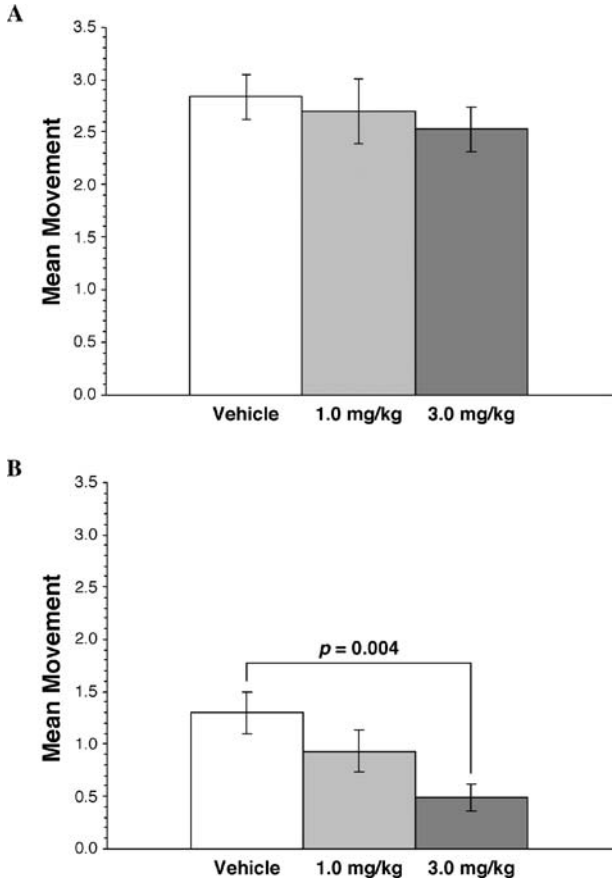

Fig. 1. Mean movement (±SEM) measured immediately before (A) or during (B) the 10-s presentation of the conditioned auditory stimulus of rats given systemic injections of either corticosterone (1.0 or 3.0 mg/kg) or vehicle immediately after the last of three tone–shock pairings. The higher dose of corticosterone induced a significant suppression of motor activity during the presentation of the tone as compared to vehicle (vehicle, $n = 24$; 1.0 mg/kg, $n = 10$; and 3.0 mg/kg, $n = 14$).

suppression of motor activity. The 3, 1 mg/kg, and vehicle groups did not differ in mean movement during the 10-s period immediately prior to the presentation of the conditioned stimulus ($F_{2,45} = 0.46$, $p = .64$; Fig. 1A). Corticosterone induced a dose-dependent enhancement of conditioned suppression during the 10-s presentation of the tone ($F_{2,45} = 4.58$, $p = .015$; Fig. 1B). Post hoc analysis with Fisher's PLSD revealed that the higher dose of corticosterone (3.0 mg/kg) produced a significant enhancement of suppression of motor activity compared to the vehicle group ($p = .004$). The lower dose of corticosterone (1.0 mg/kg) did not induce a significant enhancement of suppression ($p = .23$). Furthermore, all three treatment groups showed a significant reduction in movement during tone presentation compared to the time period prior to the conditioned stimulus presentation (paired t tests: all $p \leqslant .0002$), demonstrating that all three groups had acquired the task. Corticosterone (3.0 mg/kg) administration did not affect the mean movement, either before or during tone presentation, of rats given unpaired presentations of tone and shock, tone alone, shock alone or absence of tone/shock compared to their corresponding vehicle groups (for all groups: $p > .05$, unpaired t tests; Table 1). Furthermore, there was no significant change in the mean movement in each control group between the before and during tone presentation time periods (for all groups: $p > .05$, paired t tests). These findings indicate that suppression of motor activity to the conditioned stimulus presentation was seen only in rats given paired presentations of tone and shock during conditioning and reflect an association between the auditory stimulus and the footshock.

To examine whether the effects of corticosterone on associative learning were due to time-dependent effects on memory consolidation, other groups of rats received delayed injections of corticosterone (3.0 mg/kg) or vehicle 3 h after the last tone–shock pairing. As shown in Table 1, delayed application of corticosterone did not produce an enhancement of the conditioned responding compared to vehicle-injected rats ($p = .74$). Importantly, subjects injected with vehicle 3 h after training displayed significantly less conditioned suppression than rats

Table 1
Movement before and during conditioned tone presentation

Group[a]	Time period	Vehicle	Corticosterone	p
Unpaired	Before	2.49 ± 0.22[b]	2.76 ± 0.22	.39
	During	2.94 ± 0.26	3.32 ± 0.31	.36
Tone alone	Before	3.31 ± 0.33	3.48 ± 0.25	.67
	During	2.94 ± 0.25	3.38 ± 0.25	.23
Shock alone	Before	2.60 ± 0.27	2.46 ± 0.13	.63
	During	2.85 ± 0.21	2.51 ± 0.18	.23
No tone/shock	Before	2.95 ± 0.38	3.18 ± 0.20	.59
	During	3.04 ± 0.49	3.05 ± 0.35	.99
Delayed	Before	3.03 ± 0.32	2.70 ± 0.31	.46
	During	2.38 ± 0.38	2.22 ± 0.29	.74

[a] $n = 12$ rats per group except for unpaired vehicle group ($n = 13$) and shock alone vehicle group ($n = 11$).
[b] Mean ± standard error.

injected with vehicle immediately after training ($p = .04$, unpaired t test). To examine whether this vehicle effect on conditioning may be due to a facilitating effect of the injection procedure itself, two additional groups of rats were trained and given either a systemic injection of vehicle immediately after training ($n = 9$) or no injection ($n = 10$). The findings indicated that rats injected with vehicle displayed significantly less movement during the 24-h retention test than rats that were not injected ($p = .002$; data not shown), suggesting that emotional arousal associated with the immediate post-training injection procedure had an additive facilitating effect on fear conditioning.

4. Discussion

The main finding of the present study is that the adrenocortical hormone corticosterone administered to rats immediately after the last of three pairings of a tone with footshock enhanced retention on a 24-h test, as indicated by a facilitation of suppression of movement during the presentation of the tone in a novel test chamber. Conditioning was specific to the pairing of the tone and footshock, as the tone did not elicit suppression of movement on the retention test in vehicle control subjects that had received unpaired presentations of tone and shock, tone alone or shock alone on the training session. Furthermore, corticosterone administration did not affect retention performance in these three groups. The use of post-training administration of corticosterone suggests an effect on memory consolidation not confounded by possible effects on attentional, motivational or sensory–perceptual mechanisms at the time of conditioning or testing. As corticosterone injections administered 3 h after the tone–shock pairing did not affect performance on the retention test, the findings provide additional evidence that the stress hormone enhanced time-dependent processes underlying the consolidation of memory for the association between the tone and shock.

The effects of corticosterone on conditioned suppression of movement were dose dependent. The higher dose of 3.0 mg/kg of corticosterone enhanced memory consolidation, but the lower dose (1.0 mg/kg) was ineffective. Previous studies have shown that systemic injection of this higher dose induces plasma corticosterone levels that reflect stress levels (≈30–40 μg/dl; de Quervain et al., 1998). Systemic administration of the 1.0 mg/kg dose of corticosterone only produces modestly elevated plasma corticosterone levels compared to baseline (≈10–15 μg/dl). Corticosterone can bind to two subtypes of adrenal steroid receptors that differ in their affinity for corticosterone: the low-affinity GRs that become activated during high levels of circulating glucocorticoids and the high-affinity mineralocorticoid receptors that are almost saturated during basal levels of corticosterone (Reul & de Kloet, 1985). The present findings fit well with extensive evidence indicating that the effects of corticosterone on memory consolidation are selectively mediated by an activation of GRs (Oitzl & de Kloet, 1992; Oitzl, Reichardt, Joëls, & de Kloet, 2001; Roozendaal et al., 1996b; Sandi & Rose, 1994). These results are also consistent with previous findings indicating that corticosterone, as well as drugs that selectively activate GRs, enhance memory consolidation for several types of training, including discrimination learning, inhibitory avoidance, contextual fear conditioning, water-maze spatial training, and appetitive conditioning (Cordero & Sandi, 1998; Flood et al., 1978; Micheau et al., 1984; Roozendaal & McGaugh, 1996; Sandi & Rose, 1997).

As the hippocampus is densely populated with GRs (McEwen et al., 1969; Reul & de Kloet, 1985), it is reasonable to assume that systemic administration of glucocorticoid agonists affect memory, at least in part, by activating these receptors. Thus, it would be expected that glucocorticoids affect memory for spatial/contextual learning tasks. However, the present findings provide strong evidence for the view that glucocorticoid effects on memory consolidation are not restricted to facilitating the construction of context representations. This view is congruent with the finding that post-training administration of the synthetic glucocorticoid dexamethasone enhanced memory for both aversively as well as appetitively motivated discrete-cue conditioning (Zorawski & Killcross, 2002). Furthermore, Conrad, LeDoux, Magariños, and McEwen (1999a) found that repeated restraint stress applied for 21 days facilitated subsequent contextual and auditory fear conditioning, and that the enhancing effect depended on increased glucocorticoid actions at the time of conditioning (Conrad, Mauldin, & Hobbs, 2001). This facilitation of fear conditioning was found despite stress-induced atrophy of the CA3 field of hippocampus. As the hippocampus does not appear to play a major role in auditory fear conditioning, it seems unlikely that adrenal steroid receptors in the hippocampus were responsible for mediating such effects. In previous studies, we have found that glucocorticoids also act in other areas of the brain, including the BLA, in influencing memory consolidation for emotionally arousing experiences (Roozendaal & McGaugh, 1996, 1997b; Roozendaal et al., 2002). As there is extensive evidence that the BLA is implicated in tone–shock Pavlovian conditioning (Davis et al., 1994; Phillips & LeDoux, 1992; Wilensky et al., 1999, 2000), corticosterone-induced enhancement of auditory fear conditioning may be attributed to post-training activation of GRs located in the BLA or, alternatively, in brain regions that interact with the BLA during the consolidation of fear memory.

In sharp contrast with the view that glucocorticoids influence memory for auditory fear conditioning, Pugh et al. (1997a) and Pugh et al. (1997b) found that adrenalectomy or post-training administration of a GR antagonist failed to impair conditioned freezing induced by auditory fear conditioning. This disparity may reflect differences in the experimental conditions. For example, these studies used freezing as measure of conditioned fear whereas Zorawski and Killcross (2002) assessed suppression of lever pressing and the present study measured reduction of exploratory motor behavior in an environment enriched with toys. Additionally, the present study and that of Zorawski and Killcross (2002) examined conditioned responding during a brief time of cue presentation (i.e., 10 and 30 s, respectively), whereas those previous studies measured freezing during a 3 min auditory stimulus. It is possible that glucocorticoids induce subtle changes in conditioned responding that are diluted by extinction during a long test trial. In support of this view, a second-by-second analysis of the present findings indicated that the effect of corticosterone on the suppression of motor activity was most pronounced during the initial seconds after tone onset (data not shown). Finally, it may be that glucocorticoid-induced enhancement of fear conditioning is easier to achieve than memory impairment. Although the present study revealed that glucocorticoids enhance conditioned fear after tone–shock pairings, the findings, and those of previous studies, have not determined the specific information presented during training that is enhanced. It is possible that glucocorticoids may facilitate memory of the specific features of the conditioned stimulus (e.g., frequency, amplitude, pitch or duration) paired with the unconditioned stimulus rather than the association of tone and footshock per se. Similarly, glucocorticoids may enhance memory of the specific features of the unconditioned stimulus. Thus, after adrenocortical blockade induced by adrenalectomy or a GR antagonist, rats may remember that a tone predicts a threatening situation, but their memory for specific characteristics of either the conditioned or unconditioned stimulus may be impaired (cf. Hendersen, 1985). This interpretation is in accord with several findings from human studies demonstrating that learning during emotionally arousing experiences (often associated with elevated circulating levels of glucocorticoids) increases memory of the details of experiences (Buchanan & Lovallo, 2001; Cahill & van Stegeren, 2003; Heuer & Reisberg, 1990). Additionally, the evidence that the hippocampus is involved in coding temporal and pitch information in memory for auditory stimuli (Sakurai, 2002) suggests that glucocorticoids may influence auditory fear conditioning, at least in part, through influences involving the hippocampus.

The results reported here add to the evidence that adrenal stress hormones influence memory consolidation in various animal and human memory tasks. There is now extensive evidence that both the adrenomedullary hormone epinephrine and the adrenocortical hormone corticosterone (or cortisol) enhance memory when administered either shortly before or immediately after training (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003; Buchanan & Lovallo, 2001; Cahill & Alkire, 2003; Gold & Van Buskirk, 1975; McGaugh & Roozendaal, 2002). Additionally, memory for many kinds of training is impaired after adrenalectomy or post-training administration of adrenergic and glucocorticoid receptor antagonists (Liang, Chen, & Huang, 1995; Liang, Juler, & McGaugh, 1986; Oitzl & de Kloet, 1992; Roozendaal et al., 1996b), and the facilitating effects of stress exposure on memory consolidation are blocked by suppression of corticosterone synthesis with metyrapone (Liu, Tsuji, Takeda, Takada, & Matsumiya, 1999; Roozendaal, Carmi, & McGaugh, 1996a). Such evidence supports the view that endogenously released stress hormones normally play a role in modulating the consolidation of memory for experiences that induce their release (McGaugh & Roozendaal, 2002; Roozendaal, 2000).

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