Published in final edited form as:

Biol Psychiatry. 2008 October 15; 64(8): 701–707. doi:10.1016/j.biopsych.2008.05.007.

Effects of perceived control and cognitive coping on endocrine stress responses to pharmacological activation

James L. Abelson, M.D., Ph.D., Samir Khan, Ph.D., Israel Liberzon, M.D., Thane M. Erickson, Ph.D., and Elizabeth A. Young, M.D.

University of Michigan Department of Psychiatry, Trauma, Stress and Anxiety Research Group, Molecular and Behavioral Neuroscience Institute

Abstract

Background—The hypothalamic-pituitary adrenal (HPA) axis may mediate negative health effects of stress. It is sensitive to cognitive/emotional factors like novelty, perceived control and coping. Psychological intervention that reduces novelty, and enhances cognitive coping and sense of control can reduce cortisol responses to pentagastrin, a pharmacological HPA activator. This study attempted to identify the core factors that modulate HPA axis activity in this model.

Methods—Varying instructions were administered prior to drug exposure in a two-visit (placebo first) pentagastrin infusion paradigm. Healthy subjects (n=40) were randomly assigned to 1 of 4 instruction groups: (1) Standard instruction (SI); (2) Full cognitive intervention (CI); (3) The CI control component alone; or (4) The CI novelty reduction/coping components alone. Blood samples were obtained via intravenous catheter before and after pentagastrin.

Results—Subjects receiving an intervention had smaller cortisol responses than subjects receiving standard instructions. “Coping” alone had as strong an impact as the more complex intervention that combined “coping” and “control.” “Control alone” also reduced cortisol but its HPA impact appeared less robust.

Conclusions—Brief psychological manipulation can significantly reduce HPA activation in challenge paradigms. Cognitive preparation that focused on side effects, reduced potential surprise and enhanced cognitive coping modulated HPA axis activity as effectively as a previously tested intervention that combined coping and control manipulations. A sense of control alone also reduced cortisol release. The results support development of “control” or “coping” techniques to combat negative health effects of stress that are mediated by HPA axis activation.

Keywords

stress; cortisol; pentagastrin; control; coping; anxiety

*Corresponding author: James L. Abelson, M.D., Ph.D., Rachel Upjohn Building, 4250 Plymouth Rd (Rm. 2733), Ann Arbor, MI 48109-5765, tel: 734-764-5348; fax: 734-936-7868, jabelson@umich.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Additional details of methods and results can be found in supplementary materials on line.

Financial Disclosures and Conflicts of Interest: Dr. Abelson has received consultant fees from Pfizer Inc. Dr. Liberzon reported receiving consultant fees from Pfizer Inc. and Marinus Pharmaceuticals Inc. Drs. Young, Khan, and Erickson reported no biomedical financial interests or potential conflicts of interest.

Introduction

Stress has been linked to detrimental health effects, but the mechanisms that translate subjective “stress” into biological consequences remain unclear. The hypothalamic-pituitary adrenal (HPA) axis (1) – a critical shaper of an organism’s biobehavioral response to environmental challenge (2,3) – is one well-established mediator. This system is reactive to social contexts and cognitive/emotional inputs. Understanding social, cognitive and emotional HPA modulators could facilitate development of interventions capable of enhancing resilience and reducing negative health impacts of stress.

Novelty, unavailability of control or coping responses, and lack of social buffering are cognitive/emotional factors that enhance HPA axis responses to challenge in animals (4–8). Lack of access to behavioral responses that can control outcomes contributes to corticotropin (ACTH) and cortisol release in humans also (9,10). HPA axis activation can be reduced in humans by familiarity (reduced novelty) (11,12), access to “help” (social support) (13), and past experience suggesting a challenge can be mastered (control/coping) (14,15). These modulatory factors – identifying help as available and a challenge as familiar and perhaps able to be mastered – require cognitive processing. The importance of such factors in understanding the HPA axis is highlighted by evidence that control and familiarity are more salient to this system than fear or other negative affect (9,10,16). The role of cognition in shaping emotional, physiological, neural and neuroendocrine responses to threat and challenge is receiving increasing attention (10,17–22). Sorting out how cognitive, emotional and somatosensory processes interact in shaping stress responding may be particularly salient to developing stress reduction techniques.

We have examined psychosocial modulators of the human HPA axis using pharmacological activation paradigms (23), with particular interest in inhibitory modulation, which may be most readily detectable when studying a system that has been “turned on” systemically. The cholecystokinin-B (CCK-B) receptor agonist, pentagastrin, has proven useful for this purpose. It triggers a dose-dependent release of ACTH and cortisol (24) and produces bodily sensations accompanied by anxiety (25). It releases ACTH through direct pituitary effects, but its “side effects” may psychologically augment this response, creating multiple pathways through which activation and modulatory inhibition could occur. Its anxiogenic and HPA effects appear to be fully independent (23,24,26–28), suggesting that anxiety is not a critical factor in its HPA activating effects.

The HPA response to pharmacological activation with pentagastrin can be modulated by a brief cognitive intervention (CI), in healthy subjects and panic disorder patients (23). The intervention was developed to block anxiety in panic patients exposed to pentagastrin’s panicogenic properties, but it contained multiple components capable of modulating the HPA axis – novelty reduction, sense of control, enhanced cognitive coping. It reduced anxiety in patients, had no impact on already low anxiety levels in controls, but equally and robustly reduced cortisol response in both groups. The factors manipulated thus appear salient to the HPA axis in healthy people, and their impact is not mediated by effects on anxious distress. The compound intervention used did not allow precise dissection of the cognitive/psychological factors most salient to HPA axis activation and modulation in this model. Such dissection could facilitate efforts to identify and learn to combat those aspects of “stress” that are most health-damaging to humans. Here we sought to replicate the CI effects in a larger group of healthy controls and to initiate its dissection by separating the “control” component within it from components addressing “novelty/coping.”

Methods and Materials

Subjects

Forty subjects, aged 18 to 45, were advertisement recruited. All were medically healthy, close to ideal body weight, and not pregnant or lactating. They had no history of substance dependence or recent abuse, no recent exposure to psychoactive medication, limited tobacco and alcohol use, negative urine drug screens, and no history of psychiatric disorder or spontaneous panic attacks. Females were pre-menopausal, not using birth control pills, and studied within 10 days of menstruation onset. Subjects provided written, informed consent and were paid \$200. The study was approved by our institutional review board.

Design and Procedures

Subjects were admitted twice to a General Clinical Research Center (GCRC), receiving an intravenous injection of placebo on first visit and pentagastrin on the second (visits separated by 1–7 days). Subjects were told they might receive either substance on both visits. The placebo first design preserved equivalent uncertainty during the pre-injection phase of each visit (pentagastrin is always detectable) and delivered pentagastrin only after subjects had habituated to laboratory novelty on placebo day. Subjects were randomly assigned to 1 of 4 instruction groups: (1) Standard instructions (SI); (2) Full cognitive intervention (CI); (3) Control alone; or (4) Coping alone. Samples for cortisol and ACTH were obtained via indwelling catheter. Subjects and nurses were blind to instruction group and drug. The investigator administering drug was not. Randomization was constrained to insure comparable sex composition across groups (males and females randomized separately).

Subjects reported at 1 PM to receive instructions and were then escorted to the GCRC. An intravenous catheter was inserted into an antecubital vein at ~1:30 PM. Subjects accommodated to the setting for 1.5 hours, reading or doing homework. Baseline blood samples were drawn at 3 and 3:28 PM. At 3:20 PM, the investigator entered the room, turned on a bedside infusion pump and, for some subjects (see below), a light on top. He returned at 3:30 PM (out of subject's awareness) to inject (over 15 seconds) a placebo or pentagastrin (0.6 µg/kg). Pentagastrin was prepared by Investigational Pharmacists within one hour of injection and kept refrigerated until used. Blood samples were obtained at 3, 5, 10, 20, 30, 45, and 60 minutes after drug injection and spun in a refrigerated centrifuge within 5 minutes; plasma was separated and frozen (–70° C).

Instructions and conditions

The investigator administered instructions identically, in his office, on each visit via a 5-minute audio tape (SI, Control alone), or a 9-minute tape and 5-minute discussion (full CI, Coping alone). Standard instructions described apparatus and procedures, listed drug side effects, and disclosed risks (23). Subjects were told that drug would be delivered while the bedside infusion pump was on (3:20 to 3:40 PM). For subjects receiving standard instructions, control alone, or full intervention a light was placed on the pump. Subjects were told that if the light was lit, they could utilize pump controls to slow or stop the infusion. They were asked not to do so unless really necessary, but assured that if the light was lit, this option was available. They were told that if the light was off, they did not have this permission. For “SI” subjects, the indicator light remained off; for “Control alone” subjects (otherwise identical to SI subjects) it was turned on. The light was turned on for “full CI” subjects (giving them control), and these subjects also received (a) more detailed description of expectable responses (to reduce novelty) and (b) coaching to attribute these responses to normal reactions to pentagastrin rather than anything dangerous (to facilitate “cognitive coping”). “Coping alone” subjects received parts (a) and (b) of the full CI, but they had the indicator light removed and the possibility of control was not mentioned.

Measures and assays

Baseline measures included the Beck Depression Inventory (BDI), Anxiety Sensitivity Index (ASI), an ego resilience scale, and Spielberger State/Trait Anxiety Inventory. Symptoms, emotions and cognitions were recorded using an acute panic inventory (API) and visual analog scales (VAS). The API measured *DSM-IV* symptoms of panic on a 4-point scale (none, mild, moderate, severe). The VAS measured emotions or cognitions on 100-mm visual analog lines (“not at all” to “most ever”). Primary dependent variables were symptom intensity (sum of API symptom ratings) and subjective anxious distress (sum of VAS ratings of “anxious,” “nervous,” and “fearful” minus a rating of “calm”). Separate VAS items measured perceived dangerousness of pentagastrin, novelty, surprise, supportiveness of staff, and sense of control. Cortisol was assayed using the Coat-A-Count assay (Diagnostic Products) and ACTH using the Allegro HS IRMA (Nichols Institute).

Analyses

Primary analyses were four repeated measures analyses of variance (RM-ANOVAs) using time series data. Our interest focused primarily on cortisol and ACTH response curves on pentagastrin day, and secondarily on symptom and anxiety responses, with particular interest in group-by-time interactions, which capture differential response to pentagastrin between instruction groups. When significant group effects were found in these RM-ANOVAs, separate group comparisons were used to isolate the source of these effects. Because we expected intervention groups to differ from the SI group but not from each other, follow up analyses compared each intervention group separately to the standard instruction group.

RM-ANOVAs were supplemented by t-tests using response data that quantified change from pre- to post-pentagastrin. Hormonal responses were calculated using trapezoidal approximation of area under the response curve (AUC, post-injection levels corrected for mean baseline). Cognitive and emotional responses were calculated by subtracting mean baseline values from 3-minute post-injection levels (capturing post-pentagastrin peak subjective effects). One subject was excluded due to an ACTH peak that was > 2 standard deviations above the group mean.

Results

“Baseline” analyses

Constrained random assignment produced 4 groups with identical sex ratios (5 males and 5 females in each, except for CI group where one male was excluded), and nearly identical mean ages (~25, $p=.69$). The groups were also nearly identical in pentagastrin dose ($p=.76$, 42.0 ± 7.8 mcg), mean weight ($p=.91$), BDI ($p=.67$), ASI ($p=.35$) and ego resilience ($p=.39$). Groups differed only on Spielberger Trait Anxiety – SI subjects were elevated (34.5 ± 10.6) relative to the other groups (26.8 ± 5.0 , 26.8 ± 5.3 , and 25.8 ± 2.3 ; $F(3,35)=3.77$, $p=.02$).

Instruction groups did not differ from each other on any measure on placebo day. Cortisol declined slightly over time (Time $F(6,210)=4.58$, $p=.0002$), with no group differences in absolute level (Group $F(3,35)=1.18$, $p=.33$) or change with time (Group $\times$ Time $F(18,210)=0.79$, $p=.71$). ACTH levels were fairly flat (Time $F(6,210)=1.15$, $p=.34$). There were no group differences in ACTH level (Group $F(3,35)=0.28$, $p=.84$). Minor group differences in ACTH at first and last sampling points produced a significant Group $\times$ Time interaction ($F(18,210)=2.14$, $p=.006$). Subjective anxious distress and symptom intensity did not change over time across placebo day (Time $F(4,140)=0.26$, 1.00 , $p=.90$, $.41$, respectively), and groups did not differ significantly on either variable (Group $F(3,35)=2.26$, 1.78 , $p=.10$, $.17$; Group $\times$ Time $F(4,140)=0.37$, 0.69 , $p=.97$, $.76$).

Instruction groups did not differ on any measures at baseline on pentagastrin day (symptom intensity $F=1.58$, $p=.21$; anxious distress $F=1.13$, $p=.35$; cortisol $F=1.56$, $p=.22$; ACTH $F=1.24$, $p=.31$). The four groups thus did not differ on any pre-pentagastrin measure except trait anxiety.

Primary analyses

The main RM-ANOVA for **cortisol** showed significant Time, Group, and Group-by-Time effects suggesting that cortisol responses to pentagastrin were significantly lower relative to Standard Instructions in all three intervention groups (Figure 1). The usual rise in cortisol following pentagastrin was seen in all groups (Time $F(6,210)=45.72$, $p<.0001$). Groups differed in overall cortisol (Group $F(3,35)=3.21$, $p=.03$) and in cortisol change over time (Group $\times$ Time $F(18,210)=2.79$, $p=.0002$). The group main effect was primarily due to lower cortisol levels throughout pentagastrin day (but not significant at baseline) in the Coping alone group and to substantially lower post-pentagastrin levels in the full CI group. Follow-up RM-ANOVAs comparing each intervention group separately to the SI group showed the following: the group effect was significant for 'Coping alone' ($F(1,18)=10.03$, $p=.005$; nearly significant for 'full CI' ($F(1,17)=4.11$, $p=.06$); but not for 'Control alone' ($F(1,17)=1.62$, $p=.22$). All three intervention groups had flattened cortisol response curves relative to the SI group (Group $\times$ Time, $F(6,102)=6.06$, $p<.0001$; $F(6,108)=4.47$, $p=.0004$; $F(6,108)=3.49$, $p=.003$). The only subject given control who turned off the pump (after drug was delivered) was in the "Control alone" group. Their flattened cortisol response relative to the SI group persisted even with his exclusion ($p=.005$). See Figure 1 for time series and AUC response data. The intervention groups all differed from the SI group in AUC response ($t(17)=3.68$, $p=.002$, $t(18)=2.73$, $p=.01$, $t(18)=2.23$, $p=.04$, respectively) but did not differ from each other ($F(2,27)=0.23$, $p=.79$).

The main RM-ANOVA for **ACTH** (Figure 2) documented its usual rise following pentagastrin (Time $F(6,210)=23.17$, $p<.0001$), but group ($F(3,35)=1.95$, $p=.14$) and group-by-time interaction ($F(6,210)=1.09$, $p=.37$) effects were not significant. Full CI and Coping alone groups had flattened ACTH response curves similar to those seen for cortisol, but group differences were not significant due to higher variances. 'Control alone' did not show much ACTH flattening relative to SI, in contrast to what was seen for cortisol in this group. Because of this ACTH-cortisol difference, and because some intervention effects could be obscured in the omnibus analysis by high variance and similarities between intervention groups, we conducted follow up analyses for ACTH despite the lack of group effects in the main RM-ANOVA. When intervention groups were separately compared to the SI group in RM-ANOVAs for ACTH, the group effect was nearly significant for 'Coping alone' ($F(1,18)=4.10$, $p=.06$) and the group-by-time interaction was nearly significant for 'full CI' ($F(1,17)=2.00$, $p=.07$); but neither effect approached significance ($p>.76$) for 'Control alone'.

The main RM-ANOVA for **symptoms** showed the expected rise in symptoms following pentagastrin (Time $F(4,140)=88.28$, $p<.0001$). The intervention groups were comparable to each other and showed smaller symptom change over time than the SI group (Group $F(3,35)=3.23$, $p=.03$; Group $\times$ Time $F(12,140)=3.50$, $p=.0002$; Figure 3). The main RM-ANOVA for **subjective anxious distress** showed an increase in all groups (Time $F(4,140)=33.70$, $p<.0001$), which was smaller in intervention groups than the SI group (Group $\times$ Time $F(12,140)=2.63$, $p=.003$; Figure 3). The smaller increase in anxious distress appeared more striking for 'full CI' and 'Coping alone' than for 'Control alone,' an impression confirmed by comparison of each intervention group to SI – the group-by-time interaction was significant for both 'full CI' ($F(4,68)=4.29$, $p=.004$) and 'Coping alone' ($F(4,68)=3.92$, $p=.006$). The group effect was also significant for 'Coping alone' ($F(1,18)=5.55$, $p=.03$). Neither the group ($p=.13$) nor interaction ($p=.43$) effects were significant for 'Control alone'.

Those subjects who had permission to use the controls (full CI and Control alone) had greater subjective sense of control during exposure to pentagastrin-induced sensations than those subjects who were not specifically given control (SI and Coping alone; $t=2.09$, $p=.04$, $df=37$).

There were no significant effects of sex on subjective or hormonal responses to pentagastrin. Similar patterns were seen for both males and females, though the main cortisol finding appeared more robust for males (instruction-group effect on cortisol response remained significant for males but not females analyzed separately).

To evaluate the impact of elevated trait anxiety (in SI group), RM-ANCOVAs were run comparing the SI group and combined intervention groups on key outcomes, while controlling for trait anxiety. The time-by-group interactions remained significant for cortisol, subjective anxious distress and symptom intensity ($p<.002$).

Exploratory Analyses

We conducted exploratory regressions and path modeling to examine relationships between subjective changes (from before to just after pentagastrin) and cortisol AUC response to pentagastrin. Changes in symptom intensity and novelty significantly predicted cortisol response ($\beta=.41$, $p<.01$; $\beta=.33$, $p<.05$, respectively), but anxiety did not ($\beta=.17$, $p=.31$). Only symptom intensity remained significant in step-wise multiple regression using all subjective variables. Based on these regressions, plus theoretical assumptions about the ability of cognition to shape affect and cortisol, we tested a path analysis model (using AMOS 7.0) (29) in which cognitive change (in perceived danger, control, and novelty via control) elevates symptoms, leading separately to increases in cortisol response and anxiety. The model fit well (Figure 4), with all relevant parameters significant at $p<.05$. Adding a path between anxiety and cortisol responses did not improve fit ($\Delta\chi^2(8)=0.72$) supporting the plausibility of a model in which cognitive modulation of bodily sensations shapes cortisol response independent of anxious distress. Given the small sample, we present this analysis only as a guide for future, validating work.

Discussion

These data replicate and extend evidence that brief psychological manipulations can alter the HPA response to pharmacological activation in healthy subjects, supporting the hypothesis that novelty/familiarity and access to control or coping responses are highly salient to the HPA axis. They directly replicate our prior report (23) that a full intervention, incorporating novelty reduction, sense of control and cognitive coping components, can significantly reduce cortisol responses to pentagastrin. They also indicate that cognitive preparation alone, without direct manipulation of control, can modulate the HPA axis as effectively as the more complex intervention. There is also evidence that simply providing access to control, even if it is not utilized, can modulate HPA axis activation, though this effect may be less robust. These results further dissect psychological mechanisms of cortisol modulation in humans, supporting the separable salience of familiarity/coping and access to control.

The impact of 'Control alone' across outcome variables appeared less robust (see below), but its impact on **cortisol** was significant and comparable to that of 'full CI' or 'Coping alone' (novelty reduction plus coping instructions). Subjective data corroborated that the control manipulation in fact enhanced subjective sense of control. It would thus appear that the mere turning on or off of a light indicating presence or absence of control carried enough meaning to significantly alter cortisol release. This effect persisted with exclusion of the only subject who utilized available control. These findings suggest that believing one can control a potential threat may be a particularly salient modulator of HPA axis activation. However, we must also note that the impact of control alone was perhaps less robust than the impact of coping

instructions. The group main effect was not significant when separately comparing ‘Control alone’ to the SI group on cortisol response, whereas this comparison was significant or nearly so for the full CI and Coping alone groups, which both received coping instructions. In addition, ACTH changes for ‘Control alone’ did not parallel cortisol changes. Further study will be needed to determine the true relative potency of “coping” and “control” in modulating HPA axis activation.

Further work is also needed to separate the effects of novelty reduction and coping enhancement, since cognitive coping instructions included both factors – trying to enhance familiarity (via detailed information on expectable experiences) and cognitive coping (by helping subjects interpret these experiences as benign). As a result, these data cannot address the separable potency of these two factors in modulating HPA axis activity.

Alternative explanations for these findings must be considered and addressed in future research. Subjects receiving ‘full CI’ and ‘Coping alone’ spent an extra 9 minutes with the investigator, who was with subjects after pentagastrin injection. This could enhance sense of social support, though our subjective measure of perceived social support did not capture such an effect. Social support is a known modulator of HPA axis activity (13). Follow-up work controlling for time spent and specifically examining social support is needed. It is also possible that introducing the idea of control may have made salient the potential for lack of control and thereby enhanced HPA responding, rather than access to control reducing it. The ‘Coping alone’ group had the indicator light removed and the control concept was never introduced. Their cortisol response reduction was comparable to other intervention groups, but they had less total cortisol secretion on pentagastrin day. This was the only group with a highly significant main effect of group when separately compared to the SI group, because their cortisol levels were low throughout the experiment. We want to attribute this to the power of coping instructions, but it is conceivable that introducing the light and the possibility of control elevated cortisol in the other three groups. Given the complexity and intensity of the most robust and widely used psychosocial HPA activator, the Trier Social Stress Test (TSST, (30)), significantly elevating cortisol by adding a light and not turning it on seems far-fetched. However, the possibility that simply introducing a potential wish for control but denying it might provide an amplifying signal to the HPA axis warrants further exploration.

Further work is needed to determine if control and coping represent separate processes or two aspects of a single phenomenon. We provided direct control through access to infusion pump buttons, but coping instructions fostered cognitive control of internal responses. The salient experience for both may be a sense of mastery over side effects. In the absence of real control or coping assistance, subjects perhaps just passively endured side effects. The correlation between symptom intensity (which predominantly reflects side effects) and cortisol response, and the impact of control on cortisol via effects on symptoms (in path analysis), suggest that control was a key factor, whether it involved control over the symptom generator (drug infusion) or symptom interpretation (cognitive coping). Extensive data from other human and non-human paradigms support the importance of control, mastery, self-efficacy, and coping as modulators of HPA axis activity (19–21). Familiarity, social support, and past experience with a challenge (11–14) may all reduce HPA axis activation by enhancing “positive outcome expectancies” (10,22). Further work is needed to determine whether these indeed reflect a single underlying psychobiological mechanism or represent separable phenomena.

Future work should attempt to trace the neural pathways through which psychological processes amplify and inhibit HPA axis activity, to reveal underlying mechanisms and help optimize cognitive tools for stress modulation. In our model, pentagastrin side effects may create a signal from insula to hypothalamus that amplifies its direct pituitary effects. The insula helps to process emotion and monitor internal bodily states (31). Insula activity predicts

emotion-induced release of ACTH (32). It could well mediate side-effect-generated amplification of HPA axis activity. Positive associations between other cortical areas, insula, and ACTH response to emotional activation (32) suggest pathways through which both somatosensory and cognitive/emotional inputs (e.g., the “idea” of potential need for control discussed above) might amplify HPA axis activity.

Medial prefrontal cortex (mPFC) is a likely source for top-down inhibitory inputs that could dampen HPA responses to an activator like pentagastrin. The mPFC is a critical source for inhibitory input to “stress response” areas such as amygdala in fear conditioning models (33) and dorsal raphe in stressor control models – via glutamatergic activation of local GABAergic inhibitory neurons (34,35) – and has inhibitory control over hypothalamic outputs (36) via a similar mechanism (37), suggesting parallel inhibitory circuits from mPFC to multiple brain regions involved in emotion or stress responses. Future work may define specific prefrontal, inhibitory control pathways and ways to specifically increase activity in them, so as to enhance stress resilience (32).

Our data continue to document clear dissociation between subjective distress and HPA activity – again showing no link between anxiety and cortisol responses – consistent with extensive evidence that negative affect is not a primary driver of HPA axis reactivity in challenge paradigms (9,23). Here we report a link not previously noted (9,23) between physical symptoms and cortisol release, with path analysis support for the importance of this link. The net HPA response to pentagastrin may involve direct pituitary activation that is amplified by psychological responses to side effects. The combination of direct and indirect activation pathways may provide a particularly useful context for examining psychological modulation of the HPA axis. Psychological factors may be more salient and their impact more detectable when the system has already been turned on directly, through ‘systemic’ pathways (3). It should be illuminating to study comparable cognitive interventions in a CRH model (38), where activation is entirely direct, with no “amplifying” side effects.

One caveat in interpreting our results is the randomization failure that led to higher trait anxiety scores in the SI group. We cannot prove that trait anxiety differences did not contribute to cortisol differences, but we think it is extremely unlikely for the following reasons. Intervention groups had smaller cortisol responses to pentagastrin than the SI group even after controlling for trait anxiety. Mean trait anxiety scores were entirely within the normal range and the group difference (8 points) is not clinically meaningful. Groups did not differ on any other pre-pentagastrin measure. No linkages between trait anxiety and cortisol have been seen in any previous pentagastrin data set (24,26–28). Prior work produced strikingly similar group HPA differences without any differences in trait anxiety. We conclude that the randomization failure had no bearing on our HPA results.

These data thus confirm our prior report (23) that simple psychological manipulations can significantly reduce cortisol responses to pharmacological activation. They extend prior findings by showing that cognitive preparation alone, focusing on enhancing familiarity and preparedness to cope with drug side effects, can reduce cortisol responses. Additionally, they suggest that an ability to control drug exposure may also independently reduce cortisol responses.

Insofar as deleterious health consequences of stress may be mediated through the HPA axis (1), further dissection of psychological activators and inhibitors of this system may enhance our ability to reduce these negative effects, through laboratory-developed stress reduction and stress preparation techniques (39). The alteration of HPA axis activity by instruction-sensitive cognitive variables, even in this pharmacological activation model, also suggests that HPA abnormalities in psychiatric patients could be due to disruption in top-down modulatory inputs

to the hypothalamus, rather than to fundamental dysregulation at the level of the hypothalamus or below.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by the National Institute of Mental Health (RO1 MH052724) and a National Institute of Health General Clinical Research Center grant (M01-RR000042). Hedi Briggs, M.S.W. was essential to the execution of the study. The data could not have been collected without the superb assistance of the University of Michigan GCRC staff, particularly Kathleen Jarvenpaa, R.N., B.S.N., Judy Flaherty, R.N., and Linda Holder.

References

1. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998;338(3):171–179. [PubMed: 9428819]
2. Chrousos GP. Stressors, stress, and neuroendocrine integration of the adaptive response. The 1997 Hans Selye Memorial Lecture. *Ann N Y Acad Sci* 1998;851:311–335. [PubMed: 9668623]
3. Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci* 1997;20(2):78–84. [PubMed: 9023876]
4. Armario A, Montero JL, Balasch J. Sensitivity of corticosterone and some metabolic variables to graded levels of low intensity stresses in adult male rats. *Physiol Behav* 1986;37(4):559–561. [PubMed: 3749319]
5. Hennessy MB, Levine S. Sensitive pituitary-adrenal responsiveness to varying intensities of psychological stimulation. *Physiol Behav* 1978;21(3):295–297. [PubMed: 570273]
6. Hennessy MB, Mendoza SP, Mason WA, Moberg GP. Endocrine sensitivity to novelty in squirrel monkeys and titi monkeys: species differences in characteristic modes of responding to the environment. *Physiol Behav* 1995;57(2):331–338. [PubMed: 7716212]
7. Levine S. The psychoendocrinology of stress. *Ann N Y Acad Sci* 1993;697:61–69. [PubMed: 8257023]
8. Weiss JM. Effects of coping responses on stress. *J Comp Physiol Psychol* 1968;65(2):251–260. [PubMed: 5668311]
9. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull* 2004;130(3):355–391. [PubMed: 15122924]
10. Ursin H. The psychology in psychoneuroendocrinology. *Psychoneuroendocrinology* 1998;23(6):555–570. [PubMed: 9802127]
11. al'Absi M, Lovallo WR. Cortisol concentrations in serum of borderline hypertensive men exposed to a novel experimental setting. *Psychoneuroendocrinology* 1993;18(5–6):355–363. [PubMed: 8416046]
12. Davis HA, Gass GC, Bassett JR. Serum cortisol response to incremental work in experienced and naive subjects. *Psychosom Med* 1981;43(2):127–132. [PubMed: 7267936]
13. Kirschbaum C, Klauer T, Filipp SH, Hellhammer DH. Sex-specific effects of social support on cortisol and subjective responses to acute psychological stress. *Psychosom Med* 1995;57(1):23–31. [PubMed: 7732155]
14. Breier A, Wolkowitz OM, Doran AR, Bellar S, Pickar D. Neurobiological effects of lumbar puncture stress in psychiatric patients and healthy volunteers. *Psychiatry Res* 1988;25(2):187–194. [PubMed: 2845460]
15. Mason JW. A review of psychoendocrine research on the pituitary-adrenal cortical system. *Psychosom Med* 1968;30(5):576–607. [PubMed: 4303377]
16. Curtis GC, Nesse R, Buxton M, Lippman D. Anxiety and plasma cortisol at the crest of the circadian cycle: reappraisal of a classical hypothesis. *Psychosom Med* 1978;40(5):368–378. [PubMed: 362466]

17. Wirth MM, Welsh KM, Schultheiss OC. Salivary cortisol changes in humans after winning or losing a dominance contest depend on implicit power motivation. *Horm Behav* 2006;49(3):346–352. [PubMed: 16274692]
18. Tomaka J, Blascovich J, Kibler J, Ernst JM. Cognitive and physiological antecedents of threat and challenge appraisal. *J Pers Soc Psychol* 1997;73(1):63–72. [PubMed: 9216079]
19. Gaab J, Sonderegger L, Scherrer S, Ehler U. Psychoneuroendocrine effects of cognitive-behavioral stress management in a naturalistic setting--a randomized controlled trial. *Psychoneuroendocrinology* 2006;31(4):428–438. [PubMed: 16330155]
20. Gunnar MR, Tout K, de Haan M, Pierce S, Stansbury K. Temperament, social competence, and adrenocortical activity in preschoolers. *Dev Psychobiol* 1997;31(1):65–85. [PubMed: 9222117]
21. Breier A, Albus M, Pickar D, Zahn TP, Wolkowitz OM, Paul SM. Controllable and uncontrollable stress in humans: alterations in mood and neuroendocrine and psychophysiological function. *Am J Psychiatry* 1987;144(11):1419–1425. [PubMed: 2823617]
22. Ursin H, Eriksen HR. The cognitive activation theory of stress. *Psychoneuroendocrinology* 2004;29(5):567–592. [PubMed: 15041082]
23. Abelson JL, Liberzon I, Young EA, Khan S. Cognitive modulation of the endocrine stress response to a pharmacological challenge in normal and panic disorder subjects. *Arch Gen Psychiatry* 2005;62(6):668–675. [PubMed: 15939844]
24. Abelson JL, Liberzon I. Dose response of adrenocorticotropin and cortisol to the CCK-B agonist pentagastrin. *Neuropsychopharmacology* 1999;21(4):485–494. [PubMed: 10481831]
25. Abelson JL, Nesse RM. Pentagastrin infusions in patients with panic disorder. I. Symptoms and cardiovascular responses. *Biol Psychiatry* 1994;36(2):73–83. [PubMed: 7948449]
26. Abelson JL, Nesse RM, Vinik AI. Pentagastrin infusions in patients with panic disorder. II. Neuroendocrinology. *Biol Psychiatry* 1994;36(2):84–96. [PubMed: 7524696]
27. Khan S, Liberzon I, Abelson JL. Effects of propranolol on symptom and endocrine responses to pentagastrin. *Psychoneuroendocrinology* 2004;29(9):1163–1171. [PubMed: 15219640]
28. Khan S, Liberzon I, Abelson JL. Effect of repeat exposure on neuroendocrine and symptom responses to pentagastrin. *Psychiatry Res* 2004;126(3):189–195. [PubMed: 15157745]
29. Arbuckle, JL. Amos 7.0 [Computer software]. Spring House, PA: Amos Development Corporation; 2006.
30. Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'--a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology* 1993;28(1–2):76–81. [PubMed: 8255414]
31. Paulus MP, Stein MB. An insular view of anxiety. *Biol Psychiatry* 2006;60(4):383–387. [PubMed: 16780813]
32. Liberzon I, King AP, Britton JC, Phan KL, Abelson JL, Taylor SF. Paralimbic and medial prefrontal cortical involvement in neuroendocrine responses to traumatic stimuli. *Am J Psychiatry* 2007;164(8):1250–1258. [PubMed: 17671289]
33. Quirk GJ, Gehlert DR. Inhibition of the amygdala: key to pathological states? *Ann N Y Acad Sci* 2003;985:263–272. [PubMed: 12724164]
34. Amat J, Baratta MV, Paul E, Bland ST, Watkins LR, Maier SF. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. *Nat Neurosci* 2005;8(3):365–371. [PubMed: 15696163]
35. Amat J, Paul E, Zarza C, Watkins LR, Maier SF. Previous experience with behavioral control over stress blocks the behavioral and dorsal raphe nucleus activating effects of later uncontrollable stress: role of the ventral medial prefrontal cortex. *J Neurosci* 2006;26(51):13264–13272. [PubMed: 17182776]
36. Diorio D, Viau V, Meaney MJ. The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. *J Neurosci* 1993;13(9):3839–3847. [PubMed: 8396170]
37. Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC, Cullinan WE. Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. *Front Neuroendocrinol* 2003;24(3):151–180. [PubMed: 14596810]

38. Abelson, JL.; Khan, S.; Liberzon, I.; Young, EA. Can cognitive intervention modulate the HPA response to corticotropin-releasing hormone?. ACNP 46th Annual Meeting; Boca Raton, FL. 2007.
39. Gaab J, Blattler N, Menzi T, Pabst B, Stoyer S, Ehlert U. Randomized controlled evaluation of the effects of cognitive-behavioral stress management on cortisol responses to acute stress in healthy subjects. *Psychoneuroendocrinology* 2003;28(6):767–779. [PubMed: 12812863]

Figure 1.

Cortisol responses to pentagastrin in healthy subjects randomly assigned to standard instructions or one of three intervention groups. Left panel contains raw data (mean $\pm$ SE). Right panel shows response scores (AUC response $\pm$ SE). Asterisks indicate a significant difference ($p < .05$) from the standard instruction group.

Figure 2.

Corticotropin (ACTH) responses to pentagastrin in healthy subjects randomly assigned to standard instructions or one of three intervention groups (mean $\pm$ SE).

Figure 3. Symptom (left) and anxiety (right) responses to pentagastrin (means $\pm$ SE) in healthy subjects randomly assigned to standard instructions or one of three intervention groups.

Figure 4.

Path analysis model linking cognitive variables, bodily sensations, and cortisol responses to pentagastrin, with good fit (χ^2 (9, N = 39) = 9.23, p = .42, CFI = .99, RMSEA = .03, SRMR = .07), showing standardized partial regression coefficients. Rectangles indicate observed variables, circles indicate latent variables (d = disturbance or residual terms), curved line with double-headed arrow indicates covariance, and straight arrows indicate regressions. CFI = comparative fit index, RMSEA = root mean square error of approximation, SRMR = standardized root mean square residual, Δ = change from baseline to 5 minutes post-pentagastrin. Good fit = chi square p > .05, CFI > .90, RMSEA < .06, SRMR < .10.