

Role of Autacoids in the Development of Vulnerability and Resilience in Patients with Posttraumatic Stress Disorder (PTSD)

Shankar GS

Department of Pharmacy Practice and Administration, College of Pharmacy, Western University of Health Sciences, Pomona, CA, USA

*Corresponding author: Shankar GS, Department of Pharmacy Practice and Administration, College of Pharmacy, Western University of Health Sciences, Pomona, CA, 91766-1854, Tel: 909- 469-5459; Fax: 909- 469 -5539; E-mail: Gshankar@westernu.edu

Rec Date: Dec 15, 2014; Acc Date: Dec 18, 2014; Pub Date: Dec 22, 2014

Copyright: © 2015 Shankar GS. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Editorial

Trauma related studies indicate abnormal regulation of core neurochemicals (autacoids) through various psychobiological mechanisms that affect the vulnerability and resilience of individuals towards PTSD. These autacoids include monoamines, amino acids, peptides, opioid neurotransmitters and gonadal steroids. Same autacoids are found in various brain circuits that regulate as well as integrate stress and fear complexes. In this paper we will examine the role of monoamines, amino acids and peptides and their role in PTSD.

Monoamines

There are three monoamines in the family, including dopamine (DA), norepinephrine (NE) and serotonin (5HT). First two monoamines are catecholamines and serotonin is an indolamine. Role of DA in PTSD is not very clear even though there is evidence that exposure to stress induces mesolimbic dopamine release that may play a major role in the modulation of HPA axis and often may result some of the psychosis and paranoid behavior associated with some PTSD patients. NE is one of the principal mediators. Catecholamine neurons centrally seem to play a very important role in enhancing the levels of vigilance, alertness, selective attention, fear conditioning and cardiovascular stimuli as described elsewhere. This evidence of catecholamine dysregulation increases the vulnerability to PTSD through the mechanisms of increased heart rate and blood pressure when an individual is exposed to visual or auditory trauma. Preventing pre-synaptic NE release with alpha 2 adrenergic agonists (clonidine) or opioids, or blocking post-synaptic norepinephrine with beta adrenergic blockers (propranolol) may diminish the fear conditioning [1].

Serotonin (5HT)

Stored in the raphe nuclei in the brain stem and projects to several areas of the brain including amygdala, hippocampus, PFC, bed nucleus of stria terminalis and hypothalamus. Serotonin has around 16 receptors and 5HT_{1A} plays an important role in anxiety disorders. There is evidence of serotonergic dysregulation in PTSD and may include symptoms of aggression, depression, impulsivity and suicidality and serotonin reuptake inhibitors seem to be efficacious to control these symptoms. Studies on brain serotonin 5HT_{1A} and 5HT_{1B} suggest they potentially and specifically reduce aggressive behavior without motor slowing and sedative effects [2]. Recently research scientists have discovered the effect of low serotonin 1B levels in patients diagnosed with posttraumatic stress disorder [3]. Serotonin, along with associating brain chemicals has been the concentration of research for most of psychological anguish.

Amino acids

Gamma amino benzoic acid (GABA) is an inhibitory neurotransmitter in the brain. GABA has anxiolytic effects and diminishes the physiological effects to stress with its inhibitory response. GABA effects are mediated by GABA_A receptors that are associated with benzodiazepine receptors. Benzodiazepine receptors potentiate the effects of GABA_A. Pet studies have shown decreased receptor affinity of benzodiazepine receptors may play a role in PTSD and thus increase in vulnerability of the individual [4]. Glutamate on the contrary is the excitatory neurotransmitter in the brain. Stress releases glucocorticoids through negative feedback of cortisol production and glucocorticoids activate glutamate release in the brain. Glutamate binds to NMDA receptors in the brain and this NMDA receptor system plays an important central role in the disassociation and derealization and glutamate is excitotoxic and may contribute to the cell loss in hippocampus and PFC in patients with PTSD.

Peptides

Corticotropin-releasing hormone (CRH)

CRH neurons by assimilating the information about stress, function as the major constituent of HPA axis. CRH neurons are found throughout the brain but also in PFC, amygdala including bed nucleus of stria terminalis, raphe nucleus, LC and hippocampus. When amygdalar CRH containing neurons project to LC, that projection may create anxiety like states and increased fear response and startle response. It is known that earlier life stress associated with trauma may maintain higher levels of brain CRH activity and an organism's response to this increased allostatic load depends upon social situations, length of the stress and behavioral dominance [5]. Persistent high levels of CRH increases allostatic load and this may be implicated in PTSD [6]. Resilience in this situation is related to the ability of the organism to restrict the CRH response to stress. CRH-1 and CRH-2 receptors are found in the PFC, amygdala and hippocampus along with other areas. CRH-1 receptors may be involved in the anxiety like response and CRH-2 may be involved in anxiolytic response. However, these two receptor systems have not been evaluated in living human systems.

Galanin

It is a peptide and comprises 30 amino acids. Galanin performs a vital role in many physiological and psychological tasks. Galanin participates a part in learning, pain control, memory, and neuroendocrinology and according to recent studies it also plays a role in anxiety response [7]. Majority of the norepinephrine cells in LC co-direct Galanin and this system innervates PFC, hippocampus, amygdala and hypothalamus. In response to stress, norepinephrine

can recruit the release of galanin in the central nucleus of amygdala and PFC. From there galanin buffers the anxiogenic effects of norepinephrine. The behavior response of stress induced norepinephrine hyperactivity depends upon the balance between galanin, norepinephrine and neuropeptide y neurotransmission and this balance decides the resilience of the individual. This is a novel concept for the development of medications for PTSD or major depression.

Neuropeptide Y (NPY)

It is a 36 amino acid peptide and this is very abundant peptide in mammalian brain. Moderate levels of this peptide are available in PFC, amygdala, and hippocampus. Receptors for NPY are associated with locations in brain that are implicated in stress: amygdala, hippocampus and LC. In amygdala increased levels of NPY are associated with decreased levels and intensity of anxiety [8]. Studies have shown that NPY levels also decrease the rate of LC firing which usually results in the lower level of NE in the brain. This decrease of NE has positive effect in decreasing the damage in the brain to the prolonged stress [9]. NPY besides its effects on NE at LC also has very important interaction with CRH with positive benefits. In some of the most important parts of the brain associated with arousal, CRH and NPY counter-balance each other. NPY in amygdala decreases arousal and decreases anxiety, whereas CRH can promote activation in amygdala and increased feelings of anxiety. In LC, CRH increases the neuronal firing and increases NE levels, whereas, NPY has a balanced effect, resulting decrease in NE levels and firing [8]. In other words, it is important to have balance between CRH and NPY to maintain some sort of homeostasis of the system. CRH maintains system's response to stress, preparing the individual for the survival and NPY is in need to counterbalance the damages caused by the prolonged stress and deleterious effects of CRH. In other words, deducing from the effects of NPY, we can deduct NPY has counter regulatory effects on both CRH and LC-norepinephrine system at those areas in the brain that are cardinal in the expression of anxiety, worry, fear and also depression. This information suggests NPY system plays an important role in the psychobiology of vulnerability and resilience. In fact some studies have pointed out the higher level of performance with extreme training stress among soldiers are associated with high NPY levels. People with PTSD have shown low NPY levels in several studies and antidepressant drugs have shown to increase NPY [10].

Resilience and Vulnerability to Stress

We have examined several autacoids belonging to 3 groups and their psychobiological response to extreme stress and their contribution alone or working with other functional systems to

resilience and vulnerability in the expression of PTSD. The concept of allostatic load is very useful as an indicator to observe the changes in individual and decline in functionality caused by allostatic load. It seems like resilience to PTSD is characterized in people with high measures of DHEA, NPY, galanin, 5HT_{1b}, benzodiazepine receptor function and vulnerability increase can be observed for CRH, LC-norepinephrine activity, HPA axis. It should be noted there are only mediators discussed in the paper and the list is not exhausted. However we have an understanding about the mediators in the psychobiological system that can increase vulnerability to PTSD and about the mediators that can improve resilience for PTSD. In future the drug therapy will focus on these factors either to decrease the vulnerability or increase resilience to improve the treatment for PTSD.

References

1. Southwick SM, Bremner JD, Rasmusson A, Morgan CA, Arnsten A, et al. (1999) Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. *Biol Psychiatry* 46: 1192-1204.
2. Southwick S, Paige S, Morgan C, Bremner J, Krystal J, et al. (2005). Neurotransmitter alternations in PTSD: catecholamine's and serotonin. *CNC Spectr* 10: 99-106.
3. Murrough JW, Czermak C, Henry S, Nabulsi N, Gallezot JD, et al. (2011) The effect of early trauma exposure on serotonin type 1B receptor expression revealed by reduced selective radioligand binding. *Arch Gen Psychiatry* 68: 892-900.
4. Mellman TA, Bustamante V, David D, Fins AI (2002) Hypnotic medication in the aftermath of trauma. *J Clin Psychiatry* 63: 1183-1184.
5. Strome E, Traver G, Higley J, Liriaux D, Suomi S, et al. (2002). Intracerebroventricular corticotrophin releasing factor increased limbic glucose metabolism and has social context dependent behavioral effects in nonhuman primates. *Proc Natl Acad Sci USA*, 99, 15749-15754.
6. Nemeroff C (2002) Recent advances in the neurobiology of depression. *Psychopharmacol Bull* 36: 6-32.
7. Holmes A, Yang RJ, Crawley JN (2002) Evaluation of an anxiety-related phenotype in galanin overexpressing transgenic mice. *J Mol Neurosci* 18: 151-165.
8. Gutman AR, Yang Y, Ressler KJ, Davis M (2008) The role of neuropeptide Y in the expression and extinction of fear-potentiated startle. *J Neurosci* 28: 12682-12690.
9. Morgan CA, Rasmusson AM, Wang S, Hoyt G, Hauger RL, et al. (2002) Neuropeptide-Y, cortisol, and subjective distress in humans exposed to acute stress: replication and extension of previous report. *Biol Psychiatry* 52: 136-142.
10. Husum H, Mathé AA (2002) Early life stress changes concentrations of neuropeptide Y and corticotropin-releasing hormone in adult rat brain. Lithium treatment modifies these changes. *Neuropsychopharmacology* 27: 756-764.