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Frontiers review

Panic disorder and control of breathing

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ABSTRACT

Anxiety disorders, particularly panic disorder (PD), are associated with respiratory abnormalities. PD consists of unexpected panic attacks (PA) with anxiety, fear and many autonomic and respiratory symptoms. There is a substantial body of literature demonstrating that stimulation of respiration is a common event in panic disorder patients during PA. A number of abnormalities in respiration, such as enhanced CO_2 sensitivity, have been detected in PD patients. As a result, some investigators advanced that there is a fundamental abnormality in the physiological mechanisms that control breathing in PD. Studies indicate that PD patients with dominant respiratory symptoms are particularly sensitive to respiratory tests compared with those who do not manifest dominant respiratory symptoms, possibly representing a distinct subtype. Accumulated evidence suggests that respiratory physiology remains normal in PD patients and that their tendency to hyperventilate and to react with panic to respiratory stimulants like CO_2 represents the triggering of a hypersensitive fear network. However, some recent evidences support the presence of subclinical abnormalities in respiration and other functions related to body homeostasis. The fear network, composed by the hippocampus, the medial prefrontal cortex, the amygdala and its brainstem projections, may be abnormally sensitive in PD patients. This theory might explain why both medication and psychosocial therapies are clearly effective. The evidence of abnormalities in several neurochemical systems might be just the expression of the complex interactions among brain circuits. Our aim was to review the relationship between respiration and panic disorder, addressing the respiratory subtype of panic disorder, the hyperventilation syndrome, the respiratory challenge tests, the current mechanistic concepts and the pharmacological implications.

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1. Introduction

Panic disorder (PD) has been the fulcrum of research dealing with respiratory system and anxiety disorders (Gorman et al., 2000). Respiratory abnormalities are associated with anxiety, particularly with panic attacks (PA) (Gorman et al., 1994; Papp et al., 1997b). Achieving a deeper understanding of the nature of PD has also been important to investigate new treatments (Nardi et al., 2003b, 2005). A PA usually starts off with a sudden, surprising, unexpected rise of terror associated with many autonomic, especially cardio-respiratory symptoms (Klein and Klein, 1988). Neuroscientists have attempted to elucidate the neurobiological circuit that underlies PAs and hence sheds light on the causes of pathological anxiety states (Klein, 1993; Griez and Perna, 2003; Perna et al., 2004a).

Analyses establishing respiratory disturbances at the core of PAs are quite recent (Schwartz et al., 1996; Caldirola et al., 2004). Clinicians described a so-called hyperventilation syndrome affecting people that were believed to be either chronic or acute hyperventilators (Gorman et al., 1994). In this conceptual model, disturbed breathing is supposed to cause bursts of hyperventilation and respiratory alkalosis, triggering various somatic signs and symptoms, such as dizziness, shaking, and palpitations. These in turn are thought to precipitate fear and anxiety (Gorman et al., 2000).

Klein (1993) proposed that spontaneous PAs occur when the brain's suffocation monitor erroneously signals a lack of useful air, maladaptively triggering an evolved suffocation alarm system. Such a dysfunction would make an individual vulnerable to "false suffocation alarms", namely PAs. Respiratory tests have been fruitful in generating hypotheses about PD (Klein, 1993; Gorman et al., 2000), indicating that CO_2 sensitivity would be part of a hypersensitive suffocation detector (Klein, 1993).

PD patients exhibit both behavioral and physiological abnormal responses to respiratory challenge tests (Papp et al., 1993;

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Battaglia and Perna, 1995). Symptoms, such as shortness of breath, "empty-head" feeling, dizziness, paresthesias and tachypnea have been described both in psychiatry and respiratory physiology in relation to PD (Rapee et al., 1992; Gorman et al., 1994). PD patients report significantly more PAs and anxiety during respiratory challenges than normal volunteers (Holt and Andrews, 1989; Gorman et al., 1994; Papp et al., 1997a).

A number of agents have been reported as capable of provoking acute PAs in PD patients under laboratory conditions, including some respiratory challenge tests with carbon dioxide (Dorow et al., 1983), hyperventilation (Nardi et al., 2004), and breath-holding (Nardi et al., 2003a). These tests may induce PAs in the laboratory that are very similar to spontaneous PAs. The inhalation of high concentrations of CO_2 has consistently been shown to increase anxiety and induce PAs in PD patients (Little et al., 1987; Nutt and Lawson, 1992). Among the numerous agents capable of inducing PAs in PD patients, CO_2 represents one of the most reliable panicogenic agents (Malizia et al., 1996).

The phenomenological characterization of PAs and the response of PD patients to the respiratory tests led Briggs et al. (1993) to describe a subgroup of PD patients with prominent respiratory symptoms, who presented a larger amount of spontaneous PAs and responded better to antidepressants, while other patients had more situational PAs and responded better to benzodiazepines. In this line, Biber and Alkin (1999) found that PD patients with prominent respiratory symptoms were more sensitive to the CO_2 challenge test, presented a significantly longer duration of illness, more severe panic and phobic symptoms, and were more likely to be heavier smokers than were patients with non-respiratory symptoms.

The objective of this review is to describe the close relationship between PD and respiration. Panic disorder with prominent respiratory symptoms will be discussed in detail. The findings of the respiratory challenge tests – hyperventilation, breath-holding, and CO_2 – and their power do discriminate PD patients from normal controls and other anxiety disorder patients will be presented. The current mechanistic concepts – genetic predisposition; increased CO_2 sensitivity; exaggerated cerebrovascular responses to hypocapnia; dysfunctional serotoninergic, opioid and GABA systems; abnormalities of the central rhythm generator; neurobiologic abnormalities – and the therapeutic implications will also be discussed.

2. Panic disorder with prominent respiratory symptoms—clinical aspects

There is scientific evidence that the "respiratory symptoms" group is a distinct PD subtype (Briggs et al., 1993). These authors studied the descriptions of the most recent severe PA of 1108 PD patients and performed a principal component analysis of the symptoms. Component 2 symptoms defined a distinct group, and the absence of these symptoms defined another group. These symptoms were fear of dying, chest pain/discomfort, shortness of breath, paresthesias, and sensation of choking. Patients were considered in the respiratory subtype group if they had four or five of these respiratory symptoms during the PA, whereas patients with three or less of these symptoms were allocated in the non-respiratory subtype. The group with prominent respiratory symptoms suffered more spontaneous PAs and seemed to respond better to antidepressants, whereas patients in the non-respiratory subtype depicted more situational PAs and seemed to react better to benzodiazepines.

Valenca et al. (2002) also aimed to verify the sensitivity to CO_2 challenge test in 27 PD subjects classified into respiratory and non-respiratory subtypes. At least 15 of 16 (93.7%) respiratory PD subtype patients and 5 of 11 (43.4%) non-respiratory PD patients had a PA during one of two CO_2 challenges. Using the 35% CO_2 challenge test and the hyperventilation test, Freire et al. (2008) compared 117 PD patients belonging to the respiratory and to the non-respiratory subtypes. The respiratory group was more responsive to tests, 80.3% panicked with CO_2, and 53.0% with the hyperventilation test. Only 11.8% of the non-respiratory patients had PA during the carbon dioxide test, and 33.3% panicked during the hyperventilation test. As opposed to the subjects of the non-respiratory PD subtype, those of the respiratory PD subtype were more sensitive to the 35% CO_2 challenge test than to the hyperventilation test.

There is evidence that the respiratory and the non-respiratory subtypes respond differently to drugs (Briggs et al., 1993). In a 8-week medication trial, patients belonging to the respiratory subtype presented a better improvement with imipramine, while patients belonging to the non-respiratory subtype responded better to alprazolam (Briggs et al., 1993). In another study, the respiratory subtype patients had a faster response to treatment with nortriptyline at 8 weeks, compared to the non-respiratory subjects; however, at 52 weeks both groups had improved equally (Nardi et al., 2003b). Clonazepam yielded a similar behavior in the respiratory PD, i.e., a faster improvement of the symptoms in the beginning of the treatment and a response similar to that of the non-respiratory subtype on the long run (Nardi et al., 2005). Mavissakalian (1996) found that respiratory symptoms, particularly choking, dyspnea and fear, improved significantly at four weeks of treatment with imipramine, whereas other symptoms took longer to improve.

3. Hyperventilation syndrome

Hyperventilation is not just a simple manifestation of anxiety and there is a complex interaction among organic, respiratory, psychiatric, and physiologic disturbances (Gardner, 1996). There is a symptomatological overlap between PD and hyperventilation syndrome. Acute hyperventilation may produce anesthesia, paresthesia, sweaty hands, giddiness, loss of consciousness, visual disturbances, headache, ataxia, tremor, tinnitus, cold extremities and chest pain (Gardner, 1996), while panic attacks include most of these and other symptoms, such as breathlessness, feeling of choking, nausea, derealization, depersonalization, fear of dying or losing control (APA, 1994). Anxiety disorders, such as panic disorder are associated with both mild hyperventilation and other abnormalities of the breathing pattern (Gardner, 1996). Hyperventilation may induce, as well as being induced by, anxiety (Gardner, 1996). Asthma is one of the most relevant organic causes of the hyperventilation syndrome (Gardner, 1996), and it is also correlated to PD (Nascimento et al., 2002).

Jack et al. (2004) studied 39 subjects with idiopathic hyperventilation (IH) and found that they presented higher anxiety and depression scores than the control subjects. When submitted to normocapnic (pCO_2 ~30 mmHg) hypoxia IH subjects had a lower hyperventilation response than normal controls, but when the pCO_2 was raised to 40 mmHg there was an increase in ventilation even higher than that in control group. The ventilatory response to hypercapnia was similar in IH and control subjects. The breath-holding time in IH patients was lower than in normal controls, and did not increase with inhalation of 100% oxygen. At rest pCO_2 was significantly lower in IH patients, and during moderate exercise PET_{CO_2} remained similar to that found in resting states, i.e., approximately 30 mmHg. Subjects with IH reported a more intense dyspnea during exercise than control subjects. It remains unclear whether IH patients present hypersensitive CO_2 chemoreceptors or

if there is another cause for the lower pCO_2 levels at rest and during exercise (Jack et al., 2004).

4. Diagnostic challenge tests

4.1. Hyperventilation

The acute hyperventilation challenge test – i.e. 30 breaths per minute during 4 min – may reproduce panic-like symptoms in a significant percentage of PD patients (Garssen et al., 1983), and hyperventilation, i.e., breathing in excess to the metabolic requests, is often found in association with PAs (Cowley and Roy-Byrne, 1987). Respiration and its control mechanisms may play a prominent role in generating abnormal anxiety, particularly PD (Bellodi and Perna, 1998). Analyses locating respiratory disturbances at the core of PAs are quite recent (Anderson et al., 1984; Ley, 1985; Klein, 1993). Since then the amount of data supporting and deepening the understanding of a connection between the vital function of breathing and PD has persistently accumulated (Gorman et al., 2000).

Hyperventilation has been reported as the trigger to the development of PAs (Nardi et al., 2004): PD patients may be chronic hyperventilators that shift toward hypocapnic alkalosis as a consequence of stress-induced acute hyperventilation, thus yielding PAs. This hypothesis has been built over three main experimental evidences. Firstly, PAs and the "hyperventilation-syndrome" show common symptoms, such as dyspnea, palpitations, tremors, paresthesias, and faintness. Secondly, the hyperventilation syndrome overlaps with PD in about 40% of patients (Nardi et al., 2001b). Finally, the acute hyperventilation challenge test, in which patients hyperventilate (30 breaths per minute) during 4 min, reproduces panic-like symptoms in a significant percentage of PD patients (Garssen et al., 1983; Nardi et al., 2004). On the other hand, a growing number of studies question the ability of acute hyperventilation to induce PAs (Ley, 1985; Gorman et al., 1994). They suggest that even though it is able to induce some anxiety, hyperventilation cannot trigger a reaction similar to spontaneous PAs in PD patients. Experimental evidence suggests that hyperventilation constitutes a significant component of PD, but questions the idea of a putative causal role. It is, however, unquestionable that some PD patients show symptoms related to hyperventilation as also suggested by the evidence of a relationship between the severity of hyperventilation-induced anxiety symptoms and gradual decrease in blood cerebral flow in response to hypocapnia-induced alveolar hyperventilation (Gorman et al., 2000; Griez and Perna, 2003).

Stress-induced hyperventilation produces symptoms frequently misinterpreted as life-threatening if the patient is unaware of the consequences of overbreathing (Papp et al., 1997a). Misinterpretation of theses symptoms increases fear and activates the autonomic nervous system, thus increasing respiratory frequency that will further washout CO_2 and intensify hypocapnic symptoms (Gorman et al., 1994). Hyperventilation has been considered as a cause, a correlate, and a consequence of panic attacks (Bellodi and Perna, 1998; Nardi et al., 2000a).

Nardi et al. (2004) described the clinical features of hyperventilation-induced PAs in PD patients and compared them with their spontaneous PAs as well as with spontaneous PAs in PD patients not sensitive to the hyperventilation challenge test. Eighty-eight PD patients were submitted to a hyperventilation challenge test. A total of 51.1% ($n = 45$) PD patients developed a PA after hyperventilating. The clinical symptoms of the most severe PA were recorded by the patients that experienced hyperventilation-induced PAs and by the PD patients not sensitive to this test (non-hyperventilation-induced PA) in a diary during a 1-week period. The hyperventilation-induced PA group had more frequent and severe respiratory symptoms, fulfilling the criteria for the respiratory PD subtype (Briggs et al., 1993).

Our group has been studying the relationship between hyperventilation and PA, contrasting PD patients with normal control subjects (Nardi et al., 1999a), with healthy first-degree relatives of the patients (Nardi et al., 2000a), as well as subjects with other anxiety and mood disorders (Nardi et al., 2001a,b, 2002b). In all instances, the PD group presented a higher sensitivity to the hyperventilation challenge test. In another study, we submitted PD patients to the hyperventilation challenge test and compared the patients that developed PAs with those that did not present PAs (Nardi et al., 2004). Patients who panicked during the test had more frequently a family history of mental disorder, older age at the disorder onset, and more frequent previous depressive episodes. The spontaneous and induced PAs were very similar in those subjects that exhibited a PA, but in those individuals that did not develop panic after hyperventilating the spontaneous PAs were accompanied by a larger amount of chills/hot flushes and much less frequent respiratory symptoms, such as shortness of breath, choking sensation, chest pain/discomfort, paresthesias and fear of dying.

Although these data seem to support a causal role for hyperventilation, several pieces of evidence point against it (Gorman et al., 1984, 1988, 1994; Zandbergen et al., 1990; Van den Hout et al., 1992; Asmundson and Stein, 1994a; Antony et al., 1997) and suggest that even though it is able to induce some anxiety, hyperventilation cannot induce a reaction similar to spontaneous PAs in PD patients (Lindsay et al., 1991). Spontaneous PAs, as a rule, are not associated with a decrease in pCO_2 levels (Hibbert and Pilsbury, 1988, 1989; Buikhuisen and Garssen, 1990) and several studies report the absence of baseline chronic hyperventilation in PD patients (Woods et al., 1986; Holt and Andrews, 1989; Zandbergen et al., 1993). The studies that did find signs of chronic respiratory alkalosis were inconclusive, as far as these signs were not documented in more than 50% of the patients (Liebowitz et al., 1985; Gorman et al., 1986; Salkovskis et al., 1986). If present, chronic hyperventilation seems far from being specific for PD subjects: its frequency is similar in patients with other anxiety disorders (Van den Hout et al., 1992). Finally, many studies (Zandbergen et al., 1990; Gorman et al., 1994; Antony et al., 1997) but not all (Schmidt et al., 1996) show that hypercapnia definitely represents a stronger panicogenic challenge than hyperventilation.

4.2. Breath-holding

The understanding of the mechanisms involved in CO_2-induced anxiety could shed light on the pathophysiology of PD, and a simple method of increasing endogenous CO_2 may be the breath-holding challenge test. Breath-holding increases pCO_2 and decreases pO_2, resulting in chemoreceptor stimulation and a strong drive to resume breathing (Zandbergen et al., 1992).

Van der Does (1997) developed a breath-holding test that consists of four trials. Each of the first three trials have a 1 min anticipation period, followed by cessation of breathing at functional residual capacity, and a 2 min recovery period. In these instances, the subjects are instructed to stop breathing, then exhale normally (i.e., non-forced expiration), and maintain the apnea for as long as possible. The fourth trial consists of breath-holding after a vital capacity inspiration. A chronometer is used to measure the breath-holding time. The anxiety before and after de test, and the PD symptoms are also evaluated.

According to Klein's hypothesis (Klein, 1993), PD patients are more sensitive to the rise in CO_2, and they should not be able to hold their breath for long. In PD patients, the breath-holding time was found to be shorter (Zandbergen et al., 1992; Asmundson and Stein, 1994b; Van der Does, 1997; Rassovsky et al., 2006) and the end-tidal

pCO_2 lower than in normal controls, demonstrating the lower tolerance to CO_2 in the former group (Rassovsky et al., 2006). Some studies (Zandbergen et al., 1992; Van der Does, 1997) indicate that the breath-holding time for PD patients was similar to those found in other psychiatric disorders, but significant differences among the patients were also reported (Asmundson and Stein, 1994b). Additionally, an increase in anxiety and PAs during the breath-holding procedure was described (Roth et al., 1998; Nardi et al., 2002a, 2003a,c). These controversial findings may be explained by small and heterogeneous samples, diverse inclusion and exclusion criteria and vague criteria for laboratory-induced PA.

Comparing PD patients to those with generalized anxiety disorder (GAD), Roth et al. (1998) did not find differences regarding anxiety symptoms induced by the breath-holding procedure. Nardi et al. (2003a) reported that 44.8% of the PD patients, 14.8% of the social anxiety disorder (SAD) patients and 9.5% of the GAD patients developed a PA in the face of the breath-holding procedure. Additionally, when compared to their first-degree relatives and normal controls, PD patients had a significant increased amount of PAs (Nardi et al., 2002a). These studies indicate that the breath-holding test is very specific for PD, inducing its symptoms and an increase in anxiety levels.

4.3. Carbon dioxide

The CO_2 challenge test strongly suggests a relationship between the pathophysiology of PD and disturbances in the control of breathing (Bellodi and Perna, 1998). Schruers et al. (2004) stressed the scarcity of information on the symptomatology of real-life panic attacks and on how well they are reproduced by an experimental model, such as the 35% CO_2 test. Possibly, research on the association between CO_2 and PD will better characterize subtypes of PD with their underlying mechanisms.

Gorman et al. (1988) observed that subjects with PD, in contrast with healthy controls, develop a panic-like reaction within minutes after starting breathing a gas mixture containing 5% of CO_2. CO_2-induced PA is associated with cardiorespiratory activation including increased respiratory rate and blunted tidal volume response, tachycardia, and increased blood pressure (Gorman et al., 1988; Papp et al., 1997a; Bystritsky et al., 2000; Bailey et al., 2001). Sanderson and Wetzler (1990) concluded that despite remarkable methodological differences across various studies, it has been unequivocally established that subjects with PD are hypersensitive to hypercapnic gas mixtures.

An alternative method of doing CO_2 challenges consists of one single vital capacity breath of a gas mixture containing 35% CO_2 and 65% oxygen (Griez et al., 1987). Under these conditions, healthy subjects develop a brief but strong respiratory stimulation accompanied by neurovegetative symptoms that largely overlap with those reported by panic patients (Griez and Van den Hout, 1982; Van den Hout and Griez, 1984). In PD patients the same intervention additionally induces a sharp and transitory rise in anxiety that has been equaled with a real life PA (Griez et al., 1987; Perna et al., 1994a; Nardi et al., 2000b). Administered in a controlled laboratory environment, the single breath 35% CO_2 challenge constitutes a brief test whose effects are completely vanished in a matter of seconds. Repeated studies demonstrated that the procedure is safe and devoid of unwanted consequences both in short and long terms (Perna et al., 1999b; Nardi et al., 2007). CO_2-triggered anxiety is not merely a startle reaction generated by a strong physiological stimulus in overaroused individuals. When administered to a mixed group of patients with various anxiety disorders, all of them with comparable ratings of arousal and anticipatory anxiety, the CO_2 test affected only those with a diagnosis of PD (Griez et al., 1990b). Specifically, patients with obsessive-compulsive disorder (OCD) failed to show any significant anxiety response to the inhalation of 35% CO_2 (Griez et al., 1990a; Perna et al., 1995a). Similarly, patients with a GAD displayed only a small increase in subjective anxiety after a deep breath of CO_2 (Verburg et al., 1995; Perna et al., 1999a). Among patients with a specific phobia, making a clear-cut distinction between animal and situational phobics, the 35% CO_2 challenge did not affect animal phobics, whereas situational phobics presented a CO_2-induced reaction tending to resemble that of PD subjects (Verburg et al., 1994).

Perna et al. (2004b) studied the occurrence of dyspnea symptoms during inhalation of 35% CO_2. About 50% of the panic disorder patients reported “I cannot take a deep breath” and “my breath does not go in all the way”. The statements “I feel out of breath”, “my breathing requires more concentration” and “my breathing requires effort” were also very common, and more than 35% of the patients reported these symptoms. The symptoms reported were not influenced by gender, age or educational level. The authors identified three factors that accounted for 80% of the variance: “breathing effort”, “sense of suffocation” and “rapid breath”. The factor “breathing effort” describes the conscious awareness of muscular effort during activation of respiratory skeletal muscles that is thought to arise from a dissociation between the central respiratory motor command and the mechanical response of the respiratory muscles. A thoracic breathing pattern and a higher irregularity and instability in baseline breathing patterns, which are characteristic of patients with PD, could affect the ability of patients with PD to maintain an adequate respiratory homeostasis when external or internal changes occur. A dissociation between the increased central respiratory command stimulated by CO_2 and a decreased mechanical efficiency of the respiratory response might, therefore, lead to a heightened sense of breathing effort during the CO_2 challenge test. The factor “sense of suffocation” arises mainly from the stimulation of chemoreceptors and involves the activation of the limbic/paralimbic and cerebellar regions. The “rapid breath” factor, which describes a shallow, rapid breathing pattern in response to an excessive mechanical load, was not associated with CO_2 reactivity (Table 1). We may also understand the Perna et al. (2004b) data in other way. First, as during a CO_2 challenge test whatever it induces or not a panic attack, there is no “decrease efficiency of the respiratory response”. Indeed, while there is an increase drive, and therefore an increased effort to breath due to the CO_2-induced hyperventilation, and thus an increased load for the effector of this response, i.e., respiratory muscles, the structure or function of the latter are basically normal. Second, shallow rapid breathing is not the most characteristic response to excessive mechanical load.

Esquivel et al. (2007) studied the effects of exercise on CO_2 sensitivity. The group exposed to moderate/hard exercise presented a significant increase in lactate level and less panic attack symptoms, whereas in the PD group exposed to a very light exercise the lactate level remained low and there were more panic symptoms. After exercising, all patients were exposed to 35% CO_2 and the PD group exposed to very light exercise showed more panic attacks and scored higher in anxiety and PD symptoms scales (Esquivel et al., 2007). This differential response may be explained by an altered activity of serotonin (Greenwood et al., 2005) and endorphins (Sinha et al., 2007) during exercise in PD patients.

The effect of CO_2 challenge on the activity of the hypothalamic–pituitary–adrenal axis (HPA) has not been extensively studied yet, and the available data are conflicting. Sinha et al. (1999) found that inhalation of low doses of CO_2 (5% or 7%) did not significantly increase cortisol release in either PD patients or normal controls, suggesting that this panicogenic agent does not activate the HPA. On the other hand, Bailey et al. (2001) noticed that inhalation of 35% CO_2 increased cortisol release in normal subjects.

Table 1
The three dyspnea factors and its neurophysiologic explanations

Factor	Explained variance (%)	Symptoms/complains	Neurophysiology
Breathing effort	34	•My breathing requires effort	•The conscious awareness of muscular effort during activation of respiratory skeletal muscles that is thought to arise from dissociation between a central respiratory motor command and a mechanical response of the respiratory muscles
		•I cannot get enough air	•In PD patients, a dissociation between the increased central respiratory command stimulated by CO_2 and a decreased mechanical efficiency of the respiratory response leads to the breathing effort sensation
		•My chest is constricted	
		•I feel my breath stops	
		•My breath does not go in all the way	
		•My chest feels tight	
		•My breathing requires more concentration	
Sense of suffocation	27	•I feel that I am suffocating	•The sense of suffocation is the result of the chemoreceptors' stimulation and involves the activation of the limbic/paralimbic and cerebellar regions
		•I am gasping for breath	
		•I feel that I am smothering	
		•I feel a hunger for more air	
Rapid breath	20	•My breathing is shallow	•The shallow, rapid breathing pattern is a response to an excessive mechanical load
		•I feel that my breathing is rapid	
		•I feel out of breath	

Based on the article of Perna et al. (2004b).

Panicogenicity to CO_2 inhalation increases in the face of serotonin antagonists, such as metergoline (Ben-Zion et al., 1999) and tryptophan depletion (Schruers et al., 2000; Miller et al., 2000), whereas it decreases with the use of selective serotonin reuptake inhibitors (Pols et al., 1996a,b; Bertani et al., 1997; Perna et al., 1997). These data, together with studies demonstrating the blockade of CO_2-panic by benzodiazepines (Nardi et al., 2000b) and tricyclic antidepressants (Bertani et al., 1997), suggest that serotonin, GABA and nor-adrenergic neurotransmission play a relevant role in CO_2-induced panic.

The influence of genetics on CO_2-induced panic has also been considered. It was suggested that CO_2 sensitivity reflects a trait marker that runs in families (Perna et al., 1995b, 1999b; Bellodi et al., 1998). Hence, CO_2 sensitivity may be considered as a phenotypic expression of an underlying genetic vulnerability that may exist before the clinical onset of PD (Cavallini et al., 1999). Genetic mechanisms proposed include differential expressions of chemoreceptors and its influence on neurotransmitter systems. The ultimate isolation of genetic markers could lead to preventative measures for vulnerable individuals.

It remains to be understood whether sensitivity to CO_2 and the associated hyperventilation is a characteristic of all normal subjects and PD patients undergoing PAs. It is possible that CO_2 sensitivity relates to a specific subtype of PD, a hypersensitive homeostatic response ("suffocation alarm"), or simply an indirect cause of panic by means of a non-specific irritation of any number of chemical and/or mechanical receptors.

5. Underlying mechanistic in panic disorder

5.1. Genetic predisposition

There may be a familial association between PD and CO_2 hypersensitivity (Perna et al., 1995b; Coryell, 1997; Coryell and Arndt, 1999; Van Beek and Griez, 2000). Perna et al. (1995b) tested the reactivity to the 35% CO_2 test in a group of healthy first-degree relatives of patients with PD that had never experienced PAs during their lifetime: healthy relatives reacted significantly more than healthy subjects without a familial history of PD, with rates of CO_2-induced panic attacks of 22% in the former group and solely 2% in the latter. These results, suggesting an association between hypersensitivity to hypercapnia and familial vulnerability to PD, were confirmed by Coryell (1997), who investigated the reactivity to 35% CO_2 in groups of healthy subjects with a familial vulnerability to PD, to depressive disorders, and without a family history of panic or depressive disorders. CO_2-induced PAs were reported in 45.5% of the subjects with positive family history for PD, but none in the other two groups. Van Beek and Griez (2000) confirmed these findings by comparing an age–sex matched sample of 50 healthy first-degree relatives with 50 healthy controls. The association between familial vulnerability to PD and respiration was further reinforced by a study investigating CO_2 hypersensitivity in patients with PD or familial-genetic risk for PD. Patients hyperreactive to CO_2 showed a morbidity risk for PD (14.4%) significantly higher than that found in subjects with normal reactivity to CO_2 (3.9%), suggesting that CO_2 hyperreactivity might be associated with a subtype of PD specifically related to a greater familial genetic influence (Perna et al., 1996). A familial association between respiration and PD was also reported by Horwath et al. (1997). They showed that relatives of patients with PD with respiratory symptoms had an almost three-fold higher risk for panic and an almost six-fold higher risk for panic with smothering symptoms as compared with relatives of patients without respiratory symptoms. PD with smothering symptoms might be a subtype of PD associated with an increased familial risk, thus representing a group of interest for genetic studies. If the etiology of PD is strongly related to genetic factors and if CO_2 hypersensitivity is linked to the pathogenesis of PD, it may be presumed that CO_2 hypersensitivity is modulated by genetic influences. This hypothesis was confirmed by a study on twins (Bellodi et al., 1998) that showed a significantly higher rate of CO_2-induced panic attacks in monozigotic pairs (55.6%) than in dizigotic twins (12.5%).

The role of familial-genetic factors in the panic-respiration connection is also supported by some preliminary results in children of patients with PD. Perna et al. (2002) reported that children of PD patients exhibit higher variability of several physiological respiratory parameters compared to children of healthy individuals. Taken together, these studies (Bellodi et al., 1998; Perna et al., 2002) sup-

port the idea that the panic-respiration connection might foster a further step trying to identify a valid "gold standard" phenotype for PD. CO_2 hypersensitivity bears a relevant genetic component and seems to be significantly related to a familial vulnerability to PD. CO_2 hypersensitivity might be a phenotypical expression of a genetic vulnerability to PD, even when clinically absent, and, thus, subjects hyperreactive to hypercapnia or with respiration abnormalities might be considered "affected" members in molecular genetic studies. Alternatively, hypersensitivity to CO_2 might be considered the phenotypic expression of one of the genes involved in the "respiratory panic disease" and, thus, only the presence of both clinically expressed panic and CO_2 hypersensitivity could define the "true" phenotype for genetic studies.

5.2. Increased CO_2 sensitivity

There are two lines of evidence suggesting that PAs may originate in the brainstem (Gorman et al., 2000). The first one advances that the nature of the symptoms can be explained by a surge of impulses from the autonomic nervous system. The second line of evidence is the CO_2-mediated experimental provocation of PA itself. CO_2 primarily acts on the brainstem, especially on the respiratory center, located in the reticular substance of the medulla oblongata and the pons (Gorman et al., 2000; Griez and Perna, 2003). Considering the hyperoxic mixtures that are used in the CO_2 challenges, any stimulating influence of the peripheral oxygen chemosensitive areas is discarded. A number of studies were directed towards a possible dysfunction at the level of the central chemosensitive regions.

To explore CO_2 chemosensitivity in PD patients the ventilatory response to increasing CO_2 concentration was monitored, under the hypothesis that an exaggerated response would confirm oversensitivity. Studies on the ventilatory response to CO_2, i.e., the increase in ventilation owing to the inhalation of increasing concentrations of CO_2 yielded contradictory results (Gorman et al., 2000). This may be in part explained by a possible lack of control of confounding variables, and by the well-known wide inter-individual variability of CO_2 chemosensitivity. Klein (1993) proposed that PA results from the deregulation of a phylogenetically evolved alarm system directed to monitor suffocation signals in the organism. This alarm system has been evolutionarily programmed to fire when it senses metabolic signs of asphyxia and impending death. As a survival alert system this physiologic suffocation monitor most likely serves a deeply rooted adaptive function: its activation only occurs in extreme life threatening circumstances. The Klein's hypothesis may help to understand the preeminence of respiratory symptoms in PAs. For example, it may be of use to explain why patients with PD, in contrast to subjects with other types of anxiety, against any medical evidence, and despite repeated reassurance, invariably feel an overwhelming fear of dying and loosing control during their attacks. Klein points to the existence of the congenital central hypoventilation syndrome (Pine et al., 1994). This rare condition affects infants that apparently are born with an aberrant sensitivity to signals of hypercapnia and hypoxia. The congenital hypoventilation syndrome may be the pathophysiological mirror picture of PD (Pine et al., 1994).

A drawback of Klein's hypothesis rests on the fact that no suffocation alarm system has been anatomically or functionally identified as such within the CNS. The search for a panic circuitry in the brain should include those areas of the CNS linked to chemosensitive properties. We can understand that intermittent hypoxia may have a different effect in PD patients as compared to healthy controls, but we still have to search the specific mechanism why the PD patients are supposed to be specifically exposed to this phenomenon. These structures should logically be considered as the best candidates to fulfill the function of a suffocation detector. A few findings support the idea that CNS chemosensitive areas related to panic responses extend to several brainstem nuclei including the nucleus tractus solitarius, the locus coeruleus and the raphe nuclei, being all these structures part of a broad brainstem respiratory network (Gorman et al., 2000; Griez and Perna, 2003).

5.3. Exaggerated cerebrovascular responses to hypocapnia

PD patients experiencing recurrent PAs may display an abnormal cerebrovascular response to alkalosis and be vulnerable to brain hypoxia during hyperventilation (Bellodi and Perna, 1998). The intermittent hypoxia may disrupt homeostatic mechanisms and neuronal and glial viability within particular brain regions. Subsequent dysfunction of prefrontal cortex regions, expressed by dysfunction of a multifaceted cognitive executive system, may alter the functional recruitment of more primary cognitive abilities, resulting in maladaptive behaviors (Beebe and Gozal, 2002). In clinical practice, it is usual to find patients with a high level of dependence, a constant sense of insecurity and lack of a well-developed capacity for autonomous action, and pathological reassurance sensitivity.

5.4. Dysfunctional serotoninergic, opioid and GABA systems

The assumption that abnormalities in neurotransmitters found in PD should reflect an altered brain function and the fact that the effectiveness of drugs modulating neurotransmitters (e.g., serotonin) in the treatment of PD are related to their effect on the central nervous system are far from being demonstrated. There are growing evidences showing that classical neurotransmitters, such as serotonin or GABA, may be able to directly influence body structures other than the brain (Malizia et al., 1996; Gorman et al., 2000; Wilhelm et al., 2001.). The serotoninergic system influences the behavior of many brain areas involved in the regulation of body functions and serotonin receptors have been found in many organs other than the brain. Several evidences link the serotoninergic system to peripheral respiratory function: serotonin transporters are expressed in human pulmonary membranes (Suhara et al., 1998), are important in the maintenance of patent upper airways in obstructive sleep apnea (Veasey et al., 1996), and influence phrenic nerve activity (Holtman et al., 1984). Sertraline is able to decrease dyspnea in patients with chronic obstructive pulmonary disease (COPD) (Smoller et al., 1998) and paroxetine relieves respiratory symptoms in patients with obstructive sleep apnea (Kraiczi et al., 1999). Perna et al. (2004c) reported that the modulation of the serotoninergic system could influence positively respiratory function in patients with COPD yielding an important decrease in breathlessness and a relevant enhancement in walking ability with a net result of improved quality of life and functional status. There exist also clear evidences that serotonin influences the function of blood platelets. Similar findings also disclosed that other neurotransmitters might directly regulate body functions (Malizia et al., 1996; Gorman et al., 2000).

The endogenous opioid system was recognized as an important central regulator of respiratory drive (Akil et al., 1984). When the opioid receptors are stimulated the CO_2 sensitivity reduces and respiratory rate slows down (Fleetham et al., 1980). Conversely, naloxone, an opioid receptor antagonist, increases the ventilatory response to hypercapnic hypoxia in normal human subjects (Akiyama et al., 1993). Sinha et al. (2007) hypothesized that PD patients exhibit an opioid deficiency, which would explain why lactate induces PAs in these patients. To explore this hypothesis they administered intravenously naloxone and sodium lactate to twelve normal controls. None of the subjects felt anxiety, fear or had a PA,

but they showed panic symptoms and an increased tidal volume (Sinha et al., 2007). These findings indicate that the susceptibility of panic disorder patients to lactate-induced panic may imply a deregulation of the opioid system (Sinha et al., 2007).

5.5. Abnormalities of the central rhythm generator

Breathing pattern at rest may reveal some abnormalities in ventilatory control. Accordingly, several studies investigated PD subjects focusing on baseline respiratory physiology in the intervals between PAs (Gorman et al., 1988; Stein et al., 1995; Caldirola et al., 2004). However, caution is needed when interpreting these results, since several measurements were obtained immediately before panicogenic challenges, and procedures used to obtain these data are heterogeneous. Most of the studies performed so far failed to find significant differences in mean values of respiratory rate, tidal volume, minute ventilation and respiratory blood gases among patients with PD, healthy controls, or those with other anxiety disorders (Bellodi and Perna, 1998). The two main positive findings that have been reproduced are: patients with PD have a thoracic pattern of breathing (Beck and Scott, 1988) with a strong muscular thoracic effort and they also show an abnormal variability and irregularity in breathing both during daytime (Bystritsky and Shapiro, 1992; Schwartz et al., 1996; Papp et al., 1997a; Bystritsky et al., 2000) and sleep (Stein et al., 1995).

Since respiration is a complex physiologic function with multiple central and peripheral inputs, its pathophysiological characteristics could be more accurately investigated by the analysis of the analysis of the breathing pattern rather than by a simple measurement of the absolute values of a few parameters. Patients with PD show a larger breath-to-breath variability during a rebreathing test than is usually observed in controls (Papp et al., 1995). Compared with healthy subjects, PD patients show an increased irregularity in tidal volume and minute ventilation, and an increased rate of apneas during sleep (Stein et al., 1995; Martinez et al., 1996). In PD patients, baseline respiratory frequency was found to be more irregular than in healthy controls (Gorman et al., 1988; Bystritsky and Shapiro, 1992; Bystritsky et al., 2000). Additionally, PD patients show excessive sighing, and tidal volume irregularity significantly greater than healthy control subjects (Abelson et al., 2000, 2001) and GAD patients (Wilhelm et al., 2001). The tidal volume irregularity persists after both doxapram-induced hyperventilation and cognitive intervention, suggesting that it may be an intrinsic and stable feature of patients with PD (Abelson et al., 2001). The importance of this finding for the understanding of panic etiopathogenesis is supported by the evidence of a higher variability in respiratory pattern in response to 5% CO_2 inhalation in relatives of PD patients compared to relatives of healthy controls and of patients with affective disorders (Coryell et al., 2001). In this connection, Perna et al. (2002) suggested that variability in respiration might be higher in children of patients with PD than in those born to healthy controls. Two trials (Pine et al., 1998; Pine et al., 2000) reported more irregularities in respiratory rate in children with childhood anxiety disorders that developed panic symptoms after CO_2 inhalation than those with a healthy childhood. Respiratory irregularities and pattern variability could be a physiological trait marker of panic vulnerability able to identify subjects at risk for PD and to promote formal and molecular genetic studies in PD. Normal respiration is characterized by a synchronized action of inspiratory and expiratory neurons and, thus, the high variability observed, together with the unpleasant respiratory sensations that ensue in patients with PD, could be the results of a mismatch between the activities of inspiratory and respiratory neurons. The abnormal responses to respiratory challenges might be the expression of an unbalanced adaptation mechanism related to this disorder (Bellodi and Perna, 1998; Perna et al., 2004a).

5.6. Neurobiologic abnormalities

A recent model of PD attempts to integrate neurochemical, imaging, and treatment findings with mostly preclinical work in the neurobiology of conditioned fear responses, Fig. 1 (Gorman et al., 2000; Mezzasalma et al., 2004). The PA is speculated to originate in an abnormally sensitive fear network, centered in the central nucleus of the amygdala (CNA). The sensory input for the conditioned fear stimulus runs through the anterior thalamus to the lateral nucleus of the amygdala, thence to the central nucleus of the amygdala, where all the information is gathered and the autonomic and behavioral responses are coordinated. The CNA sends stimuli to: the parabrachial nucleus, increasing respiration rate (Takeuchi et al., 1982); the lateral nucleus of the hypothalamus, activating the sympathetic nervous system; the locus ceruleus, increasing the norepinephrine release and contributing to increases in blood pressure, heart rate and the behavioral fear response; and the paraventricular nucleus of the hypothalamus, increasing the release of adrenocorticoids. A projection from the CNA to the periaqueductal gray region is responsible for additional behavioral responses, including defensive behaviors and postural freezing. There are also important reciprocal connections between the amygdala and sensory thalamus, prefrontal cortex, insula and primary somatosensory cortex. Although the amygdala receives direct sensory input from brainstem structures and the sensory thalamus, enabling a rapid response to potentially threatening stimuli, it also receives afferents from cortical regions involved in the processing and evaluation of sensory information (Gorman et al., 2000; Mezzasalma et al., 2004). A neurocognitive deficit could result in a misinterpretation of sensory information, leading to an inappropriate activation of the "fear network" via misguided excitatory input to the amygdala. A deficiency in the coordination of the stimuli from the cortex and brainstem could lead to an abnormal activation of the amygdala, with a behavioral, autonomic and neuroendocrine stimulation. Panic originates in an abnormally sensitive fear network, which includes the prefrontal cortex, insula, thalamus, amygdala and the amygdalar projections to the brainstem and hypothalamus (Gorman et al., 2000; Mezzasalma et al., 2004).

The potential role of hypoxia as a signal of asphyxia and the suggested sensitivity of PD patients to anoxia are supported by evidences from animal studies reporting that the amygdala and the hippocampus are particularly sensitive to anoxic stimulation. Together with the evidence of strong connections between the amygdala and the carotid body, the direct sensitivity of amygdala to acid–base changes, and the interconnections between the amygdala and the parabrachial nucleus (Takeuchi et al., 1982) another pathway linking respiratory signals to panic may be suggested (Coplan and Lydiard, 1998).

6. Pharmacologic manipulations

Some trials dealt with psychotropic drugs and the changes in the respiratory response to CO_2 inhalation. Additionally, the modulation of CO_2-induced panic/anxiety by psychotropic drugs was also investigated. Some studies suggest that antipanic medication does modulate respiration physiology. Twelve weeks of antipanic treatment with tricyclic antidepressants significantly decrease CO_2 sensitivity (as expressed by minute ventilation and end-tidal CO_2) in patients with PD, whereas no significant changes were detected in healthy subjects (Gorman et al., 1997). Similarly, clomipramine reduces the ventilatory response (expressed by respiratory fre-

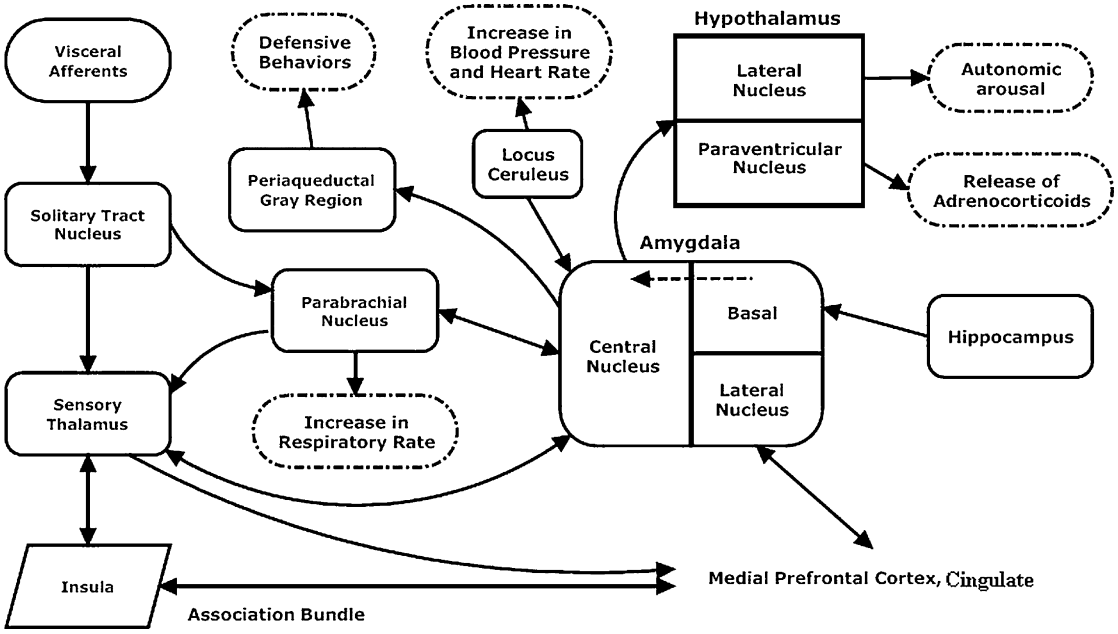

Fig. 1. The main afferent projections of the amygdala related with anxiety are towards: *locus ceruleus* (increases the release of noradrenaline, contributing to the physiological and behavioral activation), periaqueductal gray matter (promotes defensive mechanisms and postural paralysis), paraventricular nucleus of the hypothalamus (activates the hypothalamic–pituitary–adrenal axis leading to the release of adrenocorticoids), lateral hypothalamic nucleus (activates the sympathetic nervous system), and the parabrachial nucleus (influences respiratory frequency and amplitude). Viscerosensorial information is conducted towards the amygdala from the primary viscerosensory cortex through cortico-thalamic transmission, allowing cognitive processing and modulation of viscerosensory information; and from the solitarius tract through the parabrachial nucleus or the sensorial thalamus. Contextual information stored in the memory of the hippocampus is directly transmitted towards the amygdala.

quency and tidal volume) in patients with PD after 10 weeks of treatment (Pols et al., 1993), and fluoxetine expresses the same outcome after being administered for 1 month (Bocola et al., 1998).

The ability of antipanic medications to decrease panic/anxiety responses to CO_2 is well known (Sanderson et al., 1994; Nardi et al., 1999b, 2000b; Perna et al., 2004c). High potency benzodiazepines have been repeatedly shown to decrease panic/anxiety responses to hypercapnic gas mixtures. An acute dose of clonazepam (Nardi et al., 2000b), a very short treatment (10 days) with clonazepam (Nardi et al., 1999b), and a short treatment (4–8weeks) with clonazepam (Beckett et al., 1986; Pols et al., 1991) or alprazolam (Woods et al., 1986, 1989; Fishman et al., 1994) were all able to decrease CO_2-induced anxiety. On the other hand, conflicting results were reported on the effect of an acute dose of alprazolam on 35% CO_2 reactivity (Sanderson et al., 1994; Pols et al., 1996a,b). Monoamino oxidase inhibitors, tricyclic antidepressants and selective serotonin reuptake inhibitors are also able to reduce the reactivity to CO_2 (Woods et al., 1990; Perna et al., 1994b, 1997). The anxiety symptoms induced by 35% CO_2 were significantly reduced as early as 1 week of treatment with toloxatone (Perna et al., 1994b), clomipramine or fluvoxamine (Perna et al., 1997), imipramine, sertraline or paroxetine (Bertani et al., 1997), and citalopram (Bertani et al., 2001). Six weeks of treatment with fluvoxamine (Pols et al., 1996a,b) and 1 month of treatment with imipramine or paroxetine (Woods et al., 1990; Bertani et al., 1995) also significantly decreased the response to 35% CO_2 in patients with PD.

It is also noteworthy that consumption of alcohol diminishes sensitivity to CO_2 in PD patients (Kushner et al., 1996), a finding that sheds light on the mechanisms contributing to high rates of alcohol abuse in PD. Placebo has also been reported to diminish sensitivity to CO_2 in PD patients (Woods et al., 1989; Sanderson et al., 1994; Pols et al., 1996a,b; Kushner et al., 1996; Nardi et al., 2000b). In a recent study in healthy volunteers (Cosci et al., 2006), nicotine promoted autonomic activation, increased blood pressure and heart rate, and induced PA symptoms. However, this substance failed to increase the sensitivity to CO_2.

7. Conclusion

There is a substantial amount of data demonstrating that stimulation of respiration is a common event in PD patients during a PA. Some abnormalities in respiration, such as enhanced CO_2 sensitivity, have been detected in PD patients. As a result, it seems that there is a fundamental abnormality in the physiological mechanisms that control breathing in PD. Accumulated evidence suggests that respiratory physiology remains normal in PD patients and that their tendency to hyperventilate and to react with panic to respiratory stimulants like CO_2 represent the triggering of a hypersensitive fear network. However, some recent evidences support the presence of subclinical abnormalities in respiration and other functions related to body homeostasis. Hence, the role of a more primitive and lower brain center than the limbic one should be considered. The fear network anatomy has been so far gathered from preclinical studies that identified the brain pathways that promote the acquisition and maintenance of conditioned fear. The amygdala and its brain stem projections, the hippocampus, and the medial prefrontal cortex operate in this network. Although attempts to image this system in patients during panic attacks have been so far inconclusive, the theory that the fear network is operative and hyperactive in PD patients might explain why both medication and psychosocial therapies are clearly effective. Although to date it is not clear if the abnormal function underlying PAs lies in the limbic system, and mainly related to the emotion fear, or in the brainstem, and principally connected with a primal emotion, one cannot forget the complex relationships between these two brain areas and, thus, the whole picture of PD should be viewed as the complex result of multiple interactions between various brain networks. The evidence of

abnormalities in several neurochemical systems might be just the expression of the complex interaction among brain circuits. Hence, the attempt to focus on one isolated component of this complex array as the "pathogenetic" system of PD seems unwarranted.

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