

# Cognitive Modulation of the Endocrine Stress Response to a Pharmacological Challenge in Normal and Panic Disorder Subjects

James L. Abelson, MD, PhD; Israel Liberzon, MD; Elizabeth A. Young, MD; Samir Khan, PhD

**Context:** The hypothalamic-pituitary-adrenal (HPA) axis may mediate the deleterious effects of stress on health. It is sensitive to cognitive and emotional aspects of organism-environment interactions, such as familiarity, control, and social support. Scientific study of how such factors moderate human HPA axis activity has been limited. Their relevance to HPA axis disturbances in psychiatric patients is largely unexplored.

**Objective:** To determine whether cognitive manipulation can alter HPA axis activity in laboratory studies and whether patients with panic disorder are differentially sensitive to the manipulated factors.

**Design:** Pharmacological activation paradigm (cholecystokinin-B agonist pentagastrin) by which we examined symptom and endocrine effects on subjects randomly assigned to a standard introduction or a cognitive intervention.

**Setting:** Clinical research center.

**Participants:** Recruited from university clinic and newspaper advertisements. Fourteen patients with panic disorder and 14 controls, individually matched for age and sex.

**Intervention:** Half of each group received a 9-minute

cognitive intervention designed to reduce novelty, increase cognitive coping, and provide a sense of control.

**Main Outcome Measures:** Corticotropin (ACTH) and cortisol levels.

**Results:** The cognitive intervention significantly reduced cortisol ( $P=.02$ ) and ACTH ( $P=.01$ ) levels, despite pentagastrin's robust stimulation of both hormones ( $P<.001$ ). The intervention effect was evident in patients and controls, who did not differ in basal HPA axis activity or response to pentagastrin. They did differ in panic symptom responses, which were unaffected by the intervention, and in ACTH effects of the intervention. Patients' exaggerated anxiety responses to pentagastrin were normalized by the intervention.

**Conclusions:** Cognitive/emotional manipulation can substantially modulate HPA axis responses to pharmacological activation in humans, and HPA disturbances in panic disorder may be secondary to manipulable cognitive/emotional sensitivities. Further study of such factors as novelty, control, and coping may help clarify the origins of HPA axis disturbance in psychiatric disorders and the mediators linking psychosocial stress to disease.

*Arch Gen Psychiatry.* 2005;62:668-675

**Author Affiliations:**  
Department of Psychiatry and  
Mental Health Research  
Institute, Trauma, Stress and  
Anxiety Research Group,  
University of Michigan,  
Ann Arbor.

**T**HE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) axis is critical to an organism's capacity to mount an integrated biobehavioral response to environmental challenge<sup>1,2</sup> and is an important mediator linking "stress" to detrimental health consequences.<sup>3</sup> It is sensitive to social contexts and cognitive/emotional inputs as it shapes behavioral responses to environmental challenge. Such inputs, and their processing through suprahypothalamic circuits to influence hypothalamic outputs, have been well-studied in animals.<sup>4,5</sup> Similar cognitive/emotional factors contribute to endo-

crine stress activation in humans.<sup>6,7</sup> However, psychiatric studies have rarely examined the ways in which cognitive/emotional factors with particular salience to the HPA axis might shape neuroendocrine findings in clinical populations. Deeper understanding of such modulators might help clarify the origins and meaning of HPA axis abnormalities in psychiatric patients and could also facilitate efforts to ameliorate the deleterious effects of stress on health.<sup>3</sup>

Novelty, unavailability of control or coping responses, and lack of social buffering are cognitive/emotional factors known to enhance HPA axis responses to

challenge in animals.<sup>8-12</sup> Inconsistent results have characterized parallel study of “psychological stress” in humans,<sup>13</sup> but recent meta-analytic and theoretical reviews have helped link the animal and human work. Meta-analysis of 208 acute stress studies suggests that lack of access to behavioral responses that can control outcomes clearly contributes to corticotropin (ACTH) and cortisol release in humans.<sup>7</sup> Theoretical reviews also highlight the primary salience of cognitive factors—specifically defined as “acquired outcome expectancies”—in shaping stress responding.<sup>6,14</sup> A “positive outcome expectancy” based on acquired control over a potential threat is the most reliable way to reduce neuroendocrine stress responses.<sup>6</sup> Prior exposure (reduced novelty),<sup>15,16</sup> access to “help” (social support),<sup>17</sup> and past experience suggesting that a challenge can be mastered (control)<sup>18</sup> may all reduce HPA axis activation by enhancing positive outcome expectancies (coping).<sup>6,19</sup> Training in stress management or coping can in fact reduce HPA responses to acute challenge in humans,<sup>20</sup> suggesting that we can perhaps develop specific, teachable techniques to actively ameliorate the detrimental health effects of stress.

Psychiatric neuroendocrine studies have not generally considered the potential impact of novelty, social support, and access to coping or control responses within experimental paradigms. Differential sensitivity to such factors could account for some HPA abnormalities reported in psychiatric patients. This may be especially likely in an illness such as panic disorder, where HPA axis findings have been inconsistent<sup>21-24</sup> and cognitive expectancies may be particularly relevant to pathophysiological processes. Patients with panic disorder have a cognitive bias for perception of environmental threat,<sup>25,26</sup> which should heighten reactivity to novelty and undermine positive outcome expectancies and thus increase HPA axis reactivity to pharmacological and psychosocial challenges. If salient situational variables like novelty vary in uncontrolled ways across experimental paradigms, and patients and control subjects have differential sensitivity to such factors, inconsistent results can be expected. Laboratory models in which cognitive/emotional modulators can be directly studied in humans are needed to explore this possibility.

Pharmacological activation paradigms may be particularly useful because modulatory inhibition via cognitive/emotional factors may be most detectable after the system has been directly activated. The cholecystokinin-B (CCK-B) receptor agonist pentagastrin<sup>27</sup> provides an intriguing model because it releases ACTH and cortisol<sup>27,28</sup> and triggers an anxiety response.<sup>29</sup> Its anxiogenic and HPA effects are independent<sup>27,30-32</sup> and allow for multiple pathways through which modulatory inhibition could occur. Patients with panic disorder initially showed an exaggerated HPA response to pentagastrin, but interestingly, reducing novelty in the experimental paradigm normalized this response.<sup>30</sup>

To further explore the role of cognitive/emotional factors in modulating responses to pharmacological activators, we examined the impact of a cognitive intervention (CI) on symptoms and HPA axis responses to pentagastrin in patients with panic disorder and healthy

comparison subjects. The CI was designed to manipulate expectancies and facilitate stress management by increasing familiarity, control, and coping. We hypothesized that the CI would reduce the HPA axis response to pentagastrin and ameliorate CCK-B and HPA “hyper-sensitivities” in patients with panic disorder.

## METHODS

### DESIGN

Twenty-eight subjects (14 patients with panic disorder and 14 controls individually matched to patients for age and sex) received intravenous injection of placebo and pentagastrin following either standard instruction or a CI. Patient-control dyads were randomly assigned to condition. Analyses examined the effects of pentagastrin on HPA activation, CI effects, and patient-control differences in sensitivity to activation and cognitive modulation.

Subjects entered a clinical research center twice, separated by 1 to 7 days. They received placebo on the first visit and pentagastrin on the second but were told that they might receive either substance on both visits or 1 of each in either order. This preserved blind administration on both visits and separated the first exposure to the novel experimental context from the first exposure to pentagastrin. Subjects and research center nurses were blind to condition.

### SUBJECTS

Subjects were recruited through clinic referrals and advertising and diagnosed using the Structured Clinical Interview for *DSM-IV*. They were 18 to 37 years old, medically healthy, within 25% of ideal body weight, and not pregnant or lactating, and they had no history of substance dependence or recent abuse (6 months), no recent exposure (within 1 month) to psychoactive medication, low levels of tobacco use (<20 cigarettes/d) and alcohol use (<5 drinks/wk), negative urine drug screen results, and normal screening laboratory results. Females were premenopausal, not using birth control pills, and studied within 8 days of menstruation onset. Control subjects had no history of psychiatric disorder or spontaneous panic attacks and no first-degree relatives with anxiety or affective disorders. Patients had a primary diagnosis of panic disorder, with at least 2 attacks in the prior month (mean  $\pm$  SD, 21  $\pm$  22 attacks). Nine had mild to moderate agoraphobia. Five had social anxiety disorder. One had obsessive compulsive disorder. One had dysthymia. None had current depression. One had a prior depressive episode. Ten had never received psychopharmacological medications; 3 had past exposure but no daily medication for 3 years; 1 had discontinued use of a selective serotonin reuptake inhibitor, buspirone, and alprazolam 3 months earlier. Subjects provided written, informed consent and were paid \$200 each.

### PROCEDURES

Evaluations were completed 1 week before study. Subjects reported at 1 PM for experimental sessions. Use of food and tobacco was prohibited. The investigator administered instructions identically on each visit via a 5-minute audio tape for standard instructions or a 9-minute tape and 5-minute discussion for the CI. Subjects were escorted to the clinical research center. An intravenous catheter (saline drip) was inserted into an antecubital vein at approximately 1:30 PM. Subjects rested in bed for 1.5 hours, reading or watching TV, to accommodate

to the setting. Baseline blood samples were obtained at 3 PM and 3:28 PM. At 3:20 PM, the investigator entered the room briefly, turning on a bedside infusion pump and, for subjects in the CI condition, a light on top. He returned at 3:30 PM (behind a curtain, out of the subject's awareness) to inject (over 15 seconds) the placebo or pentagastrin (0.6 µg/kg; Wyeth-Ayerst, Philadelphia, Pa, or Calbiochem-Novabiochem, Laufelfingen, Switzerland). Blood samples were obtained at 3, 5, 10, 20, 30, 45, and 60 minutes after the administration of pentagastrin, drawn into vacuum tubes containing heparin (cortisol) or ethylenediaminetetraacetic acid (ACTH), and placed on ice. They were spun in a refrigerated centrifuge within 5 minutes; plasma was separated and stored at -70°C.

## INSTRUCTIONS

Instructions were presented via audio tape. The "standard" introduction was unchanged from previous studies, fully describing the apparatus and procedures and listing the common side effects of pentagastrin. The CI added 2 techniques, labeled "coping" and "control," intended to reduce anxious distress. The coping component addressed the potentially frightening misinterpretation of normal pentagastrin side effects as dangerous<sup>33</sup> by increasing familiarity with them through detailed information (reducing novelty) and reassuring subjects that side effects were normal and not adverse or dangerous reactions. It encouraged them to consciously attribute side effects to a safe, predictable response that would run its course and resolve (active coping). The control component<sup>34</sup> gave subjects the information that they could slow or stop the pentagastrin if they found it too uncomfortable. Referring to a light on the bedside infusion pump, we informed subjects that if the light was lit, they could reduce flow by decreasing the pump rate with the dial or could stop it altogether with the on/off switch. They were told that the data would be most useful if they did not use these controls, but that they were there for their use if needed. All subjects received the same description of this apparatus, but the indicator light was lit only for subjects receiving the CI. Drug was administered directly via bolus injection as previously described.<sup>35</sup> No subjects used the pump controls. All were told that they could terminate the experiment at any time. An institutional review board approved all procedures.

## MEASURES AND ASSAYS

Measures included the Sheehan Disability Scale, Beck Depression Inventory, Anxiety Sensitivity Index, and Spielberger State/Trait Anxiety Inventory. Physical and emotional symptoms were recorded at the time of each blood sample using an acute panic inventory and visual analog scale. The modified acute panic inventory<sup>36</sup> measured DSM-IV symptoms of panic on a 4-point scale (none, mild, moderate, or severe). The visual analog scale measured feeling states on 100-mm visual analog lines ("not at all" to "most ever"). Primary dependent variables were panic symptom intensity (sum of acute panic inventory symptom ratings) and subjective anxious distress (sum of visual analog scale ratings of "anxious," "nervous," and "fearful" minus a rating of "calm").

Cortisol was assayed using the Coat-A-Count assay from Diagnostic Products Corporation (Los Angeles, Calif), and ACTH using the Allegro HS IRMA from Nichols Institute (San Juan Capistrano, Calif). Sensitivities were 6 pg/mL for ACTH and 0.2 µg/dL for cortisol. Coefficients of variation were less than 10%. Patient-control dyads were always run in the same assay. Each assay run contained equal numbers of standard instruction and CI dyads.

## STATISTICAL ANALYSIS

One control (woman, CI) was excluded because of a loss of intravenous access at a critical point. Repeated-measures analyses of variance were conducted separately on placebo and pentagastrin day data to examine the effect of diagnosis (controls vs patients) and instruction (standard vs CI) on infusion-induced changes (time) in symptom and log transformed neuroendocrine responses. We also assessed hormonal responses by calculating a peak response (postpentagastrin maximum minus mean baseline) and area under the curve (AUC) response (area under the postinjection curve minus time-corrected area under the preinjection curve, using trapezoidal approximation).<sup>27</sup> The latter measures integrated secretory effects over the full course of the experiment, especially when applied to the slowly responding cortisol. Peak response captures more acute dynamics, especially when applied to the more rapidly responding ACTH. We calculated peak symptom responses, for both panic symptom intensity and subjective anxious distress, by subtracting baseline means from postpentagastrin maximums. We conducted diagnosis × instruction analyses of variance on symptom and hormonal response measures.

## RESULTS

Patient and control groups were well-matched for sex (9 men, 5 women each) and age (27.5 ± 5.78 years and 27.3 ± 5.74 years). Random assignment produced comparable sex ratios in the instruction groups (8 men, 6 women in CI; 10 men, 4 women in standard instructions;  $P = .69$ ). The CI group was slightly older (29.8 ± 5.20 years vs 25.2 ± 5.29 years,  $t_{25} = 2.25$ ,  $P = .03$ ). Patients were more depressed, anxious, and impaired than controls ( $P < .003$  for all measures). Within patients, the instruction groups did not differ ( $P > .31$ ) on any severity measure (disability, state/trait anxiety, anxiety sensitivity, depression, frequency of panic, agoraphobia rating, clinician's global severity impression). The CI patients had a later age at onset (27.3 ± 6.05 years vs 18.3 ± 4.57 years,  $t_{12} = 3.14$ ,  $P = .009$ ). Regression analyses revealed no significant relationships between age, age at onset, or any illness severity measure and the magnitude of HPA response to pentagastrin. There were no effects of sex on outcome measures; there were no significant differences between men and women in the CI effects.

## PLACEBO DAY

Patients with panic disorder had greater panic symptom intensity and higher subjective anxious distress ratings than controls (diagnosis  $F_{1,24} = 15.1$ ,  $P = .001$ ; and  $F_{1,23} = 35.9$ ,  $P < .001$ , respectively). There were no subjective responses to placebo (no time effect for either variable,  $F_{3,72} = 0.8$ ,  $P = .48$ ;  $F_{5,115} = 2.1$ ,  $P = .07$ ). The latter trend was due entirely to a drop in anxiety at the last time point, with a flat line across all earlier points. The CI had no impact on placebo day symptoms (instructions,  $F_{1,24} = 0.6$ ,  $P = .46$  for panic symptom intensity;  $F_{1,23} = 1.7$ ,  $P = .20$  for subjective anxious distress; no significant interactions).

Cortisol levels declined over the course of the placebo day (time,  $F_{6,144} = 5.1$ ,  $P < .001$ ), reflecting a normal, diurnal rhythm. There were no cortisol differences between patients and controls and no effects from the in-

structions (no significant effects or interactions involving diagnosis or instructions). Levels of ACTH did not decline with time ( $F_{6,144}=1.16, P=.33$ ). They actually rose in patients receiving standard instructions, although the time  $\times$  instruction interaction did not reach significance ( $F_{6,144}=1.89, P=.09$ ). We examined this more directly using ACTH peak response in a group  $\times$  instruction analysis of variance (**Figure 1**), which showed that the instructions had opposite effects in patients and controls on placebo day (group  $\times$  instruction interaction,  $F_{1,24}=5.1, P=.03$ ). Patients receiving standard instructions had a significant rise from first sample to peak ACTH level (paired  $t$  test,  $P=.02$ ); patients receiving the CI did not ( $P=.37$ ). For controls, the opposite was seen: controls receiving the CI showed a significant rise from first sample to peak ACTH ( $P=.01$ ), but controls receiving standard instructions did not ( $P=.34$ ). Time-course data are included in Figure 1.

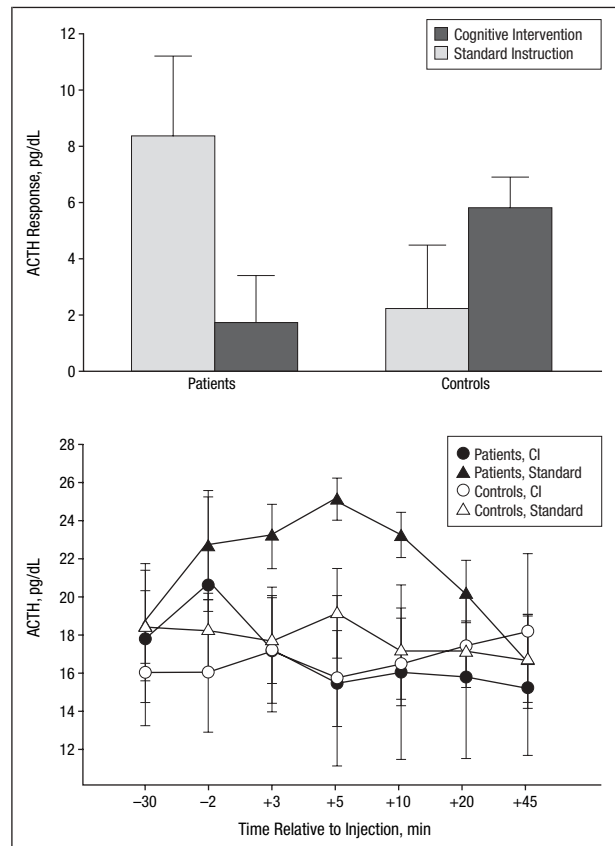
### PENTAGASTRIN DAY

On pentagastrin day, patients again showed elevated subjective ratings compared to controls (**Figure 2**), on both measures (main effect of diagnosis,  $F_{1,24}=12.9, P=.002$ ;  $F_{1,23}=23.1, P<.001$ ). Pentagastrin increased symptoms on both measures (time,  $F_{3,72}=91.3, P<.001$ ;  $F_{5,115}=26.6, P<.001$ ), and did so to a greater degree and with slower recovery in patients (diagnosis  $\times$  time interaction,  $F_{3,72}=4.99, P=.003$ ;  $F_{5,115}=3.81, P=.003$ ). The CI had no effect on either symptom measure (no effects involving instructions were significant).

Patients had greater panic symptom responses to pentagastrin (peak minus baseline) than controls (diagnosis,  $F_{1,23}=5.67, P=.03$ ), confirming increased sensitivity. Cognitive intervention had no impact on peak panic symptom response in either group (instruction,  $F_{1,23}=0.02, P=.90$ ; diagnosis  $\times$  instruction interaction,  $F_{1,23}=1.43, P=.24$ ). Similar analyses for subjective anxious distress were not significant (diagnosis,  $F_{1,23}=1.50, P=.23$ ; instruction,  $F_{1,23}=2.28, P=.14$ ; diagnosis  $\times$  instruction interaction,  $F_{1,23}=2.73, P=.11$ ). However, additional analyses confirmed the graphical impression (Figure 2) that standard instruction patients had elevated responses relative to other groups on this measure. Standard instruction patients had significantly elevated anxious distress responses compared with CI patients ( $F_{1,12}=14.1, P=.003$ ) and compared with their matched controls ( $F_{1,12}=4.56, P=.05$ ).

Pentagastrin increased cortisol and ACTH in all groups (time,  $F_{6,138}=51.6, P<.001$  for both hormones). The CI significantly reduced ACTH and cortisol levels in all groups combined (instructions,  $F_{1,23}=7.66, P=.01$ ;  $F_{1,23}=5.91, P=.02$ , respectively). The CI significantly reduced the cortisol response to pentagastrin (instruction  $\times$  time interaction,  $F_{6,138}=2.52, P=.02$ ) in both patients and controls (no significant effects involving diagnosis). Patients and controls had identical overall cortisol levels, identical cortisol responses to pentagastrin, and identical reductions in cortisol responses with CI (**Figure 3**).

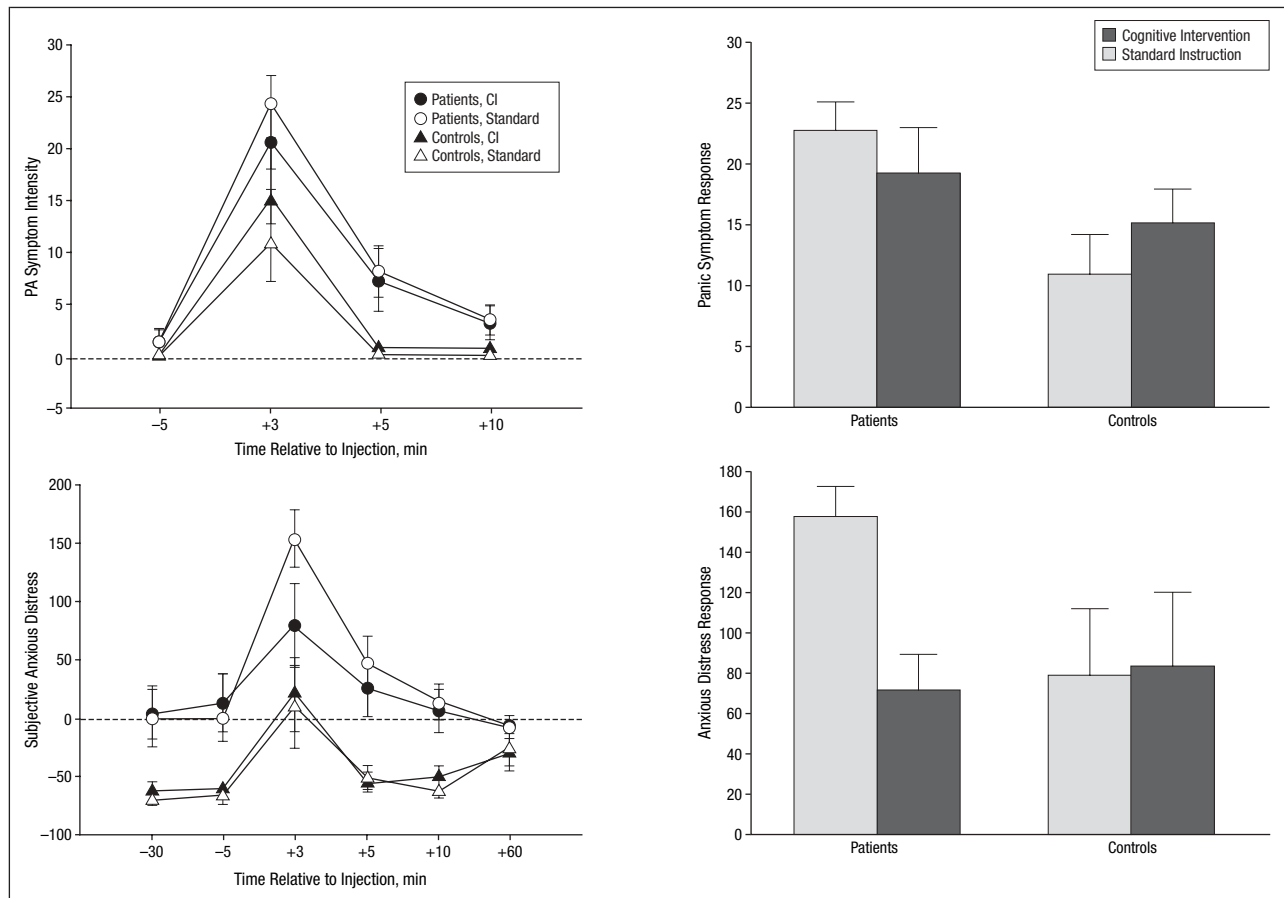
The pattern for ACTH was more complex. The CI did not reduce the overall magnitude of ACTH response to pentagastrin (nonsignificant instruction  $\times$  time interac-



**Figure 1.** Corticotropin (ACTH) levels (bottom) and responses (top, peak level minus initial level) on placebo day for 14 patients with panic disorder and 14 matched controls (means  $\pm$  SE). Half of each group received standard instructions and half received a cognitive intervention (CI) designed to reduce anxious distress.

tion,  $F_{6,138}=1.74, P=.12$ ), but it impacted patients and controls differently (significant diagnosis  $\times$  instruction interaction,  $F_{1,23}=4.28, P=.05$ ), flattening the ACTH response curve in patients alone (Figure 3).

Response measure analyses confirmed and clarified these results (Figure 3; AUC response shown for cortisol, peak response shown for ACTH). For both AUC and peak measures, ACTH and cortisol responses were smaller with the CI than standard instructions (instruction effect for peak response: ACTH,  $F_{1,23}=9.49, P=.005$ ; cortisol,  $F_{1,23}=4.30, P=.05$ ; for AUC response: ACTH,  $F_{1,23}=8.19, P=.009$ ; cortisol,  $F_{1,23}=4.47, P=.05$ ). Patients and controls did not differ on either measure for either hormone ( $P>.71$  for diagnosis in all analyses). Interaction effects were not significant ( $P>.46$ ) for these measures. However, because of the significant diagnosis  $\times$  instruction effect in the ACTH time-course data, due to greater CI-related curve flattening in patients (Figure 3), we examined patients and controls separately on the ACTH peak response measure. In patients with panic disorder, the CI significantly reduced peak ACTH response to pentagastrin, relative to standard instructions ( $F_{1,12}=5.95, P=.03$ ), but it did not have this effect in controls ( $F_{1,12}=0.51, P=.49$ ). In contrast, on a more integrated measure (cortisol total AUC), the CI significantly reduced HPA axis activity in both patients ( $F_{1,12}=7.16, P=.02$ ) and controls ( $F_{1,12}=5.42, P=.04$ ).



**Figure 2.** Panic attack (PA) symptoms (top) and anxiety (bottom) in 14 patients with panic disorder and 14 matched controls before and after pentagastrin injection (means±SE). Raw time-course data are presented on the left, and response scores (postpentagastrin peak minus baseline) are on the right. CI indicates cognitive intervention.

## CORRELATIONS

Whether examined within all subjects or patients or controls alone, clinical variables (depression, state/trait anxiety, panic attack frequency, anxiety sensitivity) showed no significant relationships with any endocrine response measure. When we examined all subjects together or controls alone, we could find no significant relationships between either panic attack symptom responses or subjective anxious distress responses to pentagastrin and any measure of ACTH or cortisol response. Examining patients alone, the anxious distress response ( $r=0.63$ ,  $P=.02$ ,  $n=14$ ) and the panic symptom response ( $r=0.54$ ,  $P=.05$ ,  $n=14$ ) both predicted the ACTH peak response; however, these could be spurious findings, given the number of correlations examined. They could also be due to group differences produced by the CI (they disappeared when we examined the 2 patient instruction groups separately).

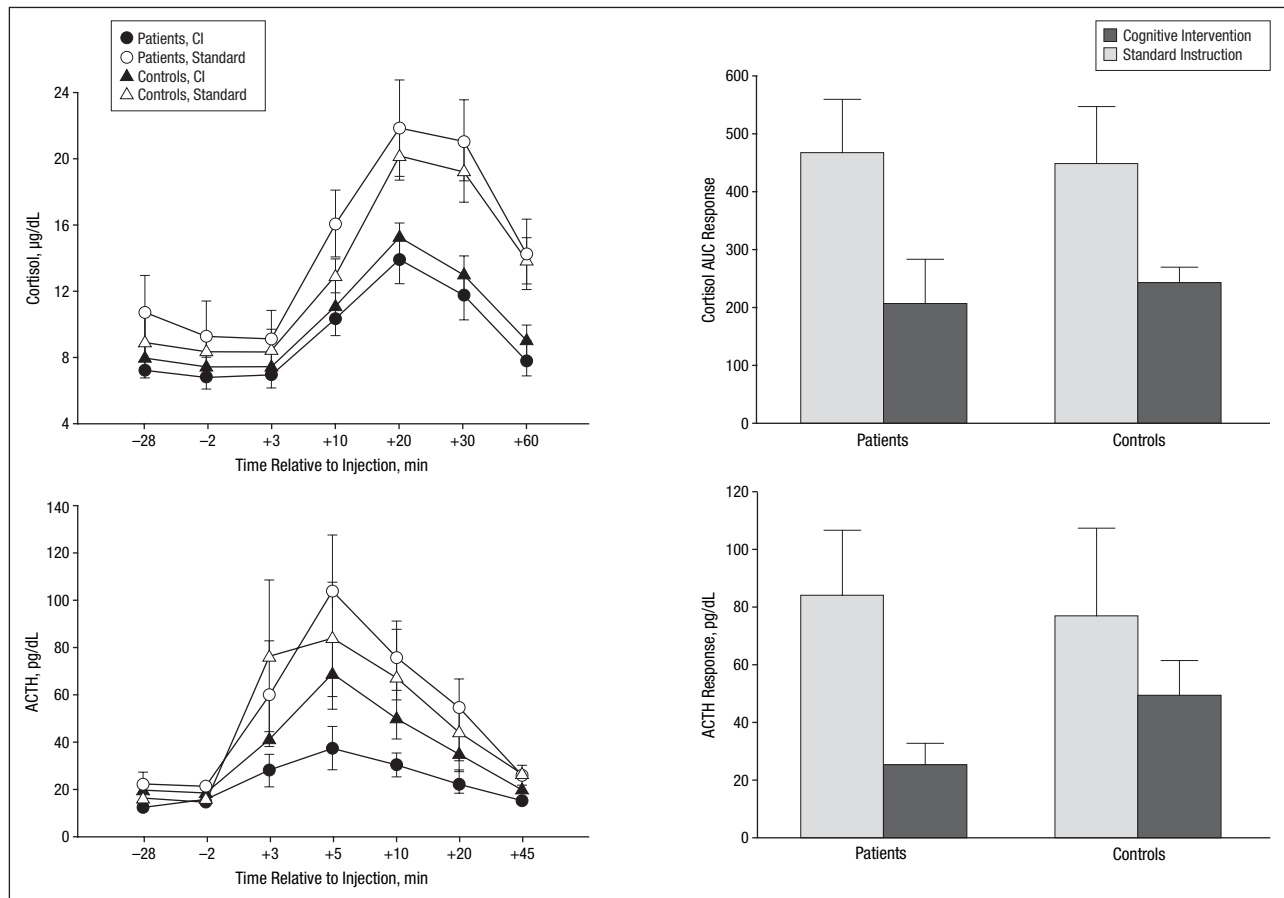
## COMMENT

These data demonstrate that varying preparatory instructions can significantly alter HPA activity in a pharmacological activation paradigm, in healthy controls as well as patients with panic disorder, indicating that cognitive vari-

ables such as familiarity or novelty and access to control or coping responses can modulate HPA axis activity in laboratory studies. An identical cognitive manipulation also significantly modulated HPA axis activity in another panicogenic model—one involving a challenge agent that, in contrast to pentagastrin, has no direct effects on ACTH and cortisol release (doxapram).<sup>37</sup> In that model, HPA axis activity is primarily shaped by psychosocial factors (doxapram does not directly activate this system), whereas in the CCK-B model used here, there is direct pharmacological activation at the level of the pituitary.<sup>27,31,32,38-40</sup>

These data suggest that suprahypothalamic inputs carrying cognitive/emotional information should be considered active in all human studies of the HPA axis, regardless of the neuroendocrine level at which a given probe is targeted. Careful attention to the expectancy milieu of an experimental paradigm may be critical to accurately understand HPA axis activity within it. These results are consistent with extensive literature documenting the importance of novelty, expectancies, control, and coping to human HPA axis stress responses<sup>6,7</sup> and demonstrate the potential particular utility of pharmacological activation paradigms for studying inhibitory, cognitive modulation of the human HPA axis.

The mechanisms whereby a brief verbal exchange robustly reduced cortisol responses in this activation para-



**Figure 3.** Cortisol (top) and corticotropin (ACTH) (bottom) responses to pentagastrin in 14 patients with panic disorder and 14 controls (means  $\pm$  SE). Left panels contain raw data, and right panels show response scores (area under curve [AUC] response for cortisol, peak response for ACTH). CI indicates cognitive intervention.

digm are of considerable interest but were not directly studied. The intervention specifically addressed factors known from prior work to be salient to the HPA axis. It was designed to provide (1) detailed information about expectable physical sensations, (2) a cognitive tool to protect against the misinterpretation of normal side effects as dangerous or unusual, and (3) a perception that control could be asserted if distress was in fact experienced. It thus reduced novelty and enhanced coping and sense of control. It may also have increased perceived social support (the investigator presenting the intervention was also present immediately after pentagastrin injection). Animal and human work has shown that familiarity, access to control or coping responses, and social buffering can all modulate HPA axis activity.<sup>6-12</sup> Our brief intervention could have reduced cortisol release through any or all of these factors.

Presumably, this type of psychological modulation must impact hypothalamic and pituitary output after processing through suprahypothalamic circuits. Animal data suggest that threats with immediate physiological relevance activate the hypothalamus fairly directly. Threats with less immediate survival relevance are processed through cortical and limbic pathways that allow interpretation of meaning and salience, influenced by past experience. When experience suggests that a challenge is familiar or can be managed or escaped, activation is modulated by extrahypothalamic (“top-down”) circuits.<sup>1,41</sup>

Our data are consistent with the hypothesis that complex psychological stimuli—in this case, a verbal discussion targeting expectancies and cognitive responses—can provide inhibitory inputs to the HPA axis, likely after processing through cortical and limbic pathways, to significantly modulate stress axis reactivity. The cognitive inputs likely shape pituitary output via hypothalamic release of corticotropin-releasing hormone or vasopressin, after integration of multiple processing loops in the “hypothalamic continuum” (bed nucleus of the stria terminalis, preoptic area, and hypothalamus).<sup>41</sup> Follow-up work using pentagastrin, which may well have both direct, pharmacological (pituitary-level) components and indirect, psychological (cognitive/emotional responses to its side effects) components to its HPA effects, could be useful in tracing psychological activation and inhibition pathways in humans, as well as in more precisely defining the specific cognitive/emotional factors that modulate human cortisol release.

Our results also demonstrate the potential relevance of cognitive factors in interpreting data from challenge studies of psychiatric disorders. Neuroendocrine challenge studies have suggested that patients with panic disorder have HPA axis abnormalities<sup>24</sup> and hypersensitive CCK-B receptors.<sup>42</sup> Pilot data suggested a link between these biological abnormalities by showing exaggerated ACTH responses to the CCK-B agonist pentagastrin<sup>30</sup> in patients with

panic disorder. However, the current data confirm subsequent evidence that patients with panic disorder in fact have normal HPA axis responses to pentagastrin<sup>30</sup> if they have prior exposure to the experimental context and procedures, suggesting that specific psychological sensitivities could shape the appearance of HPA axis and CCK-receptor abnormalities.

In the current study, patients with panic disorder had cortisol responses to pentagastrin that were identical to those of healthy comparison subjects. Patients did not differ from controls on any direct comparisons using hormonal data. The few differences detected involved CI effects. These findings suggest that patients with panic disorder have normal sensitivity of CCK-B receptors and normal pharmacological response elements within their HPA axes. The data did show some subjective hypersensitivity to the CCK-B agonist in the patients with panic disorder (greater anxiety and panic symptom intensity), as previously reported.<sup>36,42</sup> However, the normal endocrine responses argue against this being a consequence of differences in CCK-B receptor sensitivity. Intriguingly, the 2 subjective measures, anxious distress and panic symptom intensity, did not change in parallel. Panic symptom intensity, which is dominated by physical symptom ratings, was not reduced by the CI, but anxious distress, which is purely emotional, was reduced in patients with panic disorder and appeared “normalized.”

The failure of the CI to reduce panic symptom ratings could be consistent with the idea that cognitive factors are not key mediators of panic attacks produced by CCK-B agonists<sup>43</sup>; but our data suggest that although the physical “side effects” of CCK-B agonists may be resistant to cognitive manipulation, patients’ associated anxious distress responses are more malleable. The data suggest that a secondary emotional response to physical side effects, rather than a CCK-specific pharmacological effect, may account for these agents’ panicogenic potency. The specific similarity of normal CCK-B side effects to the physical manifestations of a panic attack may be the active factor. When patients with panic disorder were adequately coached to attribute the physical side effects to a normal drug effect, pentagastrin did not produce any greater rise in anxious distress in them than it did in healthy subjects, although they did start from a more anxious baseline.

The only endocrine differences detected between patients and controls involved CI effects. The CI decreased ACTH response on placebo day in patients but not in controls and had a greater impact on peak ACTH response following pentagastrin administration in patients than controls. The placebo day data suggest that the provision of detailed information and a sense of control, along with coaching in coping techniques, tended to ameliorate an acute, neuroendocrine stress response in patients that was not present in controls. On placebo day, patients may be showing a “first visit” effect, reacting with an exaggerated ACTH response to nonspecific aspects of the experimental procedures on first exposure to them, and this effect appeared correctable with cognitive preparation.

Patients with panic disorder may be hypersensitive to novelty cues, and the intervention may have reduced this

sensitivity or blocked its impact on the HPA axis, perhaps via the indirect prefrontal and limbic pathways that process complex stimuli and can inhibit hypothalamic output.<sup>4</sup> Healthy subjects, lacking this hypersensitivity, do not show a similar down modulation by the CI. Patients with panic disorder may also have overreacted to the novelty of pentagastrin side effects, so the impact of the intervention on their acute ACTH response to the drug could reflect the same process.

Peak placebo day ACTH levels, peak postpentagastrin ACTH, and anxious distress response to pentagastrin could all reflect novelty sensitivity. All were somewhat elevated in patients and significantly reduced by the intervention. Follow-up studies in panic should specifically examine novelty sensitivity and its modulation by cognitive preparation. If novelty sensitivity can explain HPA axis abnormalities in this model, similar phenomena may be at work in other paradigms and disorders. Clinical studies should examine paradigm differences in context-dependent expectancies and preparation instructions and individual differences in novelty sensitivity and control or coping expectancies. Any HPA axis abnormalities in psychiatric patients could result from heightened novelty sensitivity or impaired control or coping expectancies, rather than specific pharmacological sensitivities to particular challenge agents.

As in prior work, pentagastrin’s hormonal and subjective effects were independent. Endocrine response magnitude was not linked to the intensity of symptoms elicited or anxiety induced and thus does not appear primarily driven by these subjective experiences. The intervention reduced cortisol responses in controls without reducing anxiety, so it was clearly not anxiety reduction itself that drove the cortisol modulation noted. This is consistent with a meta-analysis showing that the nature of a threat and its controllability are more salient to HPA axis activation than the intensity of negative affect or subjective distress.<sup>7</sup>

Follow-up is needed to determine whether subjective descriptions of cognitive factors manipulated by the intervention (familiarity, surprise, control, or coping) might show a more direct link to cortisol levels than measures of physical side effects or anxious distress. Follow-up work should also examine other stress-responsive biological systems (eg, noradrenergic systems) to determine whether activity elsewhere is more closely correlated with distress and anxiety.

The impact of brief cognitive manipulation on HPA axis reactivity in both healthy subjects and patients with panic disorder has important implications for research on stress. It suggests that cognitive/emotional factors shaped by experimental contexts and instructions can alter results in studies examining HPA axis reactivity in psychiatric patients. Differential sensitivity to such variables may confound the interpretation of abnormal biological sensitivities to challenge agents.

This finding also suggests that psychologically mediated inhibition of the human stress-response system can be studied experimentally. It may be possible to empirically develop stress inoculation procedures capable of reducing cortisol responses to predictable stressors, which could help ameliorate cortisol-mediated deleterious ef-

fects of stress on health. It also provides a tool for studying the mechanisms and pathways through which cognitive/emotional processes modulate behavioral, endocrine, and physiological outputs from midbrain control centers.

Follow-up work is needed to replicate the CI effect in a larger group of healthy controls, determine the specific factors within the intervention that are most salient to HPA axis modulation, and see whether the same factors can modulate reactivity in other HPA axis activation models, both biological (eg, corticotropin-releasing hormone) and psychological (eg, the Trier Social Stress Test).

**Submitted for Publication:** May 7, 2004; final revision received October 27, 2004; accepted November 16, 2005.

**Correspondence:** James L. Abelson, MD, PhD, UH9D/0118, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109-0118 (jabelson@umich.edu).

**Funding/Support:** This research was supported by grants R29/RO1MH52724 from the National Institute of Mental Health (Bethesda, Md) and clinical research center grant MO1RR00042 from the National Institutes of Health (Bethesda, Md).

**Previous Presentation:** This study was presented at the 34th Annual Meeting of the International Society of Psychoneuroendocrinology; September 8, 2003; New York City, NY.

**Acknowledgment:** We thank Hedieh Briggs, MSW, and Kathleen Jarvenpaa, RN, whose dedication and skill were essential to the successful collection of these data.

## REFERENCES

- Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci.* 1997;20:78-84.
- 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.
- McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med.* 1998;338:171-179.
- Herman JP, Tasker JG, Ziegler DR, Cullinan WE. Local circuit regulation of paraventricular nucleus stress integration: glutamate-GABA connections. *Pharmacol Biochem Behav.* 2002;71:457-468.
- 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;24:151-180.
- Ursin H. The psychology in psychoneuroendocrinology. *Psychoneuroendocrinology.* 1998;23:555-570.
- Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull.* 2004;130: 355-391.
- Levine S. The psychoendocrinology of stress. *Ann N Y Acad Sci.* 1993;697:61-69.
- Weiss JM. Effects of coping responses on stress. *J Comp Physiol Psychol.* 1968; 65:251-260.
- 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;37:559-561.
- 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;57:331-338.
- Hennessy MB, Levine S. Sensitive pituitary-adrenal responsiveness to varying intensities of psychological stimulation. *Physiol Behav.* 1978;21:295-297.
- Biondi M, Picardi A. Psychological stress and neuroendocrine function in humans: the last two decades of research. *Psychother Psychosom.* 1999;68: 114-150.
- Ursin H, Eriksen HR. The cognitive activation theory of stress. *Psychoneuroendocrinology.* 2004;29:567-592.

- al'Absi M, Lovallo WR. Cortisol concentrations in serum of borderline hypertensive men exposed to a novel experimental setting. *Psychoneuroendocrinology.* 1993;18:355-363.
- Davis HA, Gass GC, Bassett JR. Serum cortisol response to incremental work in experienced and naive subjects. *Psychosom Med.* 1981;43:127-132.
- 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;57:23-31.
- 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;144:1419-1425.
- Levine S. Influence of psychological variables on the activity of the hypothalamic-pituitary-adrenal axis. *Eur J Pharmacol.* 2000;405:149-160.
- Gaab J, Blattler N, Menzi T, Pabst B, Stoyer S, Ehler T. Randomized controlled evaluation of the effects of cognitive-behavioral stress management on cortisol responses to acute stress in healthy subjects. *Psychoneuroendocrinology.* 2003; 28:767-779.
- Curtis GC, Abelson JL, Gold PW. ACTH and cortisol responses to CRH: changes in panic disorder and effects of alprazolam treatment. *Biol Psychiatry.* 1997; 41:76-85.
- Abelson JL, Curtis GC. Hypothalamic-pituitary-adrenal axis activity in panic disorder: 24-hour secretion of corticotropin and cortisol. *Arch Gen Psychiatry.* 1996; 53:323-331.
- Rapaport MH, Risch SC, Golshan S, Gillin JC. Neuroendocrine effects of ovine corticotropin-releasing hormone in panic disorder patients. *Biol Psychiatry.* 1989; 26:344-348.
- Roy-Byrne PP, Uhde TW, Post RM, Gallucci W, Chrousos GP, Gold PW. The corticotropin-releasing hormone stimulation test in patients with panic disorder. *Am J Psychiatry.* 1986;143:896-899.
- Orr SP, Roth WT. Psychophysiological assessment: clinical applications for PTSD. *J Affect Disord.* 2000;61:225-240.
- McNally RJ. Cognitive bias in the anxiety disorders. In: Dienstbier RA, Hope DA, eds. *Nebraska Symposium on Motivation.* Vol 43. London, England: Nebraska Press; 1996.
- Abelson JL, Liberzon I. Dose response of adrenocorticotropin and cortisol to the CCK-B agonist pentagastrin. *Neuropsychopharmacology.* 1999;21:485-494.
- Abelson JL, Le Mellédo JM, Bichet DG. Dose response of arginine vasopressin to the CCK-B agonist pentagastrin. *Neuropsychopharmacology.* 2001;24:161-169.
- Bradwejn J, Koszycki D. The cholecystokinin hypothesis of anxiety and panic disorder. *Ann N Y Acad Sci.* 1994;713:273-282.
- Abelson JL, Nesse RM, Vinik AI. Pentagastrin infusions in patients with panic disorder. II. Neuroendocrinology. *Biol Psychiatry.* 1994;36:84-96.
- Khan S, Liberzon I, Abelson JL. Effects of propranolol on symptom and endocrine responses to pentagastrin. *Psychoneuroendocrinology.* 2004;29:1163-1171.
- Khan S, Liberzon I, Abelson JL. Effect of repeat exposure on neuroendocrine and symptom responses to pentagastrin. *Psychiatry Res.* 2004;126:189-195.
- Clark DM. Cognitive mediation of panic attacks induced by biological challenge tests. *Adv Behav Res Ther.* 1993;15:75-84.
- Sanderson WC, Rapee RM, Barlow DH. The influence of an illusion of control on panic attacks induced by inhalation of 5.5% carbon dioxide-enriched air. *Arch Gen Psychiatry.* 1989;46:157-162.
- Abelson JL, Nesse RM, Weg JG, Curtis GC. Respiratory physiology and anxiety: cognitive intervention in the doxapram model of panic. *Psychosom Med.* 1996; 58:302-313.
- Abelson JL, Nesse RM. Pentagastrin infusions in patients with panic disorder. I. Symptoms and cardiovascular responses. *Biol Psychiatry.* 1994;36:73-83.
- Abelson JL, Weg JG, Nesse RM, Curtis GC. Neuroendocrine responses to laboratory panic: cognitive intervention in the doxapram model. *Psychoneuroendocrinology.* 1996;21:375-390.
- Abelson JL, Young EA. Hypothalamic-pituitary adrenal response to cholecystokinin-B receptor agonism is resistant to cortisol feedback inhibition. *Psychoneuroendocrinology.* 2003;28:169-180.
- Millington WR, Mueller GP, Lavigne GJ. Cholecystokinin type A and type B receptor antagonists produce opposing effects on cholecystokinin-stimulated  $\beta$ -endorphin secretion from the rat pituitary. *J Pharmacol Exp Ther.* 1992;261:454-461.
- Reisine T, Jensen R. Cholecystokinin-8 stimulates adrenocorticotropin release from anterior pituitary cells. *J Pharmacol Exp Ther.* 1986;236:621-626.
- Herman JP, Prewitt CM, Cullinan WE. Neuronal circuit regulation of the hypothalamo-pituitary-adrenocortical stress axis. *Crit Rev Neurobiol.* 1996;10:371-394.
- Bradwejn J, Koszycki D, Shriqui C. Enhanced sensitivity to cholecystokinin tetrapeptide in panic disorder. *Arch Gen Psychiatry.* 1991;48:603-610.
- Koszycki D, Cox BJ, Bradwejn J. Anxiety sensitivity and response to cholecystokinin tetrapeptide in healthy volunteers. *Am J Psychiatry.* 1993;150:1881-1883.