Theoretical Review

HPA AXIS ACTIVITY IN PATIENTS WITH PANIC DISORDER: REVIEW AND SYNTHESIS OF FOUR STUDIES

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Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis may play a role in panic disorder. HPA studies in patients with panic disorder, however, have produced inconsistent results. Seeking to understand the inconsistencies, we reexamined endocrine data from four studies of patients with panic disorder, in light of animal data highlighting the salience of novelty, control, and social support to HPA axis activity. Patients with panic disorder were studied (1) at rest over a full circadian cycle, (2) before and after activation by a panicogenic respiratory stimulant (doxapram) that does not directly stimulate the HPA axis, and (3) before and after a cholecystokinin B (CCK-B) agonist that is panicogenic and does directly stimulate the HPA axis. Patients with panic disorder had elevated overnight cortisol levels, which correlated with sleep disruption. ACTH and cortisol levels were higher in a challenge paradigm (doxapram) than in a resting state study, and paradigm-related ACTH secretion was exaggerated in patients with panic disorder. Panic itself could be elicited without HPA axis activation. Patients with panic disorder showed an exaggerated ACTH response to pentagastrin stimulation, but this response was normalized by prior exposure to the experimental context or psychological preparation to reduce novelty and enhance sense of control. Novelty is one of a number of contextual cues known from animal work to activate the HPA axis. The HPA axis abnormalities seen in patients with panic disorder in the four experiments reviewed here might all be due to exaggerated HPA axis reactivity to novelty cues. Most of the published panic/HPA literature is consistent with the hypothesis that HPA axis dysregulation in panic is due to hypersensitivity to contextual cues. This hypothesis requires experimental testing. Depression and Anxiety 24:66–76, 2007. *Published 2006 Wiley-Liss, Inc.*

INTRODUCTION

Hypothalamic–pituitary–adrenal (HPA) axis activity has been intensely investigated in patients with depression and anxiety disorders for decades. The HPA axis is a complex neuroendocrine "stress" system involved in biobehavioral adaptation to challenge and change. Psychiatric interest in it is not surprising given known interactions between stress, anxiety and depression. However, meaningful psychiatric study of it requires careful attention to the system's complexities. It has an intrinsic circadian rhythm, producing high "stress hormone" levels during the transition from sleep to activity and lower levels as the sleep phase again approaches, likely playing a role in entraining

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activity to the dark–light cycle. It also shows ultradian rhythms due to a pulsatile secretion pattern that can be entrained by stress exposure, creating acute reactivity to particular types of stressors. It is regulated by multiple feedback loops that prevent excessive HPA activity, which is metabolically costly and potentially damaging. A variety of probes have been used to study this system in humans, variously tapping its basal activity and circadian rhythm, its acute reactivity, or its feedback sensitivity. To capture its biological rhythms at basal state, frequent sampling over an extended period is needed. Pharmacological probes [corticotropin-releasing hormone (CRH), dexamethasone, metyrapone] are useful in assessing central drive and feedback inhibition. Acute reactivity can be captured using various laboratory or naturalistic stressor models.

HPA dysregulation was reported decades ago in patients with major depressive disorder [MDD; Carroll et al., 1981], and it is now clear that it may play an important role in the pathophysiology of depression [Young et al., 2003]. There is also considerable evidence for HPA axis dysregulation in posttraumatic stress disorder (PTSD) and some suggestion that this system may play a role in its pathophysiology [Yehuda, 2002]. For example, the dexamethasone suppression test (DST) has revealed abnormal escape from suppression in patients with MDD [Carroll et al., 1981], suggesting central overdrive of the HPA axis in this disorder, and hypersuppression in PTSD, suggesting enhanced feedback inhibition in these patients [Yehuda et al., 1993].

Panic disorder, a common anxiety disorder often associated with depression and PTSD, is responsive to similar medications. Given these associations, it is reasonable to expect HPA axis dysregulation in this disorder as well, and it has been fairly extensively studied. However, results have been strikingly inconsistent. Understanding these inconsistencies might deepen understanding of both panic disorder and the HPA axis.

Baseline or basal state activity within the HPA axis is sometimes reported as elevated and sometimes as normal in patients with panic disorder. Elevations have been reported at "baseline" before a pharmacological challenge [Roy-Byrne et al., 1986], but levels appear normal when the baseline period is more extended [Holsboer et al., 1987]. Patients with uncomplicated panic have normal "resting" cortisol levels [Kathol et al., 1988; Uhde et al., 1988], but resting state elevations have also been reported [Goldstein et al., 1987]. In a 24-hour "basal state" study with frequent sampling, patients with panic disorder had normal daytime cortisol levels but some elevation overnight [Abelson and Curtis, 1996a].

Pharmacological probes of central drive and feedback inhibition have also produced inconclusive results in patients with panic disorder. DST studies have not demonstrated clear escape or hypersuppression [Curtis et al., 1982; Goldstein et al., 1987; Lieberman et al., 1983; Poland et al., 1985; Sheehan et al., 1983], though DST results have not been entirely normal in panic [Coryell and Noyes, 1988; Coryell et al., 1989; Westberg et al., 1991]. Abnormalities seen have not been linked to anxiety or panic symptoms, but they have predicted relapse risk and long-term disability [Coryell et al., 1989, 1991]. CRH challenge has revealed blunted ACTH responses in two reports, one with elevated baseline cortisol [Roy-Byrne et al., 1986] and the other with normal baseline cortisol [Holsboer et al., 1987], but both normal [Brambilla et al., 1992; Rapaport et al., 1989] and enhanced ACTH responses to CRH have also been seen [Curtis et al., 1997; Schreiber et al., 1996].

Acute HPA axis reactivity has primarily been studied in panic in the context of laboratory panic models. Surprisingly, panicogenic stimuli (e.g., caffeine, sodium lactate, CO_2) can acutely trigger panic without a concomitant increase in cortisol release [Hollander et al., 1989; Levin et al., 1987; Liebowitz et al., 1985; Peskind et al., 1998; Seier et al., 1997; Sinha et al., 1999; van Duinen et al., 2004] or without cortisol activation that is significantly different from healthy controls [Charney et al., 1985]. However, cortisol release by some of these laboratory panicogens has occasionally been reported [Argyropoulos et al., 2002; Charney et al., 1987; Woods et al., 1988]. There are also some panicogens [e.g., cholecystokinin B (CCK-B) agonists] that can activate the HPA axis by direct pharmacological effect that is independent of panic induction [Abelson et al., 2005]. Spontaneous or natural panic attacks can occur without HPA axis activation [Cameron et al., 1987; Woods et al., 1987], though there is also evidence that cortisol levels are higher during real-life panic than they are 24 hours later, when an attack is not occurring [Bandelow et al., 2000a]. There are very few data available regarding HPA reactivity to other types of stressors in patients with panic disorder.

A variety of methodological issues likely contribute to the inconsistencies in this panic–HPA literature, but there are also potentially clarifying clues in the basic science literature on psychological factors that modulate this system. Novelty is one factor that robustly activates the HPA axis. Even benign increments in environmental novelty can evoke sustained release of cortisol in animals [Hennessy et al., 1995]. Social separation can also acutely activate the HPA axis, whereas social support can buffer the activating effects of other types of challenge [Levine, 1992, 2000]. Control over a challenge or perceived threat can also modulate the HPA axis response to it [Weiss, 1968]. Unacknowledged or unnoticed paradigm differences in novelty exposure, social support, or perceived control could thus contribute to differing results across studies done in different centers, even when basic methodologies are similar. Differences in sensitivity to any of these factors could also contribute to group differences within studies.

We have recently reexamined our own previously published data on HPA axis activity in patients with

panic disorder, to explore the hypothesis that HPA axis abnormalities in panic could be due to sensitivity to contextual cues such as novelty or lack of control. We present the results of that reexamination below. We obtained the data utilizing four different paradigms: (1) a "basal state" study over a full circadian cycle, (2) CRH infusion, (3) doxapram challenge (respiratory stimulant and panicogen without direct HPA effects), and (4) pentagastrin challenge (CCK-B agonist and panicogen that directly activates the HPA axis). We summarize shared experimental methodology, then examine each study separately, presenting a brief review of the design and results, followed by interpretive commentary related to the hypothesis. We then discuss the overall results and reexamine inconsistencies in the panic–HPA literature in light of our findings.

METHODS

Subjects: In all studies, subjects were 18–42 years of age, healthy, with no current drug or alcohol abuse, limited tobacco use, and within ±25 pounds of normal body weight. Females were premenopausal, not on oral contraceptives, and were studied within 10 days of menses onset. All subjects were administered the Structured Clinical Interview for DSM-IV (SCID). Patients met DSM-III-R or DSM-IV criteria for panic disorder, with or without agoraphobia. Control subjects who had no current psychiatric disorder and no first-degree relatives with an affective or anxiety disorder were age and sex matched to each patient.

Sampling and assays: Intravenous access, kept open with a normal saline drip, was established in an arm vein 1–2 hours before sampling began (except in the 24-hour study). Blood was drawn into vacuum tubes containing heparin or ethylenediaminetetraacetic acid (EDTA), and kept on ice until centrifuged. Plasma was stored at −70°C. We assayed cortisol using the Coat-A-Count assay from Diagnostic Products Corporation (Los Angeles, CA), and ACTH using the Allegro HS IRMA from Nichols Institute (San Juan Capistrano, CA). Sensitivities were approximately 6 pg/ml for ACTH and 0.2 μg/dl for cortisol. Coefficients of variation were generally less than 10%. Patient–control dyads were always run in the same assay.

BASAL STATE/CRH STUDY

Design. Blood samples were drawn every 15 minutes over 24 hours, beginning at 6 P.M., in 12 healthy subjects and 20 patients with panic disorder [Abelson and Curtis, 1996a]. At 6 P.M. on day 2 a CRH test was conducted, with baseline samples drawn every 5 minutes for 15 minutes, followed by intravenous injection of CRH (1 μg/kg) and additional blood sampling (+ 5, 15, 30, 60, 90, 120 minutes; Curtis et al., 1997].

Results. Cortisol levels in panic patients were significantly elevated relative to controls overnight (midnight to 6 A.M., $P<.05$), but not during the daytime. This elevation was primarily accounted for by a subset of six clinic-recruited patients who had significantly higher 24-hour cortisol than controls ($P<.01$) and than the 14 advertisement-recruited patients ($P=.03$). The clinic-recruited patients were significantly more disabled (on the Sheehan Disability Scale) than the advertisement-recruited patients ($P<.05$), but the groups did not differ significantly on any other illness severity measure. Cortisol elevations were significantly predicted by sampling-related sleep disruption, defined as shorter duration of uninterrupted sleep as recorded in nurses' sampling logs [$r=.5$, $P<.05$; Abelson and Curtis, 1996a]. Cortisol before treatment, but not illness severity, predicted total, functional disability at 2-year follow-up [$r=.7$, $P=.002$; Abelson and Curtis, 1996b].

In the CRH test, there was a significant diagnosis × time interaction ($P=.0003$) for ACTH, due to an earlier and somewhat higher peak ACTH level in patients than in controls. The patients did not differ significantly from controls in peak or total ACTH response to CRH. Their baseline cortisol and ACTH levels were also normal [Curtis et al., 1997].

Commentary. The correlation between sleep disruption and cortisol levels in our subjects may reflect the normal linkage between nocturnal awakenings and cortisol release [Leproult et al., 1997]. It is possible that some patients—particularly the more disabled, clinic-recruited subset—are more sensitive to environmental stimuli than other patients and controls, both acutely and chronically. Such sensitivity might undermine sleep continuity and produce higher nocturnal cortisol levels. Cortisol elevations were indirectly linked to functional disability at time of initial study (the clinic-recruited patients were more disabled and had higher cortisol levels) and predicted continuing disability 2 years later, independently of panic frequency or intensity. Hypersensitivity to environmental cues, reflected in novelty-associated cortisol elevations, may be a trait factor that disrupts sleep in the novel laboratory setting and links similar levels of panic to higher levels of functional disruption over time.

This same factor could create blunted ACTH responses to CRH in some contexts, because novelty sensitivity could elevate prechallenge cortisol levels, which could in turn reduce post-CRH ACTH due to feedback inhibition, as has been seen in some panic studies [Roy-Byrne et al., 1986]. In our experiment, however, the CRH challenge followed 24 hours of "accommodation," leading to normal pre-CRH cortisol levels in the panic patients, and their ACTH responses to CRH were not blunted.

DOXAPRAM STUDY

Design. Subjects were studied in a single session divided into three phases—a 5-minute accommodation period, a 15-minute placebo injection phase, and a 30-minute doxapram (0.5 mg/kg intravenously)

injection phase. Samples were obtained from the beginning of accommodation until 24 minutes post-doxapram. Half of the subjects in each group received a cognitive intervention prior to accommodation [Abelson et al., 1996].

Cognitive Intervention. Patients and their matched controls were randomly assigned to receive either standard instructions (SI) or a 9-minute cognitive intervention (CI) designed to reduce the stressfulness of the experimental procedures. The CI included the following components: (1) a more detailed description of expectable responses (to reduce novelty); (2) coaching to attribute these responses to normal reactions to doxapram rather than to anything dangerous (to facilitate "cognitive coping"); and (3) information suggesting that subjects could control exposure to doxapram (if they needed to) by using an infusion pump at their bedside.

Results. Doxapram stimulated hyperventilation and physical symptoms in all subjects and panic attacks in patients with panic disorder, but these effects were not associated with significant cortisol release. Patients had marginally higher cortisol levels than controls ($P = .06$) but did not differ from controls in cortisol response to doxapram or in CI effects on cortisol. The CI significantly altered the pattern of cortisol release in all subjects combined (time × instruction interaction, $P = .02$). With the CI, baseline levels were slightly higher and response to doxapram was lower (Fig. 1). Subject selection criteria and patient characteristics were identical between the basal state study described earlier and this doxapram challenge study. To allow a rough comparison of cortisol levels across experimental paradigms, means for the combined patient–control group from the basal state study are also included in Figure 1, using only those time points that corresponded to the exact time that samples were drawn in the doxapram study. As can be seen, cortisol levels were substantially higher in the challenge paradigm than in the resting state paradigm.

There was no ACTH response associated with doxapram-induced panic attacks. Patients with panic disorder showed a significant elevation in ACTH levels relative to controls throughout the challenge study ($P = .02$). At corresponding time points in the basal state study, patients with panic disorder and controls had identical ACTH levels [Abelson and Curtis, 1996a]. These data are shown in Figure 2.

Commentary. Dramatic physiological and emotional activation occurred in response to doxapram, without meaningful cortisol release. However, cortisol secretion patterns were significantly altered by a brief cognitive manipulation of specific psychological factors (novelty, control, coping). Cortisol levels also appear sensitive to the nature of the experimental paradigm, with higher levels seen in a challenge study than after prolonged stay in a basal state study. The ACTH data support and extend the cortisol results, confirming that doxapram-induced panic is not associated with HPA axis activation, but showing that patients with panic disorder do demonstrate an abnormal activation of the HPA axis in the context of a challenge paradigm. This abnormal activation is not present at a corresponding time of day in the context of a nonchallenge, resting state paradigm. It would thus appear that the patients with panic disorder are psychologically hypersensitive to an aspect of the experimental context (challenge) that is salient to the HPA axis.

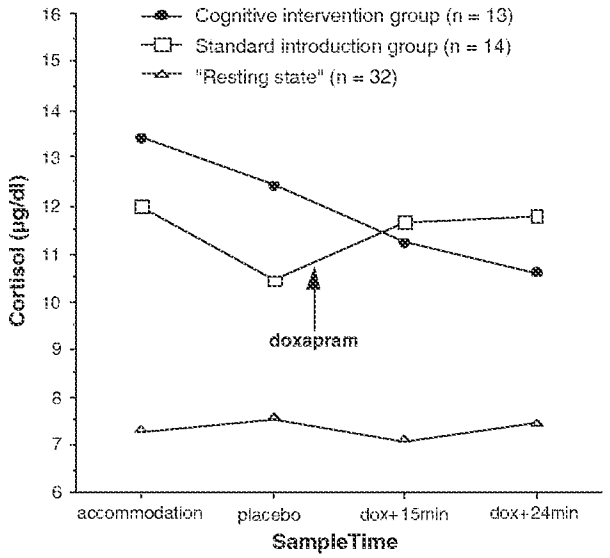

Figure 1. Mean cortisol levels before and after doxapram, in combined groups of patients with panic disorder and controls, with and without cognitive preparation. Levels for a comparable group in a basal state are included for comparison.

PENTAGASTRIN STUDY 1

Design. Cortisol and ACTH were measured before (−30 and −2 minutes) and after intravenous

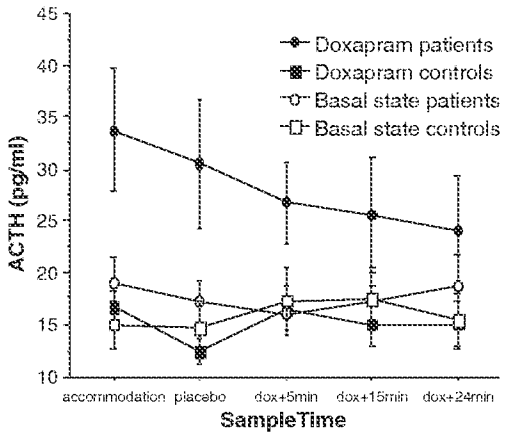

Figure 2. ACTH levels ($M \pm SE$) in panic patients and controls, before and after doxapram, compared to similar patient and control subjects from a 24-hour basal state study.

injection of placebo or pentagastrin (0.6 μg/kg). Postinjection samples were obtained at +3, 5, 10, 20, 30, 45, and 60 minutes. This experiment was conducted in two phases. In Phase 1, five patients and five controls received pentagastrin during a single research visit. In Phase 2, an additional five patients and five controls received placebo on a first visit and pentagastrin on a second visit. In Phase 1, all subjects were told that they would receive pentagastrin. In Phase 2, subjects were told that they might receive pentagastrin or placebo on either visit, and could receive pentagastrin twice, placebo twice, or one of each in either order. All visits were identically structured and included a 1- to $1\frac{1}{2}$-hour accommodation period prior to initiation of sampling [Abelson et al., 1994].

Results. Data are shown in Figure 3. Patients had greater post-pentagastrin ACTH secretion than controls in Phase 1 ($P<.05$); but their post-pentagastrin ACTH secretion was identical to controls in Phase 2. Patients were more sensitive than controls to the effects of phase (first visit effect, $P=.04$ for patients, $P=.65$ for controls). As seen in Figure 3, patients had elevated ACTH levels in Phase 1 but not in Phase 2, whereas control subjects' ACTH did not change across phases. In Phase 2, patients showed significantly elevated ACTH levels only during their first visit (placebo day peak, $P=.03$). "Baseline" ACTH prior to pentagastrin was higher in Phase 1 than in Phase 2 for all subjects ($P=.0001$).

Commentary. Prechallenge ACTH levels were higher when the challenge agent was given in the single-visit phase and subjects knew for certain that they would receive the drug, compared to the two-visit phase in which the drug was given only after a placebo day visit and subjects did not know for certain whether they would receive the drug. This suggests that anticipatory expectancies influenced HPA axis activity in all subjects. Patients with panic disorder, however, appeared more sensitive to a first-visit effect on ACTH, showing significantly greater effects of phase and elevations on first visit to the study setting regardless of phase. Patients with panic disorder thus appeared more sensitive to pentagastrin in Phase 1, but this abnormality disappeared when they were desensitized to the first-visit effect. Their sensitivity was to the experimental paradigm itself, not to the challenge agent. Patients with panic disorder thus have normal HPA response to the pharmacological effects of pentagastrin (normal CCK-B receptor sensitivity) but heightened sensitivity to paradigm factors (e.g., novelty).

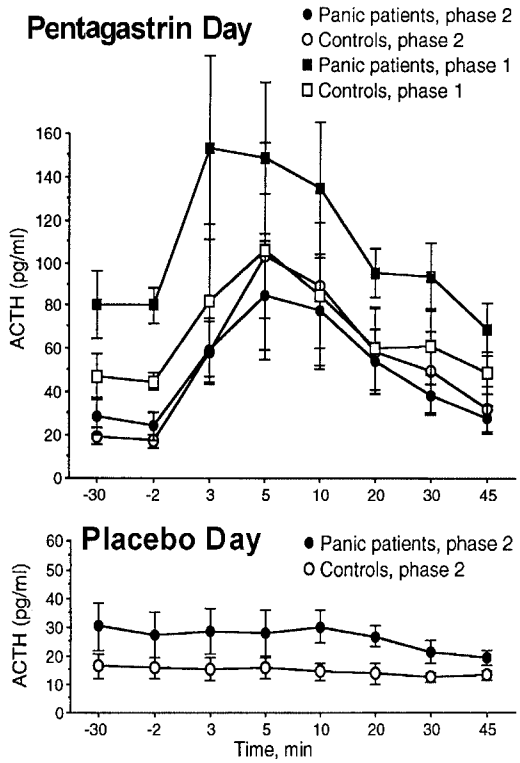

Figure 3. ACTH levels ($M \pm SE$) in panic patients and controls, before and after pentagastrin or placebo injection. In Phase 1, subjects received pentagastrin during their first visit to the research center (no placebo given). In Phase 2, subjects received placebo during their first visit to the research center and pentagastrin during a second visit.

PENTAGASTRIN STUDY 2

Design. This study [Abelson et al., 2005] was identical to Phase 2 of Pentagastrin Study 1 except for the addition of random assignment to receive SI or the same CI used in the doxapram study (described earlier). Cortisol and ACTH were measured before (−30 and −2 minutes) and after intravenous injection of placebo or pentagastrin (0.6 μg/kg). Postinjection samples were obtained at +3, 5, 10, 20, 30, 45, and 60 minutes. All subjects (14 patients, 14 controls) received placebo on their first visit and pentagastrin on their second. SI or CI was given 2.5 hours before pentagastrin injection.

Results. Data are presented in Figure 4. Patients were more symptomatically reactive to pentagastrin than controls when they received SI, but the CI completely normalized the patients' exaggerated anxiety response (Fig. 4A: SI patients > CI patients, $P=.003$; SI patients > controls, $P=.05$; CI patients = controls). The CI differentially impacted patient and control ACTH responses to pentagastrin (Fig. 4B: diagnosis × instruction interaction, $P=.05$), significantly reducing it in patients (CI < SI, $P=.03$), but not in controls (CI = SI, $P=.49$). The CI also differentially impacted patient and control ACTH responses on placebo day (Fig. 4C: diagnosis × instruction interaction, $P=.03$). SI patients had a significant rise in ACTH from initial, baseline levels on placebo day ($P=.02$), but CI patients did not show a similar rise ($P=.37$). Controls showed the opposite pattern, with a significant rise in ACTH for those receiving the CI ($P=.01$) but not for those receiving the SI ($P=.65$).

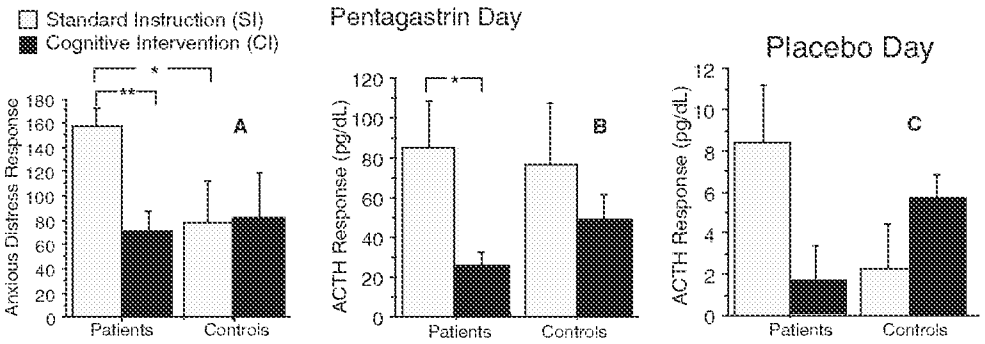

Figure 4. Symptom and ACTH ($M \pm SE$) responses (peak minus baseline) to pentagastrin or placebo in patients with panic disorder and matched controls, receiving either SI or a CI designed to reduce the stressfulness of the procedures: (A) Subjective anxious distress responses to pentagastrin; (B) ACTH responses to pentagastrin; (C) ACTH responses to placebo (first visit).

Commentary. Patients had exaggerated ACTH responses to placebo and exaggerated anxiety and ACTH responses to pentagastrin, but all of these responses were normal in patients with panic disorder who received the CI. This suggests that their HPA axes were overreacting to the experimental paradigm, and that his reactivity could be ameliorated by a brief CI. This is consistent with the hypothesis that HPA axis abnormalities in patients with panic disorder may involve heightened sensitivity to contextual factors, and suggests that this hypersensitivity can be blocked through cognitive preparation that targets factors known to be salient to the HPA axis (novelty, control, and access to coping responses).

DISCUSSION

These results suggest that experimental contexts that are novel, threatening, or uncontrollable (e.g., pharmacological challenge paradigms) can raise HPA activity above "basal" levels in all subjects, including healthy controls; but it would appear that panic patients may be more sensitive to these contextual factors. This hypersensitivity may account for HPA axis abnormalities reported in the panic disorder literature. Our findings of a normal ACTH response to CRH after an extremely prolonged period of "basal state" monitoring is consistent with this interpretation, because it suggests that when sufficiently desensitized to contextual factors, patients with panic disorder do not show evidence of central HPA axis overdrive. The blunted response to CRH reported by Roy-Byrne et al. [1986] is also consistent with this interpretation, because the short accommodation period used in that study was associated with elevated pre-CRH cortisol, likely due to unresolved hyperreactivity to entry into the challenge paradigm, and the elevated "baseline" cortisol can be expected to blunt the subsequent ACTH response to CRH. If so, then psychobiological overreactivity to novelty can account for an "abnormal" response to a biological probe like CRH. Contextual differences between paradigms (e.g., length of accommodation period) could produce inconsistencies across studies.

In our pentagastrin model, we saw an initial suggestion of exaggerated ACTH response to the CCK-B agonist, but this "abnormality" appears to have been created by the additive effects of pharmacological activation and novel exposure to a challenge paradigm. When novelty effects were diminished by prior exposure to the challenge context, the HPA responses of patients with panic disorder were normal. Exaggerated HPA activity in these patients in this model could also be normalized by a brief CI that enhanced familiarity with expectable sensations, coached subjects in cognitive coping, and provided an illusion of control.

The elevated nocturnal levels of cortisol seen in our 24-hour study [Abelson and Curtis, 1996a] seem more difficult to attribute to hypersensitivity to contextual factors; however, such sensitivity could readily produce nocturnal awakenings in the laboratory setting, and such awakenings can trigger cortisol release (Van Cauter, personal communication, 2005) and elevate overnight levels. The linkage between these overnight levels and later disability suggests trait factors at work. Animal work has shown that both developmental and genetic factors can produce chronic overreactivity to environmental novelty, physiologically and behaviorally [Caldji et al., 1998, 2000; Suomi, 1997]. Sensitized animals have normal baseline HPA axis function but heightened reactivity, and are behaviorally dysfunctional throughout their lives. Patients with panic disorder may have a similar, trait-based dysregulation, producing heightened reactivity to novelty that has both biological and behavioral repercussions—seen in enhanced HPA axis reactivity to novel experimental contexts, and elevated cortisol in some paradigms, and in heightened fear of panic in unfamiliar environments, leading to more avoidance and reduced functional capacity. Such a trait could therefore be the mediating variable creating the long-term link we saw in the 24-hour study between cortisol levels at entry and disability levels 2 years later.

A summary of HPA axis findings in panic, published by others, is presented in Table 1. It is difficult to evaluate these findings fully in light of the hypothesis presented here, because our own data show that what is said to patients with panic disorder in preparing them for their experiences within a study can make a significant difference in their HPA responses. Most reports provide little information on subject preparation procedures, and many do not provide details about accommodation periods and prior exposure to experimental contexts. As a result, study differences in novelty or familiarity, perceived controllability, and social support or assistance in coping are not readily discerned.

The findings in Table 1 highlight a failure to consistently find HPA axis abnormalities in panic. It is clear that panic attacks can occur without acute elevation in cortisol levels [Abelson et al., 1996; Cameron et al., 1987; Hollander et al., 1989; Kellner et al., 1995; Peskind et al., 1998]. When exaggerated responses have been seen in laboratory panic models, these could reflect sensitivity to the challenge paradigms themselves rather than sensitivity to the provocative agents used or correlates of the panic attacks generated. For example, exaggerated cortisol responses to yohimbine have been reported in patients with panic disorder [Gurguis et al., 1997]. However, in this study, half of the subjects received yohimbine on a first visit to the study setting and half received placebo. Analyses to detect a first-visit effect, as seen in our pentagastrin study, are not reported. The elevations in cortisol reported were fairly small (~5 μg/dl) and significant findings involved total postinjection secretion, as in our pentagastrin study. These could be due to those subjects who received yohimbine on a first visit, which combines a challenge agent effect and a novelty effect. Larger cortisol response elevations (~15 μg/dl) relative to controls were seen in a fenfluramine challenge [Targum and Marshall, 1989], but in this study, seven of the nine patients with panic disorder received the challenge on a first visit to the laboratory. Again, heightened HPA axis activity in the patients with panic disorder could be due to a first-visit sensitivity that amplifies a normal sensitivity to the provocative agent.

Pharmacological probes of intrinsic, central drive, and feedback inhibition should be less susceptible to acute reactivity effects. However, as noted earlier, even the CRH challenge can be affected by "baseline" reactivity, if feedback inhibition is intact. The DST probes feedback circuits and should be relatively insensitive to acute reactivity effects. The lack of consistently exaggerated escape from suppression or hypersuppression on the DST suggests that inhibitory components are intact in panic. When abnormalities have been detected on the DST, they appear to be associated with the presence of agoraphobia [Westberg et al., 1991] or severity of depression [Coryell et al., 1989] rather than the severity of panic. DST nonsuppression in patients with panic disorder entering a treatment study predicts greater disability at 3-year follow-up [Coryell et al., 1991], which is consistent with our report that elevated 24-hour cortisol levels at treatment entry predict follow-up disability [Abelson and Curtis, 1996b]. These HPA axis abnormalities may be marking a trait that is not disease specific but that enhances general vulnerability to psychopathology, perhaps increasing risk of comorbidity and functional impairment. Such a trait could involve heightened reactivity to or reduced ability to cope with environmental novelty. Heightened cortisol reactivity to a

TABLE 1. HPA axis findings with across multiple paradigms in panic disorder patients

Paradigms	Findings	Studies
Challenge models	No or inconsistent cortisol response with laboratory-induced panic attacks	Charney et al., 1985 (caffeine); Liebowitz et al., 1985; Levin et al., 1987; Seier et al., 1997; Peskind et al., 1998 (lactate); Sinha et al., 1999; van Duinen et al., 2004; (CO_2) Peskind et al., 1998 (hypertonic saline)
	Increased cortisol response to challenge	Woods et al., 1988 (CO_2); Gurguis et al., 1997; Charney et al., 1987 (yohimbine); Targum and Marshall, 1989 (fenfluramine); Leyton et al., 1996 (psychological stress)
CRH	Blunted ACTH response	Roy-Byrne et al., 1986; Holsboer et al., 1987
	Normal or increased ACTH response	Rapaport et al., 1989; Brambilla et al., 1992; Schreiber et al., 1996
	Change in ACTH/cortisol ratio	Brambilla et al., 1992
DST	Normal or slightly elevated rate of non-suppression	Curtis et al., 1982; Lieberman et al., 1983; Sheehan et al., 1983; Goldstein et al., 1987
	Elevated nonsuppression rate with repeat testing, linked to severity of depression	Coryell et al., 1989
Basal studies	Normal UFC (in uncomplicated panic)	Uhde et al., 1988; Kathol et al., 1988
	Elevated ACTH increased afternoon or nocturnal cortisol	Brambilla et al., 1992 Goldstein et al., 1987; Bandelow et al., 1997; Bandelow et al., 2000b
"Natural" panic	Increased cortisol	Bandelow et al., 2000a
	Inconsistent response	Cameron et al., 1987; Woods et al., 1987

novel psychological challenge has been documented in one study of patients with panic disorder [Leyton et al., 1996]. The patients in this study were in remission at the time of study, supporting the idea that HPA axis reactivity in panic may mark a trait that is not directly linked to patients' panic disorder symptoms.

Some findings in the panic–HPA literature are difficult to reconcile with the hypothesis proposed here. For example, Goldstein et al. [1987] found elevated afternoon cortisol levels in patients with panic disorder, even though DST results in these same patients were normal. Their procedure involved continuous blood extraction through an intravenous catheter over a 3-hour period, which should provide a better measure of true basal activity than levels before a challenge. However, our data suggest the even subtle aspects of the experimental context, and preparation for it, can impact the HPA axis in patients with panic disorder. Their continuous extraction procedure may be sufficiently novel to elicit an exaggerated response in patients with panic disorder relative to controls, so this "basal" abnormality could in fact reflect a reactivity effect.

The Von Bardeleben and Holsboer [1988] data showing blunted ACTH responses to CRH in patients with panic disorder even after a prolonged baseline (6 hours) are harder to reconcile. The prolonged baseline resulted in normal pre-CRH cortisol levels, similar to the normal pre-CRH baselines seen in our 24-hour study [Abelson and Curtis, 1996a], so feedback inhibition from pre-CRH cortisol elevations cannot explain the ACTH blunting. The report from this group makes it clear that they carefully controlled "exogenous stressors," because they recognized the excessive responsivity of patients with panic disorder to such stimuli [Von Bardeleben and Holsboer, 1988]. This study therefore provides the strongest evidence for intrinsically elevated central drive in the HPA axes of patients with panic disorder. However, it is a single study with a small sample, and full description of the patients with panic disorder and their comorbidities are not provided in two different publications of these data [Holsboer et al., 1987; Von Bardeleben and Holsboer, 1988]. The authors themselves conclude that patients with panic disorder do not show the same kind of clear, centrally driven overactivity of the HPA axis seen in depression, but instead show a less strictly organized and less stable endocrine response pattern [Von Bardeleben and Holsboer, 1988].

The finding of abnormal cortisol responses to a combined dexamethasone–CRH test also supports a central dysregulation of the HPA axis in panic [Schreiber et al., 1996]. However, this study also compared patients with panic disorder and those with depression, and showed that depression was associated with abnormal ACTH responses to the test, whereas patients with panic disorder had normal ACTH responses and only differed from controls in cortisol responses. The cortisol responses, however, were significantly affected by sex, and the panic group was predominantly female, whereas the control group was predominantly male. The only other HPA abnormality in the patients with panic disorder was an elevated "baseline" cortisol, but cortisol elevations with only a 30-minute accommodation following venipuncture and immediately preceding a pharmacological challenge are consistent with our environmental reactivity hypothesis.

HPA studies that use urinary or salivary collections allow assessment in more naturalistic settings and may avoid the impact of the more invasive procedures needed to obtain plasma measures. Twenty-four hour urinary free cortisol (UFC) has been shown to be normal in panic disorder [Uhde et al., 1988], or elevated only in the presence of depression or agoraphobia [Kathol et al., 1988; Lopez et al., 1990]. Bandelow et al. [1997, 2000b], on the other hand, report elevated nocturnal urinary secretion of cortisol in patients with panic disorder over multiple nights measured at home, which seems unlikely to be impacted by reactivity to novelty or contextual variables. However, Bandelow et al. [1997] note that nocturnal awakenings could explain this elevation. Using a novel design, this group also reports elevated cortisol levels in saliva samples obtained during naturally occurring panic attacks [Bandelow et al., 2000a]. The elevations reported were in comparison to samples obtained 24 hours later, when an attack was not occurring. These data may suggest that cortisol is elevated during naturalistic attacks, in contrast to laboratory attacks. However, elevations were already present in the first sample taken, immediately after attack onset, and may have been present even beforehand. In this naturalistic model, a cortisol "response" may not have been seen if levels during the attack were compared to those immediately before, as is done in the laboratory models. In the laboratory models, "elevations" would likely also be seen if the "baseline" used was cortisol measured 24 hours later at home. In at least one laboratory model, higher cortisol before challenge increases the likelihood of a panic response to the challenge [Coplan et al., 1998]. It may be that the greater subjects' novelty sensitivity, the higher their "baseline" cortisol in a challenge paradigm, and the greater their likelihood of panic. The Bandelow data may reflect a similar process, in that prepanic cortisol levels may have been elevated, and the factors contributing to this elevation (e.g., hyperreactivity to a perceived, actual, or anticipated environmental challenge) may have provided the trigger for the subsequent attack.

Our conclusion is that most of the HPA axis disturbances reported in panic could be due to heightened sensitivity to environmental cues that are salient to this neuroendocrine stress system. Animal literature suggests that novelty and threat are salient to the HPA axis, particularly in the absence of control, social support, or meaningful coping response. These are precisely the factors that were addressed by the

cognitive intervention that appeared to "correct" HPA axis abnormalities in panic in our pentagastrin model. A correctable sensitivity to one or more of these factors may explain the HPA axis abnormalities that have been reported in patients with panic disorder.

The animal literature suggests that the effects of "processive" stimuli such as novelty on the HPA axis reach the hypothalamus via "higher" level cortical and limbic circuits that allow interpretation of their meaning and salience, influenced by past experience [Herman and Cullinan, 1997]. In contrast to systemic stressors such as hypoxia, HPA responses to these behavioral stressors are altered by lesions in cortical/limbic regions [e.g., prefrontal cortex, amygdala, and hippocampus; Herman and Cullinan, 1997]. If heightened reactivity to some aspects of experimental contexts provides a parsimonious explanation for HPA axis abnormalities in patients with panic disorder, the animal literature would point us toward the cortical/limbic pathways that provide modulatory input to the hypothalamus in our search for the source of this dysregulation.

Animal models have focused attention on the amygdala as a potential site of dysregulation in anxiety disorders [Shekhar et al., 1999], and hyperactivity within the amygdala could play a role in panic. The amygdala can also influence hypothalamic activity and cortisol release [Rubin et al., 1966]. Excessive reactivity of the amygdala could contribute to panic and lead to enhanced HPA axis reactivity. However, amydgalar output is a consequence of complex, interacting activating and inhibitory inputs from multiple regions, including cortex [Shekhar et al., 1999], so enhanced amydgalar reactivity could result from dysregulation within cortical/limbic modulatory circuits.

In our work, both prior experience in the laboratory setting and verbal/cognitive manipulation were able to reduce HPA axis hyperreactivity in patients with panic disorder. These effects must also involve modulation of hypothalamic activity via "higher" brain circuits that somehow determine the salience of past experience or cognitive inputs to current challenges. Medial prefrontal cortex is a strong candidate for inclusion in such a modulatory circuit, since it is known to process emotional salience and to provide inhibitory input to the HPA axis [Diorio et al., 1993]. Such higher level inhibitory pathways may be a particularly fruitful place to look for the source of the HPA axis dysregulation seen in panic disorder. Such circuits may be of general relevance to the pathophysiology of this disorder. We propose a speculative but testable specific hypothesis—that HPA abnormalities in panic are due to dysregulation in suprahypothalamic circuits and may involve a specific hypersensitivity to novelty cues. Future work should directly test this hypothesis.

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