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Review

An animal model of panic vulnerability with chronic disinhibition of the dorsomedial/perifornical hypothalamus

Philip L. Johnson [a,b], Anantha Shekhar [a,b,c,d,*]

[a] Department of Psychiatry, Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, IN, USA
[b] Stark Neuroscience Institute, Indiana University School of Medicine, Indianapolis, IN, USA
[c] Department of Pharmacology, Indiana University School of Medicine, Indianapolis, IN, USA
[d] Indiana Clinical and Translational Sciences Institute, Indiana University School of Medicine, Indianapolis, IN, USA

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ABSTRACT

Panic disorder (PD) is a severe anxiety disorder characterized by susceptibility to induction of panic attacks by subthreshold interoceptive stimuli such as sodium lactate infusions or hypercapnia induction. Here we review a model of panic vulnerability in rats involving chronic inhibition of GABAergic tone in the dorsomedial/perifornical hypothalamic (DMH/PeF) region that produces enhanced anxiety and freezing responses in fearful situations, as well as a vulnerability to displaying acute panic-like increases in cardioexcitation, respiration activity and "flight" associated behavior following subthreshold interoceptive stimuli that do not elicit panic responses in control rats. This model of panic vulnerability was developed over 15 years ago and has provided an excellent preclinical model with robust face, predictive and construct validity. The model recapitulates many of the phenotypic features of panic attacks associated with human panic disorder (face validity) including greater sensitivity to panicogenic stimuli demonstrated by sudden onset of anxiety and autonomic activation following an administration of a sub-threshold (i.e., do not usually induce panic in healthy subjects) stimulus such as sodium lactate, CO_2, or yohimbine. The construct validity is supported by several key findings; DMH/PeF neurons regulate behavioral and autonomic components of a normal adaptive panic response, as well as being implicated in eliciting panic-like responses in humans. Additionally, patients with PD have deficits in central GABA activity and pharmacological restoration of central GABA activity prevents panic attacks, consistent with this model. The model's predictive validity is demonstrated by not only showing panic responses to several panic-inducing agents that elicit panic in patients with PD, but also by the positive therapeutic responses to clinically used agents such as alprazolam and antidepressants that attenuate panic attacks in patients. More importantly, this model has been utilized to discover novel drugs such as group II metabotropic glutamate agonists and a new class of translocator protein enhancers of GABA, both of which subsequently showed anti-panic properties in clinical trials. All of these data suggest that this preparation provides a strong preclinical model of some forms of human panic disorders.

Contents

* Corresponding author at: Indiana University School of Medicine, 1111 West 10th street, Suite 313, Indianapolis, IN 46202, USA. Tel.: +1 317 274 1246; fax: +1 317 278 4821.
E-mail address: ashekhar@iupui.edu (A. Shekhar).

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1. Panic attacks and panic disorder

Anxiety disorders are the most prevalent psychiatric disorders [1], with a life time prevalence of about 20% in the general population [2]. Currently, there is clear evidence that anxiety disorders are a heterogeneous group. Several distinct syndromes have been delineated, based primarily on clinical presentations. One severe anxiety syndrome is panic disorder where recurrent '*spontaneous*' panic attacks occur that are discrete periods of intense fear or discomfort with at least 4 characteristic symptoms such as tachycardia, hyperventilation or dyspnea, locomotor agitation, etc [1]. Current estimates are that about 7–10% of the population experience occasional panic attacks and about 2–5% of the population have panic disorder (i.e., frequent and/or disabling panic attacks) [3].

Although the cause of panic disorder and associated panic attacks is largely unknown there are predisposing factor that increase the likelihood of the development of panic attacks. The onset of panic attacks usually occurs in late adolescence or early adulthood, and women are twice as likely as men to develop recurrent panic attacks. Sexual maturation in adolescence [see review [4]], and fluctuating sex hormones in women [see review [5]] appear to play a significant role in the vulnerability to panic attacks, but other factors such as early life stress or higher incidence of trauma such as rape in women could also account for this vulnerability. Genetic factors also appear to play a significant role since it has been estimated that 30–40% of monozygotic twins of persons diagnosed with a panic disorder will experience recurrent panic attacks [6,7].

Normally an adaptive 'panic' response is a survival reflex that occurs in response to an imminent threat [8] that can be associated with either external or internal sensory stimuli (exteroceptive- or interoceptive-cues, respectively) [9,10]. For instance, normal panic is an adaptive response to imminent threats that are exteroceptive (e.g., predator attacks) or interoceptive (e.g., severe hypercapnia that leads to a suffocation sensation). However, in patients with panic disorder, the panic attacks (i.e., aberrant panic responses) often initially occur "spontaneously" in the absence of any obvious external threatening stimuli. Although panic attacks are considered "spontaneous", they can be consistently triggered in patients with panic disorder by normal interoceptive cues. For instance, patients with panic disorder are hyper-responsive to normal interoceptive cues [11,12], and are also susceptible to induction of panic attacks by subthreshold interoceptive stimuli such as 0.5 M sodium lactate (NaLac) infusions and 7.5% CO_2 inhalations, which are agents that normally do not elicit panic attacks in healthy controls [13–15]. Patients with panic disorder are also susceptible to precipitation of panic attacks by variety of other agents such as yohimbine, cholecystokinin, caffeine etc. [16], all at subthreshold doses that normally do not elicit panic attacks in most healthy controls (i.e., by subthreshold interoceptive cues). Thus, the initial pathology in these patients appears to be an alteration somewhere in the central neural pathways regulating normal panic response, thus rendering them susceptible to 'spontaneous' panic attacks [17]. These initial spontaneous attacks can eventually become associated with contextual cues where previous panic attacks have occurred such as bridges, crowded spaces, or situations where rapid exit is difficult [18]. This development of cognitive bias towards threat perception [19] and conditioning of fear responses to panic cues [20] can lead to phobias which are the likely mechanisms underlying recurrent and situational panic attacks in later stages of the illness. Within the anxiety disorder spectrum, recurrent panic attacks are the hallmark of diagnosis for panic disorder, but can also occur in other severe anxiety disorders such as post traumatic stress disorder [21], but not other anxiety disorders such as generalized anxiety and obsessive compulsive disorders [22,23], or pure depressive disorders [24].

2. Neurochemical and neuroanatomical systems implicated in panic disorder

Currently, the neuroanatomical circuits and associated neurochemicals underlying the initial vulnerability to spontaneous panic attacks in human are poorly understood. An ongoing hypothesis of ours is that an alteration in the central neural pathways regulating normal panic response underlies 'spontaneous' panic attacks and the development of panic disorder. If these putative brain areas that are postulated to be regulatory sites for a normal panic response fail to properly function, this could trigger an episodic "alarm" and activate the brain "panic circuit" resulting in a panic attack. Very little is known about such a circuit except that structures such as the periaqueductal gray (PAG), hypothalamus, amygdala and frontal cortex are frequently implicated [25–27]. While much is known about conditioned fear and induction of fear responses by contextual cues, little is known about the mechanisms underlying the vulnerability to the initial 'spontaneous' panic attacks, the true etiological basis of panic disorder [28]. A number of neurochemical hypothesis are also proposed for the etiology of panic disorder, primarily based on the therapies that work in treating panic attacks.

For example, both spontaneous and laboratory-induced panic attacks can be blocked by successful treatment of panic disorder with: 1) benzodiazepines like alprazolam [29–31]; 2) tricyclic antidepressants [32] or monoamine oxidase (MAO) inhibitors [33] that target monoaminergic systems in general (i.e., serotonin, norepinephrine, epinephrine, dopamine and histamine); 3) serotonergic (SSRI) or norephinephrine (NRI) reuptake inhibitors [see review [34]]. There is also evidence of reduced inhibitory GABAergic tone in patients