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Effects of cortisol on emotional but not on neutral memory are correlated with peripheral glucocorticoid sensitivity of inflammatory cytokine production

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ABSTRACT

Cortisol responses to stress have important physiological effects on several target tissues throughout the body, including the central nervous system and the immune system. The ability of target tissues to receive cortisol signals has been shown to vary between individuals and over time. Conflicting data exist on whether different target tissues' glucocorticoid (GC) sensitivity is related. In a double-blind, placebo-controlled design, $n=19$ participants ($n=15$ men, $n=4$ women) received an oral dose of 30 mg of cortisol and placebo in randomized order. Memory retrieval of previously learned neutral and emotional words was tested after cortisol or placebo application. Peripheral GC sensitivity was tested by measuring in-vitro stimulated production of interleukin-6 (IL-6) in whole blood before and after cortisol vs. placebo application. Cortisol treatment reduced retrieval of neutral and emotional words (marginally significant at $p=0.07$), and significantly reduced stimulated IL-6 production ($p<0.001$). Relative suppression of IL-6 production was associated with impairment of memory retrieval of emotional ($r=0.48$; $p=0.039$), but not neutral words ($r=-0.17$; $p=0.48$). In summary, results show an association of peripheral glucocorticoid sensitivity with emotional, but not neutral, memory retrieval. Given that these findings can be extended to clinical populations, the association of peripheral glucocorticoid sensitivity with emotional memory retrieval might have important implications for understanding and treatment of stress-related disorders.

1. Introduction

Glucocorticoids (GCs) are important not only as stress hormones but also in the regulation of non-stressed functioning of the organism. Cortisol released by the HPA axis impacts the central nervous system as well as the periphery of the body (e.g. Sapolsky et al., 2000). Recent evidence shows that there is a significant degree of variation in the effectiveness of glucocorticoid signaling between individuals or within individuals over time. However, little is known about the association of glucocorticoid sensitivity of different target tissues within the same individual. We don't know for example if glucocorticoid responsive tissues in the central nervous system are equally receptive for the glucocorticoid signal as tissues in the periphery. Because of its potential use in understanding and treating specific psychiatric disorders, the aim of the present study is to investigate the association of central and peripheral glucocorticoid sensitivity.

In the CNS, GCs exert negative feedback action on the pituitary and the hypothalamus (Dallman et al., 1987). In addition, GCs also act on a range of other brain structures, which are involved in HPA control, but are also crucially important for learning and memory (Gold and Chrousos, 2002; McEwen, 2002; de Kloet et al., 2005; Roozendaal et al., 2006; Wolf, 2006). In this context the hippocampus, the amygdala but also medial prefrontal regions have received the most attention. With respect to memory, GCs facilitate memory consolidation, which leads to an enhanced storage of stressful episodes (Oitzl et al., 1997; Sandi et al., 1997; Joels et al., 2006; Roozendaal et al., 2006). The size of this effect is influenced by multiple variables such as magnitude of the GC increase, coactivation of the (nor)adrenergic system, subjective arousal, but also trait-like variables like gender, age, genetic background, and concentration of local enzymes involved in GC metabolism (Abercrombie et al., 2006; de Kloet et al., 2002; Herbert et al., 2006; Holmes et al., 2003; Roozendaal et al., 2006). In contrast, other aspects of memory are functioning less efficient after stress exposure or after GC administration. Among those is memory retrieval. This has been shown repeatedly in rodents (de Quervain et al., 1998; Roozendaal et al., 2004; Diamond et al., 2006), and humans (de Quervain et al., 2000; de Quervain et al., 2003; Wolf et al., 2004). In humans the negative effect of cortisol on memory retrieval are especially pronounced for emotionally arousing material (e.g. Kuhlmann et al., 2005a; Kuhlmann et al., 2005b; Buchanan et al., 2006). The arousal induced by the testing context is another variable known to modulate GC effects (Okuda et al., 2004; Kuhlmann and Wolf, 2006; Tops et al., 2006). Even if those situational factors are controlled, a substantial amount of interindividual variance in

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the size of the GC effects on memory retrieval remains. Differences in GC sensitivity in addition to, or caused by the potential mediators mentioned above most likely contribute to the variance observed in these behavioral data. In humans, central GC effects have been indirectly assessed either by measuring the impact of GCs on cognitive function, for example learning and memory (e.g. Het et al., 2005; Lupien et al., 2005), or with neuroendocrine test paradigms, such as the dexamethasone suppression test (DST; The APA Task Force on Laboratory Tests in Psychiatry, 1987).

An important target tissue for GCs in the periphery is the immune system, where GCs have rather complex effects. While they have initially been used to suppress immune responses (Hench et al., 1949), more recent evidence gathered over the last decade(s) suggests that short-term increases in the physiological range can also stimulate immune functioning, while long-term increases or pharmacological concentrations suppress most functions (e.g. Dhabhar and McEwen, 1999; Sapolsky et al., 2000). Glucocorticoid sensitivity can be assessed by co-incubation of mitogen-stimulated whole blood or cell cultures in-vitro with different concentrations of glucocorticoids and measuring the relative suppression of stimulated cytokine production. We and others have shown that GC sensitivity of the inflammatory response is subject to inter- and intra-individual variation and responds to acute psychosocial stress and exercise (DeRijk et al., 1996; Rohleder et al., 2001; Rohleder et al., 2002; Rohleder et al., 2003a; Rohleder et al., 2003b; Rohleder et al., 2004). Long-term changes have also been documented in populations suffering from chronic stress (Miller et al., 2002) or vital exhaustion (Wirtz et al., 2003).

It has been speculated that central and peripheral GC sensitivity might be related, but this issue remains controversial. Earlier work from our group showed that GC sensitivity as measured by cortisol response to the DST was unrelated to peripheral GC sensitivity of mitogen-stimulated cytokine production in healthy young participants (Ebrecht et al., 2000). In contrast to that, Yehuda et al. have demonstrated a substantial association of the cortisol response to the DST with GC sensitivity of lysozyme activity in PBMCs in healthy participants (Yehuda et al., 2003).

In posttraumatic stress disorder (PTSD), alterations have been reported in central and peripheral GC sensitivity. Although results are not consistent, a large number of studies revealed a group of PTSD patients with a pattern of reduced basal cortisol levels, (e.g. Yehuda et al., 1995a,b; Yehuda et al., 1996; Rohleder et al., 2004; Wessa et al., 2006), increased cortisol suppression in response to the DST (e.g. Stein et al., 1997), and greater GC sensitivity of peripheral immune cells (Yehuda et al., 2004; Rohleder et al., 2004). Some studies also investigated central GC sensitivity by assessing the effects of glucocorticoids on learning and memory. Two studies reported stronger negative effects of cortisol on hippocampal dependent declarative memory (Grossman et al., 2006) or hippocampal dependent trace conditioning (Vythilingam et al., 2006) in PTSD patients, suggesting higher central GC sensitivity in PTSD. In contrast to that, Bremner et al. reported blunted effects of prolonged dexamethasone treatment on declarative memory in PTSD (Bremner et al., 2004). While these data clearly show higher GC sensitivity in the CNS and in the periphery in PTSD, heterogeneous findings exist with respect to the question if these increases are correlated. Only in one study an association between peripheral (suppression of glucocorticoid receptors) and central GC sensitivity (response to the 0.5 mg DST) was found (Yehuda et al., 1995a,b).

In light of these scarce data on association of central and peripheral GC effects, we set out in the present study to address this question in healthy young participants. We decided to assess the effect of a single dose of oral cortisol on memory retrieval as an example for GC effects on a highly relevant area of cognitive functioning. We decided to assess peripheral GC sensitivity by measuring the effect of the same oral cortisol dose on mitogen-stimulated production of the pro-inflammatory cytokine interleukin-6 in-vitro, because inflammation and its control by endogenous factors are emerging as important determinants for somatic health. In contrast to previous studies, this direct assessment of oral cortisol effects on stimulated cytokine production, instead of interpreting the effects of co-incubation with glucocorticoids in culture, was used to achieve better comparability with assessment of GC effects on memory. We hypothesized that cortisol would impair memory retrieval and suppress pro-inflammatory cytokine production, and we aimed to investigate the association of GC effects on these parameters.

2. Materials and methods

2.1. Sample

We recruited a total of $n=23$ healthy young women and men, four of which were later excluded due to problems during blood draw or laboratory procedures. The remaining sample of $n=19$ had a mean age of 27.1 years (SD=4.03; range=21 to 35) and a mean body mass index (BMI) of 22.8 kg/m^2 (SD=2.2; range=18 to 26). Four participants were women and 15 were men, and five participants reported to be habitual smokers. The female participants were part of a larger study on the acute effects of cortisol on memory retrieval (Kuhlmann et al., 2005a). All participants were Caucasian, and none of the participants reported any acute or chronic diseases or taking any medication. None of the women used hormonal contraceptives. The study protocol was approved by the local ethics committee and all participants gave written informed consent.

2.2. Procedure

The effects of oral cortisol were tested in a double-blind, cross-over, placebo-controlled experiment with randomized treatment order. Participants received either three pills containing 10 mg hydrocortisone (Hoechst, Germany) or three similar looking placebo pills. The current dose (30 mg) was chosen to be similar to previous studies showing impairing effects of cortisol on retrieval (de Quervain et al., 2000; Wolf et al., 2001). Participants were recruited through advertisements at the University of Düsseldorf and invited to the laboratory on two days with a four-week interval. Female participants were invited during the first half of their menstrual cycle to control influences of gonadal steroids on memory performance and immune measures. Upon arrival at the laboratory between 10:00 and 11:00 h participants were asked to learn a list of 15 neutral and 15 negative words (see below), after which they were allowed to leave the laboratory until the second part of the experiment began. Participants returned to the laboratory between 15:00 and 16:00 h and were instructed to refrain from smoking, eating, and drinking anything but water 30 min before their return to the laboratory. Participants provided a baseline saliva sample for assessment of baseline cortisol, after which they received an indwelling catheter into an antecubital vein of the non-dominant arm. A first blood sample was immediately taken for measurement of cytokine production. After that participants provided a second saliva sample before they received either hydrocortisone (30 mg) or placebo orally. Further saliva samples were collected 15, 30, 45, 60, 90, and 120 min after treatment, further blood samples were collected 60 and 90 min after treatment. Memory retrieval was tested 60 min after treatment as described below.

2.3. Memory testing

A detailed description of the memory test used can be found in our previous publication (Kuhlmann et al., 2005a). In brief, a word list (with two parallel versions available) containing 15 negative (e.g. pain, explosion, prison) and 15 neutral words (e.g. street, blouse, stone) was used. There were no differences between neutral and negative words or between the two lists with respect to word frequency or word length.

The word list was presented to the participants on a piece of paper with the instruction to memorize them. They were given 2 min to learn the list with immediate free recall being tested. This procedure was repeated once resulting in two learning trials. In the afternoon (5 h after initial learning, 1 h after oral cortisol or placebo treatment)