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Effects of cortisol on the laterality of the neural correlates of episodic memory

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Abstract

Alterations in the laterality of cortical activity have been shown in depressive illnesses. One possible pathophysiological mechanism for this is an effect of corticosteroids. We have previously demonstrated that endogenous cortisol concentrations correlate with the asymmetry of cortical activity related to episodic memory in healthy subjects and depressed patients. To further-examine whether this is due to a causal effect of cortisol on the laterality of episodic memory, we studied the effect of exogenous administration of cortisol in healthy subjects. Twenty-three right-handed healthy male volunteers were tested in a double-blind cross-over study. Event-related potentials (ERPs) were recorded during an episodic memory task following a four-day course of 160 mg/day cortisol or placebo. Low-resolution brain electromagnetic tomography (LORETA) was used to identify brain regions involved in the neurocognitive task. Cortisol levels were measured in saliva samples. ERP and LORETA analysis following placebo demonstrated significant left parahippocampal activation associated with successful retrieval. Cortisol led to a decrease in the mean early frontal ERP voltage and an increase in the late right ERP voltage. LORETA suggested this to be due to a significant increased late activation of the right superior frontal gyrus. There was no significant effect of cortisol on episodic memory performance. This study suggests that exogenous cortisol leads to more positive-going waveforms over the right than the left hemisphere, possibly due to increased monitoring of the products of retrieval. The results support the hypothesis of causal effects of cortisol on the laterality of cortical activity occurring during an episodic memory task.

Keywords: Cortisol; Episodic memory; Asymmetry; Stress; Electroencephalography (EEG); Event-related potentials (ERPs)

1. Introduction

Corticosteroids (cortisol in man and corticosterone in rodents) act on the brain inducing alterations in mood, emotion and neurocognitive functions. Many studies have investigated the effects of cortisol administration in healthy humans on episodic memory, memory for previously encountered events, with some demonstrating impaired memory (Newcomer et al., 1999; McAllister-Williams and Rugg, 2002). Episodic memory has also been shown to be impaired in patients with depression, a disorder that is frequently associated with increased cortisol concentration. Therefore, studies of the effects of cortisol on episodic memory are essential in full understanding the underlying mechanisms involved in the pathology associated with depressive illness. The effects of corticosteroids on neurocognitive processes have been demonstrated to be dose- and time-dependent (Lupien and McEwen, 1997). In rodents, hippocampal long-term potentiation (LTP), which may be a neurobiological correlate of memory, has been shown to have an inverted-U shape correlation with corticosteroids (Diamond et al., 1992). Similarly, some human studies have also indicated inverted-U shape correlation between exogenous cortisol dose and memory performance. Lupien and colleagues found that while a high dose

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of cortisol impaired working memory, a low dose actually improved memory performance (Lupien et al., 1999).

Cortical activity, as assessed using EEG and fMRI methodology, in general shows asymmetry during the performance of cognitive task, with this presumably reflecting the cerebral localisation of cortical networks involved in cognition. Changes in asymmetry occur in states of emotional disturbance, such as stress, anxiety and depression. Relative greater right frontal activity, demonstrated by less frontal alpha electroencephalography (EEG) frequency, has been found in fearful and distressed children (Calkins et al., 1996; Fox, 1994; Schmidt and Fox, 1998) and anxious and depressed adults (Coan and Allen, 2004; Allen et al., 2004; Davidson, 1998; Henriques and Davidson, 1991). Corticosteroids may play a part in the EEG asymmetry seen in stressful conditions. Indeed, it has been shown that 4 days of administration of 160 mg of the synthetic glucocorticoid prednisone to healthy subjects alters the laterality of alpha EEG, increasing right frontal activation (Schmidt et al., 1999). Similar findings have also been shown following acute treatment with cortisol in healthy subjects (Tops et al., 2005).

Asymmetry in the electrophysiological correlates underlying episodic memory has been shown in healthy humans (Tulving et al., 1994; Baddeley, 2001). Asymmetrical frontal and prefrontal cortex (PFC) activity, with relatively higher right hemisphere activity, has been reported in many (Tulving et al., 1994; Ragland et al., 2000; Bernard et al., 2001) but not all studies of episodic retrieval (Cabeza and Nyberg, 2000; Mayes and Montaldi, 2001). Event-related potential (ERP) data have shown differences in waveforms associated with accurate memory recollection when subjects are presented with a previously studied item compared to correct identification of new non-studied items (Wilding and Rugg, 1997; McAllister-Williams and Rugg, 2002; Alhaj et al., 2006). This "old/new" effect comprises two components: a left parietal activity, which is believed to reflect hippocampal-modulated cortical activation underlying episodic memory retrieval (Alvarez and Squire, 1994; McClelland et al., 1995) and right frontal activity, which is believed to originate from PFC and may reflect evaluation and monitoring processes that operate upon the products of memory retrieval (Rugg et al., 1996, 2002).

We have previously shown that endogenous cortisol concentrations correlate with the laterality specific to episodic memory retrieval in depressed patients and healthy subjects (Alhaj et al., 2007). In particular, cortisol concentrations were demonstrated to correlate negatively with the early left parietal and positively with the late right frontal ERP "old/new" effect components (Alhaj et al., 2007). We hypothesise that the correlation between endogenous cortisol and cortical asymmetric activity is due to a causal effect of cortisol. To test this hypothesis, we utilised a four-day exogenous cortisol administration paradigm in healthy subject who underwent an episodic memory task. The neural correlates of retrieval were assessed using ERPs and low-resolution brain electromagnetic tomography (LORETA) (Pascual-Marqui et al., 1999, 1994).

2. Subjects and methods

2.1. Subjects

Twenty-three healthy male subjects aged between 18 and 33 were recruited by advertisement from the local population. Subjects were compensated for their time and expenses. They were provided with information sheets and written informed consent was obtained. Ethical approval was granted by the Local Research Ethics Committee. Cerebral dominance was assessed using Briggs' modification of Annett's (Annett, 1967) handedness inventory (Briggs and Nebes, 1975) and only right-handed individuals were recruited.

The inclusion criteria required that all subjects had an IQ of ninety or more as assessed by the National Adult Reading Test (NART) to ensure that they comprehended the task instructions. It was also required that their first language was English in order to be familiar with all the words used in the experiment. All the subjects were healthy and not taking any medication. Females were not included in this study due to the potential interactions of the menstrual cycle with the HPA axis and because of ethical difficulties related to pregnancy checking and oral contraceptive pill interactions with the HPA axis. Subjects were excluded if there was evidence of past or present history of significant medical or psychiatric disorders (including drug and alcohol misuse) or if they had a first-degree relative with a history of a psychiatric disorder. This was ensured by a structured personal and family history administered by a research doctor. Subjects' mood was assessed using the Hamilton Depression Rating Scale (HDRS) –21 items, Beck Depression Inventory (BDI) and Profile of Mood State (POMS). In this study, subjects were excluded if they scored eight or more on HDRS.

2.2. Design

A double-blind, placebo-controlled, crossover design was used. Subjects were tested on two occasions following a four-day course of either cortisol (160 mg of hydrocortisone P.O. daily) or placebo in a random-balanced order. The cortisol was taken as 100 mg at 8:00 a.m. and 60 mg at 8:00 p.m. to mimic the circadian rhythm of endogenous cortisol secretion. The first dose was taken in the evening of day 1. A minimum of a two-week interval between treatments was used to minimise any carry-over effects of cortisol. The cortisol administration paradigm, previously used by Newcomer et al. (1999), was proposed to increase levels of cortisol to those found after severe stress. The subjects were asked to record the time they took the medication and the duration and quality of sleep (using a 100 mm. analogue scale) in a logbook. Subjects were issued with a Steroid Treatment card and a 24-h contact number for a research