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Editorial

Anxiety and Amygdalar Hyperexcitability: The Chicken or the Egg?

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Editorial

In the health sciences, we often speak of associations between physiological or pathophysiological parameters and/or symptoms. In many cases, the direction of causality in a given association is clear. For example, a headache that is associated with hypoglycemia is the result (the effect), while the hypoglycemia is the cause. In research related to the neurobiological mechanisms that underlie anxiety disorders, it is often stated that anxiety is associated with increased neuronal excitability in the amygdala. How clear is it in this case what comes first? Do intense and/or repeated anxiety states under stressful situations alter the physiology of the amygdala making it hyper excitable, or is it possible that if neuronal excitability in the amygdala is persistently increased–due to purely biological/organic causes that are independent of stress and anxiety–then anxiety will ensue?

The hyperexcitability of the amygdala in Post-Traumatic Stress Disorder (PTSD) [1-5] is probably one of the effects of the traumatic experience, and, therefore, it is a good example of stress and anxiety producing derangements in the physiology of the amygdala. Thus, exposure to intense stress induces alterations in the amygdala that make it persistently prone to high levels of activity (hyperexcitable) and exaggerated responses to fearful stimuli [1-3]. Studies in PTSD animal models have revealed possible cellular/synaptic mechanisms by which stress and anxiety can alter the excitability of neuronal networks in the amygdala; such mechanisms include impairment in the α1A adrenoceptor-mediated facilitation of GABAergic inhibition in the Basolateral Amygdala (BLA) [6,7], downregulation of the 5-HT2A serotonin receptors which also facilitate inhibitory activity in the BLA [8], and dysfunction of calcium-activated potassium channels [9]. After PTSD has developed, the hyperexcitability of the amygdala plays a central role in the expression of anxiety, but it is the initial traumatic experience and the stress and anxiety it produced that made the amygdala hyperexcitable.

Experimental evidence for the reverse directionality in the anxiety-amygdalar hyperexcitability association is also available. Thus, anxiety can be induced without previous stressful experiences, merely by increasing, through pharmacological means, excitatory activity in the BLA. For example, when kainate receptors containing the GluK1 subunit are activated by microinjection of an agonist into the rat BLA, anxiety-like behavior increases [10,11], while when these receptors are blocked by microinjection of an antagonist, anxiety-like behavior is decreased [11]. Similarly, when the activity of the acid-sensing ion channels 1a–which preferentially facilitate GABAergic inhibition in the rat BLA [12]–is increased by microinjection of an activator into the rat BLA, anxiety-like behavior decreases, and when the activity of these channels is suppressed by microinjection of an antagonist in the rat BLA, anxiety-like behavior increases [12].

Are there real-life situations where excitability of the amygdala can be increased, in long-term, by way other than stressful experiences, leading to the development of anxiety? Traumatic Brain Injury (TBI), including mild TBI, is often followed by long-term behavioral deficits, anxiety being most prevalent among them [13]. Excitability of the amygdala is altered after mild TBI [14,15]. It is difficult, however, in TBI patients to distinguish between psychogenic causes that may have increased amygdalar excitability, or organic causes resulting from the injury [13]. The experience of a life-threatening event that caused TBI, the hospitalization, the fear of possible permanent impairment, financial difficulties etc. are stressors that could alter the function of the amygdala leading to hyperexcitability and, thereby, development of anxiety. However, most of these stressors are not present in experimental animals, where mild TBI is induced under anesthesia; yet, anxiety-like behavior increases, and it is associated with loss of interneurons and reduced GABAergic activity in the BLA [15]. These findings suggest that the etiology of anxiety after TBI may also be traced to biological/organic causes that alter the physiology of the amygdala, in addition to or instead of psychogenic causes.

Anxiety is also often present in epilepsy patients and, particularly, in temporal lobe epilepsy [16-18], which involves hyperexcitability of the hippocampus and the amygdala [19]. In experimental animals, increased anxiety-like behavior is one of the behavioral consequences of prolonged status epilepticus induced by nerve agents [20,21]. These are additional examples of non-psychogenic origins of anxiety (or non-stress-induced "anxiety-like behavior" in animals), although some contribution of stress-related factors cannot be excluded. In the second example, it is conceivable that the stress component of experiencing prolonged convulsive seizures and the associated life-threat might be responsible for altering amygdalar excitability and inducing anxiety. However, the presence of anxiety is accompanied by loss of both GABAergic interneurons and principal neurons in the BLA [21,22], resulting in a significant reduction in the ratio of the number of GABAergic interneurons over the number of principal neurons [21] and a decrease in spontaneous GABAergic activity, concomitant with an increase in glutamatergic activity [23]. It is far more likely that the neuronal death was caused by the intense seizures than by the stress associated with the experience of seizures. If the seizures are controlled, even after 1 hour of ongoing status epilepticus, interneuronal death is prevented and anxiety-like behavior does not develop [20,22].

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It is noteworthy in this regard that a substantial number of the victims of the sarin attack in Tokyo, in 1995, exhibit PTSD symptoms, years later [24-27]. The development of PTSD in this case could be attributed to the one-time stressful experience of the terrorist attack and/or the stress associated with the health consequences. However, given the findings from the animal experiments, showing seizure-induced disproportional loss of GABAergic interneurons over loss of principal neurons in the BLA [21], along with the findings of amygdalar atrophy in the sarin victims who developed PTSD [27], it is necessary to consider the possibility that amygdala damage induced by seizures rather than by stress could be the primary precipitant of PTSD.

In conclusion, the association between anxiety and amygdalar hyperexcitability appears to be bidirectional. Stress and anxiety can be the cause of increased neuronal excitability in the amygdala, as in PTSD (once the disorder is established, the causality reverses direction, as the hyperexcitable amygdala sustains the anxiety disorder). However, the amygdala may also become hyperexcitable due to biological/organic causes that are independent of stress and anxiety. In those cases, anxiety is the result of the derangement in amygdala function. Recognizing the bidirectionality of the association between anxiety and amygdalar hyperexitability, and shedding light into the operating mechanisms, will reinforce the view that the underlying causes of affective disorders can sometimes be primarily or purely organic, which can help determine the correct approach to therapy.

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