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BRIEF REPORT

Acute cortisol administration reduces subjective fatigue in healthy women

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Abstract

Treatment with cortisol has been found to decrease fatigue and increase feelings of vigor in both patients and healthy male subjects. We obtained self-reports of mood before 35 mg cortisol or placebo ingestion, 70 min later, and after the healthy female subjects performed cognitive tasks for 1 h in a double-blind within-subject study. Cortisol decreased fatigue, increased vigor, and tended to decrease tension. Effects on fatigue were largest after task performance, when fatigue had increased, suggesting that improvement of fatigue by cortisol is observed when subjects are fatigued. This is the first study to demonstrate improvements in fatigue in healthy female subjects; this is particularly relevant because of the high prevalence of hypocortisolimic fatigue syndromes in women and recent evidence that many psychiatric disorders may involve stress-induced hypocortisolemia that is responsive to cortisol replacement.

Descriptors: Cortisol, Fatigue, Vigor, Healthy women, Hypocortisolemia

Clinical observations have been described of asthenia, fatigue, reduced concentration, apathy, and depression (sometimes altering with phases of tension and irritability) accompanying a pathological lack of corticosteroids. Following overdosage of corticosteroids an increased irritability and tension, hyperactivity, and also feelings of well-being have been observed (Von Zerssen, 1976; Wheatland, 2005). Patients treated with glucocorticoids suffer from sleeplessness associated with arousal and activation (Lozada, Siverman, & Migliorati, 1984; Fadeev, Gitel, & Melnichenko, 2001), and also elevated endogenous cortisol levels have been reported to be related to insomnia and arousal (Chapotot, Gronfier, Jouny, Muzet, & Brandenberger, 1998; Vgontzas, Bixler, Lin, et al., 2001; Vgontzas, Bixler, Wittman, et al., 2001). An abnormality that has been repeatedly reported in various fatigue syndromes including chronic fatigue syndrome and atypical depression is low levels of the hormone cortisol (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Gold & Chrousos, 1998). Corticosteroid supplements have been demonstrated to be an effective treatment for chronic fatigue syndrome and atypical depression, decreasing fatigue and increasing feelings of vigor (see Wheatland, 2005).

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In a recent study of 195 healthy female subjects aged 18–30 years we found that low morning cortisol was related to reports of fatigue and limpness (Tops, Riese, Oldehinkel, Fruhling, & Ormel, 2006). Similarly, the personality characteristic that has been most consistently related to low levels of cortisol, alexithymia, has also been related to high subjective fatigue and low self-rated vigor (Picardi, Toni, & Caroppo, 2005). This suggests that even in healthy people low levels of cortisol may relate to fatigue and low vigor. Indeed, administration of cortisol to healthy male subjects increased vigor and decreased fatigue (Plihal, Krug, Pietrowsky, Fehm, & Born, 1996; Reuter, 2002). In the present study we treated healthy female subjects with 35 mg of cortisol orally. Self-reports of mood were obtained before ingestion of cortisol or a placebo, 70 min later, and again 1 h later after the subjects performed cognitive tasks.

Methods

Participants

Twenty-seven healthy female volunteers aged 30–55 ($M = 39$, $SD = 7$) were enlisted by an advertisement in a local newspaper and were paid for participation. Each participant passed a health screening. Inclusion criteria included right-handedness, Dutch as their native language, normal or corrected-to-normal vision, regularly cycling or using oral contraception, and no personal history of psychiatric, metabolic, or neurological disorders. Eight

subjects were actively taking contraceptives. Volunteers who reported noxious health behaviors (drug abuse including excessive alcohol, smoking, and caffeine, and abnormal sleeping habits, e.g., too little sleep), chronic health problems, or psychopathology were excluded from the study. Participants were not on medication. Additionally, participants were screened for depression and anxiety using the 13-item Beck Depression Inventory (Bouman, Luteijn, Abersnagel, & van der Ploeg, 1985) and the State-Trait Inventory (Van der Ploeg, Defares, & Spielberger, 1980). All participants read and signed an informed consent statement approved by the Medical Ethical Committee of the University Medical Center of Groningen.

Procedure and Tests

We used a within-subject double-blind design. Placebo and treatment sessions, the order of which was counterbalanced, were separated by approximately 1 week. Subjects were asked not to use coffee, tea (unless caffeine-free), chocolate (-milk), or alcohol after 20:00 of the day preceding each session, and not to extraordinarily exert themselves physically. Compliance with these rules was checked at the beginning of the session. During the sessions subjects were not allowed to eat or smoke and were offered only water and caffeine-free tea to drink. The subjects arrived between 9:00 and 10:15. First, a capsule was ingested. In the experimental condition participants received a capsule containing cortisol (35 mg of hydrocortisone), whereas in the control condition they received a placebo (avicel capsule) double-blind orally. The participants were allowed to read while they waited 70 min for a blood sampling. Next, participants performed computer-based tasks of working memory, free recall, recognition memory, and selective attention for 1 h. Because not all subjects performed the same tasks, it is not possible to present task performance along with the present mood results.

Mood Measures

The Profile of Mood States (POMS) short version (Wald & Mellenberg, 1990) was filled out by the participants before ingestion of the capsule (T0), before the start of task performance (T1), and after the final task (T2). The POMS consists of five subscales: fatigue (range: 0–24), vigor (0–20), depression (0–32), anger (0–28), and tension (0–24), and has been translated and validated for a Dutch population.

Plasma Cortisol

The blood samples were collected in ice-chilled tubes. After centrifugation, the plasma was removed and the samples were stored at $-20°C$ until analysis. Plasma cortisol was measured by in-house radioimmunoassay at the University Medical Center of Groningen (Pratt, 1978).

Menstrual Cycle

Our female subjects self-reported the phase of their menstrual cycle (follicular, midcycle, or luteal), based on days since onset of their last menstrual period, and active contraceptive use.

Statistical Analyses

We checked for relations of menstrual phase or contraceptive use with any of the variables used in this study, but did not find any. Similarly, initial analyses controlled for the age of the subjects; however, since controlling for age did not seem to change the results, we report analyses without age as a covariate.

Multivariate analyses of covariance (MANCOVAs) for repeated measures were used to analyze mood measures, with Time (T1, T2), Measure (five subscales), and Treatment condition (cortisol treatment vs. placebo) as the within-subject factors and measures before ingestion of the capsule (at T0) as covariate. This analysis controls for differences between the sessions at baseline, that is, before ingestion of the capsule. The statistical level of significance was fixed at .05 in all tests.

Results

Plasma Cortisol

Cortisol administration increased plasma cortisol levels (placebo: $M = 201$ nmol/l, $SD = 56$; treatment: $M = 1267$, $SD = 411$; $F[1,26] = 156.73$, $p = .00001$).

Mood Measures

The means and standard deviations of the POMS mood state scores are shown in Table 1. We performed a MANCOVA repeated-measures analysis of the POMS scores that adjusted the mood scores according to the baseline T0 mood scores. The MANCOVA showed that there was a Treatment $\times$ Measure interaction, $F(4,103) = 5.51$, $p = .001$, and a Treatment $\times$ Time $\times$ Measure interaction, $F(4,103) = 2.44$, $p = .052$. Following up these interactions by performing separate analyses of each mood measure, the fatigue scores showed a significant effect of Treatment, $F(1,25) = 7.39$, $p = .012$, and Time, $F(1,25) = 17.75$, $p = .001$, and an interaction between Treatment and Time, $F(1,25) = 4.34$, $p = .047$. Analysis of the vigor scores similarly showed a significant effect of Treatment, $F(1,25) = 4.43$, $p = .046$, and Time, $F(1,25) = 13.84$, $p = .001$. Tension showed a trend of Treatment, $F(1,25) = 3.88$, $p = .060$. Performing separate analyses of the scores at T1 and T2 showed a significant effect of Treatment on fatigue at T2, $F(1,25) = 8.71$, $p = .007$, as well as on vigor at T2, $F(1,25) = 4.60$, $p = .042$, and a trend on tension at T2, $F(1,25) = 4.07$, $p = .055$. All other main or interaction effects remained nonsignificant.

As shown in Figure 1, during the session, fatigue increased and vigor decreased. Treatment with cortisol decreased fatigue and increased vigor and attenuated the increase in fatigue over time. At T2, tension was lower after cortisol treatment compared

Table 1. *Means and Standard Deviations of the Profile Of Mood States (POMS) Scores*

	Fatigue	SD	Vigor	SD	Tension	SD	Sadness	SD	Anger	SD
Placebo T0	1.42	2.91	14.26	2.97	1.12	2.23	0.62	2.02	0.15	0.61
Placebo T1	1.43	2.29	12.67	3.43	0.69	1.32	0.35	1.57	0	0
Placebo T2	3.31	3.68	10.93	4.62	0.81	1.50	0.42	1.42	0.15	0.61
Treatment T0	1.75	2.59	13.11	2.99	1.42	1.61	0.73	1.66	0.19	0.63
Treatment T1	1.42	1.95	13.26	2.92	0.46	0.99	0.38	0.90	0.12	0.59
Treatment T2	2.16	2.52	12.86	3.49	0.54	1.14	0.35	1.57	0.19	0.80

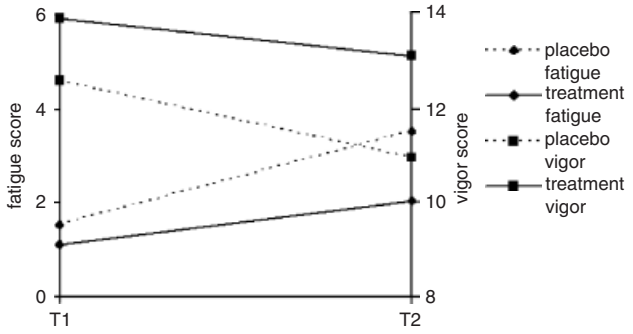

Figure 1. Means of fatigue and vigor scores before the start of a performance session (T1) and at the end of the session (T2), adjusted for the baseline scores of before capsule ingestion (T0). During the session, fatigue increased and vigor decreased. Treatment with cortisol decreased fatigue and increased vigor and attenuated the change over time.

to placebo (see Table 1). Depression and anger scores were very low and did not change during the session (see Table 1).

Discussion

In the present study we treated healthy female subjects with 35 mg of cortisol orally. Self-reports of mood were obtained before ingestion of cortisol or a placebo, 70 min later, and again 1 h later after the subjects performed cognitive tasks. Cortisol administration increased plasma cortisol levels as measured 70 min later. During the session, fatigue increased and vigor decreased. Treatment with cortisol decreased fatigue and increased vigor and attenuated the increase in fatigue and decrease in vigor over time, although this interaction between treatment and time was only significant for fatigue.

The effects of cortisol treatment on mood were largest after task performance, when in the placebo condition fatigue had increased and vigor decreased. This suggests that improvement of subjective energy by cortisol treatment is observed when conditions are less than optimal, for example, when subjects are fatigued. It should be mentioned that conditions were not necessarily optimal even at the start of sessions; for example, the subjects were asked not to consume caffeine from 20:00 the night before. Even in relatively moderate caffeine consumers, this could lead to caffeine withdrawal—a well-defined syndrome characterized by increased fatigue (Juliano & Griffiths, 2004). Nevertheless, cortisol treatment improved vigor and fatigue in healthy subjects in the morning, when endogenous cortisol levels are high. Furthermore, replicating similar results with male subjects, this study is the first one to demonstrate improvements in fatigue and vigor in healthy female subjects; this is particularly relevant because of the high prevalence of hypocortisolimic fatigue syndromes in women, and the association in healthy women between low morning cortisol levels and complaints of fatigue and muscular pain (Tops, Riese, et al., 2006).

Cortisol treatment tended to decrease tension. This finding may be related to a recent report that cortisol administration protects against the fear-arousing effect of phobia-related stimuli in subjects with social phobia or spider phobia (Soravia et al., 2006). Also, in a randomized study, patients that received cortisol during the perioperative period of cardiac surgery had lower intensity of chronic stress and posttraumatic stress disorder symptoms at 6 months after surgery (Schelling et al., 2004). Interestingly, glucocorticoid administration may also reduce fatigue in the first week after an operation (Rubin & Hotopf, 2002). We recently found preliminary evidence that the effects of cortisol treatment on cortical activity and subjective activation are state dependent and are influenced by testing conditions (Tops, van Peer, Wester, Wijers, & Korf, 2006). Perhaps cortisol administration blocks the development of whatever emotional arousal is provoked by the experimental conditions; in the studies by Soravia et al. and Schelling et al., the emotions that were aroused were fear- and trauma-related; in the present study, the testing conditions mainly aroused fatigue, a decrease in vigor, and some tension.

A similar explanation for the present results is that cortisol treatment does not directly impact on mood, but that cortisol treatment prevents conditions from having effects on the outcome measures. It may be hypothesized that the sustained, very high cortisol levels after cortisol administration may exclude both mineralocorticoid receptors and glucocorticoid receptors from further activation, thereby decreasing the responsivity of several brain systems. Changes in cortical activity and subjective activation during task performance would not take place after cortisol administration, to the extent that cortisol, or other systems that are rendered unresponsive by high cortisol levels, are normally involved in the modulation of such activity (Tops, van Peer, et al., 2006).

However, this kind of mechanism does not seem to explain the fatigue and listlessness accompanying a pathological lack of corticosteroids or the hyperarousal in patients treated with glucocorticoids or with elevated endogenous cortisol levels, described in the Introduction. Alternatively, or additionally, decreases in fatigue and tension and increases in vigor may hypothetically be explained by cortisol-induced increases in dopaminergic activity (Pruessner, Champagne, Meaney, & Dagher, 2004; Tops, Lorist, Wijers, & Meijman, 2004), metabolic agents (Sapolsky, Romero, & Munck, 2000), or of other neuromodulators, like, for example, oxytocin (Tops, van Peer, et al., 2006).

This study is the first one to demonstrate improvements in fatigue and vigor in healthy female subjects; this is particularly relevant because of the high prevalence of hypocortisolemic fatigue syndromes in women and the association in healthy women between low morning cortisol levels and complaints of fatigue and muscular pain (Tops, Riese, et al., 2006). Moreover, recent evidence suggests that many disorders labeled as psychiatric may involve stress- or trauma-induced hypocortisolemia that is responsive to cortisol replacement (Schuder, 2005). Even though the present study employed healthy subjects, the results line up with recent evidence that cortisol treatment may convey protective and therapeutic effects in some groups of patients (Schelling et al., 2004; Schuder, 2005; Soravia et al., 2006).

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