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Effects of cortisol on cognition in major depressive disorder, posttraumatic stress disorder and borderline personality disorder - 2014 Curt Richter Award Winner

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Abstract Stress hormones influence a wide range of cognitive functions, including memory performance and executive function. It is well established that glucocorticoids enhance memory consolidation but impair memory retrieval. While most of the effects have been attributed to glucocorticoid receptors (GR), the importance of mineralocorticoid receptors (MR) has been also emphasized.

Dysfunctions in hypothalamic—pituitary—adrenal (HPA) axis have been reported for several mental disorders. While major depressive disorder (MDD) as well as borderline personality disorder (BPD) seem to be characterized by enhanced cortisol release in concert with a reduced feedback sensitivity of the HPA axis, in posttraumatic stress disorder (PTSD) a contrary picture has been reported. Despite the fact that altered GR function has been discussed for these disorders only very few studies have investigated the effects of glucocorticoids on cognitive performance in these patients so far.

In a series of studies, we investigated the effects of glucocorticoids on cognition (i.e. declarative memory, working memory and response inhibition) in different mental disorders such as MDD, PTSD and BPD. While in patients with MDD cortisol administration failed to effect memory retrieval, patients with PTSD and BPD showed enhanced rather than impaired memory retrieval after cortisol administration. These results indicate an altered sensitivity to cortisol in these disorders. Results from one of our recent studies in the field of social cognition underline the importance of the MR. We found that emotional empathy was enhanced through stimulation of the MR via fludrocortisone in healthy participants and women with BPD. This review aims to integrate these findings and discuss potential mechanisms and implications.

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1. Introduction

Stress, including (early) traumatic experiences, has been associated with a higher risk of a wide range of mental disorders, such as major depressive disorder, anxiety disorders, eating disorders, somatoform disorders and personality disorders. Therefore, many studies have investigated the functioning of the hypothalamic—pituitary—adrenal (HPA) axis in these disorders. Briefly, upon stress exposure, corticotropin-releasing factor (CRF) is released from the hypothalamus which works in conjunction with arginine vasopressin (AVP) to stimulate the secretion of adrenocorticotropin (ACTH) (Holsboer and Ising, 2010). ACTH in turn stimulates the synthesis and release of glucocorticoids (GCs) from the adrenal cortex. The neuroendocrine stress response is regulated by circulating GCs via negative feedback mechanisms targeting the pituitary, hypothalamus, and hippocampus. This negative feedback loop is essential for the regulation of the HPA axis and the regulation of the stress response (de Kloet et al., 2005). GCs mediate their effects by binding to two subtypes of intracellular receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). These two receptors differ in their affinity and distribution within the brain (de Kloet et al., 2005): while MR are mainly located in the hippocampus, GR are expressed throughout the brain, e.g. the prefrontal cortex (Lupien and Lepage, 2001; de Kloet et al., 2005). In addition, also membrane-bound GR and MR have been identified (Joels et al., 2008; Roozendaal et al., 2010). Due to their prominence throughout the brain, corticoid receptors modulate several cognitive processes, including memory. While most of the effects associated with GCs — especially when related to stress — have been attributed to GR, the importance of mineralocorticoid receptors (MR) has been also emphasized (Reul et al., 2000; Joels et al., 2008; de Kloet, 2013).

It is well established that in healthy participants memory consolidation is enhanced by cortisol, whereas long-term memory retrieval is impaired after GC administration (Wolf, 2009). Similar effects on memory retrieval have been obtained after psychosocial laboratory stressors. The impairing effects of cortisol have also been found for autobiographic memory retrieval (Buss et al., 2004; Young et al., 2011) and working memory (e.g. Lupien et al., 1999; Wolf et al., 2001), although not all studies agree (Monk and Nelson, 2002; Porter et al., 2002; Oei et al., 2009). Effects of acute cortisol elevation on inhibitory control were investigated only in a few studies. Scholz et al. (2009) for example demonstrated that a psychosocial stress induction impaired go/no-go performance. In contrast, Zwissler et al. (2011) found inhibitory control of memory in a directed forgetting task not to be affected after a psychosocial stress. Using acute cortisol administration, Wolf et al. (2001) found no impairing effect of on performance in a Stroop task. Oei et al. (2009) even found an enhancing effect of cortisol on inhibitory performance when examining distracter interference in a Sternberg working memory task.

At this point it has to be emphasized that exposure to (psychosocial) stress and administration of cortisol differ markedly in several endocrine aspects: while stress exposure leads to centrally increased CRF, AVP and peripherally induced corticosteroids that penetrate into the brain, exogenous cortisol, enters the brain and decreases CRF and AVP. Thus, different and even opposite effects on cognition might occur. In contrast if both approaches induce highly similar behavioural consequences an important role of cortisol in mediating the observed effects appears likely. In the context of memory retrieval the effects of stress induced cortisol increases and exogenously administered cortisol are highly similar. Given the neuroendocrine differences between these to states this supports our conclusion that indeed cortisol is the driving factor in both scenarios (since CRH, AVP and ACTH differ).

Most of the mentioned studies used stress exposure or cortisol administration which leads to a stimulation of both glucocorticoid receptor types, GR and MR. However, some studies had a closer look at the role of the MR in terms of cognition. Indeed, it has been consistently shown that blocking the MR e.g. with spironolactone leads to impaired cognitive function in humans (Otte et al., 2007; Cornelisse et al., 2011; Rimmele et al., 2013). Interestingly, these impairing effects of MR blockade were most pronounced for emotional memory (Rimmele et al., 2013). Of note spironolactone also leads to decreases in blood pressure, which makes it difficult to clearly differentiate its MR effects from effects possibly triggered by blood pressure. However, as studies which investigated the effects of MR blockade on memory use relatively low dosages of spironolactone, effects on blood pressure and heart rate are not seen in these investigations (Otte et al., 2007; Cornelisse et al., 2011). Thus, it seems to be likely that the observed effects on cognition are indeed associated with MR function.

Alterations of the HPA axis have been reported for a wide range of mental disorders, including major depressive disorder (MDD), posttraumatic stress disorder (PTSD) and borderline personality disorder (BPD). While MDD as well as BPD seem to be characterized by enhanced cortisol release in concert with a reduced feedback sensitivity of the HPA axis, in PTSD a contrary picture has been reported (Yehuda, 2002; Parker et al., 2003; Wingenfeld et al., 2010). Recent studies also investigated the functioning of the GR directly in MDD (McGowan et al., 2009) as well as in PTSD (Rohleder et al., 2004). Of note, findings of HPA axis dysregulations in mental disorder are far from homogenous (Nemeroff, 2002; Nestler et al., 2002; Meewisse et al., 2007; Heim and Nemeroff, 2009; Wingenfeld et al., 2010). Despite the fact that altered GR functioning has been discussed for these disorders, only very few studies have investigated the effects of GCs on cognitive performance in these patients so far (Wingenfeld and Wolf, 2011).

In a series of studies, we investigated the effects of cortisol (10 mg hydrocortisone orally) on cognition, i.e. declarative memory, working memory and response inhibition, in mental disorders such as MDD, PTSD and BPD. We used the same tasks for all patient groups to be able to compare the results. In addition to a word list learning (consisting of 21 words), an autobiographical memory test was used (Buss et al., 2004). Patients with overgeneralized memory have difficulties in retrieving specific autobiographical events. Instead, they tend to reply with abstract or general memory content (e.g. they summarize several different events). To test the verbal modality of working memory, we used the self-developed Word Suppression Test (WST) in the style of the Wechsler Memory Scale. The WST consisted of two test parts - one with negative and one with neutral