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GLUCOCORTICOIDS INTERACT WITH NORADRENERGIC ACTIVATION AT ENCODING TO ENHANCE LONG-TERM MEMORY FOR EMOTIONAL MATERIAL IN WOMEN

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Abstract—Evidence from the animal literature suggests that post-training glucocorticoids (GCs) interact with noradrenergic activation at acquisition to enhance memory consolidation for emotional stimuli. While there is evidence that GCs enhance memory for emotional material in humans, the extent to which this depends on noradrenergic activation at encoding has not been explored. In this study, 20-mg hydrocortisone was administered to healthy young women (18–35 yrs old) in a double-blind fashion 10 min prior to viewing a series of emotional and neutral images. Saliva samples were taken at baseline, 10 min after drug or placebo administration, immediately after viewing the images, 10, 20, and 30 min after viewing the images. Participants returned 1 week later for a surprise recall test. Results suggest that, hydrocortisone administration resulted in emotional memory enhancement only in participants who displayed an increase in endogenous noradrenergic activation, measured via salivary alpha-amylase at encoding. These results support findings in the animal literature, and suggest that GC-induced memory enhancement relies on noradrenergic activation at encoding in women.

Key words: glucocorticoids, memory, emotion, alpha-amylase, noradrenergic activation, hydrocortisone.

INTRODUCTION

Considerable evidence in both the animal and human literature suggests that glucocorticoids (GCs) enhance long-term memory for emotionally arousing events (Buchanan and Lovallo, 2001; Okuda et al., 2004; Roozendaal et al., 2006a,b; Wichmann et al., 2012). More recent evidence indicates that corticosterone enhancement of memory depends upon the degree of arousal in animals and humans at the time of learning (Cahill and Alkire, 2003; Okuda et al., 2004). Consistent with this view, both systemic, or intra-amygdala, injections of the beta-adrenergic antagonist, propranolol, blocks corticosterone-induced memory enhancement in animals (Okuda et al., 2006b). Conversely, pharmacological adrenergic activation facilitates corticosterone enhancement of memory in animals in non-arousing learning conditions (Roozendaal et al., 2006b).

More specifically, evidence from rodent studies suggests that noradrenergic activation in the basolateral amygdala (BLA) is involved in GC influences on memory modulation. Two major brainstem noradrenergic cell groups, the nucleus of the solitary tract (NTS) and the locus coeruleus contain high concentrations of glucocorticoid receptors (GRs). Post-training activation of GRs on noradrenergic cell groups in the NTS induces dose-dependent memory enhancement in rodents (Roozendaal et al., 1999). The NTS projects directly to the amygdala and infusion of a beta-adrenergic antagonist, propranolol into the BLA blocks the GC-induced memory enhancement (Roozendaal et al., 1999). Additionally, GC activation within the BLA itself may facilitate memory consolidation by potentiating the efficacy of the norepinephrine (NE) signal cascade, by interacting with G-protein-mediated mechanisms (Roozendaal et al., 2002).

Very few studies to date have examined GC/noradrenergic interactions in human memory. Several experiments have focused solely on the role of NE in the enhancement of emotionally arousing material (Cahill and Alkire, 2001). Other studies have examined the effects of beta-adrenergic blockade on emotional memory (O'Carroll et al., 1999; van Stegeren et al., 2005). Similarly, a number of studies have examined the relationship between cortisol and memory for emotionally arousing material in humans, but have not investigated whether this memory enhancement depends on noradrenergic activation at encoding (Buchanan and Lovallo, 2001; Abercrombie et al., 2003; Kuhlmann and Wolf, 2006).

Previous research has suggested that post-learning cortisol activation may enhance memory depending upon the degree of arousal associated with initial

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Abbreviations: ANOVA, analysis of variance; BLA, basolateral amygdala; GCs, glucocorticoids; GRs, glucocorticoid receptors; IAPS, International Affective Picture Set; MANOVA, multivariate ANOVA; NE, norepinephrine; NTS, nucleus of the solitary tract.

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encoding of information. For example, a cortisol-activating stressor (Cold Pressor Stress) administered immediately after the encoding of both neutral and emotionally arousing pictures enhanced long-term memory only for the emotionally arousing pictures (Cahill et al., 2003). In another experiment, male subjects received 30 mg of cortisol 10 min prior to the viewing of emotionally arousing or neutral pictures. In a 24-h delayed recall task, cortisol administration 10 min prior to encoding enhanced memory for the emotionally arousing pictures (Kuhlmann and Wolf, 2006). Similarly, Buchanan and Lovallo (2001) reported that cortisol administration 1 h prior to encoding in men and women enhanced memory only for cued-recall emotional images.

It has been difficult to measure whether this GC-induced memory enhancement relies on noradrenergic activation in, primarily because it has been challenging to measure endogenous norepinephrine NE in humans. Salivary alpha-amylase is a known biomarker for NE (Chatterton et al., 1996). Strong evidence suggests that measurement of this salivary enzyme is a superior assessment of central endogenous noradrenergic activation, as compared with measurement of NE collected from blood plasma (Ehlert et al., 2006). Evidence from several pharmacological experiments in humans and animals suggests that sAA is a valid biomarker for noradrenergic activity. Alpha- and beta- adrenergic agonists, such as isoprenaline significantly increase sAA (Speirs et al., 1974; Ehlert et al., 2006). Conversely, beta-adrenergic antagonists, such as atenolol and propranolol significantly decrease sAA (Speirs et al., 1974; Nederfors and Dahlof, 1992; Nederfors et al., 1994; van Stegeren et al., 2005).

There has been some controversy in terms of whether sAA levels reflect alterations in plasma NE levels (Chatterton et al., 1996; Nater et al., 2006; Rohleder et al., 2004; Ehlert et al., 2006). The discrepancy in the correlations between blood plasma NE and sAA, however seems to reflect differences in origin of the sample and suggests that sAA is more reflective of central NE (Ehlert et al., 2006). Blood plasma NE levels reflect adrenomedullary NE, as well as peripheral spillover. In contrast, salivary alpha-amylase is synthesized and secreted primarily from NE released by sympathetic nerves that innervate the acinar cells in the parotid gland. Within 20 s of NE binding to g-protein-coupled receptors on the acinar cells cAMP is activated, resulting in the synthesis and secretion of alpha-amylase that can be measured in whole saliva (Yoshimura et al., 2002).

Thus it remains possible with this salivary biomarker, but untested, whether the enhancing effects of post-learning GC activation on long-term memory in humans depends specifically on noradrenergic activation at encoding. The purpose of the current study was to test this hypothesis. Based in particular on the evidence from the animal literature indicating that post-learning GC-induced memory enhancement requires noradrenergic activation during initial learning (Roozendaal et al., 2006a,b), we hypothesized that enhanced GC activity in the period after new information was acquired would enhance long-term memory only for that information only for our participants who experienced noradrenergic activation during initial encoding.

EXPERIMENTAL PROCEDURES

Study participants

Forty-four healthy women between the ages of 18 and 35 participated in this experiment. All women were naturally cycling so as to exclude influences of synthetic hormones from birth control and in the mid-luteal menstrual cycle phase (via self-report) due to evidence that cortisol increase in response to a stressor is greater during the mid-luteal phase of the menstrual cycle in naturally cycling women (Andreano and Cahill, 2006).

All participants were asked to take a pregnancy test on the day of the experiment to ensure that they were not pregnant. One participant was excluded due to reported expectation of the memory test. Two participants who received hydrocortisone were excluded because they failed to display elevated cortisol in response to the drug. Two participants who received placebo were excluded because, unlike all others in their group, they showed a markedly elevated cortisol response despite receiving only the placebo, leaving thirty-nine participants.

Experimental procedures

Participants viewed 144 slides taken from the International Affective Picture Set (IAPS) that ranged from neutral (mean arousal 3.84 ± 1.23) to strongly emotional (mean arousal 6.04 ± 1.17). Each image was presented for 3 s and the participant was asked to rate the image based on (1) how emotionally arousing the image was on a scale of 1–9 (1 = low arousal, 9 = highest arousal) and (2) valence (1 = extremely negative, 9 = extremely positive). The participant had as much time as needed to rate each image. The entire duration of the slide show was approximately 15 min long.

Participants received either 20 mg Hydrocortisone (West-ward Pharmaceutical Corporation, Eatontown, NJ, USA) or placebo orally in a double-blind fashion 10 min prior to viewing the images so as to ensure that cortisol would be significantly increased immediately after viewing the slide show. Hydrocortisone tablets were placed inside placebo gel capsules so that the drug and placebo pills appeared identical. Participants were randomly assigned to one condition, and all pills were administered by a medical doctor. Of the 39 participants, 20 received hydrocortisone and 19 received placebo.

Participants returned 1 week later for a surprise recall test and were asked to write down as many images as they could recall and to list as many details as possible for each one. Since the goal of the current study was to examine the influence of stress hormones on incidental memory, participants who anticipated a memory test were excluded.