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Review article

Translational approach to the pathophysiology of panic disorder: Focus on serotonin and endogenous opioids

Frederico G. Graeff[a,b,*]

[a] Institute of Neuroscience and Behavior – INeC, Avenida do Café, 2450, 14050-220 Ribeirão Preto, SP, Brazil
[b] Neurobiology of Emotion Research Centre (NAP-NuPNE), University of Sao Paulo, Ribeirao Preto, Brazil

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ABSTRACT

Panic patients experience recurrent panic attacks. Two main neurochemical hypotheses have been proposed to explain this vulnerability. The first suggests that panic patients have deficient serotonergic inhibition of neurons localized in the dorsal periaqueductal gray matter of the midbrain that organizes defensive reactions to cope with proximal threats as well as of sympathomotor control areas of the rostral ventrolateral medulla that generate neurovegetative symptoms of the panic attack. The second proposes that endogenous opioids buffer panic attacks in normal subjects, and their deficit results in heightened sensitivity to suffocation and separation anxiety in panic patients. Experimental results obtained in rat models of panic indicate that serotonin interacts synergistically with endogenous opioids in the dorsal periaqueductal gray through 5-HT1A and μ-opioid receptors to inhibit proximal defense and, supposedly, panic attacks. These findings allow reconciliation of the serotonergic and opioidergic hypotheses of panic pathophysiology. They also indicate that endogenous opioids are likely to participate in the panicolytic action of antidepressants and suggest that exogenous opioids may be useful for treating panic patients resistant to conventional pharmacotherapy.

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1. Introduction

The concept of panic disorder (PD) as a distinct diagnostic category is based on the pharmacological results by Klein and Fink (1962) showing that chronic administration of the antidepressant agent imipramine reduced the symptoms of patients presenting recurrent episodes of extreme fear, the so-called panic attack (PA). Although the PA is the hallmark of PD, its occurrence, alone, does not characterize the condition, since it may occur in other psychiatric disorders and even in healthy people. For PD to be diagnosed it is necessary that PA episodes are accompanied by persistent worry or anticipatory anxiety about having another attack and the consequences of such attacks, as well as by avoidance of places or situations where having a PA is embarrassing or an escape route is not easily available. When avoidance is generalized, the condition is called agoraphobia. The PA is a period of intense fear that peaks in less than 10 min and subsides in about 30 min, in

* Corresponding author at: Institute of Neuroscience and Behavior – INeC, Avenida do Café, 2450, Ribeirão Preto, 14050-220 SP, Brazil.
E-mail address: hegog@hotmail.com

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which several of the following symptoms occur: palpitation, sweating, trembling, shortness of breath, choking, chest pain, nausea or abdominal distress, dizziness, derealization or depersonalization, fear of losing control or of going crazy, fear of dying, numbness or tingling sensations, chills or hot ashes, diarrhea, cold hands, headache, insomnia, fatigue, intrusive thoughts, and ruminations. During the attack, patients often have an urge to flee and a sense of impending death from suffocation or a heart attack (American Psychiatric Association, 2013).

Theoretical constructs about the pathophysiology of PD should address the main characteristics of this condition, namely increased vulnerability to experience unexpected PAs, persistent high level of anxiety in-between PAs and avoidant behavior, as well as an abnormal sensitivity to bodily sensations that may trigger PAs (Clark et al., 1997). In addition, they should account for clinical and experimental findings that characterize PD, among which are: 1) augmented susceptibility to lactate injection or inhalation of high concentrations of CO2; 2) failure to activate the hypothalamic-pituitary-adrenal (HPA) stress hormonal axis by either experimentally-induced or natural PAs; 3) the therapeutic action of antidepressants acting primarily on the neurotransmission mediated by serotonin (5-hydroxytryptamine or 5-HT); 4) the therapeutic action of cognitive behavior therapy (CBT). Among these aspects, the most critical and best explored is the susceptibility to PA, which is the topic of the present review.

2. Vulnerability to panic attacks

Two main hypotheses have been proposed to explain why PD patients are more likely to experience PAs: 1) lack of effective 5-HT inhibition of neuronal networks that integrate defensive reactions to proximal danger, and 2) faulty buffering by endogenous opioids of an oversensitive suffocation alarm system. More recently, a reconciliation of these two proposals was suggested on the basis of experimental findings showing that 5-HT interacts with endogenous opioids in the dorsal periaqueductal gray matter (dPAG), a brain structure that is critical for regulating proximal defense and, supposedly, PAs (Graeff, 2012).

2.1. Serotonin deficiency

The idea that 5-HT restrains PAs rests on the assumption that 5-HT has a dual role in the regulation of different types of defensive reactions (Graeff, 1991). This hypothesis was elaborated to overcome apparent inconsistencies about the effects of 5-HT-acting drugs, assessed in animal models of anxiety. Thus, in experimental situations that generate suppression of instrumental responses by punishment, the so-called conflict tests, drugs that lessen 5-HT central actions release suppressed responding, an effect characteristic of anxiolytic agents like the benzodiazepines. As expected, pro-5-HT drugs enhance the response suppression induced by punishment. Although this evidence suggests that 5-HT heightens anxiety, results obtained with escape from brain aversive stimulation indicate that 5-HT lowers anxiety. As a consequence, it was proposed that the two kinds of experimental models represent different defense strategies (Graeff, 1991), as defined by the seminal work of Robert and Caroline Blanchard (Blanchard et al., 1986). Thus, conflict tests would summon neuronal networks that organize defensive reactions that cope with potential threat, i.e., when danger is not present, but may occur either because it has happened in the past in the same environment or because the situation is novel. On the other hand, escape tests would engage neuronal systems that orchestrate primitive defensive reactions that deal with danger stimuli that are near, in other words, with proximal threat.

The main brain structures involved in defense against potential threat are localized in the forebrain, comprising the prefrontal cortex (PFC), amygdala and hippocampus, whereas proximal defense is organized chiefly in the hindbrain, a key structure being the dPAG. Because the aforementioned evidence indicates that response suppression induced by conflict or inhibitory avoidance is facilitated by 5-HT, whereas proximal defense is inhibited, 5-HT was assumed to facilitate defense against potential danger, whereas at the same time inhibiting proximal defense (Graeff, 1991). The adaptive value of this neural organization in natural settings would be to restrain conspicuous behavior, such as running and jumping, in circumstances where the predator may be around (potential threat) or is at a safe distance from the prey (distant threat). Taking what now would be called a translational step, Deakin and Graeff (1991) related each animal defense strategy to a specific normal emotion and a type of anxiety disorder (Table 1), and suggested that 5-HT simultaneously heightens anxiety through actions exerted in the forebrain and holds back PAs by working on the dPAG.

The control of proximal defense by 5-HT in the dPAG has been extensively reviewed elsewhere and, in short, the pharmacological results obtained with animal models of PD (see Section 2.3) have largely fulfilled the predictions of the Deakin-Graeff proposal (Canteras and Graeff, 2014; Graeff, 2002, 2004; Zangrossi and Graeff, 2014). It is worth remarking that, as in the dPAG, electrical stimulation of the medial hypothalamus has been shown to elicit escape responses in rats (e.g., Milani and Graeff, 1987), and PA symptoms in a patient (Wilent et al., 2010). Furthermore, stimulation of 5-HT1A and 5-HT2A receptors in the dorsomedial hypothalamus impaired the escape response elicited by its electrical stimulation (De Bortoli et al., 2013), as well as escape in the ETM (Nascimento et al., 2014). Because neuroanatomical studies evidenced reciprocal connections between the medial hypothalamus and dPAG, it is likely that the two structures work together to control panic-like responses (Canteras and Graeff, 2014).

Indicating a continuity from lower animals to humans, application of a fear questionnaire to healthy subjects in dangerous scenarios varying from distant and potential to imminent and inescapable threat showed that the responses selected for each condition were similar to the types of defense observed in experimental animals (Blanchard et al., 2001; Perkins and Corr, 2006; Shuhama et al., 2008). There is also considerable human experimental evidence supporting the notion that defense against potential threat or anxiety is mainly organized in the forebrain, whereas proximal defense is regulated by hindbrain structures, e.g.: 1) Feinstein et al. (2013) reported that patients with bilateral amygdala lesion are more vulnerable to PAs induced by inhalation of 35% CO2 than healthy volunteers. Therefore, the amygdala seems to inhibit PAs, what is consistent with the earlier suggestion that the amygdala-born, persistent anxiety shown by panic patients buffers PAs (Deakin and Graeff, 1991), as well as with experimental evidence obtained in humans (Mobbs et al., 2009) and in rats (Magierek et al., 2003) suggesting mutual inhibition between the panic-encoding PAG and forebrain structures involved in anxiety; 2) results with deep brain electrical stimulation reviewed by Del-Ben and Graeff (2009) revealed that stimulation in or near the PAG causes subjective and physiological changes resembling a PA; 3) morphometric magnetic resonance imaging (MRI) studies have shown increased dorsal midbrain gray matter volume in panic patients (Protopopescu et al., 2006; Uchida et al., 2008), the severity of symptoms being positively correlated with dorsal, but not ventral PAG volume (Fujiwara et al., 2011); 4) studies with functional magnetic imaging (fMRI) have shown that neural activation shifts from the medial prefrontal cortex to the PAG as virtual or actual threatening stimuli grow nearer (Mobbs et al., 2007, 2010, 2009); 5) in panic patients treated with cognitive-behavioral therapy significant correlations have been found between the percent