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# Basolateral amygdala noradrenergic activity mediates corticosterone-induced enhancement of auditory fear conditioning

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**Abstract**

The present experiment examined whether posttraining noradrenergic activity within the basolateral complex of the amygdala (BLA) is required for mediating the facilitating effects of acutely administered glucocorticoids on memory for auditory-cue classical fear conditioning. Male Sprague–Dawley rats received five pairings of a single-frequency auditory stimulus and footshock, followed immediately by bilateral infusions of the $\beta_1$-adrenoceptor antagonist atenolol (0.5 μg in 0.2 μl) or saline into the BLA together with a subcutaneous injection of either corticosterone (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 facilitated memory as assessed by suppression of motor activity during the 10-s presentation of the auditory stimulus and intra-BLA administration of atenolol selectively blocked this corticosterone-induced memory enhancement. These findings provide evidence that, as found with other emotionally arousing tasks, the enhancing effects of corticosterone on memory consolidation of auditory-cue fear conditioning require posttraining noradrenergic activity within the BLA.


*Keywords:* Emotion; Glucocorticoids; Memory consolidation; Norepinephrine; Rat

## 1. Introduction

Glucocorticoids, released from the adrenal cortex during stressful situations, are known to facilitate the consolidation of long-term memories (de Kloet, Oitzl, & Joëls, 1999; McGaugh & Roozendaal, 2002; Roozendaal, 2000). Although most studies have investigated the memory-modulatory effects of glucocorticoids or specific glucocorticoid receptor (GR) agonists in emotionally arousing learning tasks that have a strong spatial and/or contextual component (Conrad, Lupien, & McEwen, 1999; Cordero & Sandi, 1998; Micheau, Destrade, & Soumireu-Mourat, 1985; Oitzl & de Kloet, 1992; Roozendaal & McGaugh, 1997b), recent findings indicate that they also enhance memory consolidation of other types of emotionally arousing learning experiences, including object recognition in a novel environment (Okuda, Roozendaal, & McGaugh, 2004). In contrast, glucocorticoid administration appears not to influence memory consolidation for less arousing or neutral information (Buchanan & Lovallo, 2001; Okuda et al., 2004). Extensive evidence indicates that glucocorticoids require a co-activation of noradrenergic mechanisms within the basolateral complex of the amygdala (BLA, consisting of the lateral, basal, and accessory basal nuclei) in modulating memory consolidation (Quirarte, Roozendaal, & McGaugh, 1997; Roozendaal, Nguyen, Power, & McGaugh, 1999; Roozendaal, Quirarte, & McGaugh, 2002). As emotionally arousing stimulation induces long-lasting activation of the BLA (Pelletier, Likhtik, Filali, & Paré, 2005), involving the release of norepinephrine (McIntyre, Hatfield, & McGaugh, 2002), we previously suggested that such a dependence of glucocorticoids on training-induced noradrenergic activity may underlie the selective involvement of glucocorticoids in modulating the consolidation of emotionally arousing information (Roozendaal, Okuda, de Quervain, & McGaugh, 2006).

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The present experiment investigated whether posttraining noradrenergic activity in the BLA is required for mediating the enhancing effects of glucocorticoid administration on memory for auditory-cue classical fear conditioning. In classical or Pavlovian fear conditioning, an emotionally neutral stimulus, such as a tone, acquires the capacity to elicit defensive responses after association with a noxious stimulus, such as a footshock. Some findings have suggested that auditory-cue fear conditioning may differ from other emotionally arousing tasks in that memory for tone–shock pairing may be formed instantly in the lateral subdivision of the BLA (LeDoux, 2000). As a consequence, although pretraining manipulations of BLA activity may either enhance or impair fear learning, memory of auditory-cue fear conditioning should not be susceptible to posttraining systemic or intra-BLA drug manipulations (Debiec & LeDoux, 2004; Wilensky, Schafe, & LeDoux, 1999, 2000). However, recent findings indicate that posttraining administration of glucocorticoids also enhances memory consolidation of auditory-cue fear conditioning (Hui et al., 2004; Zorawski & Killcross, 2002). Additionally, glucocorticoids enhance Pavlovian appetitive discrete-cue conditioning (Zorawski & Killcross, 2002). In the present study, immediately after pairing of a single-frequency auditory stimulus with footshock, rats received bilateral infusions of the selective $\beta_1$-adrenoceptor antagonist atenolol into the BLA together with systemic injections of corticosterone. Suppression of motor activity to the auditory stimulus was examined 24 h later in a novel test chamber and used as the measure of memory of the fear conditioning. This measure was used because it enables assessment of rapid changes in behavior in response to the onset of the conditioned stimulus. Previously, in an experiment using this measure of conditioning we reported that corticosterone selectively facilitated conditioned responding after paired presentations of the auditory stimulus and footshock without enhancing the behavioral response of rats given unpaired presentations of tone and shock (Hui et al., 2004).

## 2. Materials and methods

### 2.1. Subjects

Young adult male Sprague–Dawley rats (weighing 280–320 g at time of surgery) from Charles River Breeding 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 07:00 h) and given food and water ad libitum. Training and testing were performed between 10:00 and 15:00 h, at the rat's nadir of the 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. Surgery and cannulae implantation

Animals were adapted to the vivarium for at least 1 week before surgery. For surgery, they were anesthetized with sodium pentobarbital (50 mg/kg of body weight, i.p.), given atropine sulfate (0.4 mg/kg, i.p.) to maintain respiration, and were subsequently injected with 3.0 ml of saline to facilitate clearance of these drugs and prevent dehydration. The skull was positioned in a stereotaxic frame (David Kopf Instruments, Tujunga, CA) and two stainless-steel guide cannulae (15 mm; 23 gauge; Small Parts Inc., Miami Lakes, FL) were implanted with the cannula tips 2.0 mm above the BLA [coordinates: anteroposterior, −2.8 mm from bregma; mediolateral, ±5.0 mm from midline; dorsoventral, −6.5 mm from skull surface, with the incisor bar 3.3 mm below the interaural line (Paxinos & Watson, 1997)]. The cannulae were affixed to the skull with two anchoring screws and dental cement. Stylets (15-mm long 00-insect dissection pins) inserted into each cannula to maintain patency were removed only for the infusion of drugs. After surgery, the rats were allowed to recover a minimum of 7 days before initiation of training and were handled 3 times for 1 min each during this recovery period to habituate them to the drug administration procedures.

### 2.3. Auditory-cue fear conditioning and testing

Rats were trained in a conditioning chamber (Coulbourn Instruments, Allentown, PA; model #E10-16SC modified into a 51 cm × 29 cm × 25.5 cm single chamber) within a larger acoustically dampened isolation chamber (Industrial Acoustics Co., New York, NY). 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 shock generator (Coulbourn model #E13-14) for the delivery of scrambled footshock. A calibrated open-field speaker and tone generator (Coulbourn model #E69-20) delivered the auditory stimulus.

On the day of conditioning, the rats were transported to the laboratory 2 h before training and, subsequently, placed within the conditioning chamber for an acclimation period of 4 min. For conditioning, the subjects were given five trials consisting of a tone (6 kHz, 70 dB, 5 s) as the conditioned stimulus, co-terminating with a mild footshock (0.6 mA, 1 s, 40 Hz bipolar pulse) as the unconditioned stimulus (i.e., the interval between tone onset and shock onset was 4 s). We selected this specific footshock intensity such that control animals would show poor conditioned suppression at a 24-h retention test and, therefore, posttraining drug administration could induce memory enhancement. The intertrial interval was approximately 2 min. The animals were removed from the conditioning chamber immediately after the last tone–shock pairing and, after drug treatment, returned to their home cages. After drug administration, the rats remained in the laboratory for 1 h before being returned to the vivarium.

After 24 h, retention was tested in a novel chamber that had different dimensions than the conditioning chamber (29 cm × 29 cm × 24 cm, Coulbourn model #E10-10), placed within an isolation cubicle with high attenuation acoustical decoupling liner (Coulbourn model #H10-24A). The floor of the chamber consisted of 6.4-mm diameter steel rods spaced 17.4 mm apart. 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 test 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 rat was placed into 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 for 10 s both before and during the tone. Two subjects that ceased their exploration of the chamber prior to tone presentation, one from the vehicle–saline group and one from the corticosterone–saline group, were eliminated from further analysis because assessment of to-be-elicited reduction of movement could not be determined in a background of no movement.

### 2.4. Drugs and infusion procedure

Immediately after the last tone–shock pairing, rats were taken to an adjacent room for drug treatment. The adrenocortical hormone

corticosterone (Sigma–Aldrich Co., St. Louis, MO; 3.0 mg/kg) was injected subcutaneously in the nape of the neck in a volume of 2.0 ml/kg body weight. Corticosterone was first dissolved in 100% ethanol and then diluted 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. Bilateral infusions of the selective $\beta_1$-adrenoceptor antagonist atenolol (Sigma; 0.5 μg dissolved in saline) or an equivalent volume of saline were given into the BLA by using a 30-gauge infusion needle connected to a 10-μl Hamilton microsyringe with polyethylene (PE-20) tubing. The infusion needles protruded 2.0 mm beyond the tip of the cannulae and a 0.2-μl injection volume per hemisphere was infused over a period of 25 s by an automated syringe pump (Sage Instruments, Boston, MA). The infusion needles were retained within the cannulae for an additional 20 s after drug infusion to maximize diffusion and to prevent backflow of drug into the cannulae. Drug solutions were freshly prepared before each experiment.

### 2.5. Histology

The rats were anesthetized with an overdose of sodium pentobarbital (Sigma) and perfused intracardially with 0.9% saline. After decapitation, the brains were removed and immersed in a 4% formaldehyde solution (wt/vol). At least 24 h before sectioning, the brains were transferred to a 25% sucrose (wt/vol) solution in saline for cryoprotection. Coronal slices of 50 μm were cut on a freezing microtome, mounted on gelatin-coated slides, and stained with thionin. The sections were examined under a light microscope and the location of infusion needle tips within the BLA was determined according to the standardized atlas plates of Paxinos and Watson (1997) by an observer blind to drug treatment condition. Rats with infusion needle placements outside the BLA, or with extensive tissue damage at the infusion needle tip, were excluded from analysis. Fig. 1A shows a representative photomicrograph of an infusion needle tip in the BLA and Fig. 1B summarizes infusion needle tip placements of 30 randomly selected animals included in the analysis. There were no differences between the groups in cannulae locations within the BLA.

### 2.6. Statistical analysis

For each subject, movement during the testing phase was quantified for the time periods immediately before and during the tone presentation. Mean movement for the 10 s immediately prior to the tone and the 10 s during the tone presentation was analyzed with two-way ANOVAs with intra-BLA atenolol treatment (2 levels) and systemic corticosterone administration (2 levels) both as between-subject variables. Fisher's post hoc tests were used to determine the source of the detected significance in the ANOVAs. To ascertain whether learning had occurred, paired t-tests were used to compare the two time periods for each group. A probability level of $<.05$ was accepted as statistically significant.

## 3. Results

This experiment investigated whether glucocorticoid effects on memory consolidation for auditory-cue fear conditioning require concurrent noradrenergic activity in the BLA. As shown in Fig. 2, infusions of the $\beta_1$-adrenoceptor antagonist atenolol administered into the BLA immediately after training blocked the facilitating effect of systemic corticosterone injections on conditioned suppression of motor activity. Two-way ANOVA for mean movement during the 10-s time period immediately preceding tone presentation revealed no

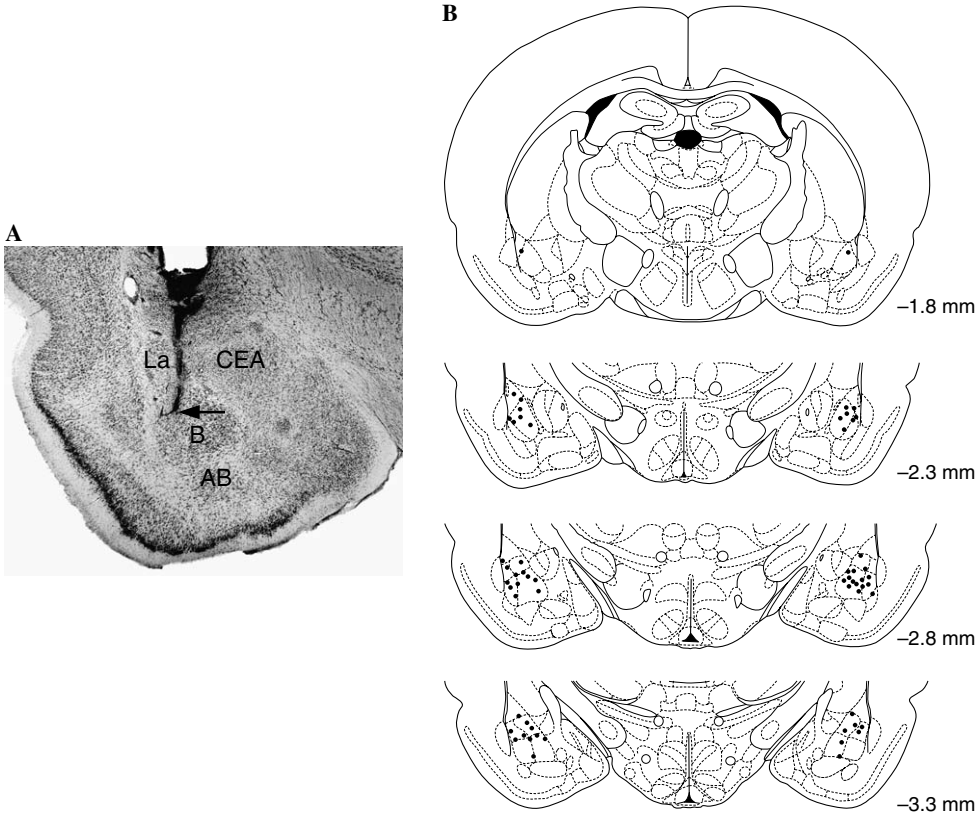


Fig. 1. Cannula placement in the BLA. (A) Representative photomicrograph illustrating the placement of a cannula and needle tip in the BLA. Arrow points to the needle tip. B, basal; AB, accessory basal; CEA, central amygdala; La, lateral amygdala. (B) Infusion needle tips in the BLA of 30 randomly selected rats included in the experiment. Adapted from Paxinos and Watson (1997).

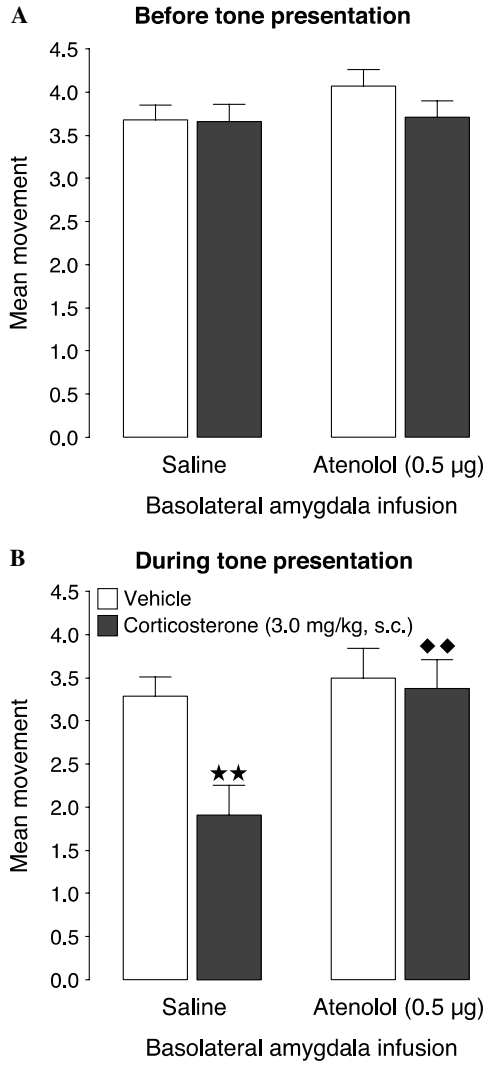


Fig. 2. Effect of immediate posttraining infusions of the $\beta_1$-adrenoceptor antagonist atenolol (0.5 µg in 0.2 µl) or saline into the BLA combined with systemic injections of corticosterone (3.0 mg/kg) or vehicle on auditory-cue fear conditioning tested 24 h later in a new environment. Data represent mean movement (±*SEM*) measured immediately before or during the 10-s presentation of the conditioned auditory stimulus. (A) Corticosterone or atenolol treatment did not alter movement during the 10-s time period immediately preceding conditioned stimulus presentation. (B) Corticosterone induced a significant suppression of motor activity during the presentation of the tone as compared to vehicle and this facilitation was selectively blocked by atenolol infusions into the BLA. ★★$p < .01$ compared with the corresponding vehicle group; ◆◆$p < .01$ compared with the corticosterone group (vehicle–saline: $n = 18$; corticosterone–saline: $n = 14$; vehicle–atenolol: $n = 9$; corticosterone–atenolol: $n = 12$).

significant corticosterone ($F_{1,49} = 0.95$, $p = .33$) or atenolol effects ($F_{1,49} = 1.21$, $p = .28$) or interaction between these factors ($F_{1,49} = 0.71$, $p = .40$; Fig. 2A), indicating that the drug treatment did not induce generalized fear or non-specific changes in motor activity 24 h later. However, two-way ANOVA for mean movement during the 10-s tone presentation revealed a significant corticosterone effect ($F_{1,49} = 5.53$, $p = .02$), a significant atenolol effect ($F_{1,49} = 7.21$, $p = .01$) and a significant interaction between both factors ($F_{1,49} = 3.93$, $p = .05$; Fig. 2B). In rats that were administered saline into the BLA, posttraining injections of corticosterone induced a significant reduction of movement during conditioned tone presentation compared to rats treated with vehicle ($p = .002$), indicating that corticosterone enhanced memory of auditory fear conditioning. Infusion of atenolol into the BLA alone did not significantly alter conditioned responding, but the atenolol administration blocked the corticosterone effect. The corticosterone–atenolol group did not differ significantly in movement scores during tone presentation from the vehicle–saline ($p = .79$) or vehicle–atenolol groups ($p = .81$). Additionally, comparison of mean movement in the period during tone presentation with that immediately before tone presentation revealed that, as was expected because of the mild footshock used in training, the vehicle–saline group only showed a weak suppression of movement that did not differ significantly from motor activity before tone presentation ($p = .10$). However, rats that had received corticosterone systemically together with saline infusions into the BLA showed a significant suppression of movement compared with the time period before tone presentation ($p < .0001$), indicating strong memory. In rats treated with atenolol in the BLA and either vehicle or corticosterone systemically, movement during tone presentation did not differ significantly from that before tone presentation (atenolol–vehicle: $p = .12$; atenolol–corticosterone: $p = .25$), indicating weak memory and thus that atenolol had blocked the facilitating effect of corticosterone on auditory fear memory consolidation.

## 4. Discussion

The main finding of the present study is that posttraining infusions of the $\beta_1$-adrenoceptor antagonist atenolol into the BLA blocked the enhancing effect of systemically administered corticosterone on memory for auditory-cue fear conditioning. These findings are consistent with previous evidence indicating that a β-adrenoceptor antagonist administered into the BLA after training blocked the enhancing effects of systemically administered glucocorticoids on memory for other kinds of emotionally arousing training (Quirarte et al., 1997; Roozendaal et al., 2002). Furthermore, the memory-modulatory effects of many other hormones and neurotransmitters have been shown to depend on an intact noradrenergic neurotransmission within the BLA (McGaugh, 2004). As norepinephrine is released into the BLA during emotionally arousing conditions (Galvez, Mesches, & McGaugh, 1996; McIntyre et al., 2002), understanding the interaction of glucocorticoids with noradrenergic mechanisms within the BLA, and their role in memory modulation, provides insight into how emotional arousal influences the formation of lasting memories.

The finding that the adrenocortical hormone corticosterone administered to rats immediately after pairing of tone with footshock enhanced retention on a 24 h test is consistent with previous reports on this task (Hui et al., 2004; Zorawski & Killcross, 2002) and with the evidence that posttraining injections of the synthetic glucocorticoid dexamethasone enhanced memory of appetitively

motivated discrete-cue Pavlovian conditioning (Zorawski & Killcross, 2002). Importantly, the Zorawski and Kilcross study also used suppression of responding as a measure of conditioned fear. Moreover, early studies reported comparable effects of pretraining manipulation of glucocorticoid levels on memory of either aversive or appetitive discrete-cue conditioning (Hennessy, Smotherman, & Levine, 1976; Mormede & Dantzer, 1977). The present findings cannot be attributed to generalized fear or non-specific changes in motor activity during testing in view of our previous finding that corticosterone administration selectively enhanced conditioned responding of rats that had received paired presentations of tone and footshock and did not affect retention performance of animals given unpaired presentations of tone and shock, or shock or tone alone (Hui et al., 2004). Moreover, as we previously found that corticosterone injections administered immediately, but not 3 h, after the tone–shock pairing enhanced performance on the retention test, the findings provide additional evidence that the stress hormone enhanced time-dependent processes underlying the consolidation of memory of the training. In the present experiment we obtained corticosterone-induced enhancement of retention under conditions that did not result in significant evidence of retention in vehicle controls, an effect seen in our previous study of corticosterone-induced enhancement of object recognition memory (Okuda et al., 2004). 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 emotionally arousing training experiences, including discrimination learning, inhibitory avoidance, contextual fear conditioning, water-maze spatial training, object recognition, and appetitive conditioning (Cordero & Sandi, 1998; Flood et al., 1978; Micheau et al., 1985; Okuda et al., 2004; Roozendaal & McGaugh, 1996).

In previous studies, we have found that glucocorticoids can act directly in the BLA in influencing memory consolidation (Roozendaal & McGaugh, 1997b; Roozendaal et al., 2002). Additionally, either lesions of or β-adrenoceptor antagonist infusions into the BLA block the memory-modulatory effects of glucocorticoids administered into other brain regions (Roozendaal & McGaugh, 1997a; Roozendaal, Nguyen, et al., 1999). In contrast, lesions of the adjacent central nucleus or infusions of a β-adrenoceptor antagonist into the central nucleus do not prevent glucocorticoid modulation of memory consolidation (Quirarte et al., 1997; Roozendaal & McGaugh, 1996). As there is extensive evidence that the BLA is the amygdala nucleus that is selectively implicated in tone–shock Pavlovian conditioning (Davis, Rainnie, & Cassell, 1994; Phillips & LeDoux, 1992; Wilensky et al., 1999, 2000), corticosterone-induced enhancement of auditory-cue fear conditioning may be attributed to posttraining activation of GRs located in the BLA or, alternatively, in brain regions that interact with the BLA during fear memory consolidation. Our current finding that a β-adrenoceptor antagonist administered into the BLA after training blocked the enhancing effect of systemically administered corticosterone on memory consolidation of auditory-cue fear conditioning supports the view that glucocorticoids require posttraining noradrenergic activation within the BLA in modulating memory consolidation of auditory fear conditioning. Numerous studies have shown that glucocorticoids are intimately linked with noradrenergic mechanisms and permissively increase noradrenergic neurotransmission in the brain during emotional arousal (McEwen, 1987; Roozendaal et al., 2002; Stone, McEwen, Herrera, & Carr, 1987). Our previous work examining glucocorticoid interactions with the noradrenergic system in the BLA in influencing memory consolidation of inhibitory avoidance indicated that glucocorticoids increase the efficacy of noradrenergic stimulation on memory consolidation via interactions with the intracellular cAMP-dependent protein kinase signaling cascade (Roozendaal et al., 2002). Recent findings indicate that GRs are also located on postsynaptic membranes in BLA principal neurons (Johnson, Farb, Morrison, McEwen, & LeDoux, 2005), supporting the view that glucocorticoids may influence memory consolidation through a mechanism other than modulation of gene transcription. However, glucocorticoids can also enhance noradrenergic neurotransmission by acting on GRs in brainstem noradrenergic cell groups that project to the BLA (Roozendaal, Williams, & McGaugh, 1999).

A wealth of data indicates that noradrenergic activation within the BLA plays a critical role in memory modulation on a wide variety of emotionally arousing tasks (McGaugh, 2004). Posttraining infusions of norepinephrine or β-adrenoceptor agonists into the BLA induce dose-dependent memory enhancement, whereas β-adrenoceptor antagonists administered into the BLA generally impair memory consolidation. Several studies investigating the effects of either pretraining or posttraining administration of β-adrenoceptor antagonists on memory for auditory fear conditioning have reported finding that whereas pretraining blockade of noradrenergic mechanisms impaired auditory-cue fear conditioning, posttraining suppression of noradrenergic neurotransmission with either systemic or intra-BLA administration of a β-adrenoceptor antagonist or an $\alpha_2$-adrenoceptor agonist was ineffective (current findings; Davies et al., 2004; Debiec & LeDoux, 2004; Lee, Berger, Stiedl, Spiess, & Kim, 2001). Additionally, Pugh, Fleshner, and Rudy (1997) and Pugh, Tremblay, Fleshner, and Rudy (1997) reported that adrenalectomy or posttraining administration of a GR antagonist failed to impair conditioned freezing induced by auditory-cue fear conditioning. Although, these findings have been used as evidence in favor of the view that posttraining manipulations of stress hormones do not affect auditory-cue fear conditioning and thus that memory of this task differs from that of other emotionally arousing tasks, it is possible that glucocorticoid and noradrenergic mechanisms within the BLA modulate memory of specific features of the conditioned stimulus

rather than the association of tone and footshock per se. Thus, after administration of an antagonist for either GRs or β-adrenoceptors, rats may retain the memory 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), which, with the use of standard auditory fear conditioning protocols, may result in unimpaired retention performance. This interpretation is in accord with several findings from human studies demonstrating that learning during emotionally arousing experiences increases memory of details of the experiences (Heuer & Reisberg, 1990).

In summary, the results reported here add to the evidence that glucocorticoids interact with noradrenergic mechanisms in the BLA in influencing memory consolidation in various animal and human memory tasks and thus indicate that modulation of memory consolidation of auditory-cue fear conditioning does not differ significantly from that of other emotionally arousing tasks. As both glucocorticoids and norepinephrine are normally activated by emotional arousal, such evidence further supports the view that endogenously released stress hormones play a role in modulating the consolidation of memory for experiences that induce their release (McGaugh & Roozendaal, 2002; Roozendaal, 2000).

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