Neuroscience and Biobehavioral Reviews 32 (2008) 1326–1335

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Neurobiology of panic disorder: From animal models to brain neuroimaging

Frederico G. Graeff*, Cristina M. Del-Ben

Department of Neurology, Psychiatry and Medical Psychology, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Av. Bandeirantes 3900, 14049-900 Ribeirão Preto, SP, Brazil

ARTICLE INFO

Keywords:
Serotonin
Defense
Animal models
Human experimental anxiety
Stress hormones
Brain neuroimaging
Periaqueductal gray matter
Insula
Anterior cingulate
Panic disorder

ABSTRACT

Evidence from animal models of anxiety has led to the hypothesis that serotonin enhances inhibitory avoidance (related to anxiety) in the forebrain, but inhibits one-way escape (panic) in the midbrain periaqueductal gray (PAG). Stressing the difference between these emotions, neuroendocrinological results indicate that the hypothalamic–pituitary–adrenal axis is activated by anticipatory anxiety, but not by panic attack nor by electrical stimulation of the rat PAG. Functional neuroimaging has shown activation of the insula and upper brain stem (including PAG), as well as deactivation of the anterior cingulated cortex (ACC) during experimental panic attacks. Voxel-based morphometric analysis of brain magnetic resonance images has shown a grey matter volume increase in the insula and upper brain stem, and a decrease in the ACC of panic patients at rest, as compared to healthy controls. The insula and the ACC detect interoceptive stimuli, which are overestimated by panic patients. It is suggested that these brain areas and the PAG are involved in the pathophysiology of panic disorder.

Contents

1. Introduction . . . 1326
2. Antipredator defense and anxiety disorders . . . 1327
3. 5-HT in defense, anxiety and panic . . . 1328
4. Human experimental anxiety . . . 1329
5. Stress hormones in anxiety and panic . . . 1330
6. Neuroimaging in experimental anxiety . . . 1330
7. Neuroimaging in panic patients . . . 1331
   7.1. Functional neuroimaging . . . 1331
   7.2. Structural neuroimaging . . . 1331
8. Conclusion . . . 1333
   Acknowledgements . . . 1333
   References . . . 1333

1. Introduction

The main characteristic of panic disorder (PD) is the unexpected and repeated occurrence of panic attacks, in which feelings of extreme fear and dread are accompanied by marked neurovegetative symptoms. Over time, anticipatory anxiety about having a further attack and avoidance of places where having an attack is embarrassing develop. Avoidance often generalizes into agoraphobia, in which case the patient is afraid of leaving home unaccompanied. In contrast, generalized anxiety disorder (GAD) is characterized by chronic worry about everyday events and decisions (American Psychiatry Association, 1994).

The present distinction between PD and TAG has originated from the results of a pharmacological study showing that panic attacks are reduced by long-term administration of imipramine, a non-selective monoamine reuptake inhibitor, but not affected by anxiolytic agents (Klein, 1964). Later on, this pharmacological discrimination between the two disorders became somewhat

* Corresponding author. Tel.: +55 16 3602 2607; fax: +55 16 3602 2544.
E-mail addresses: hegog@hotmail.com, fgraeff@keynet.com.br (F.G. Graeff).

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doi:10.1016/j.neubiorev.2008.05.017

blurred by the findings that GAD is also improved by chronic treatment with antidepressant agents (Kahn et al., 1986), and that PD responds to long-term treatment with potent benzodiazepines, such as alprazolam and clonazepam (Nutt, 2005). Nevertheless, other biological distinctions were found, among which the higher sensitivity of panic patients to panicogenic agents, such as lactate (Liebowitz et al., 1985).

The above differences between PD and GAD indicate that each disorder has its own neural basis. In this regard, theoretical constructs about the neuroanatomy and neurochemistry of PD have been generated (e.g., Coplan and Lydiard, 1998; Gorman et al., 2000). The present review focuses on hypotheses about the neural substrate of PD that are based on preclinical investigation on the role of serotonin (5-HT) in animal defense, pharmacological studies in human participants undergoing experimental anxiety tests, and neuroimaging studies performed in healthy volunteers as well as in panic patients.

2. Antipredator defense and anxiety disorders

In his seminal book "The expression of emotions in man and animals", Darwin (1872) brought emotional behavior under the biological paradigm, setting the stage for the comparative and systematic study of animal behavior (ethology), which provides the foundation of present day evolutionary psychology and psychiatry. From this perspective, the basis of anxiety and related emotions is to be found in the neural networks that organize animal defense.

A key example of this approach is the ethoexperimental analysis of defensive strategies of wild rats in response to predatory threat, originally carried out by Caroline and Robert Blanchard (Blanchard et al., 1986). From the results of their studies emerged the concept of levels of defense, which is fundamental for connecting animal defense with anxiety disorders. In brief, the defense strategies displayed by wild rats have been classified into three types, as determined by the presence or absence of the predator, and by its distance from the prey. The first defense level is potential threat, verified in novel situations or in environments where the predator had already been met, but is no longer present. The defense strategy shown in these situations consists of cautious exploration aimed at risk-assessment. The second defense level, named distal threat, occurs in face of actual danger, but placed at a safe distance from the prey. In this case, the animal becomes tense and immobile (freezing) to impair detection by the predator and prepare for further active defense. Finally, when the predator is very close or makes actual contact to the prey (circa-strike defense, according to Fanselow, 1991) vigorous flight or fight (defensive aggression) takes place, characterizing proximal threat. Comparative studies among several species led to the conclusion that although the topography of each defense strategy varies widely depending on the make up of the organism, antipredator defense is hierarchically organized from risk assessment, to tense immobility, escape, defensive threat and, finally, defensive attack. The same strategies are used when the threatening animal is of the same species, but in addition there is submission, which organizes social hierarchy and minimizes conspecific damage (for a review, see Shuhama et al., 2007).

If extrapolation is to be made from animal defense to psychiatry, the fundamental question arises of whether the same basic defense strategies displayed by nonhuman mammals can be identified in human beings. Two kinds of studies have been performed to answer this fundamental question, the first using imaginary scenarios and the second, virtual reality simulation of predation.

So far, two studies have been conducted with threat scenarios. In the first one, carried out by Caroline Blanchard and coworkers in Hawaii (Blanchard et al., 2001), 160 male and female undergraduate students were asked to read a set of 12 scenarios involving a present or potential threatening situation, and choose a primary defensive response to each. These scenarios were designed to vary features known to influence defensive responding in animals: magnitude of threat, escapability of the situation, ambiguity of the threat stimulus, distance between the threat and the subject, and presence of a hiding place. Male and female responses to the various scenarios were highly correlated, except for "yell, scream, or call for help" which was frequent for females, but rare for males. However, a combination of this response category with "attack" showed a highly positive male–female correlation, across scenarios. Significant correlations were obtained for eight specific hypotheses derived from the animal literature, with some support for two additional hypotheses. While three predicted correlations were not supported by these findings, only a single significant correlation was obtained that had not been predicted on the basis of the animal literature.

A replication of the above investigation has been carried out by Shuhama et al. (2008), in 324 students of medicine and psychology of both genders from the Ribeirão Preto Campus of the University of São Paulo, Brazil. As in the Hawaiian study, the scenarios were able to elicit different defensive responses, depending on the threat features. "Flight" was chosen as the most likely response in scenarios evaluated as unambiguous and intense threat with an available route of escape, whereas "attack" was chosen in unambiguous, intense and close dangerous situations without an escape route. Less urgent behaviors, such as "checking out", were chosen in scenarios evaluated as less intense, more distant and more ambiguous. With a few exceptions that may be due to cultural differences, our results were similar to those reported in the original study with Hawaiian students, supporting the view that the patterning of defensive behavior is similar for human and nonhuman mammals.

The results of the virtual reality study (Mobbs et al., 2007) further indicate that the defense circuits of the human brain are wired in like those of other mammals, but since brain neuroimaging is involved, these data will be considered in the appropriate section.

Table 1
Defense strategy, neural substrate, related normal and pathological emotion, and pharmacotherapy

Danger	Defense	Structure	Emotion	Disorder	Medication
Uncertain conflict	Risk assessment behavioral inhibition	Hippocampus amygdala	Anxiety	Generalized anxiety	Anxiolytics antidepressants
Warning signal (CS)	Freezing (no way out)	Amygdala PAGv	Anticipatory anxiety		
	Avoidance (way out)	Amygdala	Conditioned fear	Specific phobia	None
Distal (US)	Escape	Medial hypothalamus	Unconditioned fear	Specific phobia	None
Proximal (US)	Flight/freezing	PAGd	Dread	Panic	Antidepressants

PAG: periaqueductal gray matter; v: ventral; d: dorsal; CS: conditioned stimulus; US: unconditioned stimulus.