Psychiatry Research ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Reactivity to 35% carbon dioxide in bulimia nervosa and panic disorder

Andrea Woznica, Kristin Vickers *, Naomi Koerner, Katie Fracalanza

Department of Psychology, Ryerson University, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 19 July 2014
Received in revised form
11 March 2015
Accepted 2 May 2015

Keywords:
Carbon dioxide
Biological challenge
Panic disorder
Bulimia nervosa

ABSTRACT

The inhalation of 35% carbon dioxide (CO_2) induces panic and anxiety in people with panic disorder (PD) and in people with various other psychiatric disorders. The anxiogenic effect of CO_2 in people with eating disorders has received sparse attention despite the fact that PD and bulimia nervosa (BN) have several common psychological and neurobiological features. This study compared CO_2-reactivity across three groups of participants: females with BN, females with PD, and female controls without known risk factors for enhanced CO_2-reactivity (e.g., social anxiety disorder, first degree relatives with PD). Reactivity was measured by self-reported ratings of panic symptomatology and subjective anxiety, analyzed as both continuous variables (change from room-air to CO_2) and dichotomous variables (positive versus negative responses to CO_2). Analyses of each outcome measure demonstrated that CO_2-reactivity was similar across the BN and PD groups, and reactivity within each of these two groups was significantly stronger than that in the control group. This is the first study to demonstrate CO_2-hyperreactivity in individuals with BN, supporting the hypothesis that reactivity to this biological paradigm is not specific to PD. Further research would benefit from examining transdiagnostic mechanisms in CO_2-hyperreactivity, such as anxiety sensitivity, which may account for this study's results.

1. Introduction

A single-breath inhalation of 35% carbon dioxide (CO_2) enriched air balanced with 65% oxygen, known as the 35% CO_2 challenge, is a valid and reliable experimental procedure to provoke anxiety and panic-like symptoms (Griez et al., 1987; Vickers et al., 2012). Over two decades of research have established that people with panic disorder (PD) experience hyperreactivity to this concentration of CO_2, such that they react with significantly greater panic symptomatology and subjective anxiety compared to people without psychiatric disorders (Vickers et al., 2012). CO_2-hyperreactivity has also been observed in people with other disorders including situational and natural environment phobias (Verburg et al., 1994), social anxiety disorder (SAD; Schmidt and Richey, 2008), premenstrual dysphoric disorder (PMDD; Harrison et al., 1989), and possibly post-traumatic stress disorder (PTSD), although findings conflict (Muhtz et al., 2011; Talesnik et al., 2007). Hyperreactivity has similarly been demonstrated in those without a PD diagnosis but with sporadic unexpected panic attacks (Perna et al., 1995a) and in those with a family history of PD (van Beek and Griez, 2000). In contrast, CO_2-hyperreactivity has not been observed in other diagnostic groups, including generalized anxiety disorder (GAD; Verburg et al., 1995), obsessive–compulsive disorder (OCD; Griez et al., 1990), animal phobias (Verburg et al., 1994), and mood disorders (Perna et al., 1995b).

Only one CO_2 study has tested people with eating disorders (EDs), finding that an ED diagnosis did not predict hyperreactivity (Perna et al., 2004). At face value, this suggests that EDs are different from the aforementioned disorders in which hyperreactivity has been observed. In Perna et al.'s study, the ED group was composed of people with bulimia nervosa (BN) and people with anorexia nervosa (AN), likely on the assumption that BN and AN have more in common with one another than with other disorders. However, evidence converges to suggest that questions about CO_2-hyperreactivity should be pursued in BN specifically, as BN has much in common with PD, including a shared genetic loading (Kendler et al., 1995), serotonin deficiencies (Kaye et al., 1998), and significant anxiety symptoms produced by sodium lactate infusion (e.g., Lindy et al., 1988). Additionally, comorbidity rates between PD and EDs characterized by cycles of bingeing and purging are high relative to comorbidity between PD and restricting anorexia. For example, Godart et al. (2003) reported the prevalence of PD in an AN sample (AN-Restrictive subtype 5.4%; AN-Binge/Purge subtype 14.5%) and in a BN sample (BN-Purging subtype 20.9%). Most other studies have demonstrated similar findings (e.g., see Godart et al., 2002, Swinbourne and Touyz, 2007 for reviews; see also Kaye et al., 2004).

Accordingly, the main objective of the present study was to examine whether hyperreactivity to 35% CO_2 characterizes females

* Corresponding author. Tel.: +1 416 979 5000x7727; fax: +1 416 979 5273.
E-mail address: kvickers@psych.ryerson.ca (K. Vickers).

http://dx.doi.org/10.1016/j.psychres.2015.05.050
0165-1781/

with BN compared to females with PD and female controls who do not have known risk factors for enhanced CO_2-reactivity. One would expect high degrees of reactivity to 35% CO_2 in those with a diagnosis of PD, as the CO_2 provocation is known to aggravate panic in those with panic histories (e.g., Perna et al., 1995a). Additionally, evidence suggests that the serotonergic abnormalities that occur in PD (Coplan et al., 1992; Maron and Shlik, 2006) are associated with enhanced reactivity to CO_2. However, a history of unexpected panic attacks is an exclusionary criterion for participants with BN in the current study; thus we cannot attribute hyperreactivity in BN to panic history as we potentially could in previous studies, including those using sodium lactate (e.g., Lindy et al., 1988). Therefore, in the current study, although individuals with BN are characterized by a serotonin deficiency similar to other psychodiagnostic groups that hyper-react to CO_2 (e.g., PD, PMDD, SAD), they are without panic histories and thus cannot be expected to react to CO_2 to the same extent as individuals with PD. It was therefore hypothesized that reactivity in the BN group would be intermediate between that of the PD and control groups, such that those with PD would be most reactive and control participants least reactive to CO_2.

2. Method

2.1. Participants

Three groups of female adults were included in this study: 14 with a principal diagnosis of BN-Purging Type, 15 with a principal diagnosis of PD, and 30 controls. All participants were recruited from the community via advertisements. A total of 80 participants met inclusion criteria during a telephone screen (over 100 additional participants were screened and found ineligible). Eligible participants were invited to the laboratory. Of these, 16 were subsequently excluded for not meeting eligibility requirements (medical and/or psychological) during more rigorous in-person screening procedures. The CO_2-challenge was terminated early for two participants due to abnormal blood pressure, and for one participant with intense self-reported anxiety during the procedure. Data from two additional participants were excluded from analyses because their tidal volume during the CO_2-inhalation was less than 80% of their vital capacity. Thus a final sample size of 59 remained.

Psychiatric diagnoses according to DSM-IV-TR criteria were established using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), a widely used semi-structured diagnostic interview with psychometric properties comparable to the Structured Clinical Interview for DSM-IV-TR Axis-I Disorders (SCID-I; First et al., 2001). The MINI-Screen was first administered over the telephone along with a screening question for specific phobias from the SCID-I. The complete MINI and specific phobia section from the SCID-I were subsequently administered in the laboratory. Diagnostic criteria for each study group were confirmed: BN-P, without comorbid PD; PD, without any comorbid ED; and neither PD nor an ED. Exclusionary for all participants was the endorsement of situational or natural environmental phobias, SAD, or PMDD since individuals with these diagnoses have displayed CO_2-hyperreactivity in previous studies (Harrison et al., 1989; Schmidt and Richey, 2008; Verburg et al., 1994). Additional exclusions for the control and BN groups only were a history of sporadic unexpected panic attacks and PD in first or second-degree relatives. A senior-level doctoral student in clinical psychology was trained and supervised by PhD-level psychologists to administer this diagnostic interview.

Medical exclusion criteria were consistent with previous studies (e.g., Perna et al., 2004); they were assessed over the telephone and again in the laboratory on a self-report questionnaire. Participants were required to have been deemed healthy by a medical doctor via a physical examination within the past year, and have none of the following: cardiovascular, respiratory, renal, or neurological disorders; complicated migraines; head injury; current pregnancy; family history of cerebral aneurysm or hemorrhage, or hemiplegic migraine. Also exclusionary was the use of psychotropic medications except for benzodiazepines occasionally (less than twice/week and not within five half lives of the laboratory visit) or use of a medication that can affect heart rate (e.g., beta-blockers). Participants were asked to refrain from nicotine and caffeine for 4-hours prior to the laboratory visit, and the experiment was terminated if significant changes in blood pressure (BP) occurred during the CO_2-challenge (e.g., systolic BP reaches ≥ 170 or ≤ 90).

2.2. Self-report measures of CO_2-reactivity

CO_2-reactivity was assessed by subjective anxiety on the *Subjective Units of Distress Scale* (SUDS; Wolpe, 1973) and panic symptomatology on the *Acute Panic Inventory* (API; Liebowitz et al., 1984). Participants completed these two measures at baseline and immediately after each inhalation (room-air, CO_2-enriched air). The SUDS is a visual analog scale for anxiety (VAS-A) measuring subjective anxiety from 0 (*no anxiety at all*) to 100 (*the worst anxiety imaginable*). The API is a 17-item questionnaire assessing the symptoms of physical and cognitive arousal associated with panic attacks. Participants rate the severity of each symptom from 0 (*absent*) to 3 (*severe*) and a total symptom score (TSS) is derived. In this study, internal consistency of the API according to Cronbach's alpha (calculated at three time points) ranged from 0.81 to 0.88.

VAS-A and TSS were examined across groups in two ways: (1) as continuous variables – the change in scores from post-room-air inhalation to post-CO_2 inhalation; and (2) as dichotomous variables – the presence or absence of a positive response to CO_2. VAS-A change scores were calculated according to the method described by Perna et al. (2004), and a positive VAS-A response was defined as an increase of ≥ 26 points in anxiety from room-air to CO_2 (Battaglia and Perna, 1995). A positive TSS response was defined as an increase of ≥ 4 items on the API, regardless of the intensity of the increase on any single item.

2.3. Apparatus

Two gas mixtures were used: room-air and 35% CO_2-enriched air. A breathing circuit contained a disposable mouthpiece and bacterial/viral filter connected via tubing to a two-way non-rebreathing valve. The inspiratory valve port attached to a manual stopcock on which one port fed room-air and the other connected to a non-diffusing gas collection bag filled with CO_2-enriched air. A clinical vital signs monitor provided safety measures of BP, heart rate and oxygen saturation, and a pneumotach yielded tidal volume.

2.4. Procedure

The study consisted of one two-hour laboratory visit. After completing eligibility screening and demographic measures, participants were informed that they would be inhaling two harmless gas mixtures containing different percentages of CO_2 and O_2, which might cause transitory discomfort or panic-like symptoms. Participants were connected to the clinical monitor, which measured vitals every 60-seconds. They were then connected to the breathing circuit and vital capacity was measured. A single blind, placebo-controlled method was used for the inhalations; participants took one breath of room-air (placebo) and subsequently one breath of 35% CO_2-enriched air (e.g., Harrison et al., 1989). Only inhalations that were at least 80% of vital capacity were considered valid. Immediately following each inhalation, participants completed reactivity measures. Study procedures were approved by Ryerson University's Research Ethics Board.

2.5. Data analytic strategy

To examine group differences in CO_2-reactivity, analyses of variance (ANOVA) and Tukey's HSD pairwise comparisons were used to compare the degree of VAS-A and TSS change from room-air to CO_2. Chi-square tests were used to compare the proportions of VAS-A and TSS positive responses to CO_2.

3. Results

3.1. Preliminary analyses

Missing values (less than 10% of the total data matrix and consistent with missing-at-random data) were replaced via mean substitution. All continuous variables approximated normality in their distributions.

3.2. Demographic and characteristics of the sample

Age did not differ significantly across the BN (mean age: $25.14 \pm$ S.D. 7.67 years), PD (mean age: 26.00 ± 7.92 years), and control (mean age: 24.13 ± 5.95 years) groups, $F(2, 56) = 0.38$, $p = 0.68$, $\eta_p^2 = 0.01$. Ethnicity also did not differ significantly across the BN ($n = 6$; 42.9%), PD ($n = 10$; 66.7%) and control ($n = 9$; 30.0%) groups, $\chi^2(18) = 25.87$, $p = 0.10$, $\phi = 0.66$. In total, 18.6% ($n = 11$) of the sample reported symptoms consistent with at least one other

Please cite this article as: Woznica, A., et al., Reactivity to 35% carbon dioxide in bulimia nervosa and panic disorder. Psychiatry Research (2015), http://dx.doi.org/10.1016/j.psychres.2015.05.050