Respiratory Physiology & Neurobiology 204 (2014) 3–13

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

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

Respiratory manifestations of panic disorder in animals and humans: A unique opportunity to understand how supramedullary structures regulate breathing☆

Richard Kinkead[a,b,*], Luana Tenorio[c], Guy Drolet[a,b], Frédéric Bretzner[a,b], Luciane Gargaglioni[b]

[a] Centre de Recherche du Centre Hospitalier Universitaire de Québec, Canada
[b] Université Laval, Québec, QC, Canada
[c] Department of Animal Morphology and Physiology, Sao Paulo State University – UNESP FCAV at Jaboticabal, SP, Brazil

ARTICLE INFO

Article history:
Accepted 26 June 2014
Available online 16 July 2014

Keywords:
Control of breathing
Panic disorder
Chemoreflex
Hypercapnic response

ABSTRACT

The control of breathing is commonly viewed as being a "brainstem affair". As the topic of this special issue of Respiratory Physiology and Neurobiology indicates, we should consider broadening this notion since the act of breathing is also tightly linked to many functions other than close regulation of arterial blood gases. Accordingly, "non-brainstem" structures can exert a powerful influence on the core elements of the respiratory control network and as it is often the case, the importance of these structures is revealed when their dysfunction leads to disease. There is a clear link between respiration and anxiety and key theories of the psychopathology of anxiety (including panic disorders; PD) focus on respiratory control and related CO_2 monitoring system. With that in mind, we briefly present the respiratory manifestations of panic disorder and discuss the role of the dorso-medial/perifornical hypothalamus, the amygdalar complex, and the periaqueductal gray in respiratory control. We then present recent advances in basic research indicating how adult rodent previously subjected to neonatal stress may provide a very good model to investigate the pathophysiology of PD.

1. Introduction

The brainstem contains the core elements of neural circuits that generate and regulate breathing. Together, these structures integrate a variety of sensory signals pertaining to the respiratory tract along with O_2 and CO_2 levels within the organism to produce a rhythmic and highly coordinated motor command to activate the respiratory muscles and ultimately meet the gas exchange requirements of the organism. This component of respiratory control is vital and dysfunction of brainstem respiratory neurons can be life threatening. Consequently, much research has been devoted to deciphering the specific roles and functions of these core elements of the respiratory control system (Feldman et al., 2003, 2013). However, except for congenital central hypoventilation syndrome (a rare genetic disorder that results in failure of involuntary control of breathing (Perez and Keens, 2013)) and experimental ablation of the rhythmogenic circuits of the pre-Bötzinger complex (Gray et al., 2001), most respiratory disorders implicating dysfunction of the core elements of the respiratory control system are observed during sleep with sudden infant death syndrome, apnea of prematurity, and sleep disordered breathing being the most notable (and studied) clinical manifestations.

By contrast, respiratory activity is more robust during wakefulness owing to the increased respiratory drive originating from supra-medullary structures. Because of their functional diversity, the influence that these numerous groups of neurons exert on breathing is rich and complex. Until recently, studies addressing the role of "non-brainstem" structures on respiratory control have been sparse but as the topic of this special issue indicates, there has been a growing awareness concerning their impact on breathing. A more comprehensive view of respiratory control seems to emerge as scientists rediscover and appreciate the anatomical and functional links between rostral (non-brainstem) and classical brainstem structures and how these interactions can influence

☆ This paper is part of a special issue entitled "Non-homeostatic control of respiration", guest-edited by Dr. Eugene Nalivaiko and Dr. Paul Davenport.

* Corresponding author at: Department of Pediatrics, Université Laval, Centre de Recherche du CHU de Québec, Hôpital St-François d'Assise, 10 rue de L'Espinay, Québec, QC G1L 3L5, Canada. Tel.: +1 418 525 4444x52577; fax: +1 418 525 4195.
E-mail address: Richard.Kinkead@crsfa.ulaval.ca (R. Kinkead).

http://dx.doi.org/10.1016/j.resp.2014.06.013
1569-9048/

respiratory control across sleep/wake states. In support of this broadening view, many now argue that respiration is the best physiological marker of emotional states (Abelson et al., 2001, 2010; Wilhelm et al., 2001; Wilhelm and Roth, 2001).

It is well known that changes in arterial O_2 and/or CO_2 levels will rapidly trigger ventilatory adjustments to return arterial blood gases close to their set point but as we discuss below, a sudden drop in O_2 and/or build-up of CO_2 can also trigger significant neuroendocrine and emotional/behavioral reactions which can be very strong. Suffocation is perhaps the most powerful stressor and whenever an escape response is possible it may be the best defense strategy to avoid an improper respiratory environment. In some neurological disorders, however, these reactions may be irrelevant or disproportionate. Over the years, clinicians established a link between respiration and anxiety and today, key theories of the psychopathology of anxiety (including panic disorders) focus on respiratory control and related monitoring system (Abelson et al., 2010; Klein, 1993). Psychiatric disorders associated with respiratory dysfunction therefore provide a unique opportunity to explore the contribution of supramedullary structures in respiratory control.

With that in mind, our first objective is to briefly present the clinical manifestations of panic disorder with respiratory symptoms. We will then address the underlying neurological mechanisms by discussing the role of the amygdala, the hypothalamic defense area, and the periaqueductal gray. These structures were chosen because they stand at the interface between autonomic and emotional/behavioral function. In addition to their role in the integration of information (especially signals with an emotional connotation) and regulation of fear and anxiety responses, these structures send caudal projections to brainstem structures by which they exert commanding influence on core elements of the respiratory control system. We will then conclude this brief review by discussing how disruption of respiratory control by early exposure to stress may be a valuable experimental approach to address the pathophysiology of respiratory manifestations of panic disorder (PD) in animal models.

2. Panic disorder (PD), the "suffocation false alarm" theory, and respiratory regulation

Panic disorder (PD) is an anxiety disorder characterized by frequent panic attacks that are acute and unexpected (American Psychiatric Association, 1994; World Health Organization, 1992). A panic attack is defined as an episode of overwhelming distress and anxiety during which the patient rapidly develops symptoms such as intense air hunger, sweating, heart palpitations, shortness of breath, fear of dying, and hyperventilation (Hoppe et al., 2012). As such, it is perhaps one of the most overwhelming experiences that a person can endure (Moreira et al., 2013). Panic disorder diminishes quality of life and these patients are less productive and often miss work because of their condition. In Canada and the USA, it is estimated that PD affects ~5% of the population (Hoppe et al., 2012; Meng and D'Arcy, 2012). What is striking, however, is that the prevalence rate for women is two to three times that of men (Donner and Lowry, 2013; Pigott, 2003; Wilhelm and Roth, 2001).

Differences in the methods and criteria used for diagnosis explain the variability of prevalence rates reported for PD and because different subtypes are proposed, delineating between variants can be difficult. That being said, the respiratory subtype is the most common form mainly because respiratory distress is a prominent symptom (Hoppe et al., 2012; Wilhelm and Roth, 2001) and the respiratory component of PD has been established in epidemiological studies (Roberson-Nay and Kendler, 2011). Abnormalities in respiratory regulation are therefore central in the pathophysiology of PD (Abelson et al., 2010; Nardi et al., 2009) and symptoms include enhanced variability of breath size (due to increased sigh frequency) and hyper-responsiveness to CO_2 stimulation. Nearly a century ago, it was discovered that CO_2 inhalation can induce a panic attack and that PD patients are abnormally sensitive to this stimulus (Drury, 1918). Today, increased responsiveness to CO_2 is acknowledged as a distinctive characteristic of PD patients and CO_2 inhalation is commonly used as a diagnostic tool for PD (Gorman et al., 2001; Hoppe et al., 2012). Despite the burden that this illness represents for our society, the origins and neuroendocrine underpinnings for the sex-based difference in respiratory dysfunction observed in PD patients are poorly understood (Pigott, 2003).

Patients suffering from PD show important respiratory symptoms that result from complex interactions between emotional and physiological (respiratory) responses. When facing a stressful situation (whether real or perceived), most subjects hyperventilate to improve O_2 uptake and CO_2 excretion. This response is physiologically normal. Depending on the intensity of the response, however, the CO_2 loss (hypocapnia) that results from hyperventilation may produce a variety of symptoms such as paresthesia, sweaty hands, giddiness, loss of consciousness, visual disturbances, headaches, ataxia, tremor, cold extremities, and chest pain/discomfort (Gardner, 1996). For many patients, however, these physiological changes are misinterpreted as life-threatening symptoms and promote excessive "emotional" reactions, such that a panic attack is also associated with other conditions including fear of dying, shortness of breath, and a sensation of choking (Gardner, 1996; Gorman et al., 2000; Nardi et al., 2009). Panic disorder patients also report substantial anxiety over the possibility of experiencing another attack (Abelson et al., 2010). Accordingly, hyperventilation can be viewed as a cause, a correlate, and a consequence of panic attacks (Nardi et al., 2009). From a neural control perspective, it is interesting that PD patients show an increased rate of apnea during sleep, excessive sighing, and an abnormally elevated respiratory variability (tidal volume and breathing frequency) during both daytime and sleep (Abelson et al., 2001; Bystritsky et al., 2000; Nardi et al., 2009; Stein et al., 1995). The sum of these physiologically based symptoms indicate that regulation of breathing is dysfunctional in PD patients (Abelson et al., 2008; Gorman et al., 2000; Katzman et al., 2002; Nardi et al., 2009; Sinha et al., 2000; van Duinen et al., 2007).

Clinical observations led Klein to propose one of the major theoretical models of PD known as "the false suffocation alarm hypothesis" which states that "many spontaneous panics occur when the brain's suffocation monitor erroneously signals a lack of useful air, thereby maladaptively triggering an evolved suffocation alarm system" (Klein, 1993). After 20 years of basic and clinical research, it is now clear that disruption of respiratory control and its CO_2 sensing system is central to PD. Moreover, the intense fear and anxiety experienced by PD patients highlights the functional and anatomical overlap that exists between the neural circuits that control breathing and those that regulate fear and anxiety. While each system has been studied extensively in isolation, our understanding of the functional intersection of these systems (and circuits) is in its infancy. As we discuss in Section 7, the recent development of relevant animal models provides an excellent opportunity to further explore this highly promising research area.

3. CO_2 as a "mixed stressor": chemodetection and activation of the fear and hyperventilatory responses

Stress is commonly defined as "*an actual or anticipated disruption of homeostasis or an anticipated threat to well-being*" (Ulrich-Lai and Herman, 2009). As the definition suggests, stressful stimuli