Oxidative Stress in Panic Disorder

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Abstract
The anxiety disorder, Panic Disorder (PD) is widely distributed among the world’s population. The actual causes are poorly understood. Recent evidence suggesting that oxidative stress may develop PD in human and other animals. This paper offers shortly the findings of oxidative stress and PD association. The findings suggest that oxidative stress may have a potential connection with a number of neurological disorders, including PD.

Keywords
Nervous system, Panic disorder, Oxidative stress

Introduction
Panic Disorder (PD) is an anxiety disorder characterized by recurrent unexpected panic attacks may cause palpitations, sweating, shaking, shortness of breath, numbness, or a feeling that something really bad is going to happen [1]. PD affects about 2.5% of world populations [2] and generally it begins during adolescence or early adulthood, but less common in children, older people and male [1].

Evidence suggests that patients with PD may have a brain circuit (consists of the amygdala, central gray matter, ventromedial nucleus of the hypothalamus, and locus ceruleus) that performs improperly [3]. The misconception of bodily sensations [4], genetic inheritance [5], psychological factors, stressful life style, life transitions, environment, physical illnesses, major stress, excessive responsibilities, Post-Traumatic Stress Disorder (PTSD), certain medications, abusing illicit drugs [6], tobacco smoking (especially nicotine withdrawal) [7], caffeine ingestion [8], alcohol or sedative abuse (withdrawal), and other psychoactive drugs [9], benzodiazepine withdrawal [10], and so on the detected factors in the development of PD. The chemical imbalance within the limbic system may reduce the production of GABA-A and sends false information to the amygdala, which regulates the body’s “fight or flight” response mechanism and, in return, produces the physiological symptoms that lead to the PD [11].

Oxidative stress caused by reactive species, including Reactive Oxygen and Nitrogen Species (ROS/RNS), and unbound, adventitious metal ions (e.g. - iron [Fe] and copper [Cu]), is an underlying cause of various Neurological Disorders (NDs) [12,13]. Generally, the reactive species are an inevitable by-product of cellular respiration or other metabolic processes that may cause the oxidation of carbohydrates, proteins, lipids, and nucleic acids. Oxidative stress has recently been implicated in depression and anxiety-related disorders, including PD. This paper will discuss shortly the role of oxidative stress in the development of PD.

Oxidative Stress and PD
The human brain consumes approximately 20% of basal oxygen during metabolic processes, which makes the Central Nervous System (CNS) very sensitive to the oxidative stress [14]. Oxygen metabolism results in the production of oxygen ions and various free radicals (molecules that contain one or more unpaired electrons and are extremely reactive, with life spans of less than 10−11 s). Among the other types of radicals, oxygen-derivatives represent the most important class having an impact on
ROS are produced from both endogenous and exogenous sources [13]. On the other hand, the nervous system has tremendous reservoirs of polyunsaturated and saturated fatty acids that are extremely susceptible to the escalating effects of oxidative stress. To date, the depletion of antioxidant enzymes, such as Glutathione Peroxidase (GPx), Superoxide Dismutase (SOD), Catalase (CAT), Glutathione Reductase (GSR1), non-enzymatic components (e.g. free glutathione), various vitamins (e.g. vitamins A, C, and E) lipid and protein oxidation, DNA damage, and other redox alterations (e.g. selenium depletion and ceruloplasmin alterations) have been reported in various psychological disorders, including PD [15-17]. Decreased antioxidant enzyme (i.e. SOD, GPx) levels and consequently higher lipid peroxidation were observed in subjects with obsessive-compulsive disorder and PD. An involvement of hippocampal oxidative stress may also relate to the PD. Genetic studies established the possible role of Glyoxalase 1 (GLO1) in various neuropsychological disorders, including PD [18]. The expression of the Glutathione Reductase 1 (GSR1) gene, which encodes GSR1, and GLO1 is involved in antioxidative metabolism may relate PD. Humans with PD are evident to have altered levels of GPx, SOD and CAT antioxidant enzymes along with the Malondialdehyde (MDA) levels [19]. Politi, et al. [18] found Ala111Glu polymorphism of GLO1 gene in PD patients. However, Eser, et al. [20] did not find a correlation between GLO1 mRNA expression levels and the severity of cholecystokinin-4 (CCK-4)-induced PD. It may be a limitation of this work, however, the behavioral and cardiovascular panic symptoms elicited by CCK-4 may be different from other anxiety-related disorders, including PD. Dysregulation of the GABA system has been suggested to play an important role in the pathophysiology of PD [21], however, the casual role of methylglyoxal that acts through GABA ergic or serotonergic systems in anxious strains or lines has not been demonstrated in the literature, further complicating the relevance and understanding of the association between GLO1 and GSR1 and anxiety.

In a study, local overexpression of GLO1 and GSR1 (involve in oxidative stress metabolism) genes were seen in the mouse brain [22]. In another study, both Total Antioxidant Capacity (TAC) and oxidative stress index, and ceruloplasmin levels were found higher in PD patients (n = 19). TAC and oxidative stress index decreased after the treatment with an antioxidant, suggesting an oxidative imbalance in PD [23]. A high anxiety level is evident with an increased in the generation of ROS in the peripheral blood lymphocytes, granulocytes and monocytes of mice [24]. Agoraphobia in PD patients (n = 31) was found to alter the TAC, Paraoxonase (PON), Arylesterase (ARE) antioxidant and MDA oxidant levels in blood, suggesting oxidative/antioxidative mechanisms playing an important role in the pathogenesis of PD [25]. Paraoxonase 1 (PON1) activity may be adversely related to the oxidative stress in plasma. In a study, the PON1 192 AA genotype was found to increase the risk of PD depending on lipid peroxidation in humans (n = 42) [26]. According to Cengiz, et al. [27] a gender-specific effect of Glutathione Peroxidase-1 (GPX1) Pro198Leu C allele may be associated with PD development.

_Mimusops elengi_ Linn. traditionally is used in neurological disorders, including PD. The hydroalcoholic extract of _M. elengi_ flowers (100 and 200 mg/kg, i.p.) in rats was found to improve the ambulatory behavior, reduced lipid peroxidation and nitrite levels, and restored the enzymatic and non-enzymatic antioxidant (glutathione, total thiols, glutathione-S-transferase and CAT) status to near-normal levels, demonstrating the neuroprotective effect of the extract against excitotoxicity and oxidative stress in animals [28,29]. Generally, the antioxidants are cytoprotective at low concentration/dose, but pro-oxidative in high. Thus, this effect may be linked to the extract’s dose in the test system. For an example, fluvoxamine, a first-line treatment of PD and some other disorders. In a study, fluvoxamine (9 and 27 mg/kg, b.w., 8 weeks) was found to induce oxidative stress in a dose-dependent manner in male mice (n = 12) [30]. Some psychoactive drugs, used for recreational purposes, chron-
ic usages may also develop PD. In a recent study, patients (n = 34) using cannabis have been identified with higher levels of Interleukin (IL)-1β, -6, -8, and tumor necrosis factor-alpha (TNF-α), indicating an increased in inflammation compared to the healthy persons, suggesting cannabis may increase inflammation and impaired the oxidative balance [31]. Abadie, et al. [32] suggest that antidepressants (mainly serotonin reuptake inhibitors), mefloquine, isotretinoin, rimonabant and corticosteroids are the drugs leading to PD worldwide. Benzodiazepines or opioids are also evident to cause PD [33]. An overall sources of free radicals and their toxic effects has been shown in Figure 1.

In summary, PD has a good correlation with the oxidative stress and oxidative stress-induced events, such as inflammation, alteration of biochemical parameters, functional alteration and damage in the nervous tissue and cells.

Conflicts of Interest

The author has no interest in confliction.

References


