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Impact of exogenous cortisol on the formation of intrusive memories in healthy women

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ABSTRACT

Introduction: Stress hormones such as cortisol are involved in modulating emotional memory. However, little is known about the influence of cortisol on the formation of intrusive memories after a traumatic event. The aim of this study was to examine whether cortisol levels during encoding and consolidation of an intrusion-inducing trauma film paradigm would influence subsequent intrusion formation.
Material and Methods: In an experimental, double-blind, placebo-controlled study a trauma film paradigm was used to induce intrusions in 60 healthy women. Participants received a single dose of either 20 mg hydrocortisone or placebo before watching a trauma film. Salivary cortisol and alpha-amylase as well as blood pressure were measured during the experiment. The consecutive number of intrusions, the vividness of intrusions, and the degree of distress evoked by the intrusions resulting from the trauma film were assessed throughout the following seven days.
Results: Hydrocortisone administration before the trauma film resulted in increased salivary cortisol levels but did not affect the consecutive number of intrusions, the vividness of intrusions, and the degree of distress evoked by the intrusions throughout the following week.
Conclusions: These results indicate that pharmacologically increased cortisol levels during an experimental trauma film paradigm do not influence consecutive intrusive memories. Current data do not support a prominent role of exogenous cortisol on intrusive memories, at least in healthy young women after a relatively mild trauma equivalent.

1. Introduction

Intrusive memories in Posttraumatic Stress Disorder (PTSD) are defined as recurrent involuntary and intrusive recollections of a traumatic event (American Psychiatric Association, 2013). Increased perceptual priming, increased associative learning, and decreased memory elaboration seem to be memory mechanisms involved in intrusion formation and intrusion maintenance (Ehlers, 2010). However, little is known about the neurobiological factors influencing the formation of intrusions.

During stress the hypothalamic–pituitary–adrenal axis (HPA axis) is activated and the adrenal cortex releases cortisol (reviewed in de Quervain et al., 2009). Cortisol enters the brain where it binds to mineralocorticoid and glucocorticoid receptors (reviewed in Wolf et al., 2015). Hereby acting in brain regions like the amygdala, the hippocampus and the prefrontal cortex, brain regions closely associated with cognition (reviewed in McEwen et al., 2016). Many studies have demonstrated that released stress hormones or exogenously administered stress hormones are involved in modulating memory consolidation (reviewed in Roozendaal and McGaugh, 2011). For example, healthy female and male participants with increased cortisol levels as a response to the Trier Social Stress Test-Modified (TSST-M) showed enhanced memory for test day details after two weeks (Quas et al., 2012). Especially, cortisol enhances emotional memory consolidation (reviewed in Wolf, 2009). For instance, healthy men and women who received hydrocortisone compared to placebo showed enhanced memory for emotionally arousing pictures after one week (Buchanan and Lovallo, 2001). Further, healthy men showed enhanced memory

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for emotional material and decreased memory for neutral material 24 h after receiving hydrocortisone compared to placebo (Kuhlmann and Wolf, 2006). Also, the interaction of cortisol and noradrenalin seems to be involved in emotional memory formation (reviewed in Roozendaal and McGaugh, 2011). For example, it has been shown that memory consolidation is enhanced by glucocorticoids when noradrenergic activity is elevated during encoding of emotional stimuli (reviewed in Roozendaal et al., 2006). Further, hydrocortisone administration before encoding of emotional images leads to enhanced memory after one week, however only in participants with increased noradrenergic activity during encoding compared to participants without increased noradrenergic activity (Segal et al., 2014).

Several but not all studies have shown that cortisol levels after trauma are associated with subsequent intrusive symptoms and overall PTSD symptomatology in patients. For example, urinary cortisol assessed after a traumatic accident in children was associated with subsequent intrusive symptoms after 6 weeks (Delahanty et al., 2005). Further, women with lower serum cortisol levels measured 72 h after sexual assault showed more overall PTSD symptoms after 6 weeks compared to women with higher serum cortisol levels (Walsh et al., 2013). However, plasma, saliva, and urinary cortisol after trauma assessed in the emergency room was not associated with consecutive intrusions after 5 months (Shalev et al., 2008). The association of cortisol levels after trauma and PTSD symptomatology seems to be complex since McFarlane et al. (2011) found an association of lower morning salivary cortisol and subsequent PTSD as well as higher afternoon salivary cortisol and subsequent PTSD 48 h after trauma.

Patients who received hydrocortisone during intensive care unit treatment showed reduced PTSD symptoms (Schelling et al., 2006). For example, compared to placebo, hydrocortisone administration during septic shock (Schelling et al., 1999, 2001) and during cardiac surgery (Schelling et al., 2004) was associated with a decreased incidence of PTSD (Schelling et al., 1999, 2001) and reduced PTSD symptoms (Schelling et al., 2004). In a recent meta-analysis hydrocortisone was the only early pharmacological intervention to effectively prevent PTSD (reviewed in Sijbrandij et al., 2015). For instance, female and male patients with heterogeneous injuries after a traumatic event who received either placebo or 20 mg hydrocortisone within 12 h post trauma and subsequently every 12 h for the following 10 days reported less PTSD symptoms during the three months post trauma compared to placebo (Delahanty et al., 2013). Further, a reduced risk for subsequent PTSD 3 months after trauma was found in female and male trauma survivors who received intravenous hydrocortisone 6 h after trauma (work or vehicle accidents) compared to placebo (Zohar et al., 2011). PTSD patients show decreased basal cortisol levels in most but not all studies (Yehuda et al., 2015). Exogenous hydrocortisone in PTSD patients inhibited retrieval of trauma related memories in a case series of patients (Aerni et al., 2004), however, in a recent study no effect of exogenous hydrocortisone on intrusive memories in female PTSD patients emerged (Ludäscher et al., 2015).

Trauma film paradigms are used to examine the formation of intrusive memories by inducing short lasting intrusions in healthy participants (Holmes and Bourne, 2008). First evidence suggests that cortisol also influences intrusion formation. In a study in healthy participants using a trauma film paradigm, there was a positive correlation between post-film salivary cortisol levels and the frequency of intrusions, however this was only the case in participants with increased saliva alpha-amylase (sAA) activity (Chou et al., 2014), an indicator of enhanced noradrenergic activation (van Stegeren et al., 2006).

The present study examined the potential influence of exogenous cortisol during a trauma film paradigm on the consecutive development of intrusions. Based on the available data on emotional memory consolidation and intrusion formation, we hypothesized that an increased number of consecutive intrusions, more vivid intrusions, and more distressing intrusive memories of the trauma film would be found in participants who received hydrocortisone compared to participants who received placebo.

2. Material and Methods

2.1. Participants

The sample consisted of 60 healthy university students. Recruitment took place via flyers posted around the university, official university email lists, or postings in social network university groups. As the rape victim in the trauma film is female, only women were included. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I, German version of First et al., 1995) was conducted over the phone to exclude participants with former or present DSM IV Axis I disorders. Furthermore, physical illnesses, medication intake (except oral contraceptive), history of sexual abuse or rape, pregnancy, and lactation period led to exclusion. The HCG ULTRA pregnancy test was implemented to ensure the exclusion of pregnant woman. All participants spoke German on a native level and were between 18 and 34 years old (see Table 1).

2.2. Procedure

A double-blind, randomized, placebo-controlled study design was applied. The study was conducted at the Department of Psychiatry and Psychotherapy, Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin. All procedures were approved by the local ethics committee and participants provided written informed consent at least 24 h in advance. Participants were instructed to refrain from smoking, physical exercise, consuming caffeine, drinking alcohol or other beverages (except for water), and eating at least 1 h prior to the assessment. One participant was tested per day at 1.30 p.m.

2.2.1. Experimental phase

Participants received either hydrocortisone (2 tablets of 10 mg, Galen ®) or placebo (2 tablets of Placebo, Lichtenstein®). They were randomly allocated to one of the groups. The hydrocortisone and placebo pill looked identical. The investigator was excluded from the randomization protocol, hence ensuring that the participant and the investigator were blind to the treatment condition. Hydrocortisone or placebo was administered sixty minutes prior to the trauma film. The time of administration and the dosage have been successfully deployed in a previous study (Buchanan and Lovallo, 2001). Saliva was collected and blood pressure was measured (automatic device: boso medicus uno, Bosch + Sohn Germany) seven times throughout the study: at baseline, after medication intake, and every 15 min five times after the trauma film. Childhood trauma has been associated with increased risk to develop PTSD after trauma in adulthood (Breslau et al., 1999). To control for differences in experienced childhood events the Childhood Trauma Questionnaire (CTQ; German version of Bernstein and Fink, 1998) was applied. It has been shown that pre-trauma trait anxiety is positively related to PTSD (McNally et al., 2011). Therefore, trait anxiety was measured with the trait scale of the State-Trait Anxiety Inventory (German version of Spielberger and Gorsuch, 1983). Participants were instructed to not talk to other potential participants about the content of the study. Participants filled out the intrusion diary for 7 days subsequent to watching the trauma film.