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CRH-stimulated cortisol release and food intake in healthy, non-obese adults

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Summary

Background—There is considerable anecdotal and some scientific evidence that stress triggers eating behavior, but underlying physiological mechanisms remain uncertain. The hypothalamic-pituitary-adrenal (HPA) axis is a key mediator of physiological stress responses and may play a role in the link between stress and food intake. Cortisol responses to laboratory stressors predict consumption but it is unclear whether such responses mark a vulnerability to stress-related eating or whether cortisol directly stimulates eating in humans.

Methods—We infused healthy adults with corticotropin-releasing hormone (CRH) at a dose that is subjectively undetectable but elicits a robust endogenous cortisol response, and measured subsequent intake of snack foods, allowing analysis of HPA reactivity effects on food intake without the complex psychological effects of a stress paradigm.

Results—CRH elevated cortisol levels relative to placebo but did not impact subjective anxious distress. Subjects ate more following CRH than following placebo and peak cortisol response to CRH was strongly related to both caloric intake and total consumption.

Conclusions—These data show that HPA axis reactivity to pharmacological stimulation predicts subsequent food intake and suggest that cortisol itself may directly stimulate food consumption in humans. Understanding the physiological mechanisms that underlie stress-related eating may prove useful in efforts to attack the public health crises created by obesity.

Keywords

stress; cortisol; CRH; appetite; HPA

Introduction

The relationship between stress and appetite is complex. Stress can both increase and decrease food intake (Levine and Morley 1981; Morley et al., 1983) and might contribute to both obesity and anorexia. Appetitive responses to stress are shaped by a range of both physiological and

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psychological processes. There is growing evidence for contributions from specific psychosocial factors in stress-induced eating (Grunberg and Straub 1992; O'Connor et al., 2008; Oliver et al., 2000; Stone and Brownell 1994; Wardle et al., 2000; Weinstein et al., 1997), but less is known about underlying physiological mechanisms. The hypothalamic-pituitary-adrenal (HPA) axis is a principal mediator of physiological stress responses and may play a role in the link between stress and food intake. In response to perceived threat or challenge, corticotrophin releasing hormone (CRH) is released from the hypothalamus, triggering release of adrenocorticotrophic hormone (ACTH) from the pituitary, followed by glucocorticoid (GC) release from the adrenal cortex (Tsigos and Chrousos 2002). Glucocorticoids (cortisol in humans, corticosterone in animals) enhance availability of glucose through protein breakdown, gluconeogenesis and lipolysis, facilitating adaptation through energy mobilization.

Glucocorticoids also influence behavior and may further influence energy availability by altering food intake. In humans, chronic GC administration increases *ad libitum* food intake (Tataranni et al., 1996). In animal models, GCs appear to impact caloric intake through direct neuropharmacological effects (Dallman et al., 2007), and corticosterone has been shown to dose-dependently increase intake of palatable foods such as sucrose, saccharin (Bhatnagar et al., 2000), and lard (la Fleur et al., 2004). These findings may have relevance to the modern obesity epidemic – repeated stress-related GC release could cause excess intake of high calorie foods and contribute to weight gain. Indeed, animals prone to obesity have been shown to need circulating glucocorticoids in order for it to occur (Bray 1985) and GC receptor antagonism prevents or reverses weight gain in these animals (Okada et al., 1992). Interestingly, in humans, there is also a link between heightened HPA axis response to stress and abdominal obesity (Epel et al., 1999; Epel et al., 2000; Pasquali et al., 1993; Pasquali et al., 1999).

Thus the release of GCs, a key end product of stress-activation, produces physiological effects potentially impacting energy availability, appetitive behaviors and the maintenance of obesity. Elevated GCs in response to stress may also be a trait feature associated with abdominal obesity. However, despite this evidence, a direct relationship between stimulation of the HPA axis and increased food intake has not been demonstrated in humans. There is evidence for a link between stress reactivity and food intake, as the cortisol response to a laboratory stressor has predicted increased intake, particularly of high calorie foods, in a group of healthy adult women (Epel et al., 2001), and also predicted a link between ecologically measured daily hassles and increased snacking (Newman et al., 2007). Interestingly, in the first study, intake was significantly related to the cortisol response immediately after stress, but not to total cortisol secreted, suggesting the importance of stress reactivity.

However, it is difficult to determine from these studies whether HPA stress reactivity marks a separate vulnerability factor that contributes to stress-related eating, without being causally linked to increased consumption, or whether glucocorticoids directly stimulate eating behavior in humans, as they do in animals. While causality could perhaps be most directly assessed by acutely administering glucocorticoids and measuring food intake, exogenous drug administration has numerous differences from endogenous release and would not parallel stress-induced glucocorticoid release, which typically occurs via stimulation of the pituitary. In this study, we investigated whether endogenous cortisol release elicited by direct stimulation of the pituitary, in the absence of psychological stress, would contribute to increased food intake. We did this by infusing healthy, non-obese adults with CRH at a dose that is subjectively undetectable (eliciting no stress or anxiety) and measuring subsequent food intake.

Methods

Subjects

Fourteen subjects (8 female, 6 male) aged 18 to 42 (mean 23.3 ± 6.2) years were recruited through advertising and screened using the Structured Clinical Interview for *DSM-IV*. They were medically healthy, without history of psychiatric illness, drug or alcohol dependence, recent (6 months) drug, alcohol or tobacco abuse and reported low levels of tobacco and alcohol use. Subjects had negative urine drug screens and normal screening laboratory results and were within $+30\%/-10\%$ of ideal body weight (mean 69.4 ± 10.6 kg). Females were pre-menopausal, not using birth control pills, not pregnant or lactating, and studied within 10 days of menstruation onset. Subjects provided written, informed consent and were paid \$200 each. The study was approved by our Institutional Review Board.

Design and Procedures

Subjects reported twice to a General Clinical Research Center (GCRC) and received intravenous injections of placebo (0.9% saline) and ovine CRH (0.3 ug/kg; Acthrel, Ferring Pharmaceuticals, Tarrytown, NY) separated by 1 to 7 days. Eight subjects received placebo first and six received CRH first. They were told that they might receive either substance on both visits. Subjects and GCRC nurses were blind to condition.

Subjects reported for study at 1300h. The investigator fully described the procedures and common side effects of CRH. Subjects were escorted to the GCRC, where an intravenous catheter (saline drip) was inserted into an antecubital vein at ~1330h. Subjects rested in bed for 1.5 hours, reading or watching TV, to acclimatize to the setting. Baseline blood samples were obtained at 1500h and 1525h. At 1530h the investigator returned (behind a curtain, out of the subject's awareness) to inject saline or CRH over 10sec. CRH was prepared one hour before injection and refrigerated until used. Blood was drawn into iced vacuum tubes at 5, 10, 15, 30, 60, and 120 minutes after drug administration, spun in a refrigerated centrifuge within 5 minutes, separated and frozen (-70°C).

After the last blood sample (1730h), subjects received a basket of snacks. The basket was left in the room for 30 minutes and then removed by a dietician who weighed the food remaining. Subjects were told that eating something was recommended given the duration of the study and the repeated blood drawings, but no additional pressure was applied. They were not told that intake would be monitored. To provide variety of choice, two options of four snack types were provided in standard, pre-packaged serving sizes – two higher fat sweet snacks (chocolate and sugar cookies), two higher fat salty snacks (regular and nacho flavored potato chips), two lower fat sweet snacks (apple cinnamon and maple-flavored rice cakes), and two lower fat salty snacks, (regular and garlic flavored pretzels). Two servings of each option were presented, providing 16 servings. At 1800h on the second visit subjects were debriefed by an investigator and asked to describe which foods they had eaten and in what order on both days and to report any items they had taken off the tray to take home but had not consumed. Their measured consumption was corrected to include only food actually eaten during the snack period. Amount consumed in grams (total consumption) and calories (from nutritional labels) was calculated by subtracting weight of food remaining from weight of food delivered.

Measures and Assays

Emotional symptoms were recorded at the time of each blood sample using visual analog scales (VAS) measuring feeling states on 100-mm lines ("not at all" to "most ever"). The primary dependent variable was subjective anxious distress, calculated using the sum of VAS ratings of "anxious," "nervous," and "fearful". Cortisol was assayed using the Coat-A-Count assay

from Diagnostic Products Corporation (Los Angeles, Calif). Sensitivity was 0.2 µg/dL. Coefficients of variation were less than 10%.

Analysis

Two-factor (Time X Drug) repeated measures analyses of variance (RM-ANOVA) were used to evaluate the impact of CRH (vs placebo) on cortisol and subjective responses. Our primary interest however is the impact of cortisol on food intake, and that was examined using within-subjects RM-ANOVAs to compare food intake following CRH to food eaten following placebo. Our principle dependent variable was intake measured in calories but we also examined total intake in grams in confirmatory analyses. The relationship between food intake and cortisol levels was examined further by regressing food intake on peak cortisol response (post-CRH maximum minus mean baseline) and cortisol levels at the time of eating (120 minutes post infusion) using Pearson correlations.

Results

CRH robustly elevated cortisol levels relative to placebo (significant main effects of Drug ($F(1,12) = 177.91, p < .0001$) and Time ($F(5,60) = 35.46, p < .0001$), and significant Time-by-Drug interaction, ($F(5,60) = 24.56, p < .0001$) (Figure 1a). Separate ANOVAs for CRH and placebo days confirmed a significant rise in cortisol after CRH ($F(5,60) = 61.75, p < .0001$), but not after placebo ($F(5,65) = 1.65, p = .16$). Despite the robust impact on cortisol, CRH had no impact on subjective anxious distress ($F(10,130) = .83, p = .43$) (Figure 1b). In order to test for sex differences in intake, sex was included in the main analysis as a between-subjects factor, however, since this analysis revealed no interaction involving sex ($F(1,12) = 0.006, p = 0.94$ for calories; $F(1,12) = 0.23, p = 0.64$ for grams) this factor was excluded from all further analyses. Subjects ate more following CRH (597.5 ± 233.8 kcals, 133.8 ± 51.8 grams) than following placebo (456.5 ± 213.0 kcals, 107.6 ± 51.7 grams) and the CRH-placebo difference was significant for both variables ($F(1,13) = 7.79, p = .015$ for calories; $F(1,13) = 5.98, p = .029$ for grams). This was a highly consistent effect across subjects, with only one participant eating more after placebo than after CRH. Peak cortisol response to CRH was strongly related to both caloric intake ($r = .65, p = .011$) and total consumption ($r = .61, p = .021$) (Figure 2) after CRH administration, but not after placebo for either measure reported ($r = .14, p = .64$ for calories and $r = .15, p = .62$ for grams). To assess if age and body weight were contributing to the regression model, these factors were added in additional, multiple regression analyses. They did not provide any additional explanatory power; peak cortisol was the only significant predictor of food intake after CRH administration (analyses not shown). Cortisol levels recorded at 120 minutes post infusion were not correlated with either measure of consumption ($r = .13, p = .66$ for calories, $r = .094, p = .75$ for grams) and subjective anxious distress did not predict food intake ($r = .32, p = .26$ for calories, $r = .29, p = .31$ for grams).

Discussion

Low dose CRH administration significantly increased food intake compared to a placebo injection in healthy, non-obese adults, as measured by both calories and total grams consumed. The magnitude of the peak cortisol response to CRH was a strong predictor of subsequent food intake. These data extend growing evidence of a link between stress response systems and human eating behavior, by suggesting that activity within the HPA axis – our central, neuroendocrine stress response system – is neurobiologically linked to food consumption.

Prior human work has shown that magnitude of the HPA response to a psychosocial laboratory stressor is associated with higher food intake (Epel et al., 2001), and also predicts real life, stress-related eating during subsequent days (Newman et al., 2007). Neither of these studies, however, was able to directly associate HPA axis activity with increased food intake. In the

first study, an intense psychosocial stressor was used to activate the HPA axis but it was not known whether other, non-hormonal, aspects of the stress experience triggered both more cortisol release and increased consumption. In the second study, the magnitude of HPA reactivity to a similar psychosocial stressor predicted increased eating in association with daily hassles during following days, but in this case the HPA reactivity may have been marking a vulnerability to stress-related eating. No data on cortisol levels at the time of eating was collected, and the literature is contradictory as to whether the types of hassles documented are likely to elicit sufficient cortisol release to drive eating behavior (Dickerson and Kemeny 2004; van Eck et al., 1996). Therefore, in both cases, the mechanisms linking stress reactivity to eating behavior remained unclear.

In our data, the only stressor present was appearance in the study setting to receive a drug injection, but this was equivalent on CRH and placebo days. Because CRH is essentially undetectable at the dose administered and subjects could not subjectively differentiate CRH and placebo days, it appears likely that some biological effect of the CRH was responsible for the increased food intake. Given that we found no significant relationships between ACTH levels and food intake (data not presented) and subjective distress was minimal and did not predict intake, the most parsimonious explanation is that endogenous cortisol release was directly related to our subjects eating more food. Intriguingly, peak cortisol response to CRH, which occurred on average an hour before the food was presented, was the best predictor of intake. Cortisol levels at the time of food presentation did not significantly predict intake and levels were descending towards pre-injection baseline while the food was available. Whether the relationship between cortisol release and food intake in the current study involved direct physiological or pharmacological effects of GCs or the stimulation of other intermediary mechanisms is not clear at this point. However, the results do provide strong support for a contributing role of glucocorticoid activation in promoting food intake and perhaps thus in stimulating stress-related eating.

Factors other than stimulation of cortisol cannot be completely ruled out from the current study. The injected CRH itself could have impacted intake. Ovine CRH does not cross the blood-brain barrier, so its effects would have to be indirect. It does slow gastric emptying, but this promotes satiety and should inhibit food intake. Other physiological effects would have to be postulated, but are possible given the wide distribution of peripheral CRH receptors in reproductive, immune, renal, pulmonary and other systems. It is also possible that the cortisol response to CRH provides a marker for some other factor that influences eating behavior. Epel et al (2001) acknowledge that in their study cortisol may have directly stimulated food intake, but the cortisol response to the laboratory stressor may also be marking some other trait vulnerability that also affects appetite. Stress and cortisol reactivity were confounded, and they found no main effect of their stress manipulation on intake across days. As discussed above, the field study conducted by Newman and colleagues also provides data that is most consistent with the idea that some other aspect of trait reactivity to stress could simultaneously shape both the cortisol response to CRH and vulnerability to stress-related eating. In addition, a well-documented association between abdominal obesity in humans and exaggerated HPA reactivity (Andrew et al., 1998; Epel et al., 1999; Epel et al., 2000; Marin et al., 1992; Pasquali et al., 1993; Pasquali et al., 1999) also suggests neuroendocrine reactivity could be a trait marker for factors influencing appetite and intake. Our correlational results are consistent with a trait marker hypothesis, and future studies should examine whether high and low CRH responders differ in stress-related eating outside of the laboratory. However, the within-subject main effect of day (greater intake on CRH than placebo day) cannot be fully explained by trait variables. These data thus represent strong evidence that endogenously released cortisol might directly stimulate food consumption in humans. Whether this phenomena interacts with other established psychological moderators of the stress-eating relationship – such as eating style (emotional and external eating) and traits such as restraint and disinhibition – should be further

examined (Conner et al., 1999; Newman et al., 2008; O'Connor et al., 2008; Oliver et al., 2001).

Both animal and other human data support a direct role for glucocorticoids in appetite regulation. Administration of GCs can increase food consumption (Bell et al., 2000; Bhatnagar et al., 2000; la Fleur et al., 2004; Tataranni et al., 1996) most markedly increasing intake of palatable foods. Increased glucocorticoid levels are associated with increased insulin secretion (Strack et al., 1995). The combined effects of glucocorticoids on consumption of high energy density foods and increased likelihood that energy consumed will be stored as fat in the presence of insulin means that HPA hyperactivity may be a mechanism by which obesity both occurs and is subsequently maintained. A recent study demonstrated that people who eat in response to stress show both elevated nocturnal insulin and cortisol (Epel et al., 2004) as well as high levels of weight gain. 'Stress-eaters' might, therefore, be at particularly great risk for developing and maintaining obesity and associated health problems.

The precise mechanism linking food intake to cortisol reactivity in both psychosocial (Epel et al., 2001) and CRH challenge paradigms remains to be elucidated, but the current data support the hypothesis that cortisol itself may play a causal role in increasing food consumption. Further study is clearly needed to fully understand underlying mechanisms, but such work may prove useful in efforts to attack the severe public health crises created by obesity.

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Figure 1.

A. Cortisol responses to CRH or placebo injection (mean $\pm$ SE); B. Subjective anxiety ratings following CRH or placebo injection (mean $\pm$ SE).

Figure 2.

A. Relationship between cortisol response to CRH and number of calories consumed; B. Relationship between cortisol response to CRH and amount of food ingested.