Acute Cortisol Elevations Cause Heightened Arousal Ratings of Objectively Nonarousing Stimuli

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To test the effects of cortisol on affective experience, the authors orally administered a placebo, 20 mg cortisol, or 40 mg cortisol to 85 men. Participants' affective responses to negative and neutral stimuli were measured. Self-reported affective state was also assessed. Participants in the 40-mg group (showing extreme cortisol elevations within the physiological range) rated neutral stimuli as more highly arousing than did participants in the placebo and 20-mg groups. Furthermore, within the 20-mg group, individuals with higher cortisol elevations made higher arousal ratings of neutral stimuli. However, cortisol was unrelated to self-reported affective state. Thus, findings indicate that acute cortisol elevations cause heightened arousal in response to objectively nonarousing stimuli, in the absence of effects on mood.

Keywords: cortisol, arousal, stress, emotion

A common misconception about the adrenal hormone cortisol is that acute elevations cause feelings of stress, anxiety, or negative affect. In contrast, numerous case studies have described euphoric effects of open label treatment with cortisol or cortisone (e.g., Fox & Gifford, 1953). However, the extant double-blind placebo-controlled studies of the effects of cortisol on self-reported mood in healthy humans have not consistently confirmed euphoric or dysphoric effects of cortisol, at least for doses within the physiological range. The current literature suggests that acute pharmacologically induced cortisol elevations have varying effects on mood, often with no effect on affective state or causing only mild mood elevation (e.g., Plihal, Krug, Pietrowsky, Fehm, & Born, 1996; Wachtel & de Wit, 2001; Wolf, Convit, et al., 2001).

Although the human research on the effects of cortisol on self-reported mood has often produced null results, it is clear that cortisol has important effects on emotion-related information processing. Cortisol readily crosses the blood-brain barrier and has time-, context-, and dose-dependent effects on numerous psychological processes. For instance, extensive research implicates glucocorticoids² as an important mechanism through which stress affects memory consolidation and retrieval, and recent research suggests that glucocorticoids affect memory only in emotionally arousing contexts (Abercrombie, Speck, & Monticelli, in press; Okuda, Roozendaal, & McGaugh, 2004).

Glucocorticoids also affect anxiety. Mild systemic elevations in corticosterone can have an anxiolytic effect in rats (File, Vellucci,

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& Wendland, 1979), but corticosterone infused directly into the amygdala causes anxiogenesis (Shepard, Barron, & Myers, 2000). Anxiety-related processes in animals are often assessed by the acoustic startle reflex. Anxiogenics and fear states enhance the startle reflex but anxiolytics reduce the startle reflex. In rats, acute elevations of corticosterone have been found to reduce the amplitude of the startle reflex (Sandi, Venero, & Guaza, 1996), whereas chronic corticosterone administration potentiates the enhancement of the startle reflex by corticotropin releasing hormone (Lee, Schulkin, & Davis, 1994). In addition, Buchanan, Brechtel, Sollers, and Lovallo (2001) found effects of cortisol on the human eyeblink startle response in the absence of effects on self-reported anxiety, which suggests that cortisol may play a role in affective processing that is not reflected in changes in self-reported mood.

Furthermore, one of the primary functions of cortisol is mobilization of energy stores (Munck, Guyre, & Holbrook, 1984), and it is often assumed that acute cortisol elevations enhance feelings of arousal. However, double-blind placebo-controlled studies in humans have often failed to show effects of cortisol on self-reported experience of arousal or on cognitive tasks assessing vigilance (e.g., Lupien, Gillin, & Hauger, 1999; Wachtel & de Wit, 2001). Nonetheless, glucocorticoids have region-specific effects on brain areas subsuming arousal-related processes and appear to have subtle effects on brain excitability. For instance, glucocorticoids and corticotropin releasing hormone have important effects

¹ It should be noted that many of the studies of the effects of glucocorticoids on emotion use synthetic glucocorticoids, such as prednisone or dexamethasone. Unlike cortisol or hydrocortisone (or cortisone, which converts to cortisol), synthetic glucocorticoids do not readily cross the blood–brain barrier. Furthermore, dexamethasone exhibits different binding affinities for the two types of corticosteroid receptors than does cortisol. Thus, studies of the effects of prednisone and dexamethasone on emotion must be interpreted with extreme caution when making inferences about the effects of endogenous variation in cortisol on affect.

² Glucocorticoids are corticosterone in most rodents and cortisol in primates.

on brain stem catecholaminergic input to the cortex through their effects on the locus coeruleus, a brain stem structure essential to the maintenance of arousal (Dallman, 1993; Makino, Smith, & Gold, 2002). In rats, systemic elevations in corticosterone within the physiological range produce dose-dependent changes in the firing rate of neurons in the reticular formation, another brain stem region that regulates brain excitability and arousal (Avanzino, Celasco, Cogo, Ermirio, & Ruggeri, 1987; Dubrovsky, Williams, & Kraulis, 1985). Likewise, corticosteroids have dose-dependent, bidirectional effects on neuronal excitability and stimulus-induced cortical evoked potentials, which also suggests a role for glucocorticoids in brain excitability (Born, Hitzler, Pietrowsky, Pauschinger, & Fehm, 1988; Dubrovsky et al., 1985). Thus, although human studies often fail to observe cortisol-related changes in arousal, glucocorticoids have important effects on brain activation and arousal-related processes.

Thus, cortisol appears to have effects on the neural substrates of anxiety and arousal that are not always reflected in changes in self-reported subjective experience. Human studies may need to use measures more sensitive than the typical global self-report indices to detect the effects of cortisol on affective experience and arousal. Measurement of affective response to stimuli may provide a more sensitive index of variation in subjective experience than does measurement of self-reported mood. It is important to assess affective responses to both frank emotional stimuli as well as to more neutral stimuli because it may be that the latter in particular will be most sensitive to the impact of cortisol because of their ambiguity and low level of emotional arousal. Thus, as part of a double-blind placebo-controlled study of the effects of cortisol on emotional memory (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003), we examined the effects of pharmacologically altered cortisol levels on responses to affectively laden and neutral stimuli and on self-reported affective state. On the basis of frequent failures to observe effects of cortisol on self-reported mood, paired with data showing the importance of cortisol in the neural substrates of affective processing, we hypothesized that confrontation with challenging stimuli may more sensitively tap cortisol's effects on affective processes than do global self-report measures.

Method

Participants

Ninety normal men were recruited.³ Three participants were dropped because of abnormally high cortisol levels.⁴ Two additional participants were dropped because of failure to follow instructions. These 2 participants provided highly inconsistent ratings of stimuli, with positive stimuli often rated as highly negative, and at times the opposite. The final sample was 85 men, with 28, 28, and 29 participants in the placebo, 20-mg, and 40-mg groups, respectively. Written informed consent was obtained in accordance with the University of Wisconsin Health Sciences Human Subjects Committee guidelines (see Abercrombie et al., 2003, for an additional description of participants and methods).

Procedure

Randomized double-blind oral administration of placebo, 20 mg cortisol, or 40 mg cortisol occurred at approximately 7:15 p.m. on any night of the week (hydrocortone; Merck & Co., Inc., Whitehouse Station, NJ). The duration of the experimental session was typically 2 hr 45 min. After a 45-min drug-uptake period, each participant performed a word rating task

followed by a picture rating task, during which he was instructed to rate stimuli on the basis of how he was feeling while viewing each stimulus. Ratings were obtained for both pleasantness (negative to positive) and arousal (low to high) using 9-point numeric Likert scales. Stimuli were negative and neutral words and pictures, which were presented on a computer monitor. Words were chosen using the Affective Norms for English Words (Bradley & Lang, 1999). Pictures were chosen from the International Affective Picture System (Lang, Bradley, & Cuthbert, 1998). After the rating tasks, memory and cognitive performance were assessed, which are described elsewhere (see Abercrombie et al., 2003).

Self-reported affective state was assessed at three time points during the session, at approximately 45, 100, and 160 min after drug administration. Ratings were obtained on the Positive Affect and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) and on 11 additional emotional adjectives (Feldman Barrett & Russell, 1998), which provide separate indices of pleasantness and arousal, thus disentangling valence and arousal dimensions. Saliva samples were collected to confirm dose-related elevations in cortisol and for computation of correlations between psychological measures and cortisol levels (see Abercrombie et al., 2003, for cortisol sample collection and processing methods).

Data Analysis

The effects of dose (placebo, 20 mg, and 40 mg) on emotional responses to stimuli and on self-reported affective state were examined using an analysis of variance (ANOVA). Significant effects were followed up with tests of correlations between emotional ratings and observed postdrug salivary cortisol levels (i.e., average of cortisol samples taken after drug uptake), allowing further examination of the relation between cortisol and affective experience.

Results

Cortisol Levels

Salivary cortisol levels did not differ among the three groups at baseline, F(2, 82) = 0.63, ns, but differed after drug uptake, F(2, 82) = 55.85, p < .001. Mean salivary cortisol levels after drug uptake were $0.09 \mu g/dl$ for the placebo group, $1.62 \mu g/dl$ for the 20-mg group, and $4.04 \mu g/dl$ for the 40-mg group. Cortisol levels in the 20-mg group were commensurate with endogenous elevations occurring during moderate behavioral stressors (e.g., final exam) or moderate exercise stress (e.g., 30 min on a stationary bicycle; Kirschbaum & Hellhammer, 1994). The cortisol levels observed within the 40-mg group remained within the physiological range of cortisol but would be seen only during extreme stress, such as trauma, marathon run, or surgery (Kirschbaum & Hellhammer, 1994; Resnick, Yehuda, Pitman, & Foy, 1995).

³ Participants consisted only of men because the current study was a part of a parent project that examined the association between cortisol and memory, which varies by gender (e.g., Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001).

 $^{^4}$ Two excluded participants in the placebo group had salivary cortisol levels of 0.93 and 1.17 μ g/dl (compared with the placebo group range of 0.03–0.29 μ g/dl) and indicated that they sleep very late into the morning on a regular basis, suggesting the possibility of altered circadian rhythmicity of cortisol. One participant in the 20-mg group chewed the capsule containing the hydrocortisone tablet. His extremely high salivary cortisol level of 22.7 μ g/dl was assumed to have resulted from hydrocortisone residue left in his mouth and/or from an increased absorption rate.

⁵ See Abercrombie et al. (2003) for a further description of stimulus sets.

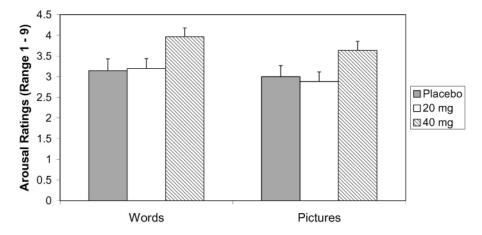


Figure 1. Arousal ratings of neutral words and pictures. The 40-mg group rated neutral words as more arousing than did the placebo and 20-mg groups, F(2, 82) = 3.50, p < .05, and a similar trend was apparent for pictures, F(2, 82) = 2.80, p = .07. Error bars represent standard error of the mean.

Self-Reported Affective State

ANOVAs examining the effects of dose (i.e., placebo, 20 mg, or 40 mg) on self-reported affective state revealed no effect of cortisol elevation on scores on the PANAS (Positive Affect, Negative Affect; Fs < 0.58) or Feldman Barrett and Russell (1998) scales (Pleasant, Unpleasant, Activated, Deactivated; Fs < 1.82).

Emotional Responses to Negative and Neutral Stimuli

Dose did not significantly affect valence ratings of negative or neutral stimuli (Fs < 0.93) or arousal ratings of negative stimuli (Fs < 0.59). However, the 40-mg group rated neutral words as more arousing than did the placebo and 20-mg groups, F(2, 82) = 3.50, p < .05, and the same pattern of results was found for pictures, but the effect fell short of significance, F(2, 82) = 2.80, p = .07 (see Figure 1). Comparison of the group means for words revealed that the 40-mg group rated neutral words as significantly more arousing than did both the 20-mg group, t(55) = 2.41, p < .02, and the placebo group, t(55) = 2.31, t > .03. The effect size for the difference between the 40-mg and placebo groups was t = 0.62, which is a medium effect size. Thus, extreme cortisol elevations caused higher arousal responses to neutral stimuli.

Correlations Between Cortisol Levels and Arousal Ratings of Neutral Stimuli

For the entire sample (N=85), individual differences in postdrug cortisol levels were positively but not significantly related to arousal ratings of neutral words ($r=.19,\ p=.08$) or neutral pictures ($r=.13,\ ns$). Within the placebo or 40-mg groups, variation in postdrug cortisol levels did not significantly predict arousal ratings of neutral stimuli (rs ranged from -.17 to .23). However, within the 20-mg group, postdrug cortisol levels were positively correlated with arousal ratings of neutral words ($r=.39,\ p<.05$), and a similar trend was apparent for pictures ($r=.32,\ p=.09$; see Figure 2). Thus, within the 20-mg group (showing moderate cortisol elevations), higher cortisol levels predicted greater arousal responses to neutral stimuli.

Discussion

Extreme cortisol elevations, which remained within the physiological range, were associated with greater arousal ratings in response to neutral stimuli. As a whole, the 40-mg group rated neutral stimuli as more arousing than did the placebo or 20-mg group. Within the 20-mg group, the individuals with higher cortisol elevations made higher arousal ratings of neutral stimuli. However, cortisol levels were unrelated to ratings of negative stimuli, and cortisol was also unrelated to self-reported affective state measured with the PANAS and Feldman Barrett and Russell (1998) scales. Thus, the data from the current study suggest that acute elevations in cortisol may be associated with feeling aroused in response to objectively nonarousing stimuli in the absence of pronounced effects on mood.

Other investigators conducting double-blind placebo-controlled studies of cortisol administration have also found no effects of cortisol on self-reported mood, anxiety, or arousal levels (Buchanan et al., 2001; Wachtel & de Wit, 2001; Wolf, Convit, et al., 2001). Thus, cortisol does not reliably change affective state. However, as outlined in the introduction, previous research shows that it alters activity in central circuitry underlying affective processes and brain activation. Cortisol's effects on brain stem regions governing brain excitability (Avanzino et al., 1987; Born et al., 1988; Dubrovsky et al., 1985; Makino et al., 2002) may cause only slight variations in arousal, which may not be reliably reflected in subjective experience or detected on global assessments of affect. The small but significant effect on arousal in the current study may be due to subtle effects of cortisol on the experience of arousal that are detectable only within the context of responses to stimuli.

⁶ A finding similar to the one presented here was included in the Abercrombie et al. (2003) article. However, 2 participants who did not follow instructions on the rating tasks were included in those analyses, and the finding fell short of significance. Here, these 2 participants are omitted, and relevant correlational analyses that were not in the prior report are included.

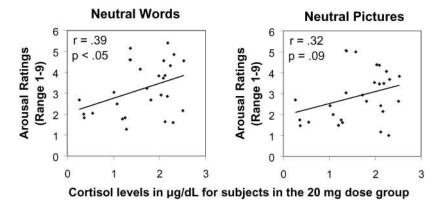


Figure 2. Scatter plot representing the correlation between postdrug cortisol levels and arousal ratings of neutral words and pictures for the 20-mg group. Within the 20-mg group, postdrug cortisol levels were positively correlated with arousal ratings of neutral words (r = .39, p < .05), and a similar trend was apparent for pictures (r = .32, p = .09).

In the current study, arousing negative stimuli were presented interspersed with neutral stimuli, which were not objectively arousing. Thus, the context in which the neutral slides were presented may interact with cortisol's effects on the affective apprehension of the stimuli. Cortisol may have increased the sensitivity to the emotional context provided by the negative stimuli, causing the experience of arousal due to the negative stimuli to generalize to the neutral stimuli. Previous research (which is outlined below) suggests that the psychological context within which cortisol elevations occur can modulate the psychological effects of the hormone. The inconsistency in the literature on cortisol's effects on human emotional experience may be due to the fact that contextual factors modulate cortisol's effects on affective processes.

The role of contextual cues in determining the affective significance of undifferentiated physiological arousal has long been an area of conceptual debate in emotion research. The well-known report by Schachter and Singer (1962) provided evidence that participants label emotional states after injection of epinephrine⁷ according to the context manipulated in the experiment. Schachter and Singer argued that cognitive attributions due to contextual cues are key. They argued that it is cognitive appraisal in combination with arousal that together form the experience of specific emotions. On this account, context is hypothesized to have an indirect effect on affective experience through higher order appraisals, which mentally define the experience of an undifferentiated state of arousal.

However, evidence suggests that cortisol directly modulates activity in brain regions that process contextual cues, the most important of which is the hippocampus. Fanselow and others (e.g., J. J. Kim & Fanselow, 1992) have differentiated two forms of fear conditioning, which depend on different neural circuitry. Cue fear conditioning constitutes the type of learning in which a neutral stimulus is paired with an aversive stimulus and after such pairing presentation of the neutral cue is sufficient to produce a fear response. Contextual fear conditioning refers to fear responses that are evoked by the background environmental cues of the location in which aversive training takes place. The hippocampus, which is rich with glucocorticoid receptors, is essential for contextual fear conditioning but not for cue conditioning (J. J. Kim & Fanselow,

1992). Pugh, Tremblay, Fleshner, and Rudy (1997) therefore tested the effects of corticosterone on both types of conditioning and found a selective role in contextual conditioning. Thus, it appears that corticosterone is essential in aversive learning that involves contextual information, and this effect may likely result from cortisol's modulatory role in hippocampal excitability.

Moreover, a recent study has shown that corticosterone may affect memory only in emotionally arousing contexts (Okuda et al., 2004). The authors performed a test of object recognition memory in groups of rats that were either previously habituated to the experimental context or for which the experimental context was novel and thus emotionally arousing. They found that cortisol dose-dependently affected memory in rats for which the experimental context was novel but had no effect in rats that were previously habituated. This study shows that the effects of cortisol on psychological processes depend on the context in which cortisol levels are manipulated. Because human studies have not yet examined the interaction of contextual factors and variation in cortisol levels, studies are needed that manipulate contextual variables and assess how participants' cognitive, affective, behavioral, and physiological responses to the context interact with cortisol's effects on psychological processes. It is known that dose and time of day are two important factors that determine the effects of cortisol on psychological processes. In addition, although affective responses may modulate cortisol's effects on memory, cortisol appears to have direct effects on the neural substrates of affective processes as described above. However, the dose response curves

⁷ Epinephrine is also an adrenal stress-related hormone but with a very different set of physiological effects than cortisol.

⁸ It is well established that the rat hippocampus is rich with glucocorticoid receptors (GR). However, the extent to which the hippocampus is a site of dense GR expression in the human is currently under debate. Primate models have provided mixed results with regard to the density of GR in the nonhuman primate hippocampus (Patel et al., 2000; Sanchez, Young, Plotsky, & Insel, 2000). Human postmortem data suggest high density of GR in the dentate gyrus, CA3, and CA4 portions of the human hippocampus (Seckl, Dickson, Yates, & Fink, 1991).

for the effects of cortisol on affect and memory may differ. For instance, in the current study the 40-mg dose caused heightened arousal in response to neutral stimuli, but the 20-mg dose produced memory facilitation for both neutral and emotional stimuli (Abercrombie et al., 2003; also see Buchanan & Lovallo, 2001). These issues require further study.

Furthermore, responses to neutral stimuli may be more susceptible than emotional stimuli to alteration by contextual factors and internal state (e.g., cortisol levels, baseline anxiety levels). Whalen and colleagues have shown that when faces with neutral expressions are interspersed with faces with emotional expressions, anxiety levels predict ventral amygdala activation in response to faces with neutral but not positive or negative expressions (H. Kim, Somerville, Johnstone, Davis, & Whalen, 2004; Somerville, Kim, Johnstone, Alexander, & Whalen, 2004). They found that those individuals with higher anxiety show greater amygdala activation to neutral pictures. They hypothesized that this effect may be due to a tendency for the ventral amygdala to track ambiguity (i.e., the uncertain predictive value associated with neutral stimuli), especially in anxious subjects (Somerville et al., 2004). The ventral amygdala is crucially important in the psychological effects of elevated cortisol levels (Roozendaal, 2000). Thus, elevated cortisol may increase ventral amygdala responsivity preferentially to stimuli whose symbolic or predictive value is uncertain (such as neutral stimuli), causing heightened arousal in response to these stimuli. Further research is required to test this hypothesis and to examine whether cortisol's effects are isolated to arousal ratings (rather than valence) as the current data suggest.

Limitations

A significant positive association between individual differences in postdrug cortisol levels and arousal ratings of neutral stimuli would be consistent with the hypothesis that cortisol elevations cause heightened arousal ratings of objectively neutral stimuli. For the entire sample, however, our data did not reveal significant correlations between cortisol levels and arousal ratings of neutral stimuli. In our study, it was only within the 20-mg group that variability in cortisol levels predicted arousal ratings. Aggregation of group data by dose (such as in the ANOVA) was required in order to reveal the relation between cortisol levels and arousal ratings of neutral stimuli for the entire sample.

As mentioned above, a limitation of the present study and other similar studies is that contextual factors have not been specifically examined. Furthermore, because only negative and neutral stimuli were presented, the effects of cortisol on responses to positive stimuli are not addressed by the current study. In addition, research on the differential roles of acute versus chronic variation in cortisol on affective processes is needed. Such research is particularly important because the possible role of chronic elevations of cortisol in the affective and cognitive deficits that occur in major depressive disorder is not yet well understood.

The current study is also limited in that one of the major findings is the null result of cortisol's lack of effects on self-reported affective state. Heeding a null finding is always dangerous because experimental shortcomings can cause failure to reject an incorrect null hypothesis. In addition, predrug affective state was not measured. Therefore, change in affective state due to the drug cannot be fully assessed. However, the null finding for

affective state is highlighted here because of the preponderance of similar null findings in the literature.

Because only men were tested, it is unknown whether the current results generalize to women. In addition, if ratings of stimuli were obtained at a different time point with respect to the rise in cortisol levels, results may have differed. These issues require further study.

Furthermore, two types of stimuli were studied (words and pictures) in the current study, but corrections for multiple comparisons were not applied. Having two stimulus sets (which were presented separately) allows for examination of the consistency of results for pictures and words. The fact that the results were similar for the two stimulus sets suggests that results are generalizable.

Summary

Past research suggests that cortisol modulates activity in brain structures that govern affective processes, and human studies have at times shown effects of glucocorticoids on self-reported affective experience. Conversely, many studies have shown null effects of cortisol on self-reported emotional experience in humans, and the current study replicates such findings. Measures of affective experience in response to negatively valenced stimuli in the current study also showed no effects of cortisol on affective responses. However, cortisol elevations caused heightened arousal in response to neutral stimuli. We speculate that our results may have occurred because our neutral stimuli were presented within the context of emotionally arousing stimuli. Because cortisol's role in psychological processes has been shown to depend on contextual factors, we speculate that cortisol's effects on emotional experience depend on context. The inconsistency in the human literature of the effects of cortisol on affective processes may be due in part to variation among studies in contextual factors that occur along with cortisol manipulation. Future research is needed in humans, which manipulates context and examines interactions with cortisol's effects on psychological processes.

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