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Research paper

Effects of cortisol on hippocampal subfields volumes and memory performance in healthy control subjects and patients with major depressive disorder

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ABSTRACT

Overactivity of the hypothalamic-pituitary-adrenal (HPA) axis in major depressive disorder (MDD) is among the most consistently replicated biological findings in psychiatry. Magnetic resonance imaging (MRI) studies have consistently demonstrated that hippocampal (HC) volume is decreased in patients with MDD. The improved spatial resolution of high field strength MRI has recently enabled measurements of HC subfield volumes in vivo. The main goal of the present study was to examine the relationship between cortisol concentrations over a day and HC subfield volumes in patients with MDD compared to healthy controls and to investigate whether diurnal cortisol measures are related to memory performance.

Fourteen MDD patients with moderate or severe episodes were recruited, together with 14 healthy controls. Imaging was performed using a 4.7 T whole-body imaging system. HC subfields and subregions were segmented manually using previously defined protocol. Memory performance was assessed using the Wechsler Memory Scale IV. The salivary cortisol levels were measured over the course of one day.

We found that cortisol awakening response to 8 h (CAR-8 h) was higher in MDD patients compared to controls and that this increase in CAR-8 h in MDD patients correlated negatively with left total Cornu Ammonis (CA)1–3 and left HC head volume. In healthy controls mean cortisol levels were negatively associated with right total CA1–3, right HC head, and right total HC volume. In addition, in healthy controls higher CAR-8 h was related to worse performance on the immediate content memory. These results provide the first in vivo evidence of the negative associations between cortisol level, CA1-3 HC subfield volume and memory performance in patients with MDD and healthy controls.

1. Introduction

Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the release of corticosteroid hormones. While brief HPA axis activation in an acutely stressful situation is important for optimal performance, continuous hyperactivation of the axis can be maladaptive and eventually lead to mental and physical health conditions. Overactivity of the HPA axis in major depressive disorder (MDD) is among the most consistently replicated biological findings in psychiatry as is most evident from increased basal cortisol levels, escape from dexamethasone suppression, and exaggerated responses in the combined dexamethasone-CRH challenge test (Barden, 2004). However, the recent meta-analyses pointed to the modest effect size and the large heterogeneity of results (Knorr et al., 2010; Stetler and Miller, 2011). For instance, the first study of a large cohort (n=1293) of MDD patients (Knorr et al., 2010) detected a small but statistically significant mean difference of morning and evening salivary cortisol levels between depressed patients and controls. However, this effect was modest and there was a large heterogeneity between the studies of salivary cortisol as well as a substantial overlap between values for patients and controls. In the second study (Stetler and Miller, 2011) of 18,454 individuals it was found that approximately 73% of depressed individuals had cortisol values greater than the median cortisol value among non-depressed individuals. In addition,

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cortisol differences between depressed and healthy individuals usually were smallest in the morning and largest when assessed continuously throughout the day (Stetler and Miller, 2011), suggesting the importance of measuring cortisol concentrations over a day.

Manipulation of the HPA axis has been shown to have putative therapeutic effects in both preclinical and clinical studies, and it has been suggested that both glucocorticoid receptor antagonists and steroid synthesis inhibitors may be useful in the treatment of mood disorders (Young, 2006). Successful antidepressant treatment has been associated with resolution of impairment in HPA axis negative feedback and normalizing the HPA axis in depressed patients (Heuser et al., 1996; Nickel et al., 2003).

Stress and glucocorticoid overexposure affect hippocampal (HC) neuroplasticity, neuronal survival, and glial survival via mechanisms that are at least in part localized to specific hippocampal (HC) subfields (Sapolsky, 2000; Czéh and Lucassen, 2007; Pittenger and Duman, 2008). These mechanisms include dendritic retraction (Czéh and Lucassen, 2007) neuronal death, and suppressed neurogenesis (Pittenger and Duman, 2008). The cornu ammonis (CA3) pyramidal cells have also been found to be most susceptible to neuronal damage and cell loss associated with prolonged social stress and glucocorticoid overexposure, in both rats and primates (Sapolsky, 2000).

Magnetic resonance imaging studies (MRI) have consistently demonstrated that HC volume is decreased in patients with MDD (Videbech and Ravnkilde, 2004; McKinnon et al., 2009; Malykhin and Coupland, 2015) and that those reductions have been associated with episode recurrence, history of childhood maltreatment, and deficit in memory function. Furthermore, both prenatal stress and childhood maltreatment are associated with abnormally developing HPA function, as well as with HC volume reduction (Frodl and O'Keane, 2013).

Recent studies of the relationship between HC volume and cortisol levels indicated that measuring cortisol at awakening is not a very stable index of cortisol functioning as linked to brain structures whereas cortisol awakening response (CAR) with several measures after awakening and cortisol response after stress tests might have better potential to reflect the physiology of the system (Dedovic et al., 2010; Frodl and O'Keane, 2013). The most consistent findings from a recent review (Frodl and O'Keane, 2013) is that an association between higher cortisol levels and smaller HC volumes arise from continuous measures of cortisol levels over a day, rather than a single measure taken at one time of the day only. The authors concluded that continuous measures of cortisol over a day are natural measures of feedback mechanisms. The single study in MDD that investigated the association between 24-hour urinary cortisol and the HC did not report significant associations in MDD patients, while it was seen in the healthy comparison group (Vythilingam et al., 2004). In general, both passive measures of cortisol levels (reflective of basal activity and diurnal rhythm) and challenge tests (reflective of the ability of the HPA axis to turn on and importantly to turn off) can be used to evaluate the HPA function.

The improved spatial resolution of high field strength MRI has recently enabled measurements of HC subfield volumes in vivo in MDD patients (Huang et al., 2013; Lindqvist et al., 2014; Travis et al., 2014a). The findings from these studies indicated that HC volume reductions in MDD are specific to the CA1-3 and dentate gyrus (DG) subfields, findings that appear consistent with preclinical evidence for localized mechanisms of HC neuroplasticity. However, whether those reductions are directly related to glucocorticoid-induced neuronal damage of the HC in MDD remains to be determined. A single study that investigated relationship between cortisol level and HC subfields volumes, found that smaller volumes in the CA2-3-DG area of the HC were linked to depressive symptoms and were associated with hyper-reactivity of cortisol secretion during the day in patients with Multiple Sclerosis (MS) (Gold et al., 2010) suggesting region-specific effects of stress on daily cortisol levels in controls vulnerable for depression. However, it remains unclear if measures of the HPA axis that incorporate daily cortisol measures are associated with reductions in HC subfields volumes observed in MDD patients.

The damaging effects of glucocorticoids on memory and learning are mediated through the HC (Goosens and Sapolsky, 2007). Despite the fact that increased levels of cortisol is associated with impairments in verbal and spatial episodic memory (Wolf, 2009) in healthy subjects and multiple evidence suggesting that patients with MDD have worse performance than healthy controls on memory tests (Lee et al., 2012) it remains unclear whether overall increased cortisol level or CAR or both are associated with memory impairment. Therefore, the main goal of the present paper was to examine the relationship between cortisol concentrations over a day and CA1-3 and DG HC subfield volumes in MDD patients compared to healthy controls. The second goal was to investigate whether diurnal cortisol measures are related to memory performance. We hypothesized that both mean cortisol level and CAR would be increased in MDD patients compared to controls and these increases will be associated with reductions in CA1-3 and DG subfields volumes and worse performance on episodic memory tests.

2. Materials and methods

2.1. Participants

Fourteen patients (4 males, 10 females) meeting DSM-IV criteria for MDD with moderate or severe episodes were recruited, based on full clinical assessment and the Structured Clinical Interview for Diagnosis for DSM-IV (SCID) (First et al., 1997), together with 14 healthy controls (5 males, 9 females). Participants were males or premenopausal females aged 18–50. Two women (one patient and one healthy control) were older than 45 years of age. The groups were similar in age, sex, education, and smoker status. MDD patients were recruited via local notices or directly referred from the outpatient psychiatry department by the authors (N. J. C. and P. H. S.). Symptom severity was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D). Healthy controls were recruited through advertisements in the community as well as word-of-mouth. The cohort of MDD patients and controls was a subset taken from our two previous studies (Huang et al., 2013; Travis et al., 2014). Those included had completed salivary cortisol tests (14 out of 35 MDD patients). The number of MDD patients included in the study is approximately 10% of the number of psychiatric patients screened and assessed to meet inclusion/exclusion criteria for this study. Detailed results on volumetric changes in HC subfields and their associations with memory performance in two independent MDD cohorts had been previously reported (Huang et al., 2013; Travis et al., 2014). 8 MDD patients included in this study appeared in Travis et al. (2014) and 6 patients in Huang et al. (2013).

Of the 14 MDD participants, 2 were antidepressant naïve or medication free $\geq$6 months, and 12 reported continuous use of antidepressant treatment for more than 6 months. The majority of MDD patients were non-responders. Exclusion criteria were MDD with only mild episodes, psychotic or atypical features, postpartum depression, seasonal affective disorder, lifetime schizophrenia, bipolar disorder, alcohol or substance dependence, anorexia nervosa, predominant personality or anxiety disorder, systemic corticosteroid use, significant medical or neurological disease, pregnancy or lactation, or treatment with mood stabilizers