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Carbon Dioxide Provocation of Anxiety and Respiratory Response in Bipolar Disorder

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Abstract

Background—Frequent bipolar/panic comorbidity implies bipolar individuals may experience CO₂-provoked anxiety and changes in respiratory patterns similar to those experienced by individuals with panic disorder.

Methods—16 euthymic bipolar individuals breathed air and air combined with 5% CO₂ for 15 minutes each. Respiratory and subjective anxiety measures were collected.

Results—On CO₂ subjects were more anxious and breathed more deeply and rapidly than with air; the degree of increase in anxiety attributable to CO₂ was directly correlated with the degree of increase in minute ventilation. Five individuals were assessed as having a panic attack. Panic response to CO₂ was predicted by the degree of anxiety experienced with air alone.

Conclusions—Comparison with the results of similar panic studies shows bipolar disorder is associated with enhanced respiratory response to CO₂. Hypersensitivity to CO₂ among bipolar individuals suggests a possible pathological mechanism common to both bipolar and panic disorders. These preliminary data support the expanded application of CO₂ challenges in bipolar subjects.

Keywords

Affective disorders; psychophysiology; panic disorder; hypercapnia; hyperventilation

Introduction

The rate of panic disorder among individuals with bipolar disorder is higher by an order of magnitude than among the population in general (Freeman et al. 2002). Familiality of bipolar/panic comorbidity implies a biological basis for the association (MacKinnon et al. 2002). Physiological evidence that panic disorder patients are hyperreactive to mild hypercapnea (Papp et al. 1997) suggests the possibility that bipolar patients may have similar vulnerability. In this pilot study, individuals ascertained for bipolar disorder genetic linkage study were given 5% carbon dioxide over 15 minutes and evaluated for the emergence of anxiety, panic symptoms, and changes in respiratory function akin to those experienced by individuals with panic.

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Methods and Materials

Study subjects

Sixteen unrelated euthymic individuals with bipolar disorder were included. All had been interviewed by a research psychiatrist using a version of the Diagnostic Interview for Genetic Studies (Nurnberger et al. 1994). Thirteen had bipolar I, three had bipolar II with recurrent depression. Nine subjects had experienced at least one prior panic attack, and three of these subjects had a lifetime diagnosis of panic disorder. There were 9 females. Thirteen were currently taking psychotropic medications indicated for bipolar disorder (lithium, anticonvulsants, atypical neuroleptics); 7 of the 13 were also medicated (not necessarily for panic) with antidepressants; one had taken a single small dose of a benzodiazepine in the week prior to the study. No subject had an active substance use disorder or had taken alcohol or illicit drugs in the 48 hours prior to the study.

Study procedures

After providing informed consent both in writing and by discussion with the investigator, each subject was to have two 15 minute sessions with a facemask. During one, compressed air was inspired, during the other 5% carbon dioxide in air was inspired; the order was applied randomly across subjects and subjects were not informed which gas they were receiving. All subjects were able to complete 15 minutes with carbon dioxide. A rest period of at least 5 minutes without the mask was included between sessions. Respiratory function was measured with Korr RSS 100 flow spirometer, which yielded continuous information on the timing and volume of inspiration, and generated data files with raw and breath-by-breath data on tidal volume and breath frequency. Before, after, and at three points within each trial, subjects were asked to rate their level of anxiety on an analog scale of 0–100 mm, and after each trial to note on a checklist the presence and intensity (on a scale of 1–4) of any of the characteristic symptoms of a panic attack. After both trials were completed the investigator asked subjects whether they thought they had experienced a panic attack during the experiment.

Data processing and analysis

Subjective data—A subject was assessed as having a panic attack when either the subject reported having a panic attack or the subject reported an anxiety rating of at least 50/100 and had four of the characteristic symptoms of a panic attack.

Respiratory data—Data were inspected visually and cleaned of artifact, and then divided into three five minute intervals (1st, 2nd, and last five minutes) for each arm of the trial.

Exploratory analyses were conducted to examine patterns in anxiety and respiratory measures to air and carbon dioxide separately. Statistical analyses were performed using Statistica (Statsoft) for correlations and t-tests.

Results

Response to Air versus Carbon Dioxide

Mean maximum anxiety on 15 minutes of carbon dioxide was two and a half times the maximum anxiety experienced with air alone (40.4 (± 23.2) vs 15.8 (± 12.7)), paired $T(15)=5.32$, $p<0.0001$). Mean minute ventilation on carbon dioxide was elevated consistently with respect to minute ventilation on air (Table 1). The degree of difference in anxiety attributable to carbon dioxide was correlated with the minute ventilation difference between air and carbon dioxide ($r=0.71$; $p<0.05$). The difference in minute ventilation between air and carbon dioxide was significant in the first five minutes (8.9 (± 2.4) l/minute on air vs 14.7 (± 4.7) l/min on CO₂ ($T(15)=6.39$, $p<0.00005$)) and continued to expand through the last 5 minutes (7.7 (± 2.5) l/min

vs 16.4 (± 6.1) l/min, $T(15)=6.80$, $p<0.00001$). In the first five minutes, the air versus carbon dioxide difference in minute ventilation was associated almost entirely with an elevation of tidal volume. As tidal volume changed little over the remaining time on carbon dioxide, the increasing minute ventilation was a product of increasing respiratory rate through the course of the trial.

Lifetime history of panic disorder appeared to have no influence on the results, which were virtually identical when these three individuals were removed from the analysis. Lifetime history of any panic attacks similarly did not predict carbon dioxide reactivity; the nine individuals with prior panic attacks were in fact slightly less anxious and breathed slightly less frequently on carbon dioxide than did individuals with no prior panic experience.

Panic Response to Carbon Dioxide

Five individuals experienced a panic attack on carbon dioxide. These individuals also had higher anxiety with air alone (27.6 (± 5.9) vs 10.5 (± 11.3); $T(14)=3.17$, $p<0.01$). As illustrated in Figure 1, there were no obvious differences between panickers and nonpanickers in terms of bipolar subtype, lifetime anxiety disorder diagnosis, current pharmacotherapy, age, or sex. One potentially noteworthy pattern differentiating panickers from nonpanickers is that panickers in every case increased their minute ventilation between the first and last five minutes on CO₂, whereas this was not the case for five of the eleven nonpanickers.

Discussion

In these individuals with bipolar disorder, 5% carbon dioxide strongly stimulated respiratory function and had a potent effect on subjective anxiety. The additional anxiety attributable to carbon dioxide correlated with the additional respiratory function. Five of 16 individuals were found to have a panic response. The likelihood of a panic response was associated primarily with the degree of anxiety experienced by a given subject on air alone, which may be taken as an indicator of anxiety sensitivity in a given subject (e.g., triggered by wearing a face mask).

We lacked a comparison group of unaffected individuals, however there are several studies that used similar methods with panic patients and healthy controls. The patterns from these studies reflect relatively greater increases in respiratory rate among individuals with panic (Bystritsky et al. 1992; Rapee et al. 1992), as well as individuals without a panic diagnosis who experienced panic with carbon dioxide (Gorman et al. 2001). In each of these studies, the rate among panic patients significantly exceeded the rate among (nonpanicking) controls. The mean rate achieved by our subjects exceeded the rate for CO₂-sensitive subjects in these studies of panic disorder.

One observes in these results that mildly hypercapnic individuals with bipolar disorder mount a respiratory response more like individuals with panic than like normal controls. However, the rate of panic response was modest, compared to other studies of panic patients (Rassovsky et al. 2003). The decoupling of panic from heightened respiratory response might be the result of pharmacologic blockade, or it might denote the absence in our subjects of some non-respiratory factor (present in panic patients but not necessarily in bipolar patients) that produces a panic response, or our failure to detect a significant association of respiratory reactivity and panic may be a function of our small sample size. Although these are preliminary findings, the results suggest an extension of the hypothesis that carbon dioxide induced hyperventilation triggers arousal of the conditioned fear response in panic patients (Sinha et al. 2000). Functionally and anatomically, the most obvious point of intersection between anxiety and affective disorders is in the processes of threat and reward assessment (MacKinnon et al. 2006). Both functions appear to depend on amygdala-mediated conditioned learning of the appropriate threat and reward value of present objects and experience. One can understand one

aspect of affective states—the manic incorrigibility of efforts to satisfy certain appetites and the depressive inability to mount a behavioral response to appetite—as a broken connection in the cognitive process driving behavior with respect to appetite and the anticipated consequences of pursuing the behavior. Similarly, one can understand the intense and prolonged hyperventilatory response seen with panic (and bipolar) disorder as a deficit in the ability to satisfy or quell the “appetite” for fresh air under conditions where less sensitive individuals learn that hyperventilation is an uncomfortable and ineffective strategy to restore a resting carbon dioxide level.

Compared to most psychophysiologic study groups, this is a heterogeneous set of individuals, older on average than subjects in other studies, many taking medications that can potentially affect the response to physiologic challenge. The panic and anxiety response observed despite medication suggests this study underestimates the true carbon dioxide sensitivity of bipolar individuals, however the pharmacologic effect, if any, was not uniform across subjects and so remains a potential source of noise. The study of unmedicated subjects would be preferable. However, unlike panic patients, who are generally studied in an unmedicated state, it is rarer to find and potentially riskier to study unmedicated bipolar patients.

Several other limitations warrant discussion. The absence of a control group requires us to compare these data with other studies and thus introduces the possibility that comparisons are skewed by local differences in measurement. We did not perform a standardized baseline assessment of anxiety or mood state. This limits comparison of the affective state of our subjects with subjects in other studies. Measures of end-tidal CO₂ and psychometric data on the perception of threat and reward would be helpful in elaborating on the hypothesis that differences in respiratory function result from factors other than physiologic drive to maintain eucardia. The sample size was underpowered to detect different responses among subgroups, hence the lack of association on any anxiety or respiratory variable to differences in sex, prior anxiety or panic disorder diagnosis, current psychotropic treatment, bipolar subdiagnosis (I vs II), or priority of air versus carbon dioxide is inconclusive. It must be noted that statistical tests were not corrected for multiple testing, in order to highlight potential questions that arise from this exploratory study.

Nevertheless, this preliminary evidence showing similarities in the hypercapneic response of subjects with bipolar disorder to the abnormally high response seen with panic disorder suggests that further application of symptom provocations methods in use for anxiety disorder may be a fruitful approach with which to explore the pathophysiology of bipolar disorder as well.

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Reference List

- Bystritsky A, Shapiro D. Continuous physiological changes and subjective reports in panic patients: a preliminary methodological report. *BiolPsychiatry* 1992;32:766–777.
- Freeman MP, Freeman SA, McElroy SL. The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology, and treatment issues. *J AffectDisord* 2002;68:1–23.
- Gorman JM, Kent J, Martinez J, Browne S, Coplan J, Papp LA. Physiological changes during carbon dioxide inhalation in patients with panic disorder, major depression, and premenstrual dysphoric disorder: evidence for a central fear mechanism. *ArchGenPsychiatry* 2001;58:125–131.

- MacKinnon DF, Zamoiski R. Panic comorbidity with bipolar disorder: what is the manic-panic connection? *Bipolar Disord*. 2006Ref Type: In Press
- MacKinnon DF, Zandi PP, Cooper J, Potash JB, Simpson SG, Gershon E, et al. Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. *Am J Psychiatry* 2002;159:30–35. [PubMed: 11772686]
- Nurnberger JII, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, et al. Diagnostic interview for genetic studies. Rationale, unique features, and training NIMH Genetics Initiative. *Arch Gen Psychiatry* 1994;51:849–859. [PubMed: 7944874]
- Papp LA, Martinez JM, Klein DF, Coplan JD, Norman RG, Cole R, et al. Respiratory psychophysiology of panic disorder: three respiratory challenges in 98 subjects. *Am J Psychiatry* 1997;154:1557–1565. [PubMed: 9356564]
- Rapee RM, Brown TA, Antony MM, Barlow DH. Response to hyperventilation and inhalation of 5.5% carbon dioxide-enriched air across the DSM-III-R anxiety disorders. *J Abnorm Psychol* 1992;101:538–552.
- Rassovsky Y, Kushner MG. Carbon dioxide in the study of panic disorder: issues of definition, methodology, and outcome. *J Anxiety Disord* 2003;17:1–32.
- Sinha S, Papp LA, Gorman JM. How study of respiratory physiology aided our understanding of abnormal brain function in panic disorder. *J Affect Disord* 2000;61:191–200.

Figure 1.

Minute ventilation and anxiety during each of the three five minute periods on carbon dioxide. Each column of data points represents one subject. The first (left) dark circle in each segment is respiratory data from the first 5 minutes on carbon dioxide, the middle is the second five minutes, and the third (right) circle is from the last 5 minutes. Open circles represent the mean minute ventilation breathing air alone. Gray columns represent anxiety ratings from the periods of time corresponding to the respiratory data points. Short horizontal lines denote the maximum anxiety reported during the 15 minutes on air alone. White space after the 5th subject divides panic responsive subjects on the left from the rest. Codes beneath the chart by line: Line 1 is the sex and age, line 2 the bipolar subtype (B1 for bipolar type I, B2 for bipolar II with recurrent major depression). Line 3 marks lifetime anxiety disorder diagnosis: pa=any panic attack, PD=panic disorder, AD=other anxiety disorder. Line 4 marks pharmacotherapy: PT=panic treatment—treatment with anti-panic agent (any antidepressant or benzodiazepine); OM=other medication—use of any other prescription psychotropic medication.

Anxiety and Respiratory Response by Individuals with Bipolar Disorder to Air and 5% Carbon Dioxide over 15 Minutes

	AIR		5% CARBON DIOXIDE		Last 5 minutes	
	1 st 5 minutes		2 nd 5 minutes		Mean	SD
Anxiety (VAS)	Mean	11.4	Mean	35.1	Mean	30.5
	SD	10.8	SD	17.8	SD	22.2
Respiratory rate (breath/min)		4.9		957		18.9
Tidal volume (ml)		316		16.0		925
Minute ventilation (l/min)		2.4				417
						6.1

* Differences in results for air at different time periods were trivial, so only the first 5 minutes are presented.