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ORIGINAL INVESTIGATION

Working memory performance and cognitive flexibility after dexamethasone or hydrocortisone administration in healthy volunteers

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Abstract
Objective Several studies have shown that glucocorticoids can impair declarative memory retrieval and working memory (WM) performance. The aim of the present study was to investigate the impact of a high dose of hydrocortisone on WM, as well as to examine the effects of cortisol suppression via treatment with a high dose of dexamethasone (DEX). We hypothesized that hydrocortisone treatment results in an impaired cognitive function compared with placebo. We further expected that dexamethasone treatment is also followed by cognitive impairment, due to the hypothesis that very low levels of cortisol are also associated with alterations in memory performance.
Methods In a placebo-controlled study with a within-subject design, 16 healthy volunteers received placebo or 120 mg of hydrocortisone (two boluses of 60 mg) directly before neuropsychological testing or 4 mg of DEX the day before testing.
Results We did not find any effect of hydrocortisone on WM and cognitive flexibility, even though cortisol levels were high at the time of testing. Furthermore, we did not find any effect of DEX treatment on WM and reaction time in a cognitive flexibility test. However, cognitive flexibility was negatively correlated with adrenocorticotropin (ACTH) in the DEX condition.
Conclusions Our results found no clear effect of hydrocortisone and dexamethasone treatment on WM. These results emphasize the need for further research on the association between hypothalamic–pituitary–adrenal axis activity and cognition. These studies should investigate the hypotheses of dose-dependent associations in more detail and should also include analyses on ACTH and cognition.

Keywords Working memory · Selective attention · Hydrocortisone · Dexamethasone · Cortisol · ACTH

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Introduction

The hypothalamic–pituitary–adrenal (HPA) axis is an important part of the neuroendocrine system involved in the coordination of the stress response (de Kloet et al. 2005). Briefly, upon stress exposure, corticotropin-releasing hormone is released from the hypothalamus and is transported to the anterior pituitary, where it stimulates the secretion of adrenocorticotropin (ACTH), which, in turn, stimulates the synthesis and release of glucocorticoids (GCs) from the adrenal cortex. The neuroendocrine stress response is counter-regulated by circulating glucocorticoids via negative feedback mechanisms targeting the pituitary, hypothalamus, and hippocampus as well as the prefrontal cortex (Lupien et al. 1999). This negative feedback loop is essential for the regulation of the HPA axis and, therefore, for the regulation of the stress response (Carrasco and Van de Kar 2003). GCs can pass the blood–brain barrier and mediate their effects by binding to two subtypes of intracellular receptors, the mineralocorticoid receptor

(MR) and the glucocorticoid receptor (GR; de Kloet et al. 2005). GRs have their highest density in the hippocampus (de Kloet 2003; Seckl et al. 1991) but are also prominent in the prefrontal cortex (Diorio et al. 1993; Lupien and Lepage 2001; Meaney and Aitken 1985), which both are brain regions of substantial importance for memory function. While the hippocampus is especially important for declarative memory, the prefrontal cortex is crucial for working memory (WM; Wolf 2009).

In healthy subjects, there is compelling evidence that acute administration of GCs impairs retrieval from long-term memory (Buchanan 2007; Het et al. 2005; Roozendaal 2002). Similar effects have been obtained using psychosocial laboratory stressors (Elzinga et al. 2005; Kuhlmann et al. 2005a). Memory consolidation, on the other hand, seems to be positively influenced by higher cortisol levels shortly after encoding (Roozendaal 2002; Wolf 2009), while consolidation during sleep requires rather low cortisol (Wagner and Born 2008).

The effect of stress and stress hormones has also been investigated for WM, even though fewer data exist. Animal studies, for example, have revealed that chronic stress or GC treatment impair WM (Arnsten 2000; Cerqueira et al. 2007; Mizoguchi et al. 2000; Shansky et al. 2006).

In humans, pharmacological studies observed that both acute and chronic cortisol administration led to poorer WM performance (Lupien et al. 1999; Wolf et al. 2001; Young et al. 1999), although not all studies agree. In a sample of healthy elderly, no effects of GCs on WM could be revealed (Porter et al. 2002), which is in line with the study of Wolf et al. (2001). They found an impairing effect of hydrocortisone only in young men, but the sample size in this study was very small. Another study reported even an enhanced memory performance after hydrocortisone treatment in healthy young men (Oei et al. 2009b), while still others did not find any effect of hydrocortisone treatment on WM (Monk and Nelson 2002). These studies used nearly comparable doses of hydrocortisone (approximately 35–40 mg). One study investigated the effect of repeated administrations (Young et al. 1999): In a placebo-controlled design, they administrated 20 mg hydrocortisone twice a day over 10 consecutive days and found cognitive impairments including WM. Lupien et al. (1999) examined the effects of various doses of hydrocortisone on WM using an item recognition task with a different load. They found reaction times to be negatively affected by high doses of GCs, but predominantly in the more difficult trials of the WM test. Furthermore, they reported an inverted U-shaped curve function between the magnitude of changes in cortisol levels and WM performance. Thus, the effects of GCs seem to cause an increase or a decrease in WM as a function of drug dose (Lupien et al. 1999). The idea that the relationship between cortisol and cognition appears to follow an inverted U-shape dose–response curve with extremely high and low levels of cortisol impairing memory and intermediate levels enhancing memory consolidation has also been emphasized by others (Belanoff et al. 2001; de Kloet et al. 1999). Consistently, basal levels of GCs are essential for effective long-term potentiation, while higher levels impair it (Lorenzetti et al. 2009).

In this context, studies which have investigated memory performance when cortisol is suppressed are of great interest. Recently, an impairing effect of metyrapone-induced suppression of morning cortisol levels on memory retrieval has been found (Rimmele et al. 2010) as well as an impairment of sleep dependent memory consolidation (Wagner and Born 2008). Furthermore, cognitive impairments have been reported after blocking MRs with spironolactone (Otte et al. 2007), which is also in line with the idea that extremely low cortisol levels have negative effects on memory.

In addition, the impact of acute stress-induced GC elevations has been investigated, but also yielded mixed results: One study in healthy individuals found an impaired WM performance after stress, but only at high working memory load (Oei et al. 2006), while others did not find stress-related deficits in WM (Kuhlmann et al. 2005b; Smeets et al. 2006). Recently, Schoofs et al. (2008) found an impaired WM performance after stress, using an *n*-back paradigm. Furthermore, a stress-induced impairment in a working memory test with verbal stimuli has been reported (Luethi et al. 2009). The paradigms (item recognition task, *n*-back task, reading span task) used in the studies, which found an effect of stress-induced cortisol elevation on WM (Luethi et al. 2009; Oei et al. 2006; Schoofs et al. 2008), differed from those studies, which could not confirm these results. In these studies (Kuhlmann et al. 2005a; Smeets et al. 2006), a digit span task was used (Wechsler 1987). However, these studies showed that a moderate but physiological cortisol enhancement has an impact on WM in humans.

The aim of the present study was not only to investigate the impact of a high dose (120 mg) of hydrocortisone on WM but also to examine the effects of cortisol suppression via treatment with a high dose (4 mg) of dexamethasone (DEX), a GC which cannot pass the blood–brain barrier. This dose was used to fully suppress cortisol the following day. Besides a WM paradigm which has been also investigated in former studies, we further investigated cognitive flexibility (attention shifting), which is an important part of WM. We hypothesized first that hydrocortisone treatment results in an impaired cognitive function compared with placebo. Second, we expected that dexamethasone treatment and therefore reduced cortisol levels when testing is also followed by cognitive impairment, due to the hypothesis that very low levels of cortisol are also associated with alterations in memory performance.

Materials and methods

Participants

Sixteen healthy volunteers, seven men and nine women, participated in the study. The mean age was 38.4 years (5.0) with a range from 31 to 50 years.

Exclusion criteria were the following: any severe disease during the prior 6 months, i.e., CNS relevant somatic diseases (e.g., neurological diseases), metabolic diseases (e.g., thyroid disease, diabetes), organic shift in cortisol secretion (e.g., Morbus Cushing), immune-mediated diseases, cardiovascular diseases, or other current infections. Further exclusion criteria were pregnancy, current infection, use of medication, any current or lifetime psychiatric disorders, or cognitive impairment.

The protocol was approved by the ethics committee of the medical faculty of the University of Marburg, Germany. All subjects gave written informed consent and received a 125-euro incentive.

Procedure

A double-blind placebo controlled study design was used. All participants were tested three times (within-subject design) with a minimum of 72 h between the examinations. The participants were randomly allocated to the treatments. The study protocol is presented in Table 1. The day before testing, a pill containing either placebo or 4 mg dexamethasone was taken at 11 p.m. at home. The day after, subjects received an intravenous catheter 1 h prior to the test. At 2 p.m., they took the second pill, containing 60 mg of hydrocortisone or placebo, respectively, which was repeated at 3 p.m. Two oral boluses were given separated by 1 h to prevent blood concentrations of hydrocortisone from decreasing too early. Blood samples were drawn at 30-min intervals with the first sample drawn at 2 p.m. (0, +30, +60, +90, +120, +150, +180, +210 min). The test on cognitive flexibility was run at +110 min, while working memory was tested +170 min after the first drug/placebo intake. In the two sessions with active agents, increased or reduced levels of cortisol could be expected to be similar at both post-drug intervals (+110 or +170 min).

Tests of working memory and cognitive flexibility (shifting)

Two subtests from the "Test for Attentional Performance" (Zimmerman and Fimm 1993) were used in this study.

In the working memory task, a sequence of numbers is presented to the subject on a computer screen. The subject is required to determine in each trial whether the present number corresponds with the one before the previous number (2-back task). Such a correspondence represents the target succession. Within the sequence of 100 numbers, the target succession was presented 15 times.

To test cognitive flexibility, we decided to examine attention shifting. In this test, two stimuli (target and distractor) were presented simultaneously left and right from a fixation point. The participant was asked to press one of two buttons (left and right) in concordance with the position of the target stimulus. The target stimuli were alternately a number and a letter whereas the other stimulus at a time was the distractor. Accordingly, continuous requirement to engage with and disengage from target stimulus was imposed. Overall, 100 stimuli were presented. In both tests, the mean reaction times of correct responses as well as the number of correct responses were analyzed.

Biochemical analyses

Blood was collected in EDTA tubes, immediately centrifuged, and the plasma was stored at −80°C until assayed. Plasma samples were assayed by using commercial enzyme immunoassay for cortisol and chemiluminescence immunoassay for ACTH. Inter- and intra-assay coefficients of variance were below 7% for all analyses.

Statistics

Statistical analyses were performed using SPSS Version 15.0. Cortisol and ACTH release was analyzed via ANOVA

Table 1 Study protocol

Treatment condition	First drug/placebo intake 11 p.m. (the day before)	Second drug/ placebo intake 2 p.m. (0 min)	Third drug/placebo intake 3 p.m. (+60 min)	+110 min	+170 min
High cortisol condition	Placebo	60 mg hydrocortisone	60 mg hydrocortisone	Cognitive flexibility test	Working memory test
Cortisol suppression	4 mg dexamethasone	Placebo	Placebo	Cognitive flexibility test	Working memory test
Control condition	Placebo	Placebo	Placebo	Cognitive flexibility test	Working memory test

with repeated measurements. As measure for total cortisol and ACTH release, the area under the curve (AUC) with respect to increase was calculated using the following formula (Pruessner et al. 2003): $\mathrm{AUC} = \frac{C_n - C_1}{2} + \sum_{i=1}^{n-1} C_i$. Data from the cognitive flexibility test and the working memory test were also analyzed using univariate ANOVA with repeated measurement. Furthermore, Pearson's correlation analysis was used to analyze associations between neuropsychological and endocrine data (AUC). The level of significance level was set at α=0.05 for all analyses.

Results

ACTH and cortisol release

Cortisol and ACTH release were analyzed with a 3×8 ANOVA with repeated measurements, with the two main factors being treatment condition (placebo, hydrocortisone, and dexamethasone) and time (eight measurement points). The endocrine data are presented in Fig. 1. Concerning ACTH release, the following significant effects have been found: a main effect of treatment condition ($F_{df1,\ 15}$=63, 93, p<0.001), a main effect of time ($F_{df1,\ 15}$=20, 78, p<0.001), and a treatment by time interaction effect ($F_{df1,\ 15}$=15, 84, p<0.001). Post hoc ANOVA showed that all treatment conditions differed from each other (all p<0.001). For cortisol release, we also found significant effects of the main factors treatment condition ($F_{df1,\ 15}$=46, 33, p<0.001) and time ($F_{df1,\ 15}$=28, 36, p< 0.001), as well as a significant treatment×time interaction effect ($F_{df1,\ 15}$=31, 73, p<0.001). Again, all treatment conditions differed significantly from each other (all p< 0.001). Differences between the treatment conditions were also seen when analyzing the AUC for cortisol and ACTH via ANOVA with repeated measurement (cortisol: $F_{df2,\ 30}$= 41, 08, p<0.001, ACTH: $F_{df2,\ 30}$=61, 36, p<0.001).

Thus, the intended manipulation was successful: After dexamethasone treatment, cortisol and ACTH levels were suppressed at the time of testing. After hydrocortisone treatment, cortisol was markedly enhanced, while ACTH levels showed a decrease over time.

Working memory and cognitive flexibility (attention shifting)

Concerning working memory performance, no differences among the three treatment conditions could be revealed, neither for reaction time ($F_{df2,\ 30}$=1, 89, p=0.17) nor for the number of correct responses ($F_{df2,\ 30}$=0, 14, p=0.87). The results are presented in Table 2.

There were also no differences in mean reaction time among the treatment conditions in the attention shifting test ($F_{df2,\ 30}$=0, 65, p=0.63; see also Table 2). When analyzing the number of correct responses, a significant effect of treatment could be revealed ($F_{df2,\ 30}$=4, 10, p=0.03). Post hoc ANOVAs showed that the dexamethasone condition differed from the placebo condition (p=0.02), with fewer correct responses in the dexamethasone condition. There were no differences between the placebo and the hydrocortisone condition (p=0.12) nor between the hydrocortisone and the dexamethasone condition (p=0.29).

For explorative purposes, we analyzed whether the treatment order influenced the results. There were no such effects.

Associations between working memory, attention shifting, and endocrine data

We computed correlations between the AUCs for ACTH and cortisol release on the one hand and the neuropsycho-

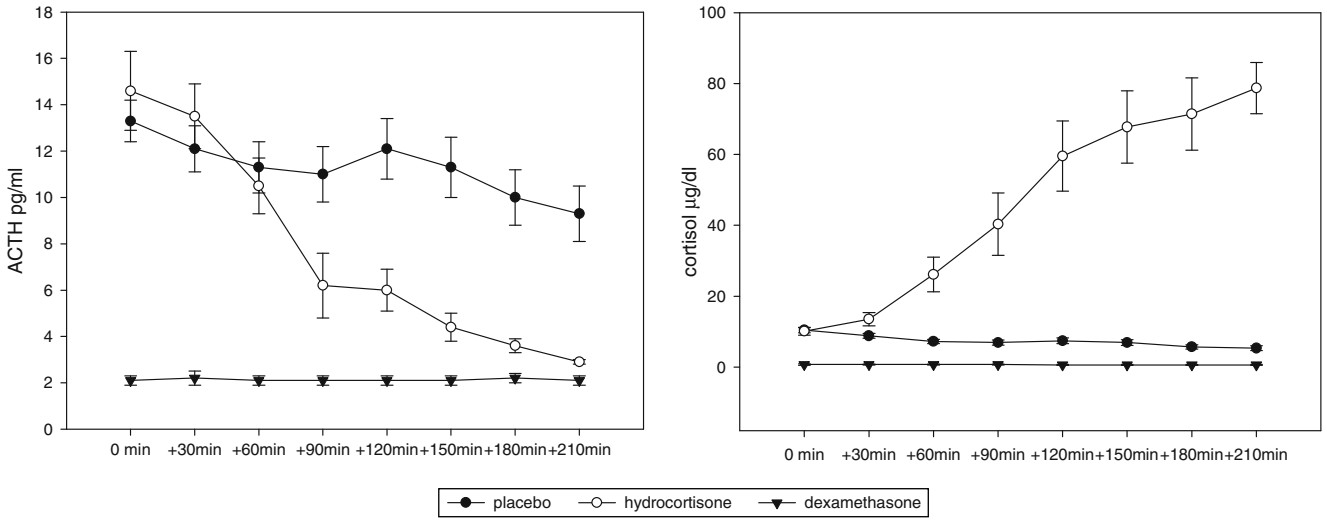

Fig. 1 ACTH and cortisol release (mean/SEM) in the three treatment conditions: dexamethasone, hydrocortisone, and placebo (N=16)

Table 2 Cognitive flexibility and working memory after placebo, hydrocortisone, and dexamethasone

	WM mean reaction time	WM number of correct responses	CF mean reaction time	CF number of correct responses
Placebo	597.2 (156.0)	13.1 (1.7)	713.5 (139.5)	95.9 (2.3)
Hydrocortisone	663.1 (156.2)	13.1 (1.6)	747.1 (172.1)	94.2 (3.0)
Dexamethasone	644.3 (163.2)	12.9 (1.9)	739.9 (143.1)	93.4 (3.2)*

CF cognitive flexibility, *WM* working memory

*$p=0.02$ (significant difference between the placebo and the dexamethasone condition concerning number of correct responses in the cognitive flexibility test)

logical data on the other for each treatment condition. There were no significant associations between working memory, cognitive flexibility, and both AUCs in the placebo and in the hydrocortisone condition (all $p>0.39$). In the dexamethasone condition, there was a significant correlation between the reaction time in the test on cognitive flexibility and ACTH release ($r=-0.67$, $p<0.001$). All other correlations failed to be significant also in this session.

Discussion

In the current study, we investigated the effects of high and low cortisol levels on working memory performance, also measuring cognitive flexibility. Contrary to our expectations, we did not find an effect of hydrocortisone treatment on WM and cognitive flexibility, even though cortisol levels were high at the time of testing. Furthermore, we did not find any effect of DEX treatment, resulting in low cortisol levels at the time of testing, on WM and reaction time in a cognitive flexibility test.

A study, which has investigated different dosages of cortisol on WM performance, reported reaction times to be negatively affected only by high doses of GC (Lupien et al. 1999). This effect was predominantly found in the trials with a high task load. While the cortisol levels in our study were comparable with the high dose group in the study by Lupien, the tasks we used might be of lower difficulty, which might explain the divergent findings. Contrary to this finding, another study, in which an effect of stress-induced cortisol elevations on WM was found, also used an *n*-back task (2-back and 3-back task; Schoofs, et al. 2008). Thus, the differences to the Lupien study might not only be interpreted in terms of task difficulty. Overall, after psychosocial stress, those studies, in which a more complex cognitive task was used, found an impaired WM performance, while no effects were found by easier tasks, e.g., digit span task (Kuhlmann et al. 2005b; Luethi et al. 2009; Oei et al. 2006; Schoofs et al. 2008; Smeets et al. 2006). It has to be mentioned that psychosocial stress paradigms result in more physiological cortisol levels, which are much lower than those in our study. Studies, which used a pharmacological stimulation to elevate cortisol levels and produced thus higher cortisol levels compared with psychosocial stress, also yielded divergent results (Monk and Nelson 2002; Oei et al. 2009a; Porter et al. 2002; Wolf et al. 2001). One of these studies even reported an enhanced WM performance after hydrocortisone treatment (Oei et al. 2009b).

In a recent study, it could be shown that the administration of GCs led to significant impairment on WM only when emotionally distractors, i.e., distractors with a negative valence, were integrated into the task (Terfehr et al. in press). This is in line with studies on declarative memory performance, showing that cortisol significantly impaired retrieval of negative words, while in contrast it had only a minor or no effect on neutral words (de Quervain et al. 2007; Kuhlmann et al. 2005a).

Under the hypothesis of an inverted U-shaped function between cortisol levels and memory function, studies are also needed which investigate memory performance when cortisol is suppressed. In this study, we did not find any effect of DEX treatment, resulting into low cortisol levels at the time of testing, on WM. Accordingly, we were not able to verify the hypothesis of negative effects of low cortisol levels on memory function. Another study, in which cortisol levels had also been suppressed, found contrary results (Rimmele et al. 2010). They reported an impairing effect of metyrapone-induced suppressed morning cortisol on memory retrieval. Furthermore, cognitive impairments have been reported after blocking MRs with spironolactone (Otte et al. 2007). Both observations are in line with the hypothesis that low cortisol levels also negatively influence memory performance. Otte et al. (2007) found an effect of MR blockade predominantly in more complex tasks, i.e., the Test d2 and the Trail Making Test B, but not in the Trail Making Test A, which is much easier compared with version A, and in a simple digit span task. Consistently, our findings of deteriorating effects of DEX treatment on the number of correct responses in the cognitive flexibility task suggest that tasks, which in contrast to our less demanding WM paradigm additionally involve a continuous attention shifting, are sensitive enough to demonstrate an action.

In summary, the results of the Lupien study, suggesting an inverted U-shaped curve function between the magnitude of changes in cortisol levels and WM performance (Lupien et al. 1999), have to be replicated, and further research is needed to understand the relationship between cortisol levels and working memory performance, including the effects of task difficulty and the emotional valence of stimuli. A further explanation for the divergent findings in the literature might be derived from the time of testing. Especially in the afternoon, cortisol effects might be more variable compared with morning effects.

When cortisol levels are high, cortisol mostly acts via GRs, which have a much lower affinity for cortisol than MRs. MRs are already occupied to a great extent under basal conditions (De Kloet et al. 1998). In the study presented here, effects of MRs and GRs are nor clearly distinguishable. However, in the hydrocortisone condition, one might assume that MRs and GRs are occupied, while in the dexamethasone condition, some, if any, of the MRs might be occupied. The MR/GR balance seems to be very important for cognitive functioning (De Kloet et al. 1998). It has been assumed that a fully occupation of MRs in concert with a 50% occupation of GRs might lead to optimal cognitive performance (De Kloet et al. 1998). Possibly, the higher number of mistakes in the cognitive flexibility task after dexamethasone treatment might be due to missing the MR effect. Interestingly, the blockade of MRs has been reported to have anxiolytic effects, which also follow a dose-depended inverted U-shaped function (Bitran et al. 1998). In summary, the effects of MR/GR balance on cognition need further evaluation.

Another unexpected finding was that cognitive flexibility was highly negatively correlated with ACTH but not with cortisol in the dexamethasone condition. While many studies have investigated the association between cortisol and cognitive function, there is a lack of studies on the relationship between ACTH and memory. Our results suggest that a less effective suppression of the HPA axis at the pituitary level, which indicates a less effective GR regulation, might be associated with less cognitive flexibility. Of course, this idea is very speculative and needs further scrutiny.

There are some limitations of the study which should be mentioned: First, the sample size of our study is very small, and thus, it was not possible to control for gender and age. Therefore, it cannot be excluded that we missed effects on WM and cognitive flexibility due to the small and heterogeneous sample and, accordingly, to a lack of statistical power. Furthermore, we were not able to control for potential confounders as menstrual cycle phase, intake of oral contraceptives, smoking, and coffee consumption (Kirschbaum et al. 1999). Therefore, our result needs to be replicated in a larger sample. Second, we investigated only three conditions, i.e., very high levels of cortisol, suppressed cortisol levels, and normal cortisol levels (placebo condition) at the time of cognitive testing. To test the hypothesis that cortisol levels and WM performance are associated in the form of an inverted U-shaped curve function, a condition with moderately enhanced cortisol levels is needed. Third, we did not assess self-reported mood and arousal in response to the treatments, which might have influenced the results (Abercrombie et al. 2006; Elzinga and Roelofs 2005; Tops et al. 2006).

In summary, our results emphasize the need for further research on the association between HPA axis activity and cognition. Those studies should investigate the hypothesis of dose-dependent associations in more detail and should also include analyses on ACTH and cognition.

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Conflict of interest There were no conflicts of interest, financial or otherwise, to declare.

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