Progress in Neurobiology 129 (2015) 58–78

Contents lists available at ScienceDirect

Progress in Neurobiology

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

The brain acid–base homeostasis and serotonin: A perspective on the use of carbon dioxide as human and rodent experimental model of panic

N.K. Leibold [a,b,c,*], D.L.A. van den Hove [a,b,c,1], G. Esquivel [a,b,2], K. De Cort [a,b,3], L. Goossens [a,b,4], E. Strackx [d,5], G.F. Buchanan [e,6], H.W.M. Steinbusch [a,b,7], K.P. Lesch [a,b,c,8], K.R.J. Schruers [a,f,9]

[a] Department of Psychiatry and Neuropsychology, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands
[b] School for Mental Health and Neuroscience (MHeNS), Maastricht University, European Graduate School of Neuroscience (EURON), P.O. Box 616, 6200 MD Maastricht, The Netherlands
[c] Division of Molecular Psychiatry, Laboratory of Translational Neuroscience, Center of Mental Health, University of Wuerzburg, Fuechsleinstrasse 15, 97080 Wuerzburg, Germany
[d] Department of Health and Technology, Leuven University College, Herestraat 49, 3000 Leuven, Belgium
[e] Department of Neurology, Yale University School of Medicine, P.O. Box 208018, 15 York Street, New Haven, CT 06520-8018, USA
[f] Center for the Psychology of Learning and Experimental Psychopathology, Department of Psychology, University of Leuven, Tiensestraat 102, P.O. Box 3726, 3000 Leuven, Belgium

ARTICLE INFO

Article history:
Received 2 December 2014
Received in revised form 16 April 2015
Accepted 20 April 2015
Available online 27 April 2015

Keywords:
Panic disorder
Brain pH
CO_2
Human models
Animal models
Serotonin

ABSTRACT

Panic attacks (PAs), the core feature of panic disorder, represent a common phenomenon in the general adult population and are associated with a considerable decrease in quality of life and high health care costs. To date, the underlying pathophysiology of PAs is not well understood. A unique feature of PAs is that they represent a rare example of a psychopathological phenomenon that can be reliably modeled in the laboratory in panic disorder patients and healthy volunteers. The most effective techniques to experimentally trigger PAs are those that acutely disturb the acid–base homeostasis in the brain: inhalation of carbon dioxide (CO_2), hyperventilation, and lactate infusion. This review particularly focuses on the use of CO_2 inhalation in humans and rodents as an experimental model of panic. Besides highlighting the different methodological approaches, the cardio-respiratory and the endocrine responses to CO_2 inhalation are summarized. In addition, the relationships between CO_2 level, changes in brain pH, the serotonergic system, and adaptive physiological and behavioral responses to CO_2 exposure are presented. We aim to present an integrated psychological and neurobiological perspective. Remaining gaps in the literature and future perspectives are discussed.

Abbreviations: ACCN2, amiloride-cation channel 2; ASIC, amiloride-sensitive ion channel; CO_2, carbon dioxide; DSM, Diagnostic and Statistical Manual of Mental Disorders; $EtCO_2$, end-tidal CO_2; GABA, gamma-aminobutyric acid; GAD, generalized anxiety disorder; HPA axis, hypothalamo-pituitary–adrenal axis; O_2, oxygen; PA, panic attack; pCO_2, partial pressure of CO_2; PD, panic disorder; SSRI, selective serotonin reuptake inhibitor; TASK, TWIK-related acid sensitive K^+ channel; TPH2, tryptophan hydroxylase 2; 5-HT, serotonin; 5-HTT, serotonin transporter; 5-HTTLPR, serotonin transporter gene-linked polymorphic region.

* Corresponding author at: Department of Psychiatry and Neuropsychology, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands. Tel.: +31 43 3883875.
E-mail addresses: nicole.leibold@maastrichtuniversity.nl (N.K. Leibold), d.vandenhove@maastrichtuniversity.nl (D.L.A. van den Hove), gabriel.esquivel@maastrichtuniversity.nl (G. Esquivel), klara.decort@maastrichtuniversity.nl (K. De Cort), lies.goossens@maastrichtuniversity.nl (L. Goossens), eveline.strackx@khleuven.be (E. Strackx), gordon.buchanan@yale.edu (G.F. Buchanan), h.steinbusch@maastrichtuniversity.nl (H.W.M. Steinbusch), kplesch@mail.uni-wuerzburg.de (K.P. Lesch), koen.schruers@maastrichtuniversity.nl (K.R.J. Schruers).
[1] Tel.: +31 43 3881021.
[2] Tel.: +31 43 3883511.
[3] Tel.: +31 43 3883511.
[4] Tel.: +31 43 3883511.
[5] Tel.: +32 16 375200.
[6] Tel.: +1 203 7854085.
[7] Tel.: +31 43 3881021.
[8] Tel.: +49 931 20177610.
[9] Tel.: +31 43 3883511.

http://dx.doi.org/10.1016/j.pneurobio.2015.04.001
0301-0082/

Contents

1. Introduction

Panic attacks (PAs) are common psychopathological phenomena that affect about 23% of the general population at least once in their lifetime (Kessler et al., 2006). PAs represent abrupt surges of intense fear or discomfort, even though no real danger is present, accompanied by various physical or cognitive symptoms. According to the current criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 (American Psychiatric Association, 2013), at least four out of the following thirteen symptoms have to develop abruptly with a symptomatic peak within a few minutes after onset: palpitations or pounding heart; sweating; trembling or shaking; sensation of shortness of breath or smothering; feeling of choking; chest pain or discomfort; nausea or abdominal distress; feeling of dizziness, lightheadedness or faintness; depersonalization (feeling of being detached from oneself) or derealization (feeling of unreality); fear of losing control or going crazy; fear of dying; paresthesia (numbness or tingling sensations); and chills or hot flushes. As several symptoms closely resemble those of a cardiac arrest or acute asthma, cardiac- and/or emergency departments are frequently visited. Patients often receive costly tests such as angiography and echocardiography (Zaubler and Katon, 1998), without finding an explanation for their complaints.

PAs can occur in any anxiety or mental disorder as well as in many medical conditions (American Psychiatric Association, 2013), but are most prominent in panic disorder (PD). PD occurs in about 4% in the general population (Norton et al., 2008; Pane-Farre et al., 2014), with the onset commonly between the ages of 25–34 years in women and 30–44 years in men (Wittchen and Essau, 1993). PD has a high heritability of about 40% (Hettema et al., 2001; Maron et al., 2010) and is characterized by PAs that occur more than once and unexpectedly (i.e., 'out of the blue' and not caused by a medical condition or the use or withdrawal of a drug) (American Psychiatric Association, 2013). The frequency of the attacks can vary widely: a few attacks a month, several attacks each week or having periods with frequent attacks separated by weeks or months with less or no attack (Faravelli and Paionni, 2001). In addition to recurrent unexpected PAs, at least one of the following criteria is required for a period of at least one month: persistent concern about having additional attacks or the implications of the attack (anticipatory anxiety), and/or a significant maladaptive change in behavior related to the attacks. Frequently, patients develop agoraphobia, the avoidance of places and situations that are associated with the occurrence of previous attacks or in which having an attack may be embarrassing or in which it may be difficult to get help (for instance, being alone outside the home, being in a crowd or traveling in a bus or car). This avoidance behavior can become so severe that patients are confined to their homes. Due to the unpredictability of PAs, avoidance behavior, and the common comorbid anxiety disorders (Tilli et al., 2012), patients experience a marked decrease in their quality of life (Mendlowicz and Stein, 2000). Therefore, costs associated with an individual having PD are substantial (Salvador-Carulla et al., 1995). At the population level, the costs associated with PD are comparable with the combined costs associated with social phobia, simple phobia, and generalized anxiety disorder (GAD) (Batelaan et al., 2007).

1.1. Etiology of panic from a neurobiological perspective: the concepts of anxiety, fear, and panic

According to the current DSM-5 (American Psychiatric Association, 2013), PD is classified as an anxiety disorder and is characterized by unexpected PAs (including intense fear) as well as anticipatory anxiety. Research has indicated that anxiety, fear, and panic are distinct entities involving divergent brain structures and behaviors. The main factor that determines the specific behavioral response is the 'defensive distance' to the threat (e.g., a predator). According to this concept, first introduced by Blanchard