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SHORT COMMUNICATION

No morning cortisol response in patients with severe global amnesia

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Summary Activity of the hypothalamus pituitary adrenal (HPA) axis is characterized by a pronounced circadian rhythm. An acute increase in cortisol levels occurs after awakening in the morning with continuously declining levels over the course of the remaining day. The morning cortisol increase probably reflects an activational response of the HPA axis aimed at preparing the body for the day. Some studies found patterns of enhanced or blunted waking cortisol responses observed under chronic stress, burnout, or post traumatic stress disorder.

The present study wanted to characterize the morning cortisol response and the circadian cortisol day profile in a sample of six male patients with severe amnesia due to hypoxia, herpes simplex encephalitis or closed head injury. Age and gender matched relatives or friends served as controls. Cortisol was measured from saliva samples collected at home on two consecutive days. The patients were woken up in the morning by their partners or caregivers. The morning cortisol increase typically observed in healthy subjects and also observed in the control group was absent in the amnesic patients. In contrast, a normal circadian day profile was found in the amnesic patients, with a pronounced circadian cortisol decrease. Further studies are needed to understand the neurological or psychological mechanisms leading to a missing morning cortisol response in amnesic patients.
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1. Introduction

Cortisol secretion is characterized by a strong circadian rhythm. The levels peak in the first 30 min after awakening (cortisol awakening response; Pruessner et al., 1997) and thereafter

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decline gradually over the course of the day. The lowest levels occur in the first part of the night (nadir). The free cortisol response to awakening has received considerable attention over the last few years and many modulating factors have been established. In addition to a genetic component (Wust et al., 2000), psychological and situational factors are known to influence the magnitude of the morning cortisol increase. An enhanced morning cortisol increase has been observed in subjects reporting chronic work stress (Wust et al., 2000; Steptoe et al., 2003). In contrast, a blunted morning cortisol response has been found in teachers with burnout (Pruessner et al., 1999), even though this finding could not be replicated in another study with burnout patients (De Vente et al., 2003). War refugees with post traumatic stress disorder (PTSD) also showed a reduced morning cortisol response (Rohleder et al., 2004). In addition, situational factors determine the size of the morning cortisol response. For example, a larger cortisol response occurs on work days compared to the weekend (Kunz-Ebrecht et al., 2004). Likewise an early wake-up time causes a more pronounced morning cortisol increase (Edwards et al., 2001).

Brain lesions due to insults in humans (Tchiteya et al., 2003) or due to localized experimental lesions in animals (Roozendaal et al., 2001) impact on cortisol secretion. Special emphasis has been placed on the role of the hippocampus. However, more recent data has provided evidence that other brain structures, especially the prefrontral cortex and the amygdala, are not only main target areas of glucocorticoids, but are also critically involved in the regulation of the hypothalamus–pituitary–adrenal axis (see for reviews Lupien and Lepage, 2001; Gold et al., 2002).

Global amnesia is caused by extensive lesions to several cortical and subcortical brain areas. These include bilateral medial temporal or medial diencephalic regions often extending to the frontal lobes or the basal forebrain. Etiologies can comprise insult, hypoxia, encephalitis, or severe closed head injury (Markowitsch, 2000). The aim of the present study was to characterize the morning cortisol response as well as the circadian day profile in a small sample of severely amnesic patients. The brain lesions of these patients might lead to elevated cortisol levels, which in turn could negatively impact on their memory performance (Roozendaal et al., 2001). On the other hand, the deteriorated spatial and temporal orientation of these patients might lead to a blunted awakening response due to the missing anticipatory response to the upcoming day.

2. Material and methods

2.1. Subjects

Patients and caregivers contacted the University of Bielefeld for a detailed neuropsychological diagnostic work up and provided written informed consent. Six severely amnesic patients (mean age 37.0±4.80 (SE)) and six healthy control subjects (mean age 38.7±3.41) participated in the study. All patients and control subjects were males. Control subjects were either friends or relatives of the patients. In the patient group, etiology of amnesia comprised hypoxia ($n=4$), herpes simplex encephalitis ($n=1$), and closed head injury ($n=1$). The occurrence of the amnesia was 2.98 years (±0.98) ago with a range of 0.9–6.33 years. Patients showed normal intelligence with an average IQ of 103.2 (±6.16) points assessed by a German adaptation of the National Adult Reading Test (Nelson, 1982). In contrast, as tested with the Wechsler Memory Scale-Revised (WMS-R), memory for verbal and non-verbal materials was severely impaired. Their IQ-scaled general memory quotient (MQ) was 50.7 (±0.67) points (normal average: 100 points), and their delayed MQ was similarly highly deficient (50.0±0.00). A quotient of 50 points is the weakest score that can be reached in the WMS-R. Since the patients also could not recall large portions of their previous life, the results clearly indicate severe global amnesia. The memory deficits were observed in the absence of general cognitive decline given their discrepancy between IQ and MQ, a profile typically seen in amnesic patients (Markowitsch et al., 1993).

Data from previous neuroradiological examinations with computer-tomography and in three cases with additional measures of resting state brain perfusion (SPECT) or glucose metabolism (PET) were available. Affected brain regions included basal frontal and medial temporal lobes, extending to basal ganglia, thalamus or brain stem.

Patients were tested under their current medication. All but one patient had antihypertensive, and/or lipid-lowering treatment. Two patients were further treated with antidepressants (tricyclic antidepressant and 5HT-/NA-reuptake inhibitor) and one patient received opioid analgesics. Control subjects were free of medication at the time of testing.

2.2. Cortisol measurements

Cortisol levels were assessed out of saliva samples obtained using Salivette sampling devices (Sarstedt, Rommelsdorf, Germany). Amnesic patients and their controls sampled saliva at home on two consecutive days. Amnesic patients were woken up in the morning by their partners or caregivers and were reminded repeatedly throughout the day to sample saliva. The cortisol response to awakening and a daytime cortisol profile was collected. For the cortisol response to awakening, all participants obtained the first saliva sample immediately

after awakening, and further samples 15, 30, and 45 min thereafter (Pruessner et al., 1997). A daytime profile of cortisol secretion was obtained by additional saliva samples at 09:00, 11:00, 15:00, 20:00 and 23:00 h. Free cortisol levels in saliva were measured using a commercially available immunoassay (IBL, Hamburg, Germany). For each sampling point, cortisol levels were averaged for the two consecutive sampling days. Reports of wake-up times were recorded to control for possible influences of this factor. For statistical analysis of the morning cortisol response, the global area under the curve (AUCg) and the area under the response curve (AUCi) were computed (Pruessner et al., 2003).

2.3. Sleep quality

Participants were asked to rate the quality of their last night's sleep on a 10-point scale (0=very bad, 10=very good). The average rating of the two test days was used for analysis. In addition, the partners or caregivers were asked to report the presence of any general sleep problems of the patients.

2.4. Statistical analysis

Cortisol levels were analysed with an analysis of variance (ANOVA) with the grouping factor DIAGNOSIS (patient versus relative) and the within subject factor TIME. Reported p values were corrected with the Huynh-Feldt procedure, where appropriate. The AUC values and the subjective sleep ratings were analysed using t-tests.

3. Results

3.1. Wake-up time

Controls tended to wake-up 30 min earlier than patients (controls: 7:15; patients 7:50).

3.2. Sleep quality

Five of the six patients reported subjective sleep ratings. Ratings of the patients (6.75 ± 0.94) did not differ significantly from those of the controls (5.90 ± 0.48). The partners or caregivers stated that none of the patients had any general noticeable sleep disturbance.

3.3. Morning cortisol response

The morning cortisol increase observed in the control group was completely absent in the amnesic patients (Fig. 1). ANOVA revealed a significant main effect of TIME ($F(3,30)=4.2$, $p<0.05$) and a significant TIME by DIAGNOSIS interaction ($F(3,30)=3.7$, $p<0.05$).

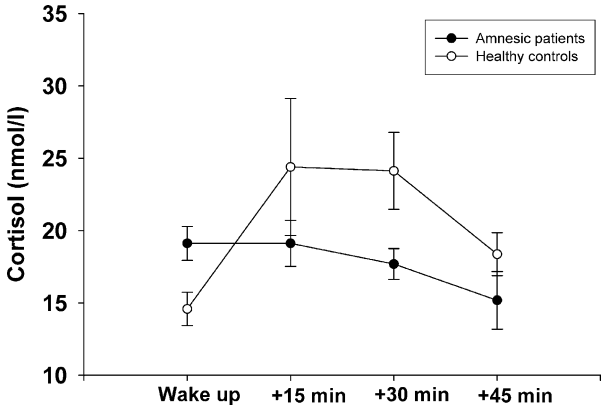

Figure 1 Morning cortisol response of amnesic patients and healthy controls (mean ± SE). Data represent the mean values of two sampling days.

Analysis of the AUCs revealed that both groups did not differ in the global AUC (patients: 53.96 ± 3.5, controls: 65.00 ± 7.5; $t(10)=-1.3$, p=n.s.). They did, however, differ significantly in the area under the response (or increase) curve AUCi (patients: -3.39 ± 2.5, controls: 21.25 ± 6.25; $t(10)=-3.66$, $p<.01$). Inspection of the individual data revealed that only one subject from the control group overlapped with the low AUCi values of the patients. The data range for the patients was -15.30 to 2.28, while the data range for the controls was -0.97 to 39.20.

3.4. Circadian cortisol profile

Both groups showed a similar circadian cortisol profile with the typical strong circadian decrease (Fig. 2). ANOVA revealed a significant main effect of TIME ($F(4,40)=16.08$, $p<0.01$) in the absence of a significant TIME by DIAGNOSIS interaction

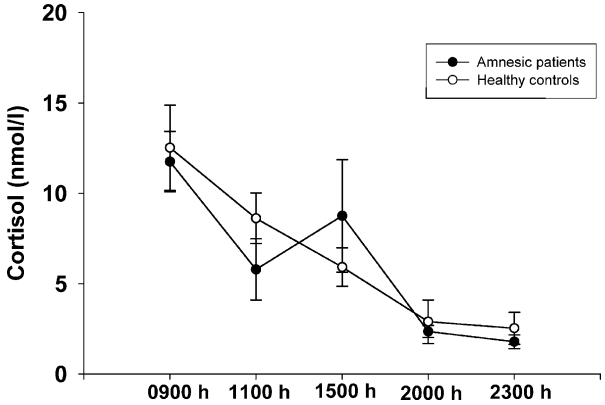

Figure 2 Circadian cortisol day profile of amnesic patients and healthy controls (mean ± SE). Data represent the mean values of two sampling days.

($F(4,40) = 1.00$). The non-significant elevation observed in the patient group at 1500 h was the result of one patient having a very high cortisol level (44.8 nmol/l) on one of the two sampling days.

4. Discussion

The main finding of the current small study in patients with severe global amnesia is an absent morning cortisol response despite an otherwise normal circadian cortisol day profile. Since patients were woken up by their caregivers or spouses who monitored the saliva sampling according to the fixed sampling protocol it appears unlikely that incorrect sampling is the reason for the missing morning cortisol response. In support of this notion is the fact that the morning response was absent in all six patients but clearly visible in five out of the six control subjects.

Another obvious problem with the patient sample is that most of them took various medications (antihypertensives, lipid-lowering substances or antidepressants). The effects of those medications on the morning cortisol rise have not been investigated systematically to the best of our knowledge. Unpublished data in older subjects at least suggest that antihypertensives have no strong effect on the morning cortisol rise (Wolf and Kirschbaum, unpublished observation). Also arguing against a major influence of this confound is the fact that all six patients had a missing morning cortisol response independently of the specific medications used. Future studies should try to study an additional patient group matched for medication use, however, this was not feasible within the frame of the current small pilot study.

A next potential confound is sleep quality and the possibility that the patients had woken up spontaneously earlier and thereafter had only superficially returned to sleep. Subjective sleep quality ratings did not differ between the patients and controls, even though the validity of this rating in the patient group can be questioned. The partners or caregivers of the patients did not report any substantial or repeated sleeping problems of the patients, but again this information might not be error-free. At least the repeated observation of the missing morning cortisol response in all six patients argues indirectly against such a situational explanation of the results. Nevertheless, a replication of the current finding is needed. A sleep laboratory study would be ideal, even though patient recruitment for such a study could be a challenge.

Previous studies from our group have observed blunted or missing cortisol responses in patients with burnout or PTSD (Pruessner et al., 1999; Rohleder et al., 2004). The current study extends these findings to patients with severe amnesia. We can, of course, only speculate about the possible underlying mechanism mediating this phenomenon in those patients. A direct effect of the brain damage is certainly possible even though brain lesions often lead to increased rather than decreased cortisol levels (Tchiteya et al., 2003). Moreover, the morning cortisol increase was missing in all patients despite their heterogeneous lesion sites. Nevertheless, it might be that damage to any one of the major memory-relevant brain structures (e.g. medial temporal regions, medial diencephalic regions, frontal lobes, or the basal forebrain; see Markowitsch, 2000) leads to a blunted morning cortisol response. Alternatively, it might be that the patients had an overlapping damaged region, and that this particular region is 'the one' region crucial for the morning cortisol rise. Future studies in patients with more circumscribed lesions and a more detailed neuroimaging workup will be able to answer the question of brain areas required for a regular morning cortisol response. Indeed the present results parallel recent findings obtained in an independent study with patients with hippocampal damage. Patients with damage to the hippocampus showed no awakening cortisol rise but, as in the present study, had unaltered cortisol levels during the remainder of the day (Buchanan et al., submitted).

In light of the issues discussed above an alternative, psychological explanation could be put forward. Namely the possibility that the morning cortisol response requires an intact spatial and temporal orientation and that subjects with severe amnesia do not show the anticipatory and activating hormonal response at the beginning of the day. Future studies including patients with 'psychogenic' amnesia could be one venue to test this hypothesis (Markowitsch, 2003).

In sum, the current small study on six patients with severe global amnesia documents an intact circadian cortisol rhythm and no evidence for elevated hypothalamus pituitary adrenal (HPA) activity. However, the morning cortisol response typically observed during the first 30 min after awakening and also observed in the control subjects was completely absent in these patients. Future studies are needed to understand the neurological or psychological mechanisms involved.

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