PSYCHOBIOLOGY OF FEAR AND ANXIETY

Marcus Lira BRANDÃO

Faculty of Philosophy, Sciences and Languages of Ribeirão Preto / University of São Paulo (USP)

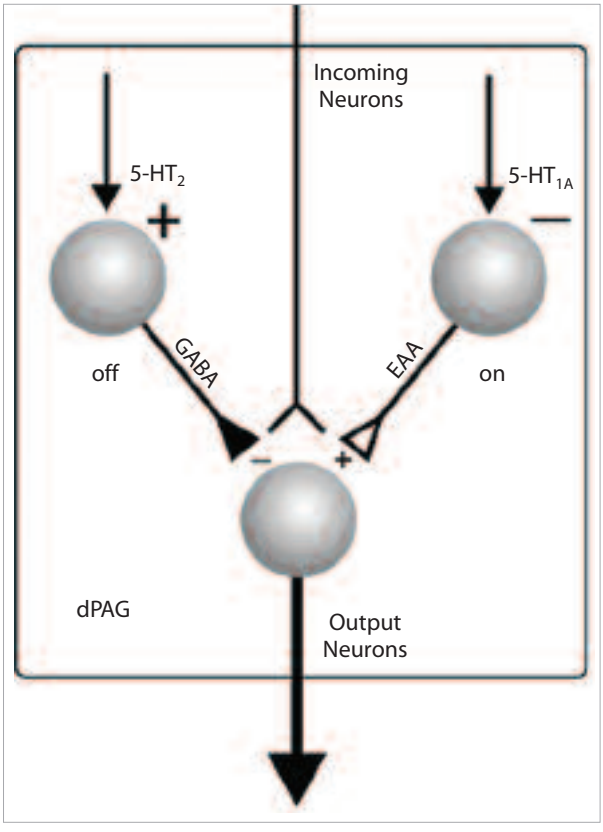

Figure depicting the defense modulating neurons in the dorsal periaqueductal gray (dPAG)). Both off- and on-cells are intrinsic neurons of the dPAG, where they exert a dual control over output neurons; on-cells excite and off-cells inhibit these neurons. Excitatory amino acids and GABA could be the neurotransmitter of on- and off-cells, respectively. While on-cells are excited by 5-HT2A agonists, off-cells are inhibited by 5-HT1A agonists. As a result both 5-HT1A and 5-HT2A mechanisms cooperate in the regulation of the neural substrates of fear in the dPAG. EAA= excitatory amino acids. 5-HT= serotonin.

The medial hypothalamus, amygdala and dorsal periaqueductal gray (dPAG) have been traditionally grouped together as a "brain aversion system". More recently, a continuos strip of midbrain structures composed of superior and inferior colliculi have also been proposed as parts of this "system". In this project we will focus on the neural substrates of defensive behavior in the midbrain tectum (dPAG, superior and inferior colliculi), and their relevance for understanding fear and anxiety. The proposed link between the defense behavior, fear and anxiety is consistent with many behavioral, electrophysiological and immunohistochemical studies showing expressive activation of these regions by threatening stimuli or conditions. The present project further investigates general principles that regulate the sensory information input and the behavioral output that animals present in fearful situations as well as the neurochemical mechanisms underlying the aversive responses associated with fear and anxiety. The presentation of these studies is organized in nine groups representing the behavioral (I, II and III), immunohistochemical (IV), sensorimotor (V and VI), electrophysiological (VII) and neurochemical (VIII) approaches to the defense reaction. The last subproject (IX) is an atempt to make a multifaceted approach to the neurobiology of fear so as to produce scientific material with enough impact to contribute to this field of enquiry.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Freezing defined as the complete absence of body movements is a normal response of animals to unavoidable fear stimuli. In the present project we have obtained a series of evidence relating different defensive patterns with specific anxiety disorders. There are at least four different kinds of freezing with specific neural substrates. The immobility induced by stimulation of the ventral column of the periaqueductal gray (vPAG) has been considered a quiescence characteristic of the recovery component of defense–recuperative processes. There is an isomorphism between freezing response to contextual stimuli paired with electrical shocks and generalized anxiety disorder. Besides, two types of freezing emerge with the electrical stimulation of the dorsal aspects of the periaqueductal gray (dPAG): the dPAG-evoked freezing and the dPAG post-stimulation freezing. Evidence is presented in support of the hypothesis that whereas dPAG-evoked freezing would serve as a model of panic attacks, the dPAG post-stimulation freezing appears to be a model of panic disorder. It is also proposed that conditioned freezing plus dPAG electrical stimulation might also mimic panic disorder with agoraphobia. It has also been possible to present a model of serotoninergic modulation through on- and off-cells of the defense reaction generated in the dPAG. The understanding of how the periaqueductal gray generates and elaborates different types of freezing is of relevance for our better knowledge of distinct types of anxiety such as panic disorder or generalized anxiety disorder.

MAIN PUBLICATIONS

Martinez RC, Oliveira AR, Brandão ML. 2007. Serotonergic mechanisms in the basolateral amygdala differentially regulate the conditioned and unconditioned fear organized in the periaqueductal gray. *European Neuropsychopharmacology*. **17**:717-724.

Zanoveli JM, Ferreira-Netto C, Brandão ML. 2007. Conditioned place aversion organized in the dorsal periaqueductal gray recruits the laterodorsal nucleus of the thalamus and the basolateral amygdala. *Experimental Neurology*. **208**:127-136.

Oliveira LC, Broiz AC, De Macedo CE, Landeira-Fernandez J, Brandão ML. 2007. 5-HT2 receptor mechanisms of the dorsal periaqueductal gray in the conditioned and unconditioned fear in rats. *Psychopharmacology (Berl)*. **191**:253-262.

Bassi GS, Nobre MJ, De Araújo JE, Brandão ML. 2007. Anxiogenic effects of activation of NK-1 receptors of the dorsal periaqueductal gray as assessed by the elevated plus-maze, ultrasound vocalizations and tail-flick tests. *Neuropeptides*. **41(6)**:365-74.

Broiz AC, Oliveira LC, Brandão ML. 2008. Regulation of conditioned and unconditioned fear in rats by 5-HT1A receptors in the dorsal periaqueductal gray. *Pharmacology Biochemistry & Behavior*. **89**:76-84.

Brandão ML, Zanoveli JM, Ruiz-Martinez RC, Oliveira LC, Landeira-Fernandez J. 2008. Different patterns of freezing behavior organized in the periaqueductal gray of rats: association with different types of anxiety. *Behavioural Brain Research*. **188**:1-13.

Borelli KG, Brandão ML. 2008. Effects of ovine CRF injections into the dorsomedial, dorsolateral and lateral columns of the periaqueductal gray: a functional role for the dorsomedial column. *Hormones & Behavior*. **53**:40-50.

Marcus Lira BRANDÃO

Faculdade de Filosofia, Ciências e Letras
de Ribeirão Preto / Universidade de São Paulo (USP)
Avenida Bandeirantes, 3900 – Monte Alegre
CEP 14049-901 – Ribeirão Preto, SP – Brasil

+55-16-3602-3638
mbrandao@usp.br