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Enhanced memory for emotional material following stress-level cortisol treatment in humans

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Abstract

Memory tends to be better for emotionally arousing information than for neutral information. Evidence from animal studies indicates that corticosteroids may be necessary for this memory enhancement to occur. We extend these findings to human memory performance. Following administration of cortisol (20 mg) or placebo, participants were exposed to pictures varying in emotional arousal. Incidental memory for the pictures was assessed one week later. We show that elevated cortisol levels during memory encoding enhances the long-term recall performance of emotionally arousing pictures relative to neutral pictures. These results extend previous work on corticosteroid enhancement of memory and suggest that high cortisol levels during arousing events result in enhanced memory in humans. Published by Elsevier Science Ltd.

Keywords: Cortisol; Memory; Emotion; Emotional memory

While several studies of the effects of acute stress and corticosteroids on human cognition have documented a deleterious effect on declarative memory performance (de Quervain et al., 2000; Kirschbaum et al., 1996; Newcomer et al., 1999), this

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finding is not unequivocal (Beckwith et al., 1986; de Kloet et al., 1999; Lupien et al., 1999). On the contrary, a great deal of animal research documents a facilitating effect of corticosteroids on memory performance (Micco and McEwen, 1980; Borrell et al., 1983, 1984; see Roozendaal, 2000 for review). Most of these experiments used aversive conditioning paradigms in which emotional arousal was a key component of the learning experience and memory enhancement. It is postulated that this enhanced memory for emotional events is due to an interaction between amygdala activity and the stress hormones — both epinephrine and corticosteroids (see McGaugh, 2000).

Epinephrine and corticosteroids are released as part of the response to emotionally arousing or stressful situations (see Lovallo and Thomas, 2000). In the rat, the combination of epinephrine and corticosterone is necessary for the facilitation of the learning of an inhibitory avoidance task (Borrell et al., 1983, 1984). These effects are dependent upon the integrity of the basolateral amygdala (BLA; Roozendaal and McGaugh, 1997a), and they may be blocked by antagonists of β -adrenergic (Liang et al., 1986) or glucocorticoid (GR; Roozendaal and McGaugh, 1997b) receptors. Adrenergic mechanisms also play a role in memory formation in humans (Cahill et al., 1994; O'Carroll et al., 1999; van Stegeren et al., 1998). Specifically, increased adrenergic activity enhances (O'Carroll et al., 1999) while blockade of adrenergic activity reduces (Cahill et al., 1994) memory for emotional materials.

The association between corticosteroids and memory for emotional material has not been addressed in humans. The aforementioned animal studies suggest an interaction between corticosteroids and adrenergic activity during emotionally arousing situations in the formation of memory for these situations. In this experiment, separate groups of participants received either 20 mg of cortisol or placebo and viewed both emotionally arousing and neutral pictures. Emotionally arousing pictures included pleasant (eg, appetizing food, mountain scenery) and unpleasant (eg, disfigured people, threatening weapons) scenes. One week later, participants' memories for the pictures was examined. We tested the hypothesis that cortisol is part of an endogenous neurobiological system active during arousing learning situations to enhance memory for these events (see McGaugh, 2000). We predicted that cortisol would enhance memory performance of emotionally arousing pictures but not for emotionally neutral pictures.

1. Methods

1.1. Participants

Forty-eight healthy volunteers (24 women and 24 men) between the ages of 20 and 40 (mean age=26.7 years) who had been screened to exclude psychiatric, metabolic, and neurological conditions were recruited from the university community. The study was approved by the Institutional Review Boards of the University of Oklahoma Health Sciences Center and the Veterans Affairs Medical Center; written informed consent was obtained from all participants.

1.2. Cortisol administration and measurement

We used a double-blind, placebo controlled, between-subject design. Twenty-four participants (12 men, 12 women) were randomly assigned to receive hydrocortisone (20 mg; Hawkins Chemical Company, Minneapolis, MN) and the other 24 participants received placebo (identically appearing caplets) in oral form one hour before stimulus presentation.

Saliva samples were collected before drug administration, 50 min postdrug administration, and after stimulus presentation using a commercially available collection device (Salivette®, Sarstedt, Germany), centrifuged and stored at -70°C until assayed. Cortisol concentrations were measured by a radioimmunoassay technique with a commercially available kit (Orion Diagnostica, Espoo, Finland) adapted to measure the low cortisol concentrations observed in saliva. Saliva samples were mixed with a fixed amount of ^{125}I -labelled cortisol derivative and cortisol antiserum. The labelled and unlabelled antigens were then allowed to compete for the high affinity binding sites of the antibody during an incubation period. The separation of bound and unbound antigen was performed with polyethylene glycol. The amount of labelled antigen in the sample is inversely proportional to the concentration of the unlabelled antigen. The actual concentrations in the unknown samples were obtained by means of a standard curve based on known concentrations of unlabelled antigen analyzed in parallel of the unknown. Intra- and inter-assay coefficient of variations were 6% and 12%, respectively.

1.3. Stimulus presentation

Sixty emotionally arousing and neutral pictures selected from a standard set of affective pictures (International Affective Picture System [IAPS], Center for the Study of Emotion and Attention [CSEA–NIMH], 1995, University of Florida, Gainesville, FL, USA) were presented to participants on a television monitor. Each picture was presented for 12 s, with 12–16 s between pictures. Participants were told “devote all your attention to each picture for the entire time that it is on screen.” No mention of the memory tests was made. Pictures were divided into three sets of 20 slides containing approximately equal numbers of arousing pleasant, arousing unpleasant and nonarousing neutral pictures, with the order of picture sets counterbalanced across participants. Measure of electromyographic (EMG) activity in response to startling noise bursts was recorded during presentation of the pictures. These data will be reported elsewhere.

1.4. Memory measures

Participants returned to the laboratory exactly one week after the initial stimulus presentation for incidental memory tests. A free-recall test in which participants were asked to write down words or phrases describing all the pictures that they could recollect was followed by a cued recall test in which participants were provided with 11 different descriptors (eg, injured people, people by themselves, couples, sports

and leisure activities, food, animals, household objects, scenery, building exteriors, building interiors, and weapons) into which all the pictures could be categorized and asked to write down as many of the pictures as could be recalled. Two independent scorers, blind to drug assignment, determined which pictures were described in free and cued recall tests. A correct recall was scored if the participant's description of a specific picture could be clearly linked by both scorers to a picture that had been shown. Most of the responses given in the recall tests could be clearly linked to a particular picture: there was a high degree of agreement between the two scorers (89%). Picture descriptions that could not be clearly linked to a particular picture by both scorers were scored as a nonresponse and not included in the analyses. In cases of similar pictures (i.e., aimed gun and sideview gun), if only one was remembered, recall was noted for the picture that was remembered most often by all participants. Recognition was then assessed via the presentation of all 60 previously seen pictures randomly mixed with 60 new pictures which were similar to those previously seen. Participants were asked to respond 'yes' if they remembered seeing the picture or 'no' if they did not.

1.5. Affective picture ratings

During the recognition procedure, participants rated each picture on standardized, 9-point Likert scales of emotional arousal (1, lowest; 9 highest) and emotional valence (1, most unpleasant; 5, neutral; 9 most pleasant; see Bradley and Lang, 1994). Mean ratings of the pictures for both drug groups are shown in Table 1. The mean rated emotional valence was used to categorize each picture as pleasant, neutral or unpleasant by splitting the slides into thirds with the lowest one-third of the slides categorized as unpleasant, the middle one-third as neutral and the highest one-third as pleasant. Categorization of pictures by emotional arousal into high and low arousing pictures was based on a median split within each drug group due to differences between the cortisol and placebo groups on this measure (see Table 2).

Table 1
Salivary cortisol levels^a

Group	Period ^b		
	Predrug	50 min postdrug	80 min postdrug
Cortisol	4.9±0.3	49.6±11.2**	59.9±10.4**
Placebo	6.2±0.7	5.6±0.9**	5.0±1.4**

^a Entries show mean±standard error of the mean of salivary cortisol in nmol/l.

^b **Significant group difference at $P < 0.0001$.

Table 2
Affective picture ratings^a

	Stimulus type ^b		
	Pleasant	Neutral	Unpleasant
Emotional arousal			
Cortisol group	4.8±0.4	2.3±0.2	5.6±0.4*
Placebo group	5.1±0.3	2.8±0.2	6.6±0.2*
Emotional valence			
Cortisol group	7.0±0.2	4.8±0.1	2.0±0.2
Placebo group	6.7±0.2	4.9±0.1	2.1±0.1

^a Numbers following the \pm sign indicate the standard error of the mean.

^b *Significant group difference at $P < 0.05$.

2. Results

2.1. Salivary cortisol levels

Cortisol levels measured in saliva at 50 min (immediately before picture viewing) and 80 min postdrug (immediately after picture viewing) were significantly elevated in the cortisol group compared to placebo group, $F(1,46)=28.1$, $P < 0.0001$, and within the range of cortisol measured after psychological stress (see Table 1; Lovallo and Thomas, 2000).

2.2. Recall performance

Free and cued recall performance was analyzed using a multivariate analysis of variance (MANOVA) with drug group (cortisol or placebo) and gender as between-subjects factors and free and cued recall performance as the within-subjects factor. We observed better performance on the cued recall test compared to free recall, $F(1,44)=125.5$, $P < 0.0001$, as one would expect. The cortisol group remembered more pictures in the cued recall test than did the placebo group, as evidenced by a significant group \times recall interaction ($F(1,44)=7.3$, $P < 0.01$; see Fig. 1). Men and women did not differ significantly in recall performance.

2.3. Recognition performance

Recognition memory performance was assessed between drug groups and genders. There was no difference in recognition performance between the cortisol and placebo groups, neither was there a gender difference ($F_s(1,44) < 1.3$, $P_s > 0.1$; See Fig. 1).

2.4. Effects of emotional arousal and valence on memory

Memory performance was then analyzed according to the ratings of emotional arousal that participants gave to the stimuli (see Table 2). Highly arousing slides

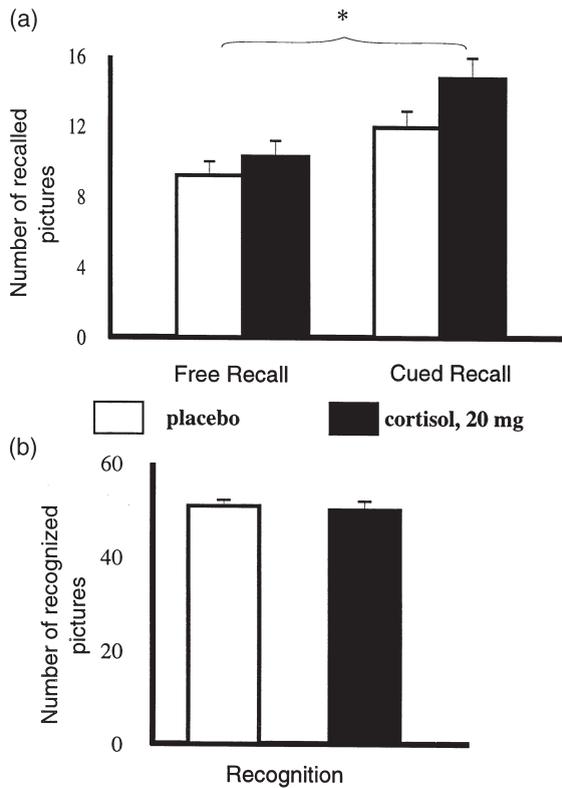


Fig. 1. Effects of cortisol on picture recall and recognition. (a) Mean (\pm SEM) correct recall of pictures from placebo and cortisol groups on the free and cued recall tests. *Significant interaction of cortisol and test, $P < 0.01$. (b) Mean (\pm SEM) correct recognition of pictures from placebo and cortisol groups.

were remembered significantly better on all three tests of memory ($F_s(1,43) > 79$, $P_s < 0.0001$). For cued recall performance, there was a significant cortisol by arousal interaction, $F(1,44) = 4.7$, $P = 0.035$, post-hoc tests performed on this interaction showed that the cortisol group recalled significantly more highly arousing slides than those in the placebo group ($F(1,44) = 5.9$, $P < 0.02$; see Fig. 2). Emotional valence also had a significant effect on memory performance, with both the unpleasant and pleasant pictures remembered more often than the emotionally neutral pictures ($F_s(2,43) > 27$, $P_s < 0.0001$). The cortisol group did not specifically show enhanced memory for either unpleasant or pleasant pictures compared to the placebo group ($F_s(1,44) < 2.1$, $P_s > 0.1$).

2.5. Affective picture ratings

Table 2 shows means (standard error of the mean) for arousal and valence ratings of the pictures across both drug groups. There were no differences in valence reports between the drug groups ($F_s(1,46) < 1$). The cortisol group rated the unpleasant pic-

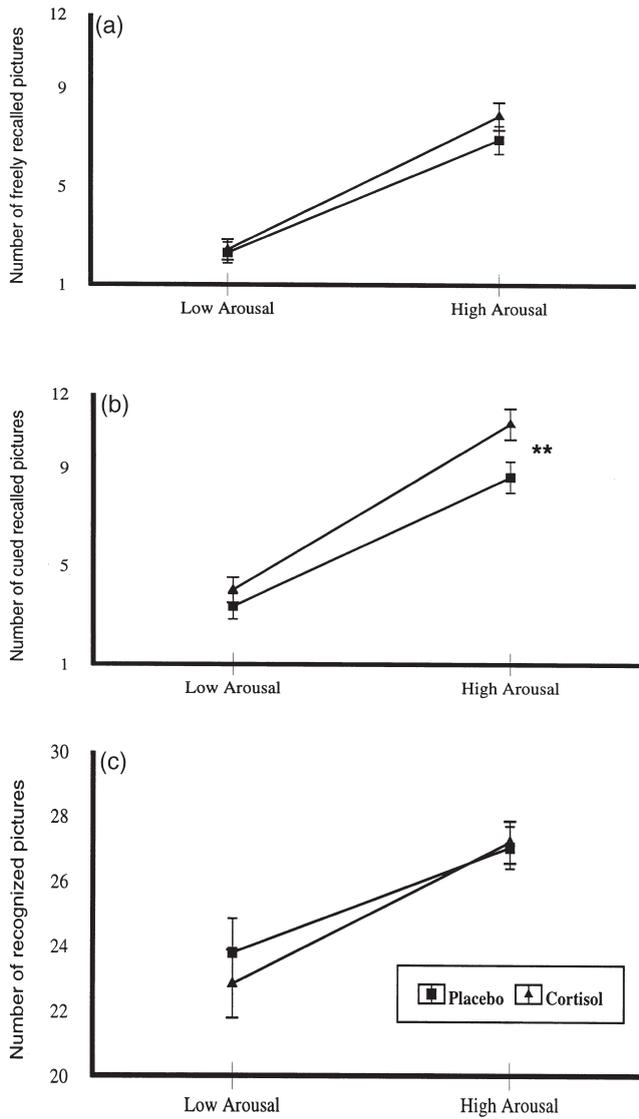


Fig. 2. Effects of cortisol and emotional arousal on picture recall and recognition. (a) Mean (\pm SEM) correct free recall by arousal median split. (b) Mean (\pm SEM) correct cued recall by arousal median split. **Significant group difference at $P < 0.02$. (c) Mean (\pm SEM) correct recognition by arousal median split.

tures as significantly less arousing than did the placebo group, $F(1,46)=4.1$, $P < 0.05$, although the drug groups did not differ in ratings of the pleasant or neutral pictures ($F_s(1,46) < 1.5$).

3. Discussion

This experiment investigated whether the stress hormone cortisol is involved in the formation of emotionally arousing memories. We found that a single dose of 20 mg given one hour before exposure to emotionally arousing pictures increased memory for those pictures in a cued recall test one week later. Modest, nonsignificant, memory facilitation was also found in a free recall test, although no improvement was found during recognition, where a ceiling effect may have operated. Although research has suggested that cortisol impairs memory for emotionally neutral materials, the present findings suggest that the hormone enhances the long-term recall of emotionally arousing stimuli. These results are consistent with animal research which suggests that corticosteroids play an integral role in an endogenous neurobiological system active during arousing learning situations to enhance memory for these events (see McGaugh, 2000).

A large body of research has focused on the modulatory effects of corticosteroids on memory (see Lupien and McEwen, 1997; de Kloet et al., 1999; McEwen and Sapolsky, 1995). In humans, cortisol can impair performance on tests of declarative memory (Kirschbaum et al., 1996; Newcomer et al., 1999). Recently, de Quervain et al. (2000) showed that this impairment may be specific to retrieval processes. Three groups learning word lists received cortisol, either: 1) before learning, 2) immediately after learning, or 3) immediately prior to a recall test 24 hours later. Cortisol impaired performance if given prior to recall, while it had no effect before or after initial exposure to the materials. In the studies of Kirschbaum et al. (1996) and Newcomer et al. (1999), cortisol levels were elevated during both acquisition and retrieval, making it unclear which processes were affected. However, their findings, and those of de Quervain et al. (2000) are consistent with a potential cortisol-induced impairment of retrieval processes.

The present results amplify these prior studies, indicating that cortisol can have effects during acquisition and consolidation, but only if the materials are emotionally arousing. The present study and that of de Quervain et al. (2000) are consistent in finding no effect of cortisol given prior to or just after exposure to emotionally neutral material. Neither study addressed possible effects of elevated cortisol during retrieval of emotionally arousing material. Future research should address cortisol effects at each stage in memory formation and retrieval and use materials varying in emotional arousal.

Studies in animals have shown that corticosterone, in combination with central adrenergic activity can enhance performance on inhibitory avoidance tasks involving possible exposure to aversive stimuli (Borrell et al., 1983, 1984; see Roozendaal, 2000 for review). These effects are dependent upon the integrity of the basolateral nucleus of the amygdala (Roozendaal and McGaugh, 1997a), which is thought to enhance memory consolidation via effects on other structures such as the hippocampus and caudate/putamen (Packard, Cahill & McGaugh, 1994). While epinephrine does not readily cross the blood brain barrier, it may affect memory centrally via feedback mediated by peripheral beta adrenoreceptors (McGaugh, 2000). Corticosteroids freely enter the brain and act on intracellular receptors distributed throughout

the central nervous system, including the hippocampus and amygdala (Allen and Allen, 1974; McEwen and Sapolsky, 1995). The interaction between corticosteroids and adrenergic mechanisms is thought to occur at the level of the amygdala (see McGaugh, 2000). The facilitation of emotional memory by central adrenergic mechanisms in humans is well-established (Cahill et al., 1994; van Stegeren et al., 1998; O'Carroll et al., 1999). The present findings extend our understanding of this facilitation to the action of corticosteroids in humans. A possible mechanism for our reported effect may be through activation of central adrenergic mechanisms via the arousing nature of the learning conditions which, through interaction with the increased circulating cortisol, resulted in increased encoding and/or consolidation of the materials. Future work could explicitly test this hypothesis in humans by including measures of adrenergic function.

The apparent ability of cortisol to improve acquisition or consolidation of memories for arousing, emotionally charged material assessed one week later, has implications for our understanding of memories for stressful or traumatic experiences. Along these lines, posttraumatic stress disorder (PTSD) involves alterations in both memory (Pitman, 1989; Hembree and Foa, 2000) and cortisol function (Yehuda, 1997). If cortisol enhances memory for emotionally arousing events, then it may play a role in the formation of persistent intrusive memories characteristic of PTSD (see Schelling et al., 1999, for an example of a protective effect of cortisol in PTSD). Additional experiments are required to test this hypothesis and to further understand the complex effects of corticosteroids on memory function.

Studies of picture recall in persons without manipulation of cortisol also highlight the effect of arousal on recall. Pictures rated as either highly pleasant or unpleasant on the valence scale were remembered more often than neutral pictures (Bradley et al., 1992), but this effect was stronger for highly arousing pictures, and arousal tended to be a better predictor of memory performance than did valence (Bradley et al., 1992; Bradley and Lang, 2000). In the present study, cortisol's effects on emotional memory were not specific to either positive or negatively affective materials, but influenced memory for arousing stimuli, regardless of valence. Interestingly, the cortisol group rated the unpleasant pictures significantly less arousing than did the placebo group. In light of the increased memory performance associated with both high arousal and cortisol group membership, this group difference in ratings seems paradoxical. If the cortisol group experienced the pictures as less arousing, it would be predicted that they would remember fewer of these pictures, but the results show the opposite pattern. This suggests that experienced arousal is not the primary cause of the effect reported here. Future research should address the effects of cortisol on the recognition and experience of arousal in combination with its role in memory formation.

Results from this experiment extend previously reported work in animals suggesting that corticosteroids may enhance the formation of memory for emotionally relevant events. This is, to our knowledge, the first study to document such an effect in humans. Future studies in humans should separately investigate cortisol's effects on acquisition, consolidation and retrieval in conjunction with explicit manipulation of the adrenergic state of the participants.

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