Available online at www.sciencedirect.com
ScienceDirect
Psychiatry Research 151 (2007) 173–176
PSYCHIATRY RESEARCH
www.elsevier.com/locate/psychres

Brief report

Reactivity to challenge with carbon dioxide as a prospective predictor of panic attacks

Norman B. Schmidt [a,*], Jon K. Maner [a], Michael J. Zvolensky [b]

[a] Department of Psychology, Florida State University, Tallahassee, FL 32306, United States
[b] Department of Psychology, University of Vermont, Burlington, VT, United States

Received 11 May 2006; received in revised form 21 September 2006; accepted 9 November 2006

Abstract

Fear responding induced by carbon dioxide was prospectively evaluated as a risk factor for the development of anxiety pathology in a nonclinical sample (N=404) followed for 2 years. Baseline response to a CO_2 challenge was a very strong predictor of future panic attacks (though not for panic disorder or other anxiety disorders).

Keywords: Carbon dioxide; Panic attack; Longitudinal

1. Introduction

Carbon dioxide challenge has been extensively used to explore the nature of panic and panic disorder. The current study addresses one of the main limitations of the literature exploring CO_2-reactivity as a risk factor for panic-related pathology. The primary question of interest is whether CO_2-induced reactivity is predictive of the later development of panic attacks, panic disorder, or other anxiety disorder diagnoses. Studies have shown that patients with panic disorder exhibit increased rates of panic and fear responding to CO_2 inhalation (Papp et al., 1993), suggesting that CO_2 hypersensitivity may be a risk marker for the development of panic disorder. However, such studies have relied on cross-sectional designs and therefore leave unanswered the question of whether CO_2 reactivity truly serves as a risk factor for panic-related symptoms and diagnoses, or whether it is merely concomitant to the experience of panic symptoms. The current research thus used a prospective design to redress this limitation.

A second, related aim of the current research pertains to the link between family history of anxiety and CO_2 reactivity. We evaluated 1) whether a family history of anxiety is associated with CO_2-induced reactivity and 2) whether family history of anxiety might modulate the influence of CO_2-induced reactivity on the later development of anxiety pathology. The previous literature provides mixed support for the link between family history of anxiety and CO_2 reactivity. Exaggerated CO_2-induced fear reactivity has been found in unaffected first-degree relatives of patients with panic disorder (Coryell et al., 2001; Perna et al., 1995; Perna et al., 2002), suggesting that CO_2 reactivity is a familial marker for the development of panic pathology. Such studies, however, have focused largely on healthy adult relatives who have presumably passed through the highest risk period for panic disorder. Therefore, evidence for CO_2 reactivity as a premorbid indicator of familial risk is limited. Indeed, a

* Corresponding author. Tel.: +1 850 664 1707; fax: +1 850 644 7739.
E-mail address: schmidt@psy.fsu.edu (N.B. Schmidt).

0165-1781/$ - see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2006.11.006

recent report evaluated healthy children and adolescents using a 5% CO_2 challenge (Pine et al., 2005). This study observed no link between offspring of patients with panic disorder or other anxiety disorders and enhanced fear responding to the CO_2 challenge.

2. Method

2.1. Assessments

2.1.1. Diagnostic interview

Psychiatric diagnoses were made using the Structured Clinical Interview for DSM-IV, Nonpatient Version (SCID-NP). Interviews were conducted by research assistants with extensive training in SCID administration and scoring.

2.1.2. Assessment of family history of anxiety

A semi-structured interview was used to ascertain lifetime history of significant anxiety problems in first-degree relatives of the participants. This method is widely used and has been found to be reliable and valid for most Axis I conditions, including anxiety disorders (Nardi et al., 2005; Zvolensky and Raulin, 1999). The interview was developed for this study based on similar research. Participants are essentially asked whether their mother, father and siblings had ever either been hospitalized or treated for an anxiety problem. Positive responses were queried to obtain more detailed information though no specific diagnoses were assigned. Lifetime hospitalization or treatment for an anxiety problem was endorsed for one first-degree relative in 22.7% ($n=86$) of the sample (an additional 4.0% ($n=15$) endorsed anxiety treatment in two first-degree relatives). For analytic purposes, this variable was collapsed indicating either a positive or negative family history of anxiety problems.

2.1.3. Acute panic inventory (API)

The API has been commonly used in prior studies evaluating panic provocation as well as those investigating familial CO_2 hypersensitivity. Participants rate the severity of each symptom from 0 (absent) to 3 (severe). The API also includes a Subjective Units of Distress (SUDS) rating of self-reported anxiety (0–No Anxiety, 100–Extreme Anxiety). In the present report, API reactivity indices (pre–post CO_2 challenge in API total symptoms and API–SUDS) were the primary predictors of interest.

2.1.4. 20% CO_2 challenge

Participants underwent a 20-s gas inhalation (20% CO_2, 80% O_2) administered through a continuous positive air pressure Downs C-Pap Mask with nose clip and head strap to assess CO_2 reactivity. The 20% CO_2 challenge has been increasingly used in recent years, with well over 20 empirical studies now available on this topic (Lejuez et al., 2000). Work using 20% CO_2 suggests it is a powerful panicogenic agent that can be administered repeatedly, for various durations of time (see Zvolensky and Eifert, 2000, for a review).

2.2. Procedure

Individuals were recruited from the Columbus, OH metropolitan area school system ($n=46$), the Ohio State University ($n=263$), and the Columbus, OH community ($n=96$). Eligibility criteria included age (range=15–30), scoring >1.5 standard deviations above the mean on the Anxiety Sensitivity Index for a nonclinical community sample (Schmidt and Joiner, 2002), and no current or recent psychiatric history (no diagnoses in the past 12 months and no current Axis I diagnosis). This young adult sample (age $M=19.3$, S.D.=3.9; Female=61%) was followed for approximately 24 months (see (Schmidt et al., in press) for more details). Participants initially completed the SCID and, if eligible, completed a CO_2 challenge. Participants completed an API following a 5-minute adaptation period. After approximately 3 min, participants received a 20-s inhalation of CO_2-enriched air. Immediately following the inhalation, participants returned to breathing normal room air and completed another API. Participants were followed for up to 24 months (average=18 months). During the follow-up evaluations, the SCID was readministered to assess for the occurrence of spontaneous panic attacks and Axis I disorders during the follow-up interval.

Table 1
Zero-order correlations for main study variables

	Panic attacks	Panic disorder	Any anxiety Dx
1. Family history of anxiety	0.00	0.10	−0.01
2. CO_2 reactivity–SUDS	0.55*	0.03	0.11
3. CO_2 reactivity–API	0.47*	−0.01	0.00

Note. 1–Family history of anxiety–any anxiety problems endorsed in first-degree relatives; 2–SUDS–change in anxiety in response during the CO_2 challenge; 3–API–change in API symptoms in response during the CO_2 challenge; Panic attacks–spontaneous panic attacks during follow-up; Panic disorder–panic disorder diagnoses during follow-up; Any anxiety Dx–any anxiety disorder diagnosis during follow-up.
n range=241–379.
* Correlation is significant at the 0.001 level (2-tailed).