available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

The relation of cortisol levels with hippocampus volumes under baseline and challenge conditions

Kevin D. Tessner[a,*], *Elaine F. Walker*[a], *Shivali H. Dhruv*[b], *Karen Hochman*[c], *Stephan Hamann*[a]

[a]*Department of Psychology, Emory University, Atlanta, GA 30322, USA*
[b]*Graduate Division of Biological and Biomedical Sciences, Emory University, Atlanta, GA 30322, USA*
[c]*Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30322, USA*

ARTICLE INFO

Article history:
Accepted 19 May 2007
Available online 26 May 2007

Keywords:
Hippocampus
Hydrocortisone
Glucocorticoid
Hypothalamic–pituitary–adrenal
HPA axis
MRI

ABSTRACT

Several studies using animal models have revealed an inverse relation between glucocorticoid levels and hippocampus volumes. This inverse relation has been interpreted as reflecting the role of the hippocampus in modulating glucocorticoid secretion, as well as the effect of glucocorticoids on the hippocampus. The objective of this study was to examine the relation between hippocampus volumes and baseline and post-challenge salivary cortisol levels in healthy young adults. A double-blind, placebo controlled design was used in which 14 males between 18 and 30 years of age received either 100 mg hydrocortisone or placebo on separate occasions approximately 1 week apart. Baseline and post-challenge cortisol levels were assessed prior to and after magnetic resonance imaging. Volumetric analyses of the hippocampus revealed no differences between the hydrocortisone and placebo conditions; however, post-challenge cortisol levels were inversely associated with total and right hippocampus volumes. Cortisol levels were not associated with the volume of the hippocampus in the placebo condition (i.e. under baseline conditions). The present findings are consistent with other evidence that the hippocampus, as reflected in volume, partially determines the efficacy of negative feedback in modulating cortisol levels.

1. Introduction

The hippocampus plays a role in modulating activity of the hypothalamic–pituitary–adrenal (HPA) axis via a negative feedback system that involves glucocorticoid binding to receptors in the hippocampus (Herman et al., 2005; Jacobson and Sapolsky, 1991). In rodents, smaller hippocampal volume is associated with heightened glucocorticoid levels and blunted negative feedback (Hibberd et al., 2000; Meaney et al., 1996; Meaney et al., 1995). This has also been shown in the rhesus (Coe et al., 2003) and tree shrew (Ohl et al., 2000), and a recent study of pigs exposed to chronic stress revealed that basal cortisol was negatively correlated with volume and neuron number of the hippocampal dentate gyrus on the left side, but not the right (van der Beek et al., 2004). Likewise, the density of hippocampal astrocytes was decreased in male tree shrews undergoing psychosocial stress, and these changes correlated strongly with hippocampal volume (Czeh et al., 2006).

Several neuroimaging studies of human subjects, typically clinical samples, have explored the relation between

* *Corresponding author*. Fax: +1 404 727 1284.
E-mail address: ktessne@emory.edu (K.D. Tessner).

0006-8993/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2007.05.027

glucocorticoid secretion and hippocampal volume. Again, the findings generally show an inverse relation, although some do not find this association (MacLullich et al., 2005; Vythilingam et al., 2004). In patients with dementia (Alzheimer's type), for instance, higher serum cortisol concentrations were associated with smaller hippocampal volume (Ferrari et al., 2000). Similarly, a longitudinal study revealed that in aged humans hippocampal atrophy was associated with higher basal cortisol and greater increases in cortisol over time (Lupien et al., 1998). However, MacLullich and colleagues (2005) failed to replicate this finding in a sample of healthy elderly men aged 65–70 years. In this study, the volume of the right and left hippocampus did not correlate with morning, afternoon, or post-dexamethasone plasma cortisol levels. Similarly, 24-h urinary free cortisol were not inversely associated with right and left hippocampus in middle-aged subjects with major depressive disorder, however, a negative correlation was identified in age-matched healthy subjects (Vythilingam et al., 2004). Likewise, a 6-month longitudinal study of elderly depressed subjects revealed that hippocampal volume reduction was not associated with increased cortisol levels (O'Brien et al., 2004). More recently, a study of healthy preadolescent children found no association between baseline cortisol and overall hippocampal volume, although a subregional analysis revealed significant inverse associations between baseline cortisol and the lateral aspects of the anterior, medial, and posterior portions of the hippocampus, with the most pronounced associations corresponding to the CA1 subfield (Wiedenmayer et al., 2006).

Animal studies have revealed that neurons in the hippocampus contain a high density of glucocorticoid receptors that are targets for steroids (Aronsson et al., 1988; de Kloet et al., 1994, 2000), and evidence indicates that hippocampal input from these principle neurons to the bed nucleus of the stria terminalis and subsequent projections to the paraventricular nucleus of the hypothalamus is important in feedback regulation of the stress response (Petrovich et al., 2001). Negative feedback effects in the HPA axis also occurs at the level of the pituitary as well as other cortical sites including regions in the frontal cortex (Diorio et al., 1993). For example, recent studies in rats suggest that the medial frontal cortex and anterior cingulate is involved in glucocorticoid regulation (Diorio et al., 1993; Sullivan and Gratton, 2002; Brake et al., 2000), and it appears that smaller cingulate cortex volumes may be associated with HPA axis dysregulation in humans (MacLullich et al., 2006). Further, in some reports, selective lesions of the hippocampal formation have been shown to increase basal glucocorticoid secretion (Sapolsky et al., 1984; Herman et al., 1989), although other studies have failed to replicate this finding (Tuvnes et al., 2003; Bradbury et al., 1993).

It is generally assumed that the functions of the hippocampus in modulating HPA activity and glucocorticoid secretion are mediated by both glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) (Bradbury et al., 1993; Keller-Wood and Dallman, 1984; van Haarst et al., 1997). Recent evidence from rodent studies suggests a distinction between "proactive" glucocorticoid negative feedback that maintains the HPA axis under baseline conditions, and "reactive" negative feedback that modulates activity of the HPA axis following acute HPA activation (Ladd et al., 2004). Reactive negative feedback may be more dependent on the hippocampus than proactive baseline modulation. The specific neural mechanisms distinguishing these two feedback processes are not fully understood, however, they are presumed to be differentially mediated by GR and MR. Further, although there is no documentation of these two processes in humans, there is reason to believe that there may be counterparts in human hippocampus feedback mechanisms (van Haarst et al., 1997).

We are aware of only one published study that has examined the relation of cortisol with hippocampal volume under challenge conditions. This investigation included both young (19–30 years) and older (59–76 years) healthy male subjects, and showed that total hippocampal volume was inversely associated with 24-h urinary cortisol and basal corticotropin (ACTH) levels, after controlling for age and total cerebral volume (Wolf et al., 2002). This same study also included a condition in which the investigators also administered hydrocortisone to challenge the HPA axis. Wolf and colleagues found no relation between post-challenge ACTH and hippocampal volume, but they did not report on the relation with post-challenge cortisol levels.

In summary, there is evidence of a relation between circulating glucocorticoids and hippocampal morphology. Consistent with the role of the hippocampus in modulating HPA activity, hippocampal volume is typically found to be inversely correlated with glucocorticoid levels, and this may partially reflect a reduction in negative feedback to the HPA axis in animals with reduced hippocampal volume. The present study extends previous investigations of this relation in healthy young adults. Using a double-blind, placebo-controlled paradigm, we examined the relation between hippocampal volume and cortisol levels under both placebo and challenge (hydrocortisone administration) conditions. First, it was predicted that cortisol secretion would be inversely correlated with hippocampal volume. Second, the assumption that "reactive" negative feedback is more dependent on hippocampal integrity leads to the prediction that the inverse relation between hippocampal volume and cortisol secretion will be more pronounced in the hydrocortisone challenge condition.

There is no animal data that suggests that a single exposure of corticosterone in adulthood would altar the volume of the hippocampus (Sousa et al., 1998a,b). In addition, Sousa et al. (1998a,b) report that hippocampal volume reductions occur after 3 months, but not 1 month of high-dose corticosterone administration. Generally, reductions in hippocampal volumes occur as a consequence of very high doses of glucocorticoid treatment over prolonged periods of time. Therefore, we do not expect to find hippocampal volume reductions following the administration of hydrocortisone in the participants in this study.

2. Results

2.1. *Salivary cortisol*

Mean raw salivary cortisol levels for the two experimental conditions are displayed in Table 1. As shown, the administration of hydrocortisone resulted in an increase in salivary cortisol that peaks between 1 and 2 h post-administration. It is important to note that these values reflect both endogenous