Exogenous cortisol acutely influences motivated decision making in healthy young men

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Abstract

Background The glucocorticoid (GC) hormone cortisol is the end product of the hypothalamic–pituitary–adrenal axis (HPA axis). Acute psychological stress increases HPA activity and GC release. In humans, chronic disturbances in HPA activity have been observed in affective disorders and in addictive behaviour. Recent research indicates that acute effects of GCs may be anxiolytic and increase reward sensitivity. Furthermore, cortisol acutely influences early cognitive processing of emotional stimuli.

Methods In order to extend such findings to more complex emotional-cognitive behaviour, the present study tested acute effects of 40 mg cortisol on motivated decision making in 30 healthy young men.

Results Results showed that cortisol indeed increased risky decision making, as predicted. This effect occurred for decisions where making a risky choice could potentially yield a big reward. These results are discussed with respect to currently proposed mechanisms for cortisol’s potential anxiolytic effect and GCs’ involvement in reward systems.

Keywords Cortisol · HPA axis · Emotion · Anxiolytic · Reward · Decision making

Introduction

The glucocorticoid hormones (GCs; cortisol in humans) are produced as the end product of the hypothalamic–pituitary–adrenal axis (HPA axis). After a physiologic or psychological stressor, corticotropin-releasing factor (CRF), synthesised in the paraventricular nucleus of the hypothalamus, is released into the anterior pituitary, which responds by increasing its output of adrenocorticotropic hormone (ACTH). ACTH is then released into the bloodstream and stimulates the release of cortisol by the adrenal glands. When central cortisol concentrations are elevated to stress levels, cortisol binds to GC receptors (GRs), whose density is purportedly highest in limbic and prefrontal areas where they probably influence reciprocal prefrontal-limbic circuits of emotion regulation (de Kloet et al. 1999; Sapolsky 2000; de Kloet et al. 2005; Ochsner and Gross 2005; Urry et al. 2006). Because of the involvement of the HPA axis in psychological stress, its relation to psychopathology has been studied extensively. Chronic HPA dysregulation (mainly hypercortisolism) has been reported for mood and anxiety disorders (Yehuda et al. 1996; Yehuda 2001; Young and Breslau 2004; Takahashi et al. 2005; Mantella et al. 2008; Vreeburg et al. 2009). Addictive behaviour is also associated with disturbances of HPA functioning and HPA-induced sensitisation of the dopaminergic (DA) mesolimbic ‘reward’ system (Marinelli and Piazza 2002; Koob and Kreek 2007; Sinha 2008). Acute effects of GCs may also contribute to increased reward-seeking and risk-taking behaviour related to substance abuse and pathological gambling (Marinelli et al. 1998; Mantsch and Katz 2007; Wohl et al. 2008; van den Bos et al. 2009). For stress-related psychopathology, the observed long-term alterations of HPA functioning may be partly due to...
dysregulation of the HPA negative feedback system as a result of unduly wear and tear on GRs (Yehuda 2004). Much less is known about acute effects of cortisol on emotion regulation and the manifestation of negative affect, sensitivity to punishment and anxiety.

Several recent publications suggest that exogenous GCs may reduce fear and biased attentional and working-memory processing of threat-related stimuli (Soravia et al. 2006; Het and Wolf 2007; Putman et al. 2007a, b; Oei et al. 2009; Vasa et al. 2009). This may be taken to suggest that cortisol acutely alters cognitive processing (attention, working memory, or memory retrieval) of threat- and withdrawal-related negative arousing information (see Putman et al. 2007a; de Quervain and Margraf 2008). However, it may also be the case that cortisol acutely influences bottom-up affective state, resulting in altered performance on sensitive emotional-cognitive experimental tasks only as a secondary effect. This may not be restricted to anxiolytic-like effects, but cortisol may also promote a more reward-driven or approach-motivated affective state. Animal models indeed suggest that high levels of GCs increase reward- and approach-related behaviour, likely due to increased DA activity (Marinelli et al. 1998; Marinelli and Piazza 2002; Mikics et al. 2007).

Hence, the present study sought to establish if cortisol acutely influences performance on a motivated decision-making task wherein choice behaviour is influenced by sensitivity to cues of punishment and reward. This motivated decision-making task (Rogers et al. 2003) presents subjects with 80 rounds of a gambling game in which they have to choose to play a control gamble with a fixed expectancy value or to play experimental gambles, which vary in their associated potential losses, potential gains and the probability of losing/winning. Choice between playing the control gamble or the experimental gamble is dictated by the perceived attractiveness of the experimental gamble relative to the control gamble and so depends on the attention that subjects pay to these cues of potential punishment and reward and on how they weigh their relative importance. This task has been utilised repeatedly to assess effects of different psychopharmacological manipulations (e.g. Rogers et al. 2003, 2004; Antypa et al. 2009). Since cortisol may also acutely promote reward-driven behaviour (though there is less empirical support for such a prediction from research in humans), we also tested if cortisol administration would result in increased sensitivity to reward. No effects on self-reported state anxiety were expected (as also reported in, for instance, Buchanan et al. 2001; Abercrombie et al. 2003; Tops et al. 2003; Putman et al. 2007a, b; Oei et al. 2009).

**Methods**

**Subjects**

Thirty healthy young men were recruited on campus and were paid for their participation. Exclusion criteria were drug use, habitual smoking, alcoholism, any past or current psychiatric, endocrine or neurological illness and excessive physical exercise. One participant demonstrated abnormal performance on the decision-making task (see below) and only data of the 29 remaining men are reported. Mean (M) age was 22.7 years [range, 20–30 with a standard deviation (SD) of 2.5]. The study was approved by the local review board, and all subjects provided written informed consent.

**Design and procedures**

Performance on various instruments was measured after subjects were orally administered two different capsules, identical in appearance, containing 40 mg hydrocortisone+320 mg Primogel or 360 mg Primogel on two separate testing sessions in a double-blind, placebo-controlled crossover design. Order of drug administration was counterbalanced across the subjects with 15 subjects receiving placebo on the first day of testing and 14 subjects receiving cortisol on the first day; (washout≥72 h). Curvilinear dose–response effects of GCs have been reported for some cognitive effects of cortisol. Buchanan et al. (2001) compared effects of 5 and 20 mg cortisol on a psychophysiological fear index and also suggested a nonlinear dose–response with apparent fear-reducing effects after the higher dose. The present dose of 40 mg was chosen as the highest level tested so far in human research for anxiolytic-like effects. In addition, this administration procedure is exactly as in our previous studies (Putman et al. 2007a, b, 2009). Testing was done between 1300 and 2000 hours at the same time on both days. Subjects were required to refrain from intake of any nutrients for at least 1.5 h prior to the start of the lab session. On arrival, they first completed a questionnaire to assess state anxiety (the STAI-s; van der Ploeg et al. 1980; Spielberger 1983) after which the capsule was administered. One hour later, another STAI-s was administered, after which computerised testing began. Participants then performed two experimental tasks designed to assess attentional processing of neutral and emotional pictorial stimuli, some of which may have been stressful to watch (data reported elsewhere). The decision-making task was administered last, approximately 2 h after capsule administration.
Decision-making task

This task contains 80 trials in which subjects have to choose between two gambles with the aim of earning as many game credits as possible. Coloured vertical bars of varying length indicate the probability of winning/losing, and the amount of credits that can be gained/lost is indicated at the top and bottom of the bars. Subjects were told that they would be paid a small amount of money for earned game credits to increase motivation to perform well on the task. Each trial lets the participant choose between a control gamble and an experimental gamble. For all trials other than the wins only and losses only trials (see below), this control gamble predicts a 0.5 probability of winning and a 0.5 probability of losing ten credits. Experimental gambles vary in the probability of losing or winning (0.4 probability of losing versus 0.6 probability of losing), the amount of expected gains (30 versus 70 credits) and the amount of expected losses (30 versus 70 credits), yielding a total of eight trial types that are each presented eight times (see Table 1). In addition, there are eight ‘wins only’ and eight ‘losses only’ trials. Wins only trials present the subjects with a choice between a guaranteed win of 30 credits and a gamble with 0.5 probability of winning 60 credits versus a 0.5 probability of winning nothing. The losses only trials present a choice between a guaranteed loss of 30 credits and a gamble representing a 0.5 probability of losing nothing and 0.5 probability of losing 60 credits. Typically, subjects choose the guaranteed win in wins only trials and gamble on the losses only trials. Order of trial types is randomised within four continuously presented blocks of 20 trials presenting each trial type twice per block. Dependent measures are proportionate choice scores—the number of times the participant chooses a certain experimental gamble relative to the frequency of occurrence of that trial type. For the wins/losses only trials, proportionate scores reflect the number of times the subjects chose the guaranteed win/loss relative to the number of trials of that condition.

Data reduction

Data from one participant were discarded; this participant took on average more than 13 s to choose on one of the testing days versus an average of approximately 2 s for the other subjects. Distributions of raw, log-transformed and arc sine-transformed performance scores for the decision-making task all differed significantly from normal, so only non-parametric statistical tests were performed for this experimental task. In order to test interactions between various conditions, contrast scores were calculated by subtracting the number of proportionate choice scores for various trial types. To test the effects of drug on probability of losing, scores for high probability of losing were subtracted from scores for low probability of losing for the two drug conditions separately. To calculate the expected gains contrast score, scores for low expected gains were subtracted from scores for high expected gains. An expected losses contrast score was similarly calculated for high versus low expected losses. Note that for all these contrast scores, larger scores indicate stronger preference for less risky and more rewarding choices.

Within-subject comparisons between the various proportionate choice scores and contrast scores were performed with Wilcoxon rank tests. Between-subject comparisons for the effects of order of administration (either placebo or cortisol on the first day of testing) were performed with Mann–Whitney U tests, but since no relevant comparisons showed an effect of order, these tests are not further mentioned below. State anxiety measures and salivary cortisol concentrations were tested in repeated measures ANOVA’s with drug (2; placebo versus cortisol) and time (2; before and after drug administration) as within subject factors. Initially, order was entered as a between-subject factor, but since order showed no effects, it was removed from the analyses and is not further reported below. Paired-sample t tests were used for simple mean comparisons of cortisol concentrations.

Results

Cortisol

One saliva sample for one participant was lost (the pre-administration sample in the placebo session). A repeated

Table 1 The eight conditions in the decision-making task where participants have to chose between playing a control gamble or an experimental gamble

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Probability</th>
<th>Expected gains</th>
<th>Expected losses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High (60%)</td>
<td>Large (70)</td>
<td>Large (70)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Small (30)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Small (30)</td>
<td>Large (70)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Small (30)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Low (40%)</td>
<td>Large (70)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Small (30)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Small (30)</td>
<td>Large (70)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Small (30)</td>
<td></td>
</tr>
</tbody>
</table>

The control gamble predicts a 0.5 probability of winning and a 0.5 probability of losing ten credits. Experimental gambles vary in the probability of losing/winning, the amount of expected gains and the amount of expected losses, yielding a total of eight trial types...
measures ANOVA was performed with drug and time as within-subjects factors and salivary cortisol concentrations as dependent variable. This showed a significant main effect of drug \( F(1,27)=53.96; p<0.001 \), a significant main effect of time \( F(1,27)=52.84; p<0.001 \), and a significant drug\times time interaction \( F(1,27)=55.68; p<0.001 \). The main effects of drug and time are carried by the high cortisol condition in the post-administration sample in the cortisol condition. In the placebo condition, mean cortisol concentration dropped from 7.73 nmol/L before administration to 3.89 nmol/L after administration, ~1 h later \( t(27)=3.17; p<0.005 \). In the cortisol condition, mean cortisol concentration rose from 6.47 nmol/L before administration to 116.4 nmol/L after administration \( t(28)=7.44; p<0.001 \). Post-administration cortisol concentrations differed significantly between placebo and cortisol conditions \( t(28)=7.50; p<0.001 \).

State anxiety

STAI-s data for one participant were removed before analyses because his STAI-s scores were extremely high (>2 SDs above the mean on all measurements). For the remaining subjects, a repeated measures ANOVA with time (before or after drug administration) and drug (placebo or cortisol) as within-subject factors and STAI-s score as dependent variable was performed. This showed no main effect of drug \( F(1,27)=0.063; p>0.05 \), no time\times drug interaction \( F(1,27)=0.140; p>0.05 \), but a borderline significant main effect of time \( F(1,27)=4.185; p<0.1 \). This trend-level main effect reflected a slight drop in STAI-s between the first and second measurement across both drug conditions: from \( M=30.9 \) (SD=5.4) to \( M=29.8 \) (SD=5.5).

Gambling task

Median proportionate choice scores are presented in Fig. 1a. Cortisol had no effect on overall frequency of choice for experimental gambles \( z=0.901; p>0.05 \). Subjects more often preferred to gamble on the losses only than on the wins only trials \( z=3.977; p<0.001 \), but this was not influenced by drug condition \( z=0.299; p>0.05 \). More experimental gambles were made for trials with small expected losses than large expected losses \( z=4.5345; p<0.001 \). Drug condition had no significant effect on the expected losses contrast score reflecting this risk avoidant choice pattern \( z=0.272; p>0.05 \). More experimental gambles were made for trials with large expected gains than for trials with small expected gains \( z=4.628; p<0.001 \). The expected gains contrast score reflecting this reward-driven choice pattern was not influenced by drug condition \( z=1.039; p>0.05 \). More experimental gambles were made for trials with a low probability of losing than for trials with a high probability of losing \( z=4.705; p<0.001 \). Drug condition significantly influenced the probability of losing contrast score \( z=2.106; p<0.05 \). Subjects made more high-risk experimental gambles after cortisol than after placebo. To clarify the nature of this effect of drug, low and high probability of losing conditions were analysed separately. Although cortisol had no effect on choice pattern in the low probability of losing condition \( z=0.396; p>0.05 \), it significantly increased risk-seeking when the probability of losing was high \( z=1.763; p<0.05 \; one tailed \). We further explored this effect and analyses of the separate trial types with a high probability of losing showed that cortisol significantly increased the number of experimental gambles of the most risky kind, i.e. when there was a high probability of losing a large amount of credits \( z=2.519; p<0.025 \), especially when there was also a large possible gain \( z=2.802; p<0.05 \). Since this last test concerns effect of cortisol on but one of eight experimental trial types, it is important to note that it also proves significant when using a Bonferroni-corrected alpha of 0.006 (see Fig. 1b).

Discussion

Our main hypothesis was that 40 mg of cortisol would acutely decrease punishment-sensitive behaviour on the gambling task. We also thought it was possible that cortisol would increase reward-sensitive behaviour. Results showed that cortisol changed motivated decision-making in a manner compatible with both notions.

Analysis of salivary cortisol samples confirmed that the cortisol manipulation was successful in significantly raising cortisol concentrations to levels very similar to those reported earlier for single oral 40 mg administrations (see, e.g. Abercrombie et al. 2003; Putman et al. 2007a). Results also showed a slight cortisol drop between the first and second salivary samples in the placebo condition, which probably reflects normal diurnal variation and/or habituation to the slight initial stress of coming to the lab for an administration study (cf. Putman et al. 2007a).

As expected, no effect on self-reported anxiety was observed. Only under very stressful circumstances (exposure to phobic stimuli, exposure to a strong laboratory stressor, or yohimbine-induced panic attack; Soravia et al. 2006; Het and Wolf 2007; Vasa et al. 2009) does cortisol seem to influence self-reported affective state. Several studies in healthy participants have reported that administrations of up to 40 mg cortisol does affect performance on more sensitive experimental measures of affect and emotional cognition in the absence of effects on non-challenged self-reported affective state (e.g. Tops et al.
This suggests that cortisol does not work by directly altering affective state but, rather, by altering the cognitive processing of emotional information that people encounter during their ongoing interactions with the environment [see de Quervain and Margraf (2008) for a different instance of such a biological-cognitive hypothesis, which applies specifically to phobic memories and also see Harmer (2008)].

Presently, as expected, cortisol reduced the influence of perceived probability of losing on performance of the gambling task. Although subjects typically shun the gambles with a high probability of losing compared to gambles with a low probability of losing, this risk-avoidant behaviour was reduced by cortisol. Rogers et al. (2004) reported that administration of a beta-adrenergic antagonist had the clearest effect on performance of this task when the probability of losing as well as the amount of potential losses were high, as was presently found. Interestingly, administration of such beta-adrenergic antagonists tends to acutely increase cortisol levels (see, e.g. Kizildere et al. 2003). Closer inspection of the present effect on the compound variable of probability of losing showed that the effect was carried by an increased proportion of risky choices in a single condition where the experimental gamble also offers a large potential gain. This behavioural pattern is probably best understood as reflecting a combined effect of reduced sensitivity to cues of punishment and increased sensitivity to reward.

Only little human research into potential acute effects of cortisol on reward-driven behaviour has been reported. Tops et al. (2006) reported increased approach-motivated locomotor behaviour. Putman et al. (2007b) reported increased selective processing of angry faces after cortisol administration. This was assumed to reflect increased socially agonistic motivational tendencies that have been linked to approach- and reward-driven behaviour (van Honk et al. 2001; d’Alfonso et al. 2000; Putman et al. 2004; Wirth and Schultheiss 2007; Beaver et al. 2008; Hermans et al. 2008; Passamonti et al. 2008; Carver and Harmon-Jones 2009). Most recently, van den Bos et al. (2009) reported cortisol effects on another motivated decision-making task (the Iowa gambling task or IGT; Bechara et al. 1996) in participants who had been subjected to a psychological stressor. The subjects with larger cortisol responses to the stressor demonstrated a performance pattern that reflects perseverance in making decisions that not only yield high immediate reward but also result in more severe punishment. Such a pattern of IGT performance is typical for less anxiously inhibited more reward-oriented participants (e.g. van Honk et al. 2002). Therefore, it is highly likely that the data reported by van den Bos et al. truly reflect effects of neuroendocrine agents involved in the stress response and do not merely result as a psychological response to the stressor. As such, their results showing that higher cortisol levels predict more reward and less punishment sensitivity are very much in line with the present results. Finally, it has also been demonstrated that administration of GCs increases self-administration of psychostimulant drugs in rodents (Marinelli et al. 1998; Mantsch and Katz 2007). A mechanism likely causing such increased reward-seeking behaviour is GCs’ acute increase of DA activity in the nucleus accumbens (NAcc), a vital structure in the mesolimbic DA reward pathway (Marinelli and Piazza 2002).

It seems quite possible then that relations between HPA activity and pathological gambling (Wohl et al. 2008), reward-driven and punishment-insensitive effects as ob-

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**Fig. 1 a** Median proportionate choice scores and 25th and 75th percentile limits for the eight experimental conditions. **b** Proportionate choice scores for the high-risk situation where there is a large probability of losing. For wins only and losses only, a higher score indicates fewer participants chose to gamble instead of taking the guaranteed win/loss. For all other measures, a higher score indicates that participants more often chose experimental gambles over than control gambles.
served by van den Bos et al., as well as the present results, may be mediated by cortisol’s effect on NAcc DA activity. Both the results of van den Bos et al. with the IGT and the present results constitute an effect of cortisol on conditions that simultaneously present a great risk and a great reward cue. These are high arousing situations likely involving simultaneous activation of neuroendocrine stress and reward systems, both of which may be involved in cortisol’s apparent stress-reducing effects. CRF, an important neurohormone in the HPA stress cascade, has been reported to have anxiogenic and depressogenic effects in non-human primates (Strome et al. 2002), so increased negative feedback resulting from our cortisol administration may influence sensitivity to arousing cues of punishment. Cortisol itself may also affect stress directly via stimulation of GRs in limbic-prefrontal emotion regulation circuits (e.g. de Kloet et al. 1999, 2005; Etkin et al. 2006; Libezon et al. 2007). Alternatively, potentially anxiolytic interactions between cortisol and its metabolites and GABA are possible. (see Putman et al. 2007a). Finally, NAcc DA-stimulating properties of cortisol have been proposed to reduce stress through reward sensitisation (see Marinelli and Piazza 2002). Possibly then, subtle effects of cortisol on the decision-making task may only become observable when both reward and stress systems involved in cortisol’s affective properties are triggered, as also inherent in performance of the IGT. Of course, all this remains speculative, and it is possible that different mechanisms are needed to explain the diversity of abovementioned findings. An alternative to this speculative explanation of the apparent specificity of the observed effect is to interpret it as a mere chance finding in a single condition. However, the effect remains significant after chance-level correction, so the finding is statistically sound and not likely spurious.

Several factors limit the interpretation of this study and its results. Firstly, in order to exclude possibly confounding influences of menstrual endocrine fluctuations and as a replication of several relevant previous studies (e.g. Putman et al. 2007a, b; Oei et al. 2009), only men were tested. These results may not generalise to women. Secondly, only a dose of 40 mg of cortisol was tested. Because the relation between cortisol levels and (cognitive) behaviour may be nonlinear (see e.g. Buchanan et al. 2001; Lupien et al. 1999), future studies may address the issue of dose-response relation.

The potential therapeutic value of GC administration in the treatment of anxiety disorders is an important current issue (Aerni et al. 2004; Soravia et al. 2006; Schelling et al. 2006; de Quervain and Margraf 2008). The present study adds to our knowledge of possible anxiolytic properties of cortisol by being the first to demonstrate that cortisol affects more complex-motivated behaviour in healthy subjects.

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References


