Dysregulation within both respiratory control systems and the hypothalamic-pituitary adrenal (HPA) axis has been implicated in the pathophysiology of panic disorder. However, potential linkages between respiration and the HPA axis have rarely been examined in panic patients. We have previously published neuroendocrine and psychophysiological response data from a laboratory panic model using the respiratory stimulant doxapram. We now present a new, theoretically driven re-examination of linkages between HPA axis and respiratory measures in this model. Previous analyses showed elevated corticotropin (ACTH) and persistent tidal volume irregularity in panic patients, due to a high frequency of sighs. Regression analyses now show that tidal volume irregularity and sigh frequency were strongly predicted by pre-challenge ACTH levels, but not by subjective distress or panic symptoms. We predicted this relationship on the basis of our hypothesis that both the HPA axis and respiratory control systems may be reactive to contextual cues such as novelty or anticipation of future challenge. Follow-up work is needed to directly test this hypothesis.


Key words: corticotropin; respiration; breathing; panic disorder; stress

INTRODUCTION

Dysregulation within brainstem respiratory control systems may play a central role in the etiology or pathophysiology of panic disorder [Klein, 1993]. Considerable evidence in fact supports the presence of dysregulated respiratory control in panic patients [Papp et al., 1997]. Another etiologic theory suggests that panic disorder may be due to dysregulation within central stress response circuits mediated by corticotropin-releasing hormone (CRH) [Schreiber et al., 1996]. There is evidence that panic disorder patients do have abnormalities within the hypothalamic-pituitary adrenal (HPA) axis, which is controlled by CRH [Abelson and Curtis, 1996]. We have made contributions to both sets of literature. We have shown that panic patients have persistent respiratory (tidal volume) irregularity, characterized by a high frequency of sighing breaths. This irregularity is relatively immutable even when respiration is driven exogenously; and it is unaffected by cognitive manipulation that significantly alters other respiratory measures as well as panic attack vulnerability [Abelson et al., 1996a; Abelson et al., 2001]. We have also shown that panic patients have abnormal HPA axis activity in a 24 hr basal state study [Abelson and Curtis, 1996] and in a panicogenic laboratory model [Abelson et al., 1991]. In the original publications of these data, we speculated

Department of Psychiatry, Trauma, Stress and Anxiety Research Group, Drive, University of Michigan, Ann Arbor, Michigan

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*Correspondence to: Dr. James L. Abelson, 4250 Plymouth Road, Ann Arbor, MI 48109-5765. E-mail: jabelson@umich.edu

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that both the respiratory irregularity and HPA axis
disturbances could be secondary phenomena and not
primary factors in disease pathology [Abelson and
Curtis, 1996; Abelson et al., 2001].

In a recent review of our panic-HPA work [Abelson
et al., 2006], we suggest that HPA axis abnormalities in
panic are secondary to hyper-reactivity to specific
environmental triggers that are known to be highly
salient to this system, such as novelty, and that HPA
axis abnormalities in panic may thus originate in supra-
hypothalamic brain areas that modulate the HPA axis
rather than within its core components. We have
subsequently revisited our respiratory irregularity data
[Abelson, 2006]. We had originally speculated that
respiratory irregularity in panic might represent a
secondary effort to use intrinsic anti-dyspneic effects
of sighs to combat anxious distress associated with
subjective dyspnea [Abelson et al., 2001]. Noting that
(a) panic patients had elevated ACTH levels through-
out our doxapram challenge study, relative to levels at
the same time of day in a separate basal state study; (b)
that they had elevated tidal volume irregularity and
elevated sigh frequency relative to controls throughout
the challenge study; and (c) that both ACTH and
respiratory irregularity were unaffected by dramatic,
drug-induced hyperventilation accompanied by panic
attacks, we hypothesized that the elevated ACTH levels
were marking a psychological-somatic hyper-reactivity
to the novelty-induced stress of participating in a
challenge study and that tidal volume irregularity could
be a physiological reaction to the same sensitivity
[Abelson, 2006]. If so, they should be significantly
related to each other, and examination of this correla-
tion (not previously done) could provide a very
preliminary test of the hypothesis. We now present
results of new correlational analyses examining the
relationships between ACTH, tidal volume irregularity
and symptom responses in the doxapram challenge
study.

METHODS

The experiment compared 16 panic patients and 16
healthy controls on neuroendocrine, psychological and
physiological responses to the respiratory stimulant
doxapram, in a single session involving three phases—
an accommodation phase (5 min), a placebo phase
(12 min), and a doxapram phase (25 min). Our primary
prediction was that pre-challenge ACTH levels, which
we thought best captured the HPA axis reactivity of
subjects to the novelty stress of the challenge paradigm,
would be strongly related to tidal volume irregularity
and sigh frequency throughout the experiment.

Pre-challenge ACTH was calculated as the mean of
two samples taken during the accommodation and
placebo phases, before doxapram injection. The injec-
tions were done out of sight of subjects, so subjective
experiences during accommodation and placebo phases
were identical, and the mean of these two samples
provides the best measure of HPA activity during
the first 15 min of data collection. Tidal volume
irregularity was quantified by von Neumann’s statistic
[Abelson et al., 1996a] separately for the accommodation,
placebo and doxapram phases. Subjects were
recruited from a clinical population and through
newspaper advertising, screened by structured diag-
nostic interview, and met strict entry criteria (including
no daily medication for 2 months prior to study).

All patients met DSM-III-R criteria for panic disorder,
with or without agoraphobia. For methodological
details and overall results, see previous publications
[Abelson et al., 1996a,b].

RESULTS

ACTH levels and tidal volume irregularity did not
change significantly over the three phases and were
elevated in panic patients relative to controls in
all phases (see Table 1). Pre-challenge ACTH was
strongly related to tidal volume irregularity during all
three phases \( r = .67, P < .0001; r = .58, P = .0009; \)
\( r = .63, P = .0002 \), for accommodation, placebo and
doxapram phases, respectively, \( n = 29 \). It was also
significantly related to sigh frequency during all phases
(e.g., \( r = .53, P = .006, n = 25 \) for total sighs, \( r = .56, \)
\( r = .002, n = 29 \) for sigh frequency after doxapram
injection). To insure that these relationships were not a
consequence of group differences on both variables,
the relationships between pre-challenge ACTH and
tidal volume irregularity during accommodation

| TABLE 1. Mean (SD) ACTH and tidal volume irregularity over three phases in patients and control subjects, with repeated measures analysis of variance results |

<table>
<thead>
<tr>
<th>Phase</th>
<th>Patients</th>
<th>Controls</th>
<th>Tidal volume irregularity</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accommodation</td>
<td>32 (20)</td>
<td>17 (5)</td>
<td>517 (422)</td>
<td>175 (111)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>29 (21)</td>
<td>12 (4)</td>
<td>464 (396)</td>
<td>153 (117)</td>
<td></td>
</tr>
<tr>
<td>Doxapram</td>
<td>34 (16)</td>
<td>16 (7)</td>
<td>495 (339)</td>
<td>192 (101)</td>
<td></td>
</tr>
</tbody>
</table>

ANOVA: \( F(p) \)

<table>
<thead>
<tr>
<th>Group</th>
<th>7.1 (.01)</th>
<th>11.2 (.002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>2.5 (.10)</td>
<td>1.1 (.33)</td>
</tr>
<tr>
<td>Group × phase</td>
<td>1.7 (.19)</td>
<td>0.3 (.76)</td>
</tr>
</tbody>
</table>

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DISCUSSION

Pre-challenge ACTH levels and respiratory irregularity were strongly and consistently linked to each other in this study, whether irregularity was quantified by tidal volume variability or sigh frequency. ACTH explained nearly half the variance in tidal volume irregularity, and this link was independent of subjectively reported symptom and distress levels. The relationship between ACTH and respiratory irregularity was not examined in initial analyses because we had no theoretical reason at that time to expect that HPA axis activity and breathing patterns should be linked to each other. When prompted to look at this now by the realization that both could reflect sensitivity to contextual stress cues (e.g., novelty, anticipation of upcoming challenge), we were quite struck by the strength and robustness of the relationship we found in this data set. There is one prior report in the literature [Coplan et al., 1998] showing a parallel finding in a lactate challenge—elevated pre-challenge cortisol predicted greater fear, subjective dyspnea, lactate-induced panic, and hyperventilation (lower pCO₂). Tidal volume irregularity and sighs were not reported, but our data would predict that their reduced pCO₂ was due to more frequent sighs and that associated tidal volume irregularity would be strongly linked to pre-challenge cortisol. We hypothesize that this relationship appears primarily in the context of activation, as it was only absent in our data set for the control subjects during accommodation. We suspect that the control subjects were in a fairly basal state during accommodation but were activated by doxapram, whereas panic patients were activated in both phases due to hypersensitivity to paradigm novelty.

Though these post-hoc analyses can only provide the most preliminary kind of support for our hypothesis, it does suggest that follow-up work is indicated to directly test the proposal that both HPA axis activity and tidal volume irregularity (created by high rates of sighing) can be markers or consequences of hypersensitivity to factors such as novelty or anticipation of future challenge. Such work may help illuminate the neurobiology of panic disorder. This follow-up work must consider competing hypotheses as well, such as the possibility that HPA axis hormones themselves may directly modulate respiratory patterns.

REFERENCES


