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Neuroanatomy of panic disorder

Marco Andre Mezzasalma,[a] Alexandre M Valença,[a] Fabiana L Lopes,[a] Isabella Nascimento,[a] Walter A Zin[b] and Antonio E Nardi[a]

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[a]Laboratory of Panic and Respiration. Institute of Psychiatry. Federal University of Rio de Janeiro, Brazil
[b]Laboratory of Respiratory Physiology. Institute of Biophysics Carlos Chagas Filho. Federal University of Rio de Janeiro, Brazil

Abstract

Objectives: *Animal model studies may allow greater elucidation of the cerebral circuits involved in the genesis of panic disorder (PD), but these studies have not yet been fully analyzed.*

Methods: *The authors review recent literature on the neurobiology and neuroanatomy of PD.*

Results: *In this update, the authors present a revision of data that demonstrates the existence of a "fear network", which has as its main point the central nucleus of the amygdale and includes the hypothalamus, the thalamus, the hippocampus, the periaqueductal gray region, the locus ceruleus and other brainstem structures. Its existence is evidenced in animal studies of emotional and behavioral states, and its presence and importance can be extrapolated to the study of PD in humans.*

Conclusion: *This fear network can allow new progresses and studies using neuroimaging techniques and/or psychopharmacological trials, further elucidating the cerebral circuits of PD.*

Keywords: *Neurobiology; Panic disorder; Neuroanatomy; Fear; Anxiety; Conditioning (psychology)*

Introduction

Panic disorder (PD) is characterized by the sudden and unexpected occurrence of panic attacks (PA), which may be as frequent as having several attacks in the same day up to few attacks during a year. PA are defined by the DSM-IV[1] as a discrete period of intense fear or discomfort, in which four (or more) of the following symptoms appear abruptly such as: pounding heart, palpitations, trembling, sensations of shortness of breath, sweating, feeling of choking, fear of dying, fear of losing control, among others.

In 1989, Gorman et al[2] elaborated a neuroanatomic hypothesis for PD aiming to explain how two different treatments – psychopharmacotherapy and cognitive-behavioral psychotherapy – were efficient in its treatment. This theory presupposed that: PA originated from points in the brainstem which encompass the serotonergic, noradrenergic transmission and the respiratory control; that anticipatory anxiety arises after the activation of the limbic system structures and, finally, that phobic avoidance stemmed from precortical activation. This hypothesis therefore explained that the medication acted through the normalization of the brainstem activity in PD patients, while cognitive-behavioral therapy would act on the cortex.

Psychopharmacs, especially those that affect the serotonergic transmission[3] and cognitive-behavioral therapy[4] are effective in the treatment of PD patients. The theories which postulate alterations in the respiratory[5,6] and cardiovascular[7] reactivity, which therefore imply an impairment in the brainstem, were also reinforced.

Recent studies performed in basic and pre-clinical research accomplished the mapping of the neuroanatomic basis of fear, and these findings should be correlated to the previously described hypotheses. The result of this correlation proposes that PD can compromise the same pathways involved in conditioned fear in animals, including the central amygdaloid nucleus and its afferent and efferent projections, as well as the septo-hipoccampal system and the cingulate.

Our objective is to perform an update in the neurobiology of panic

disorder based on the neuroanatomic hypothesis presented by Gorman et al,[2] correlating it to the studies that have been performed since then in pre-clinic and basic research, especially in the areas of fear and avoidance.

Neuroanatomy of fear

One of the great challenges of modern psychiatry consists of the use of advanced information from pre-clinical research in basic neuroscience. Progress has been obtained in the development of animal models of emotional and behavioral states, but it is not easy to understand how an animal, unable to verbally express its emotional state, could reflect in a significant way the human psychopathology. This can be a limitation when trying to conceive an animal model for the assessment of depression or psychoses, which depend on the patient's capability of verbally informing us about the symptoms needed for the diagnosis.

Animal models can be used for the study of anxiety in human beings. Fear, flight, avoidance behaviors and responses similar to panic attacks occur in all animal philogenesis. It is almost intuitive that a rodent, which avoids entering into a cage where it was previously submitted to an adverse stimulus, is similar to a patient who refuses to cross a bridge in which he/she had already suffered a panic attack. Similarly, an animal shows an increase in the heart rate, blood pressure and release of glucocorticoid when it hears a sonorous tune that was previously matched with a mild adverse stimulus, demonstrating several autonomic alterations which are characteristic of panic attacks. However, the analogy between PA in humans and fear and avoidance behaviors in animals is not perfect. Most animal models of anxious states presuppose the conditioning (the correlation with the previous exposition to an adverse stimulus), what does not occur in any other anxiety disorder, except for post-traumatic stress disorder. The incapability of animals to provide verbal information from the subjective point of view is other important limitation to the study of fear. Besides, some authors propose that the models of animal fear do not reflect anxious states, such as Klein[8] who describes the biological differences between fear and the manifestations of anxiety disorders in human beings.

Nonetheless, there are aspects of conditioned fear in animals which make their analogy to PA be practically irresistible. The analysis of the neuroanatomy of conditioned fear among rodents and other animals can provide important data to be used as a basis for the study of PD patients.

The paradigm of conditioned fear used in neurobiological studies originates in Pavlov's work.[9] Normally, it consists of exposing an animal to a neutral stimulus – a sonorous tune or a lightening flash – at the same time in which a slight adverse stimulus is applied. The former is called conditioned stimulus and the latter, non-conditioned stimulus. After several paired exposures, the animal learns to respond to the conditioned stimulus with the same autonomic and behavioral response of that of the non-conditioned stimulus, even though this is not present.

The central network of fear

Currently we have a greater elucidation of the neurotransmitters and the brain pathway needed for the acquisition of conditioned fear (see Figure 1). The sensorial information for the conditioned stimulus passes through the anterior thalamus up to the lateral amygdaloid nucleus, being then transferred to its central nucleus,[10] which acts as the central point for the dissemination of information, coordinating thus autonomic and behavioral responses.[11-12] In pre-clinical studies, projections of the amygdale were identified and related to those responses. The efferent projections of the central amygdaloid nucleus have different destinies: the parabrachial nucleus, producing an increase in the respiratory rhythm;[13] the lateral hypothalamic nucleus, activating the sympathetic nervous system and causing autonomic activation and sympatic discharge;[14] the locus ceruleus, increasing the release of norepinephrine with the consequent rise in blood pressure, heart frequency and behavioral response to fear;[15] and the paraventricular nucleus of the hypothalamus, causing a higher release of adrenocorticoids;[16] the periaqueductal gray region, responsible for additional behavioral responses, including defensive behaviors and postural paralysis, which may be the animal equivalent to phobic avoidance.[17] The autonomic, neuroendocrine and behavioral responses which occur during PA are incredibly similar to the symptoms that occur in animals as a result of the activity in these brain regions while facing the conditioned stimulus. Although suggestive, the overlap between the consequences of the stimulation of brainstem structures by the central amygdaloid nucleus and the biological events, which occur during PA among human beings, does not take into account the important reciprocal connections between the amygdale and the sensorial thalamus, pre-frontal cortex, insula and the primary somatosensorial cortex[18] Therefore, the amygdale receives directly the sensorial information from the brainstem and the sensorial thalamus structures, enabling thus a rapid response to potentially dangerous stimuli, but also receives afferences from the cortical regions responsible for the processing and assessment of the sensorial information. If a neurocognitive deficit occurs in these cortical processing pathways, it could result in an error in the processing of sensorial information (corporal sensations), which is one of the components of PD, leading to an inappropriate activation of this 'fear network' through erroneous excitatory stimuli for the amygdale. Although the role of the amygdale in PD has only started to be studied, we can speculate that there may be a deficit in the transmission and coordination of the 'upward' (cortical) and 'downward' (brainstem) sensorial information, resulting in an increased activity of the amygdale with consequent behavioral and autonomic neuroendocrine activation.

Nevertheless, we should take into account the frequency in which PD patients actually demonstrate neuroendocrine and autonomic activation during PA. The studies performed in this area are incomplete and sometimes contradictory. For example, some ambulatorial monitoring studies show that there is an increase in heart[19] and respiratory[20] frequencies during spontaneous PA. PD patients respond to the inhalation of CO_2 with more anxiety, PA and increase in the respiratory frequency than normal volunteers or patients with other psychiatric disorders.[5,21-22] Nevertheless, studies performed to measure the ratio of change in the ventilation rate according to the alteration in the final concentration of CO_2 – which is the most sensitive physiological response to CO_2 – have found conflicting results.[23] Some researchers have found evidence of hypersensitivity to CO_2, whereas others have found results in which PD patients showed normal variations in this measure. The eleva-

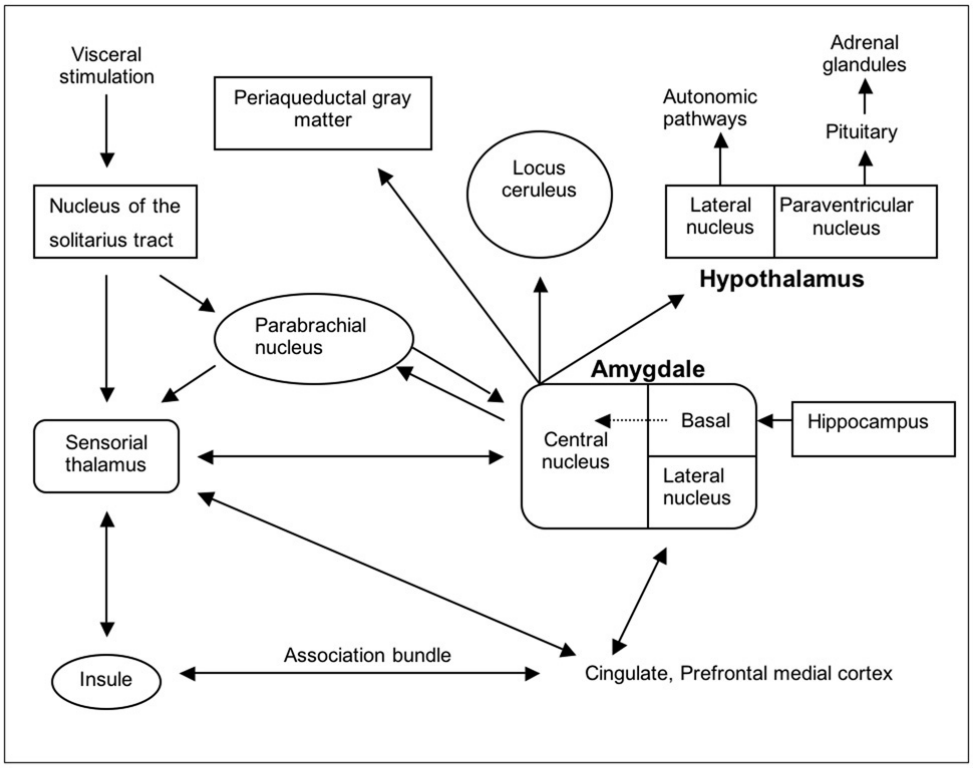

Figure 1 - Brain neuroanatomic pathways of viscerosensorial information

Viscerosensorial information is conducted towards the amygdale by two pathways: one 'downwards', from the solitarius tract through the parabrachial nucleus or the sensorial thalamus; other 'upwards', from the primary viscerosensorial cortex through cortico-thalamic transmission, allowing cognitive processing and modulation of viscerosensorial information. Contextual information stored in the memory of the hippocampus is directly transmitted towards the amygdale. The main afferent projections of the amygdale related with anxiety are towards: *locus ceruleus* (increases the release of noradrenaline, contributing for the physiological and behavioral activation), periacheductal gray matter (promotes defensive mechanisms and postural paralysis), paraventricular nucleus of the hypothalamus (activates the hypothalamic-hypophyseal-adrenal axis leading to the release of adrenocorticoids), lateral hypothalamic nucleus (activates the sympathetic nervous system), and the parabrachial nucleus (it influences respiratory and frequency and amplitude).

tion of cortisol in PD patients is reliably observed during the anticipation of PA,[24] but not during PA proper.[25] Analyzing all these pieces of evidence we may conclude that not all PA show neuroendocrine and autonomic activation.

Therefore, this conclusion suggests that if PA were the direct result of an alteration in the brainstem autonomic control, we would have observed a neuroendocrine autonomic alteration in all of them. Thus, brainstem activation would probably be a manifestation of the activity of other brain area. The findings of pre-clinical research that the activity of the central amygdaloid nucleus starts the stimulation of all relevant brainstem centers and that the manipulation of specific projections of the central amygdaloid nucleus into brainstem neurons interferes selectively with the autonomic responses reinforces this concept.

Other finding that contradicts again the idea that there is a specific abnormality in the brainstem autonomic control in PD is the diversity of agents with distinct biological properties which produce PA in PD patients, but not in normal subjects or patients with other psychiatric disorders. The list of these agents is large and seems to grow with time, including: sodium lactate,[26] CO_2,[22,27-28] iohimbine,[29] noradrenaline,[30] adrenaline[31] among others. Based on the diversity of these substances, it is difficult to conclude which brainstem anomalous nucleus could be specifically activated.

We should take into account the studies with animal models of Gray,[32] McNaughton,[33] Ledoux,[34-35] Deakin,[37] Graeff[38-40] and Blanchard and Blanchard[40-41] on the neural organization of defensive mechanisms which are organized according to concepts such as distance and defensive direction. Synthetically, we may say that the lowest neural levels of the system (especially the periaqueductal gray) control easily and immediately the responses when the

defensive distance is very small (proximal threat). As this distance grows, more complex defensive strategies arise and are controlled by progressively higher levels of the system, with the cingulate representing the highest levels (distal threat). Avoidance or defensive avoidance ('fear') is controlled by the amygdale and by the anterior cingulate. The defensive approximation ('anxiety') occurs when a strong trend to gratification conflicts with avoidance, being characterized by high levels of risk assessment behaviors, being controlled by the septo-hipoccampal system and by the posterior cingulate. The model developed by Gray[32] suggests that the cholinergic transmission occurs from the sept towards the hippocampus, whereas data from Degroot & Treit[42] suggest that it proceeds from the hippocampus towards the sept. This and other findings do not invalidate Gray's model, but reinforce the role of the medial sept in the control of anxiety.

Pre-clinical and clinical findings are compatible with the hypothesis of Deakin & Graeff[36] that different neurotransmitters and modulators have distinct and opposed effects in the modulation of varied types of anxiety in different brain regions. The opposed response patterns observed using agonists and antagonists of serotoninergic receptors in different models are not mutually exclusive, but, on the contrary, suggest that the subtypes of serotoninergic receptors have an elaborated form of controlling the different types of anxiety. Based on this complex neural mechanism of anxiety, serotonin could facilitate or inhibit different types of fear in different brain regions.

Conclusion

PA originate in a fear network which has its sensitivity altered, including in this network the pre-frontal cortex and the cingulate, the insule, the thalamus, the amygdale and the projections of the amygdale into the brainstem, the hypothalamus and the septo-hippocampal system. When administering a panicogenic agent, we would not be acting on a specific brainstem autonomic area, but we would be activating all the fear network; in this way, we would explain the inconsistence of autonomic responses and the heterogeneity of panicogenic agents. PD patients frequently complain about uncomfortable somatic sensations. The administration of a panicogenic agent would correspond to a non-specific activation; as all those agents acutely produce unpleasant physical sensations, the hypothesis is that they act stimulating a sensitive brain network which was conditioned to respond to harmful stimuli. Along time, the projections of the central amygdaloid nucleus towards brainstem centers such as the locus ceruleus, the periaqueductal gray and the hypothalamus can become more or less sensitive. There may also be an inter-individual difference in the strength of these afferent projections. Therefore, the pattern of neuroendocrine and autonomic responses presented during panic attacks may vary from one patient to the other, and in the same patient along time.

This model suggests many possibilities for experimental tests. Neuroimaging studies may show in greater detail the neuroanatomic substrates of panic attacks, of phobic avoidance and also the site of specific activity of efficient forms of treatment. The study of animal models may allow a deeper elucidation of the neural mechanisms which transform stress factors in the development of permanent behavioral and neurobiological disorders.

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Correspondence
Marco A Mezzasalma
Laboratório de Pânico e Respiração
Universidade Federal do Rio de Janeiro
R. Visconde de Pirajá, 407 / 702
22410-003 Rio de Janeiro, RJ, Brazil
Phone: (21) 5521- 2521-6147
Fax: (21) 5521-2523-6839
E-mail: aenardi@novanet.com.br