Carbon Dioxide Hypersensitivity in Separation-Anxious Offspring of Parents with Panic Disorder

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Background: Similar patterns of vulnerability to carbon dioxide (CO_2) inhalation have been reported in adults with panic disorder (PD) and children with separation anxiety disorder (SAD), suggesting a link between the adult and child conditions. This study examines the influence of familial risk for PD on CO_2 responses in children with SAD. We hypothesized that offspring with SAD of parents with PD would have distinct CO_2 responses.

Methods: Two hundred twelve 9- to 20-year-old offspring of parents with or without PD were exposed to maintained 5% CO_2 inhalation in the participants' homes. Anxiety symptoms, panic attacks, and respiratory physiology (respiratory frequency and tidal volume) were monitored during baseline and 15-min maintained CO_2 breathing.

Results: As hypothesized, significant offspring SAD × parent PD interactions were obtained for anxiety symptoms, respiratory frequency, tidal volume, and a panting index during CO_2 inhalation. Offspring with both SAD and parental PD exhibited more anxiety symptoms at termination of 5% CO_2 breathing than the other offspring groups and had the most extreme values on measures of respiratory physiology.

Conclusions: Youth with both SAD and parental PD have respiratory responses to CO_2 similar to adult PD. They might be a subtype of SAD at particularly high risk for adult PD.

Key Words: At risk, carbon dioxide hypersensitivity, panic disorder, respiratory frequency, separation anxiety disorder, tidal volume

Uncued panic attacks, the defining clinical features of panic disorder (PD), have been the focus of active research. An early view proposed hyperventilation as the proximate causal mechanism of panic attacks. During hyperventilation, more carbon dioxide (CO_2) is eliminated than produced, thus inducing respiratory alkalosis, a putative panicogen. The hyperventilation hypothesis was previously tested by having patients with PD hyperventilate both in room air and in 5% CO_2-enriched air (1). Five percent CO_2 was chosen because this level approximates the usual lung concentration of CO_2. It was predicted that breathing 5% CO_2 air would prevent panic by respiratory alkalosis, whereas hyperventilating in ambient air would induce panic. Surprisingly, the opposite was found. The connection between PD and CO_2 hypersensitivity has now been well-documented, characterized by perturbed ventilation and increased panic attacks and anxiety symptoms (2–11). Perturbed ventilation includes increased respiratory frequency, coupled with lowered tidal volume (8–9,12–14). This respiratory response pattern during CO_2 exposure is akin to "panting," which decreases gas exchange by increasing the dead space proportion of each breath.

Klein hypothesized a specific, evolved suffocation alarm system (15). The initial adaptive response to smothering (e.g., maternal overlay of neonate or sudden exposure to high CO_2 environment) would be hyperventilation combined with escape and protest. However, if hyperventilation and escape failed, because the asphyxiating environment was inescapable, panting would be the default adaptive response, in an attempt to prevent a further rise in partial pressure of CO_2 and increased respiratory acidosis. Klein hypothesized that a hypersensitive suffocation alarm system would lead to false alarms manifested as "uncued" panic attacks (15).

Family studies suggest that CO_2 hypersensitivity represents a vulnerability marker for PD. For instance, increased minute ventilation has been observed in relatives of PD probands compared with relatives of low-risk subjects (16). Healthy relatives of PD patients also report more anxiety compared with healthy relatives of healthy subjects after inhalation of 35% CO_2 (17). Moreover, patients with PD who are hypersensitive to CO_2 are three times more likely to have a first-degree relative with PD than those without CO_2 hypersensitivity (18). A recent twin study showed higher concordance for CO_2-induced panic attacks among monozygotic than dizygotic twins (55.6% vs. 12.5%) (19). Given that the major source of familial risk for PD seems to be genetic (19,20), heritable aspects of CO_2-hypersensitivity and PD might overlap significantly. Findings from a recent population-based twin study of shared genetic influence for CO_2 hypersensitivity and uncued panic attacks support this hypothesis (21). This study also suggests that, among adults, a prior history of separation anxiety disorder (SAD) moderates the association between genetic risk for PD and CO_2-hypersensitivity. A more recent adult twin study by the same team found that genetic factors strongly influence the covariation among childhood separation anxiety disorder, CO_2 hypersensitivity, and adult PD (22). The familiality of anxiety disorders and the putative relationship between PD and SAD prompted the current study that relates CO_2 hypersensitivity to familial risk for PD in children with SAD.

Studies examining CO_2 hypersensitivity in children with anxiety disorders or at risk for PD have relied on maintained 5% CO_2 protocols that expose subjects to room air, followed by 5%

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CO_2-enriched air for various time periods (23–25). Clinical samples of children with anxiety disorders have been found to request termination of the CO_2 task at higher rates, report more panic symptoms, and exhibit more rapid respiratory rate in response to CO_2 than healthy peers (23). Children with SAD exhibit signs of CO_2 hypersensitivity consisting of relatively greater reports of dyspnea and steeper respiratory frequency slopes (24), much like patients with PD during exposure to maintained 5% CO_2. In contrast, this response does not occur in children with social phobia. Children with generalized anxiety disorder do not differ from healthy subjects on respiratory-rate or dyspnea response to CO_2 but do report increased anxiety. In sum, SAD but not social phobia or generalized anxiety disorder is more consistently associated with CO_2 hypersensitivity.

Only a subset of children with SAD develop PD (26,27). It might be that it is those individuals at familial risk for later-life PD who selectively exhibit respiratory correlates of PD at an early age. We hypothesized that children with SAD who also have parents with PD would experience greater symptomatic change and respiratory perturbations (i.e., increased respiratory rate and decreased tidal volume) during CO_2 inhalation, compared with other offspring (i.e., offspring without SAD who are at high risk for PD [parents have PD], offspring with SAD who are at low risk for PD [no parental PD], and offspring with neither risk factor [no SAD and no parental PD]). We also tested the hypothesis that, during CO_2 breathing, conversion to panting respiration, indexed by a decreasing ratio of tidal volume to respiratory frequency over time, would be significantly greater in offspring at genetic risk for PD and SAD than in the other offspring groups.

We previously reported the separate main effects of offspring SAD and parental PD on CO_2 effects in a partial sample of 142 offspring (24). This sample was too small to test an SAD × parental PD interaction. This report is based on the completed sample of 212 offspring from this same high-risk study.

Methods and Materials

Participants

Two hundred twelve biological offspring of 135 families were recruited, with at least one parent with a lifetime diagnosis of PD (n = 57 PD+ families; n = 88 offspring) or neither parent with a history of PD (n = 78 PD− families; n = 124 offspring). Of the 57 families in which at least one parent met criteria for PD (n mothers = 47; n fathers = 11), there was only 1 family in which both the father and mother had a history of PD. Age of PD onset was 27.30 years (SD = 9.69) for mothers and 28.73 for fathers (SD = 9.40). Twenty of 47 mothers (41.7%) and 5 of 11 fathers (45.5%) with PD were currently symptomatic. Demographic data of parents with and without PD did not differ significantly (Table 1).

Subjects also included offspring of parents with a history of major depression (MD). In a series of separate analyses, parental MD was not associated with any measure of offspring CO_2 hypersensitivity. Therefore, parental MD was not included in the statistical models, and this report focuses on whether measures of CO_2 sensitivity are influenced by an interaction between offspring SAD and parental PD, regardless of parental MD.

Offspring (n = 212) were classified on the basis of the presence or absence of a lifetime parental diagnosis of PD and cross-classified on the basis of current SAD, irrespective of other ongoing anxiety disorders. The four cross-tabulated groups were: 1) offspring with both SAD and PD (SAD+/PD+, n = 13); 2) offspring with SAD but no parental PD (SAD+/PD−, n = 10); 3) offspring with parental PD but not SAD (SAD−/PD+, n = 75); and 4) offspring with neither SAD nor parental PD (n = 114, SAD−/PD−). As presented in Table 2, the four risk groups did not differ significantly on gender composition or percent of parents with a history of MD, but children with SAD+ (SAD+/PD− and SAD+/PD+) were younger than those without SAD (SAD−/PD− and SAD−/PD+).

Table 1. Parent Demographic Data

	Parent Diagnostic Group	
	PD− (n = 78)	PD+ (n = 57)
Mother's Ethnicity *n* (%)		
African-American	5 (6.9)	2 (3.8)
Asian/Pacific islander	2 (2.8)	1 (1.9)
Caucasian	62 (86.1)	46 (88.5)
Latino/Latina	3 (4.2)	3 (5.8)
Father's Ethnicity *n* (%)		
African-American	6 (8.3)	3 (5.8)
Asian/Pacific islander	1 (1.4)	1 (1.9)
Caucasian	60 (83.3)	46 (88.5)
Latino/Latina	4 (5.6)	2 (3.8)
Mother's Age, mean yrs (SD)	45.68 (5.41)	46.04 (5.91)
Father's Age, mean yrs (SD)	47.39 (6.55)	48.69 (7.11)
Family SES *n* (%)		
1 (11–17)	4 (5.6)	2 (3.8)
2 (18–31)	31 (43.1)	20 (38.5)
3 (32–47)	26 (36.1)	22 (42.3)
4 (48–63)	9 (12.5)	5 (9.6)
5 (64+)	2 (2.8)	3 (5.8)

Score on 5-factor Hollingshead scale (33); + denotes presence of panic disorder (PD), and − denotes absence of PD. Missing demographic data for 6 PD− families and 5 PD+ families.

SES, socioeconomic status.

Fourteen subjects had missing respiratory data, due to technical difficulties. The 198 offspring with respiratory data came from 126 families. Those included in respiratory data analyses were: 1) SAD+/PD+, n = 11; 2) SAD+/PD−, n = 9; 3) SAD−/PD+, n = 69; and 4) SAD−/PD−, n = 109. The 14 subjects with missing respiratory data were included in all analyses of symptom-based responding to CO_2. The 14 offspring without respiratory data did not differ significantly from the others with regard to demographic data or psychopathology measures, p values > .05.

Offspring exclusionary criteria were psychosis, mania, pervasive developmental disorder, use of psychotropic medication, IQ <70, or an acute medical condition. Parents with PD were past or current outpatients identified via chart review from the New York State Psychiatric Institute (New York, New York), Long Island Jewish Medical Center (New Hyde Park, New York), or Freedom From Fear (Staten Island, New York). Approximately one-half of healthy parents were recruited through a pediatric dental clinic, with the remaining one-half recruited through acquaintances of parents. Inclusion/exclusion criteria were the same for parent and comparison parents with the exception that comparison parents could not qualify for a past or present mood or anxiety disorder.

Full disclosure of study procedures was provided to all families. Written informed consent was obtained from parents and offspring 18 years and older. Offspring ages 9–17 provided assent. Participants were informed that the CO_2 task would include periods of breathing room-air and a 5% CO_2-enriched air mixture and that they might experience anxiety during CO_2 inhalation. This study was approved by an institutional review board.