NEUROENDOCRINE RESPONSES TO LABORATORY PANIC: COGNITIVE INTERVENTION IN THE DOXAPRAM MODEL

James L. Abelson¹, John G. Weg², Randolph M. Nesse¹ and George C. Curtis¹
¹University of Michigan Department of Psychiatry, Anxiety Disorders Program, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0840; and ²University of Michigan, Department of Internal Medicine, Pulmonary Division, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0024, USA

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SUMMARY

Doxapram is a respiratory stimulant that appears to be a potent and specific panicogenic agent. It also elicits an abnormal ventilatory response in patients with panic. A replication study confirmed these findings and demonstrated that behavioral and ventilatory responses to doxapram were significantly modified by a psychological intervention designed to cognitively block panic. The replication study provided an opportunity to simultaneously investigate the neuroendocrine effects of the illness, the drug, the drug-induced panic attacks, and the cognitive intervention. Epinephrine (EPI), norepinephrine (NE), growth hormone (GH), adrenocorticotropic (ACTH), and cortisol were studied in patients with panic and control subjects given placebo and doxapram injections after receiving either standard instructions or a brief cognitive intervention. Patients with panic had elevated levels of EPI, ACTH, and cortisol throughout the study. Doxapram had little or no detectable effects on plasma NE, GH, ACTH, and cortisol. Doxapram-induced panic attacks were not associated with elevations in NE, GH, ACTH, or cortisol. Doxapram led to a rapid and very brief rise in plasma EPI, which was small in subjects who did not panic and pronounced in patients who did panic. The cognitive intervention attenuated the EPI response to doxapram, perhaps through its effect on panic, and modified the temporal pattern of ACTH and cortisol secretion. These results suggest that: (1) further study of catecholamine responses within the first few minutes after panic induction is needed; (2) intense panic can occur without significant activation of the hypothalamic–pituitary–adrenal axis; and (3) cognitive factors can modulate neuroendocrine activity in laboratory studies of patients with panic.

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Keywords—Panic disorder; Doxapram; Cortisol; Catecholamines; Growth hormone; Cognition.

INTRODUCTION

Doxapram is a respiratory stimulant that provides a new laboratory model for the study of panic attacks. It appears to be a potent and specific panicogenic agent, triggering panic attacks in 80% of patients and 20% of controls (Lee et al., 1993). It also produced an exaggerated ventilatory response in patients (Lee et al., 1993), supporting the hypothesis that patients with panic attacks have hypersensitive respiratory control centers (Papp et al.,

Address correspondence and reprint requests to: James L. Abelson, University of Michigan Department of Psychiatry, Anxiety Disorders Program, Rm C435, Med Inn Bldg/0840 1500 E. Medical Center Drive Ann Arbor, MI 48109-0840, USA (Tel: 313 764 5348; Fax: 313 936 7868).
1993). Doxapram acts on both peripheral and medullary oxygen and carbon dioxide (CO₂) chemoreceptors to increase the rate and depth of breathing (Burki, 1984; Calverley et al., 1983; Folgering et al., 1981; Winnie, 1973). It has no known interactions with any of the neurotransmitter receptor systems that have thus far been implicated in the control of anxiety or anxiety-related neuroendocrine parameters (Curtis and Moyer, unpublished data).

We conducted a replication study to confirm doxapram’s panicogenic activity and to investigate the effectiveness of a cognitive intervention in attenuating patients’ exaggerated behavioral and respiratory responses (Abelson et al., in press). This study provided an opportunity to simultaneously investigate neuroendocrine effects of the illness, the drug, the drug-induced panic attacks, and the cognitive intervention. The doxapram model is advantageous for such a study in that it produces a high rate of panic, the onset of panic is rapid and predictable, it allows blood sampling during the panic itself without subject awareness, and there are no volume-loading effects that might dilute hormone concentrations or block hormone release.

We examined levels of norepinephrine (NE), epinephrine (EPI), growth hormone (GH), adrenocorticotropic (ACTH), and cortisol. Catecholamines are of interest because noradrenergic hyperactivity has long been thought to play a role in panic disorder (Uhde, 1987). Rises in plasma NE, but not EPI, have been seen in spontaneous and CO₂-induced panic (Cameron et al., 1987; Gorman et al., 1988) and following yohimbine and caffeine provocation (Albus et al., 1992; Uhde et al., 1984), raising the question as to whether a similar pattern would be seen with doxapram. Blunted GH responses to clonidine are a robust feature of patients with panic disorder, suggesting reduced sensitivity of α₂-adrenoreceptors (Uhde et al., 1992) and supporting the noradrenergic hyperactivity hypothesis. However, panicogenic agents such as yohimbine and caffeine may also elicit a GH response that is blunted in patients with panic disorder, raising the possibility that anxiety states may generally be associated with transient GH release but patients with panic attacks may have a widely hyporesponsive hypothalamic–GH system (Uhde et al., 1992). Examination of the GH response to doxapram-induced panic is relevant to this hypothesis.

Numerous studies have examined hypothalamic–pituitary–adrenal (HPA) axis activity associated with panic attacks. Naturally occurring attacks (Cameron et al., 1987) and attacks elicited by behavioral challenge (Woods et al., 1987) have not been associated with consistent or clearly abnormal elevations in cortisol. Neither lactate- nor CO₂-induced panic is accompanied by consistent elevations in ACTH or cortisol (Aronson et al., 1989; Gorman et al., 1988; Levin et al., 1987). Other panicogenic agents, such as yohimbine (Charney et al., 1984), caffeine (Uhde et al., 1984), β-carboline (Insel et al., 1984), and cholecystokinin (CCK) agonists (Abelson et al., 1994), do activate the HPA axis, but they may do so independently of their anxiogenic activity. However, patients panicking in response to yohimbine show an enhanced rise in cortisol (Charney et al., 1984). Fenfluramine produces greater anxiety and a greater elevation of cortisol in patients with panic disorder than controls (Targum, 1992).

These and other data have led to the hypothesis that panic attacks are not necessarily accompanied by HPA axis activation, but that such activation is a more common accompaniment of anticipatory or generalized anxiety (Carr et al., 1986; Klein, 1993; Targum, 1992). Klein (1993, 1994) has gone further and suggested that true panic, best modeled by lactate and CO₂, always involves a respiratory mechanism and is not accompanied by HPA axis activation. Agents such as yohimbine, which do activate the HPA axis, may be modeling anticipatory anxiety rather than panic. Although vulnerable to a variety of
critiques, this hypothesis does lead to the specific, testable prediction that panic attacks provoked through a primarily respiratory mechanism should not activate the HPA axis. Examination of ACTH and cortisol responses to doxapram provides a test of this prediction.

Basic research on the psychoneuroendocrinology of stress has emphasized the impact of psychological mediators, such as the predictability and controllability of a stressor, on endocrine stress responses (Breier et al., 1987; Levine, 1992; Weinberg & Levine, 1980). Few studies, however, have directly addressed the potential impact of such factors on neuroendocrine results in studies of patients with psychiatric disorders. Our study design allowed us to examine whether a simple manipulation of perceived predictability and controllability of a stressor would alter neuroendocrine responses to a panicogenic agent.

SUBJECTS AND METHODS

Patients and Controls
Sixteen patients with panic disorder and 16 normal control subjects were evaluated by structured interview (SCID-UP) (Spitzer & Williams, 1986). They were 19–39 years of age, medically healthy and normotensive, not pregnant or lactating, free of any medication that might affect endocrine measures, and reported no exposure to psychoactive medication for at least 2 weeks prior to the study. Control subjects additionally had no life history of any Axis I psychiatric disorder and had no first-degree relatives with panic or an affective disorder. They were matched by sex and age (within 4 years) to enrolled patients. All patients met DSM-III-R criteria for panic disorder, with or without agoraphobia, and had at least four panic attacks during the month prior to study. One patient was in a major depressive episode at the time of study and two others had prior depressive episodes. In all cases the panic symptoms had occurred first and predominated the clinical picture. None of the patients had been taking any daily medication within 2 months of being studied and all reported no medication intake whatsoever for at least 2 weeks prior to study.

Design
Each subject was studied in a single experimental session that included an accommodation phase, a placebo phase, and a doxapram phase. The accommodation phase occurred first and subjects were informed that it was for acclimatization only. They were told that in the subsequent two phases they might receive two placebo infusions, two doxapram infusions, or one of each in any order. All actually received placebo followed by doxapram, as doxapram’s effects make its blind administration impossible. Patients were randomly assigned to either ‘standard’ or ‘experimental’ conditions (eight patients in each), which differed in the orientation that was given prior to the experiment. The experimental condition applied a cognitive intervention designed to reduce subjective anxiety and panic responses to the infusion (see below) by altering cognitive set. Control subjects were assigned to the same cognitive set condition as their paired patient. The design thus included four cells, created by two diagnoses (patients vs. controls) crossed with two conditions (standard vs. experimental). The experimenter who recorded symptoms and debriefed subjects was blind to condition assignment.

Cognitive Intervention
An introduction to the experiment was presented to all subjects via a prerecorded audio tape. The standard introduction paralleled the control instructions used in prior studies of
cognitive factors in laboratory-induced panic (Clark, 1993; Sanderson et al., 1989). It lasted 4 min and described the apparatus, all procedures, and all common side effects of doxapram. The experimental introduction began identically, but then manipulated the cognitive set by incorporating two techniques intended to reduce subjective symptoms and frequency of panic attacks. The first technique inoculates against ‘catastrophic misinterpretation’ of bodily sensations by providing a detailed description of the somatic symptoms to be expected in response to the infusion and repeatedly emphasizing that these symptoms represent a normal response and do not indicate an adverse or dangerous bodily reaction (Clark, 1993). This portion of the introduction involved an additional 3 min of recorded explanation and 5–10 min of open discussion during which the subjects’ own experiences were used to help them see how normal bodily sensations could become frightening and develop into anxiety triggers. The second technique reduces the stressfulness of the procedure by giving subjects an illusory belief that they can control their exposure to the drug should they find it too uncomfortable (Sanderson et al., 1989). This was accomplished by providing an infusion control apparatus (infusion pump) with a light on top that was used to indicate when this control system was activated for use. When the light was lit, subjects believed that they could slow the infusion using a dial on the pump or turn it off altogether. The light was lit only for subjects in the experimental condition. In reality, the doxapram was administered as a bolus injection through tubing that bypassed the control apparatus. Because it was given as a bolus injection, by the time any subject could note any symptom responses and decide to turn off the ‘infusion’, they would have received their full dose of doxapram. As a result, our deception never extended to the point of giving the drug to someone who believed they had stopped its administration. All subjects were also told that they could terminate the procedures at any time by raising their arm to signal to the experimenter. The illusion of control manipulation was identical to that previously employed by Sanderson and this type of deception is a standard approach in psychological studies (Sanderson et al., 1989). This and all procedures were reviewed in detail and approved by the university institutional review board.

Procedures

Approximately 1 week before the experimental session, clinical evaluations were completed and informed consent obtained, after full description of the procedures. Subjects reported for the experiment at 1330h and received either the standard introduction or the cognitive intervention. They were then escorted to a pulmonary laboratory and seated in a semireclining position. An intravenous catheter was placed in an arm vein and connected to a normal saline drip. Electrocardiograph leads were attached. A nose clip and plastic mouthpiece for breathing were put in place and connected to a CAD*NET SYSTEM 2001 (Medical Graphics Corp., St Paul, MN, USA) for respiratory measurements. During the monitoring phases, room lights were dimmed and the experimenters sat behind and out-of-sight of the subject. The accommodation phase lasted for 5 min during which subjects were left at rest to allow habituation to the monitoring apparatus. The placebo and doxapram phases began with approximately 5 min of baseline monitoring, followed by an intravenous injection (over 15 s) of a 5 ml normal saline (NS) solution in the placebo phase and of doxapram (0.5 mg/kg in NS to make 5 ml) in the doxapram phase. Data collection continued for approximately 8 min following the placebo injection and 25 min following the doxapram injection.
Blood samples were drawn 4 min after initiation of the accommodation phase, 7 min after the placebo injection, and 2, 5, 15, and 24 min after the doxapram injection. The accommodation and placebo phase samples were considered baselines and were assayed for ACTH, cortisol, EPI, NE, and GH. The catecholamines were also measured at 2 and 5 min after doxapram. ACTH and GH were measured at 5, 15, and 24 min after injection. Cortisol was measured at 15 and 24 min postdoxapram. All manipulations of the intravenous system (blood sampling, injections, and changes in flow rates) were accomplished outside of the subjects' awareness. Four of the 32 subjects did not have full endocrine profiles drawn. When blood samples could not be easily obtained without disruption of respiratory monitoring they were abandoned. As a result, there is some sample size variation in the endocrine analyses.

Immediately before beginning the accommodation period and at the end of each phase a semistructured interview was used to obtain descriptions and ratings of the subject's experiences. Panic attacks were judged to have occurred when subjects: (a) identified their experience as a panic attack; (b) rated four or more DSM-III-R symptoms as at least moderate (3 on the 4-point scale) in severity (excluding 'hot and cold flushes', as all subjects experienced a sensation of heat from the drug); and (c) rated the experience as highly similar to a spontaneous attack (rating of 5 or more on a similarity scale ranging from 1, not at all similar, to 7, identical; criterion (c) was not applied to control subjects).

**Assays**

Samples for ACTH and GH were drawn into tubes containing heparin and ethylene-diaminetetraacetic acid. Both were measured using an immunoradiometric (IRMA) assay kit from Nichols Institute (San Juan Capistrano, CA, USA). For ACTH, the sensitivity was 1.0 pg/ml and intra- and interassay coefficients of variation (CVs) were less than 4 and 8%, respectively. For GH, the sensitivity was 0.2 ng/ml and CVs were less than 5%. Samples for cortisol and catecholamines were drawn into tubes containing heparin alone. Cortisol was measured by radioimmunoassay using the Diagnostic Products, (Los Angeles, CA, USA) Coat-A-Count kit. The sensitivity was 0.2 μg/dl and CVs were less than 6%. Catecholamines were measured by high-performance liquid chromatography with electrochemical detection. The sensitivities were 6 pg/ml for EPI and 3 pg/ml for NE. The CVs were all less than 12%. Clinical and respiratory measures are described and reported in detail elsewhere (Abelson et al., in press).

**Data Analyses**

The hormone data were log-transformed prior to analysis to normalize distributions. The main analyses were three-way repeated measure analyses of variance (ANOVA) conducted on data for each hormone. ‘Time’ was the within-group factor, utilizing accommodation, placebo, and postdoxapram measures and reflecting changes in hormone levels over the course of the experiment. A significant time effect in the ANOVAs might suggest an endocrine response to the doxapram injection, but other factors, such as circadian rhythm, could also produce a significant main effect of time. The between group factors were diagnosis and cognitive set. Differences between patients and controls in response to doxapram or cognitive set should appear as interactions between diagnosis and time or cognitive set. A significant time-by-cognitive set interaction would reflect an impact of the cognitive intervention on fluctuations in endocrine levels.
Table I. Mean (± SD) norepinephrine, epinephrine, and cortisol levels in four experimental cells during baseline phases (accommodation and placebo) and at various intervals after doxapram (dox) infusion

<table>
<thead>
<tr>
<th></th>
<th>Norepinephrine (pg/ml)</th>
<th>Epinephrine (pg/ml)</th>
<th>Cortisol (µg/dl)</th>
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<tr>
<td></td>
<td>Accommodation</td>
<td>Placebo</td>
<td>Dox+2 min</td>
</tr>
<tr>
<td>Patients-experimental (n = 6)</td>
<td>153.3 ± 50.7</td>
<td>136.7 ± 42.5</td>
<td>117.5 ± 35.4</td>
</tr>
<tr>
<td>Patients-standard (n = 6)</td>
<td>110.8 ± 53.2</td>
<td>125.3 ± 79.9</td>
<td>139.5 ± 94.0</td>
</tr>
<tr>
<td>Controls-experimental (n = 6)</td>
<td>169.7 ± 111.9</td>
<td>173.3 ± 122.5</td>
<td>205.3 ± 138.6</td>
</tr>
<tr>
<td>Controls-standard (n = 5)</td>
<td>151.2 ± 55.1</td>
<td>140.2 ± 41.9</td>
<td>151.2 ± 33.3</td>
</tr>
<tr>
<td>Mean (all subjects)</td>
<td>146.0 ± 71.7</td>
<td>144.4 ± 77.1</td>
<td>153.5 ± 89.5</td>
</tr>
</tbody>
</table>
To assess response to drug more directly and to maximize the probability of detecting any measurable response, we also compared maximum postdoxapram levels to predoxapram baselines using paired t-tests, for all subjects combined and then separately within each experimental cell. Subjects' experiences during the accommodation and placebo phases were essentially identical and we saw no differences between these phases in NE, EPI, or GH levels. We therefore used the mean of the accommodation and placebo phase levels as the baseline measure for these hormones. Both ACTH and cortisol were significantly lower during the placebo phase than the accommodation phase (p < .002 for both), probably due to an HPA response to venipuncture and entry into the novel laboratory setting that raised levels during the accommodation phase. We therefore used the lower placebo phase level as the predoxapram baseline for these two hormones.

To determine specifically whether panic attacks were associated with endocrine responses, we used t-tests to compare the endocrine responses of patients who panicked (n = 8) to those of controls, and to those of patients who did not panic. The response measures were maximum postdoxapram levels minus predoxapram baselines.

RESULTS

The four experimental cells (patients-standard, patients-experimental, controls-standard, controls-experimental) did not differ in the mean age of subjects (27.4 ± 5.2, 26.9 ± 4.9, 29.5 ± 5.9, and 26.5 ± 4.6 years, respectively). The sex ratio in each cell was 3:5 (male:female). Patients in the two conditions (standard and experimental) did not differ in age of illness onset (22.1 ± 5.1 and 20.1 ± 4.4 years, respectively), duration of illness (5.2 ± 4.2 and 6.8 ± 7.7 years), or panic attack frequency (4.7 ± 2.3 and 6.2 ± 5.0 attacks/week).

Under standard conditions, panic attacks occurred in 75% of patients (six of eight) and 12.5% of controls (one of eight). After cognitive intervention, panic occurred in 25% of patients (two of eight) and 12.5% of controls (one of eight). Respiratory and behavioral results are reported in detail elsewhere (Abelson et al., in press).

NE and EPI data are presented in Table I. For NE, the ANOVA revealed only a significant effect of time (F = 3.28, p = .03, df = 3, 57). NE levels were stable from accommodation to 2 min after doxapram, but declined at 5 min after drug. Changes were very small and there was no clear NE release in response to the injection. There was no significant change from baseline to maximum postdoxapram levels for the total subject group (t = 1.0, p = .33, df = 23) or for the four experimental cells analyzed separately. Panicking patients did not differ significantly from nonpanicking patients or control subjects (p > .51) in the NE response.

For EPI, the ANOVA revealed significant main effects of diagnosis (F = 9.01, p = .007, df = 1, 19) and time (F = 11.29, p = .0001, df = 3, 57), and a significant time-by-cognitive set interaction (F = 3.09, p = .03, df = 3, 57). Patients had elevated EPI relative to controls at all time points, levels increased sharply from placebo phase to 2 min after doxapram, and the cognitive intervention attenuated this EPI response to drug. As can be seen in Fig. 1, there was an EPI response to doxapram regardless of cognitive set, but the size of the response was substantially smaller in subjects who received the cognitive intervention. The EPI response to doxapram was confirmed by the significant rise from baseline to the postdoxapram maximum (t = 6.7, p = .0001, df = 23) for all subjects combined. This rise remained significant (p < .04) for each of the four cells analyzed separately. Patients who had
panic attacks had larger EPI responses to doxapram than controls \((t = 2.8, p = .01, df = 17; 100.5 \pm 104.6 \text{ vs. } 18.5 \pm 15.8 \text{ pg/ml, respectively})\), although they did not differ significantly from the nonpanicking patients \((28.5 \pm 36.6 \text{ pg/ml; } t = 1.7, p = .12, df = 12)\). The nonpanicking patients did not differ from controls in EPI response to doxapram \((t = 0.8, p = .43)\).

GH data are presented in Table II. The ANOVA revealed only a significant effect of time \((F = 2.75, p = .03, df = 4, 76)\), due to declining levels from accommodation to 5 min after doxapram, and rising levels from 5 to 24 min after injection, but the changes were very small and no clear response to the drug was seen. The lack of significant change from baseline to postdoxapram maximum in the total subject group \((t = 1.2, p = .23, df = 25)\), and in each cell analyzed separately, confirms the lack of a drug effect on GH levels. Panicking patients did not differ significantly from nonpanicking patients or control subjects \((p > .20)\) in GH response.

ACTH data are also presented in Table II. The ANOVA revealed significant main effects of diagnosis \((F = 6.35, p = .02, df = 1, 20)\) and time \((F = 3.89, p = .006, df = 4, 80)\), and a significant time-by-cognitive set interaction \((F = 3.34, p = .01, df = 4, 80)\). Patients had elevated ACTH levels relative to the controls at all time points. The main effect of time primarily reflected the overall declining levels from beginning to end of the study (see Table II, total group means). The time-by-cognitive set interaction reflects the impact of the cognitive intervention on the pattern of ACTH change over time (see Fig. 2). Under standard conditions, ACTH levels declined over the baseline phases and increased slightly after doxapram injection. With the cognitive intervention, ACTH levels started higher and declined steadily from beginning to end, with no increase after doxapram. An apparent ACTH response to doxapram, reflected in the significant rise from baseline to postdoxapram
Table II. Mean (± SD) growth hormone and adrenocorticotropic (ACTH) levels in four experimental cells during baseline phases (accommodation and placebo) and at various intervals after doxapram (dox) infusion

<table>
<thead>
<tr>
<th></th>
<th>Growth hormone (ng/ml)</th>
<th>ACTH (pg/ml)</th>
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<tr>
<td></td>
<td>Accommodation</td>
<td>Placebo</td>
</tr>
<tr>
<td>Patients-experimental (n = 6)</td>
<td>2.4 ± 2.5</td>
<td>1.04 ± 0.96</td>
</tr>
<tr>
<td>Patients-standard (n = 6)</td>
<td>1.7 ± 1.8</td>
<td>1.2 ± 1.6</td>
</tr>
<tr>
<td>Controls-experimental (n = 6)</td>
<td>0.62 ± 0.57</td>
<td>0.91 ± 1.6</td>
</tr>
<tr>
<td>Controls-standard (n = 5)</td>
<td>0.20 ± 0.15</td>
<td>1.5 ± 2.9</td>
</tr>
<tr>
<td>Mean (all subjects)</td>
<td>1.3 ± 1.7</td>
<td>1.2 ± 1.7</td>
</tr>
</tbody>
</table>
Fig. 2. Adrenocorticotropic (ACTH) levels (mean ± SE) during baseline phases (accommodation and placebo) and at 5, 15, and 24 min after doxapram infusion in subjects (patients and controls) receiving either a cognitive intervention designed to reduce panic response to the challenge agent or a ‘standard’ introduction to the experiment.

maximum levels for all subjects ($t = 3.0, p = .007, df = 23$), was mainly due to a significant rise ($p = .01$) in the standard condition control subjects. None of the other cells showed a significant change when analyzed separately. Panicking patients did not differ significantly from nonpanicking patients or control subjects ($p > .36$) in ACTH response. The mean response was in fact smaller in panicking patients than controls ($4.3 ± 8.4$ vs. $7.0 ± 6.1$ pg/ml, respectively).

The pattern seen for cortisol (Table I) was similar to ACTH, although the main effects of diagnosis and time did not quite reach significance ($F = 3.49, p = .07, df = 1, 23; F = 2.54, p = .06, df = 3, 69$, respectively). The time-by-cognitive set interaction was significant ($F = 3.28, p = .02, df = 3, 69$). Overall, cortisol levels declined from the beginning to the end of the study (see Table I, total group means), and patients had higher levels than the controls at every measurement point. As with ACTH, the significant time-by-cognitive set interaction was due to the fact that, under standard conditions, cortisol levels declined over the baseline phases but rose slightly after doxapram, whereas they started higher but declined steadily despite the doxapram injection in subjects who received the cognitive intervention (see Fig. 3). There was no significant change from baseline to maximum postdoxapram level for cortisol, for the total subject group ($t = 1.2, p = .23, df = 25$) or for any of the four cells analyzed separately. Panicking patients did not differ significantly from nonpanicking patients ($p = .06$) or controls ($p = .26$) in cortisol response. Panicking patients and controls showed small rises in cortisol from baseline to the postdoxapram maximum ($4.4 ± 6.7$ μg/dl and $1.2 ± 2.5$ μg/dl, respectively), while nonpanicking patients had a slight decline ($-1.6$ μg/dl).
Fig. 3. Cortisol levels (mean ± SE) during baseline phases (accommodation and placebo) and at 15 and 24 min after doxapram infusion in subjects (patients and controls) receiving either a cognitive intervention designed to reduce panic response to the challenge agent or a ‘standard’ introduction to the experiment.

DISCUSSION

Briefly summarized, our principal findings are as follows: (1) patients with panic disorder had elevated levels of EPI, ACTH, and cortisol throughout the study; (2) doxapram per se, at a dose of 0.5 mg/kg, had little or no detectable effects on plasma NE, GH, ACTH, and cortisol; (3) doxapram-induced panic attacks were not associated with elevations in NE, GH, ACTH, or cortisol levels; (4) doxapram produced a rapid and very brief rise in plasma EPI, which was small in subjects who did not panic and pronounced in patients who did panic; and (5) the cognitive intervention attenuated the EPI response to doxapram, perhaps through its effect on panic, and modified the temporal pattern but not the overall levels of ACTH and cortisol.

In contrast to the NE release that has been reported in spontaneous and CO₂-induced panic (Cameron et al., 1987; Gorman et al., 1988), and following yohimbine and caffeine provocation (Albus et al., 1992; Uhde et al., 1984), we saw no significant NE response to doxapram or doxapram-induced panic. We did see a brief but robust EPI response to doxapram that was strikingly similar to the EPI response we previously reported in response to another panicogen, pentagastrin (Abelson et al., 1994). Similar responses have not been reported in response to other laboratory panicogens. However, other studies have not consistently sampled blood within the first few minutes of pharmacological stimulation or panic onset, as would be continuous to capture the response that we have seen. One unpublished study using continuous venous sampling suggests that with adequate frequency of measurements, both NE and EPI responses may be seen in spontaneous and imagery-induced panic (cited in Veith, 1991)). Further study using continuous sampling techniques
(Dimsdale & Moss, 1980) in all models may be necessary to clarify catecholamine activity in laboratory panic. Our data suggest that laboratory panic can occur in the absence of significant NE release. Other models need to be examined for early, brief pulses of EPI.

The EPI response in our subjects could be a direct pharmacological effect of doxapram or a nonspecific effect from injection of a foreign substance. It could also be a specific concomitant of panic onset or a more general concomitant of a startle response, elicited by sudden symptom induction. The facts that it (a) appeared in all four experimental groups and in most but not all subjects, (b) has been seen in response to pentagastrin, a panicogen with an entirely different pharmacology but a similar abrupt onset of symptoms and panic (Abelson et al., 1994), and (c) was clearly alterable by cognitive expectancies and perceived control, which reduced the rate of panic and the intensity of panic symptoms (Abelson et al., in press), may be most consistent with the hypothesis that it is linked to panic onset or sudden symptom induction. Although the EPI response was clearly larger in panicking patients than either controls or nonpanicking patients, we cannot disentangle the effects of panic from other effects of the cognitive intervention, as the intervention so effectively reduced panic symptoms (Abelson et al., in press). Future research should further explore this rapid and brief EPI release, its modulation by cognitive factors, and the possibility that it is a marker of panic onset.

We detected no significant effects of diagnosis, doxapram, panic, or cognitive intervention on GH levels. The data do not support the hypothesis that anxiety states are generally associated with transient GH release (Uhde et al., 1992). Despite the induction of typical and intense panic attacks, doxapram did not produce elevations in GH. Because of the extremely low levels of GH seen throughout our sampling period, the data cannot address the hypothesis that patients with panic may have a widely hyporesponsive hypothalamic–GH system.

In this paradigm, panic disorder was associated with elevated levels of ACTH and cortisol, but we did not see robust elevations in either hormone in response to doxapram or doxapram-induced panic. Significant effects of time in the repeated measure ANOVAs reflected declining levels over the course of the procedures, and attempts to maximize response detection by comparing postinjection maximum levels to preinjection baselines did not reveal a consistent overall doxapram effect. A small but significant ACTH rise in control subjects in the standard cognitive set condition raises the possibility of a small drug effect, but there was clearly no panic-related ACTH response. Changes in cortisol were quite small and, except for the main effect of time in the ANOVA due to the overall decline in cortisol, did not achieve statistical significance. A possibly greater rise in cortisol in panicking than nonpanicking patients just missed reaching statistical significance, but the rise in cortisol was quite small, did not differ between panicking patients and control subjects, and was not accompanied by any parallel change in ACTH.

The panic attacks induced by doxapram were intense, rated as very similar to patients' naturally occurring attacks, and were accompanied by striking elevations in ventilation and heart rate (Abelson et al., in press). The physiological responses to doxapram began within 1–3 min of the injection and, when panic attacks occurred, they coincided with this physiological activity, so our sampling times should have captured any associated ACTH or cortisol responses. The data thus confirm that fairly intense panic, accompanied by strong physiological reactions, can occur in a stressful laboratory paradigm without clearly measurable activation of the HPA axis.
These data are consistent with other results that have failed to demonstrate significant HPA axis activation in lactate (Carr et al., 1986) and CO₂ (Gorman et al., 1988) models of panic or in clinical or spontaneous panic attacks (Cameron et al., 1987; Woods et al., 1987). Although not a definitive test of the entire theory, this study supports the prediction, based on Klein’s suffocation alarm hypothesis of panic, that respiratory stimulant-induced panic attacks should not activate the HPA axis (Klein, 1993).

Recent evidence raises the possibility that our inability to detect HPA axis activation in laboratory models of panic may not be due to an absence of panic-related stimulatory input to central corticotropin-releasing hormone (CRH) neurons, but rather to a simultaneous inhibition of these neurons by atrial natriuretic hormone (Kellner et al., 1995). This hormone suppresses HPA axis activity (Kellner et al., 1992), is secreted in excess in response to lactate-induced panic (Kellner et al., 1995), and could therefore obscure ACTH and cortisol responses to panic that might otherwise be seen. Examination of the atrial natriuretic hormone response to doxapram-induced panic is needed to determine whether release of this hormone is specific to lactate panic or is associated more generally with panic attacks, and whether its release may inhibit HPA axis activation in the doxapram model.

Whether the mechanism involves absence of activation or modulatory inhibition, the fact remains that intense panic anxiety can occur without the striking activation of the HPA axis that so many observers have expected (Kellner et al., 1995). Similarly, and also contrary to initial expectations and prior conventional wisdom, intense phobic anxiety is not accompanied by HPA axis activation (Curtis et al., 1978). It thus appears that severity or intensity of anxiety or distress are not key factors in HPA axis activation. This may seem counterintuitive if one thinks simplistically about ACTH and cortisol as ‘stress’ response hormones, but basic research has demonstrated repeatedly that the nature of the ‘stressor’ is important and that psychological factors such as novelty, expectancies, and perceived control may be more critical to stress-related modulation of the HPA axis than overall distress intensity (Levine, 1992).

Although the importance of cognitive/psychological processing of aversive stimuli in modulating HPA axis responses is well-established in the preclinical literature (Breier et al., 1987; Kirschbaum et al., 1992; Levine, 1992), its relevance to clinical studies has perhaps not been fully recognized and has only rarely been directly addressed (Croes et al., 1993). Our data confirm that expectancies, perceived control, and anticipatory anxiety can modulate neuroendocrine activity in a laboratory model of panic and appear to have a more robust impact on HPA axis activity than the panic attacks themselves. Future studies of the neuroendocrinology of panic cannot ignore these factors and their examination in studies of HPA axis activity in patients with other psychiatric disorders may also be revealing.

It is of interest that the three hormones that were affected by the cognitive manipulation (ACTH, cortisol, EPI) were also consistently elevated in patients with panic disorder relative to the controls. For all three of these hormones, the main effect of diagnosis was significant in the repeated measure ANOVA and patients had higher mean values than the controls at every time point. It has been difficult to determine whether patients with panic disorder truly have elevated basal levels of ‘stress-reactive’ hormones because their level of reactivity to environmental perturbations may make the circumstances of blood sampling a sufficient stressor to remove them from the basal states. Examination of reports of ACTH and cortisol levels in patients with panic disorder suggests that elevations are more likely to be seen when ‘baseline’ levels are measured just prior to an infusion paradigm (Roy-Byrne et al., 1986) than when they are measured in less invasive paradigms (Gurguis et al., 1991), or over
a longer period of time prior to an infusion (Holsboer et al., 1987). The fact that patients with panic disorder showed elevations relative to the controls in this study on only those endocrine measures which were impacted by cognitive manipulations is consistent with the hypothesis that endocrine abnormalities in panic may be at least partially tied to cognitive processing abnormalities.

This study has a number of weaknesses that must be acknowledged. Behavioral and respiratory findings (Abelson et al., in press) strongly replicate earlier work (Lee et al., 1993), but this is the first study to examine neuroendocrine measures in this paradigm and full endocrine profiles were not obtained on every subject studied. Replication is clearly needed. Furthermore, a single dose of doxapram was utilized, and neuroendocrine responses may be dose dependent. The apparent lack of response in some cases could also be due to Type II error. Comparisons between the total patient group and the total control group, and between cognitive set groups with diagnoses combined, probably have adequate sample sizes to suggest some robustness to the findings that patients had elevated levels of ACTH, cortisol, and EPI relative to controls and that cognitive set affected these three hormones. Comparisons involving just panicking patients or diagnosis-by-cognitive set interactions, however, had very small sample sizes and particularly need confirmation with larger samples. The conclusion that psychological factors may be important modulators of neuroendocrine activity in laboratory panic paradigms rests on the comparative finding that we could more robustly detect an impact of cognitive set on ACTH and cortisol than an impact of doxapram or doxapram-induced panic, and is thus less vulnerable to Type II error. However, we also failed to include a group of comparison subjects who were subjected to the same procedures but did not receive doxapram. Such a control group is needed to determine whether, in the absence of doxapram, more substantial declines in ACTH and cortisol would have been seen. If so, then the lack of greater declines in hormone levels in our subjects could reflect HPA axis activation. The paradigm itself appears to have been fairly activating of the HPA axis, most likely because it presented a novel experience to most subjects. Substantially lower ACTH and cortisol levels are seen during this time period when patients with panic disorder and controls are studied while at rest over a full circadian cycle (Abelson & Curtis, 1996). Although these factors may have obscured HPA axis responses to doxapram or doxapram-induced panic, the data still demonstrate that a fairly simple cognitive manipulation of expectancies/perceived control does influence HPA axis activity and EPI release, and that any doxapram or panic effects on the HPA axis are too subtle to overcome the impact of novelty exposure and perceived predictability or controllability.

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