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Oxidative Stress and the Central Nervous System

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Running Title Page

Running title: Oxidative stress regulates neuro-behavioral function

Abbreviations: LMWA: low-molecular-weight antioxidants, SOD: superoxide dismutase, GLO: glyoxalase, GSR: glutathione reductase, GPx: glutathione peroxidase, CAT: catalase, ROS: reactive oxygen species, RNS: reactive nitrogen species, BDNF: brain derived neurotrophic factor.

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Abstract

Biochemical integrity of the brain is vital for normal functioning of the central nervous system (CNS). One of the contributing factors of cerebral biochemical impairment is a chemical process called oxidative stress. Oxidative stress occurs upon excessive free radical production due to insufficiency of counteracting antioxidant response system. The brain with its high oxygen consumption and lipid-rich content is highly susceptible to oxidative stress. Therefore, oxidative stress-induced damage to the brain has a strong potential to negatively impact normal CNS functions. While oxidative stress is historically considered to be involved mainly in neurodegenerative disorders such as Alzheimer's disease, Huntington's disease and Parkinson's disease, its involvement in neuropsychiatric disorders including anxiety disorders and depression is beginning to be recognized. This review is a discussion of relevance of cerebral oxidative stress to impairment of emotional and mental wellbeing.

Introduction

Oxidative phosphorylation occurring in the mitochondria is a major source of ATP. As a by-product, it produces free radicals or reactive oxygen species (ROS), reactive nitrogen species (RNS), carbon-centered and sulfur-centered radicals (Pero et al., 1990). In moderate or low amounts, ROS are considered essential for neuronal development and function, while excessive levels are hazardous. ROS-generated nitrous oxide (NO), and carbon monoxide (CO) promote important physiological functions such as long-term potentiation (LTP) via glutamate dependent mechanisms (Knapp and Klann, 2002; Verma et al., 1993; O'Dell et al., 1991; Stevens and Wang, 1993; Zhuo et al., 1993). Under normal conditions, deleterious effects of ROS production during aerobic metabolism are neutralized by antioxidant system and in this manner the brain effectively regulates its oxygen consumption and redox generation capacity. When ROS production exceeds scavenging capacity of antioxidant response system, extensive protein oxidation and lipid peroxidation occurs causing oxidative damage, cellular degeneration, and even functional decline. For example, high ROS concentrations reportedly diminish LTP and synaptic signaling and brain plasticity mechanisms (Knapp and Klann, 2002; Verma et al., 1993; O'Dell et al., 1991; Stevens and Wang, 1993; Zhuo et al., 1993). This is regarded as a state of *oxidative stress* and becomes particularly hazardous for normal functioning of the brain.

Oxidative stress is often described as a self-propagating phenomenon. This is based upon the observations that when oxidative stress-induced excessive ROS release triggers cellular damage then damaged macromolecules themselves behave as and/or become ROS. Consequently, the brain, with its rich lipid content, high energy demand and weak antioxidant capacity becomes an easy target of excessive oxidative insult (Hulbert et al., 2007). Phospholipids in the brain are particularly vulnerable entities for ROS-mediated peroxidation,

but proteins and DNA also are targeted by ROS, which becomes particularly problematic during aging as aged brains have been reported to exhibit high levels of oxidative stress-induced DNA mutations in the mitochondrial DNA (Chomyn and Attardi, 2003; Kraysberg et al., 2003; Trifunovic et al., 2004; Gross et al., 1969). Therefore, ROS accumulation is a cellular threat, which if it exceeds or bypasses counteracting mechanisms, can cause significant neuronal damage.

Two kinds of protective mechanisms operate in the brain to tackle the threat posed by ROS, the antioxidant enzyme system and the low-molecular-weight antioxidants (LMWA) (Kohen et al., 1999; 2000). The antioxidant enzyme system includes superoxide dismutase (SOD), glyoxalase (GLO), glutathione reductase (GSR), glutathione peroxidase (GPx) and catalase (CAT) (Griendling et al., 2000). SOD enzymes including Cu-Zn SOD and Mn-SOD facilitate spontaneous dismutation of superoxide radicals to generate H₂O₂, which is further removed by catalase and glutathione peroxidase enzymes (Saso and Firuzi, 2014). The LMWA including glutathione, uric acid, ascorbic acid and melatonin offer neutralizing function by causing chelation of transition metals (Chance et al., 1979). Glutathione, which occurs in reduced (GSH) and also in oxidized form (GSSG) is the most important non-enzymatic endogenous antioxidant and can be regenerated by glutathione reductase (GSR) with the consumption of nicotinamide adenosine dinucleotide phosphate (NADPH) (Gul et al., 2000). In this manner optimum levels of reduced GSH are maintained (Halliwell, 2006; Kohen and Nyska, 2002). The endogenous ratio of GSH:GSSG is considered as an indicator of redox homeostasis within a cell. Higher levels of GSH also serve as a cofactor for other enzymes including glyoxalase and peroxidase (Kohen and Nyska, 2002).

In response to oxidative and nitrosative stress, cells increase their antioxidant defenses through activation of nuclear factor erythroid 2-related factor (Nrf2), an important transcription factor (Maes et al., 2011). Nrf2 is a key component of this control system and recognizes the antioxidant response element (ARE) found in the promoter regions of many genes encoding antioxidants and detoxification enzymes such as Heme oxygenase 1 (HO-1), NAD(P)H dehydrogenase quinone 1 (NQO-1), superoxide dismutase 1 (SOD1), glutathione peroxidase 1 (GPx1) and catalase (Itoh et al., 1997). Thus, Nrf2 pathway activation occurs to combat the accumulation of reactive oxygen (ROS) and nitrogen (RNS) species. Due to its protective properties, Nrf2 has been proposed as a pharmacological target in pathologies with neuroinflammatory and oxidative features, including neurodegenerative and neuropsychiatric diseases. When activated, Nrf2 increases the expression of several endogenous antioxidants. And, upon persistent inflammation and increased ROS levels, as observed during several psychiatric episodes, tissue antioxidant defenses mechanisms are saturated to the point they become ineffective (Anderson and Maes 2014). Cytosolic enzymes such as Glyoxalase I (GLO-1) by detoxifying methylglyoxal (MG) offer protection from oxidative damage (Distler and Palmer, 2010). MG generates highly oxidative advanced glycation end products (AGEs) and can further induce oxidative stress and cause cell death (Uribarri et al., 2010).

It is clear that ROS play a crucial pathophysiological role (Campese et al., 2004) and that ROS accumulation increases the susceptibility of brain tissue to damage. Mechanisms of how ROS cause cerebral tissue damage are not well understood but ROS are reported to trigger a variety of molecular cascades that by increasing blood-brain barrier permeability, alter brain morphology, cause neuroinflammation, and also neuronal death (Gu et al., 2011). Involvement of hypothalamic–pituitary–adrenal (HPA) axis mediated glucocorticoid receptor signaling,

glutamate toxicity and NMDA receptor signaling systems has been suggested (Albrecht et al., 2010; Nguyen et al., 2011; Okamoto et al., 1999; Tanaka et al., 1999; Makino et al., 1996). Thus, evidence of increased brain oxidative damage in the development of CNS pathologies has been reported for neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, cerebrovascular disorders, demyelinating diseases, and psychiatric disorders (Scorce and Krause, 2009).

Oxidative stress and neurodegenerative disorders

Neurodegenerative disorders commonly associated with muscular, dementic and cognitive deficits exhibit brain atrophy, neurofibrillary tangles, plaques and aggregates as pathological hallmarks of the disease (Gandhi and Abramov 2012; Obeso et al., 2008; Kipps et al., 2005). Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) are commonly occurring neurodegenerative disorders, which involve neurotoxic aggregation of specific proteins in the brain. Accumulation of misfolded Tau and amyloid beta occurs in AD, while alpha-synuclein and mutant Huntington protein (mHtt) accumulate in PD and HD respectively. Cause and effect relationship between oxidative stress and these protein aggregates has been theorized. While some studies have reported age-associated increase in oxidative stress-related ROS as a contributor to neuronal plaque, synuclein and mHtt formation (Li et al., 2013), other studies have suggested role of amyloid beta protein formation in ROS production (Shelat et al., 2008; Abramov and Duchon 2005; Behl et al., 1997). Similarly with regards to Parkinson's disease pathology, it is reported that oxidative stress promotes alpha-synuclein aggregation in dopaminergic neurons, and that alpha-synuclein further generates intracellular ROS (Xiang et al., 2013). Furthermore, neuronal cell culture studies have implicated free radicals in misfolding and accumulation of mHtt-induced neurotoxicity in PC12 cells. While accumulation of mHtt led to

decrease in antioxidant protein peroxiredoxin Prx1, the overexpressed wildtype Prx1 significantly reduced mHtt-induced toxicity (Pitts et al., 2012). Amyloid B-mediated ROS production is reported to induce lipid peroxidation causing impaired membrane permeability activating excitotoxicity mechanisms due to increased calcium (Ca^{2+}) influx. This is believed to significantly alter neurotransmission and alter cognitive functions. In fact, several studies have implicated ROS in amyloid β -induced impairment in long-term potentiation (LTP), a cellular correlate of learning and memory (Ma et al., 2011; 2012; Parajuli et al., 2013; Dumont et al., 2009), also a consequence of aberrant neuronal transmission.

Oxidative stress and neuropsychiatric disorders

Neuropsychiatric disorders are complex and heterogeneous disorders that not only negatively impact quality of life but also significantly affect behavior and cognitive functions (Kessler, 1997; Post, 1992). Several pathophysiological mechanisms have been implicated in these orders including genetic predisposition, monoamine deficiency, circadian disruptions, hypercortisolemia, and inflammation (Belmaker and Agam 2008). Oxidative stress mechanisms also have been suggested to be involved in some psychiatric illnesses including depression, anxiety disorders, schizophrenia and autism spectrum disorders (Ng et al. 2008; Bouayed et al., 2009; Valko et al., 2007). Increased levels of ROS and RNS (Maes et al., 2011; Suzuki et al., 2001; Dhir et al., 2011) and altered levels of antioxidant glutathione (GSH) were reported in postmortem brain samples of depressed individuals (Gawryluk et al., 2011). Actually, oxidative stress mechanisms have been suggested as targets for novel antidepressants (Lee et al. 2013). This seems reasonable considering reported occurrence of inflammation, oxidative and nitrosative stress as well as declining levels of plasma concentrations and activity of several key antioxidants in sample from depressed subjects (Meas et al., 2011).

Association between depression and polymorphisms in superoxide dismutase (SOD) and catalase (CAT) genes is also known (Meas et al., 2011). The hypothesis is that the antidepressants exert their therapeutic effect by suppressing pro-inflammatory cytokines and ROS/RNS production or enhancing antioxidant defense (Behr et al., 2012). There seems to be strong data to support that depression is accompanied with oxidative stress and that perhaps augmentation of antioxidant defenses is one of the mechanisms underlying the neuroprotective effects of antidepressants (Wu et al., 2013). Oxidative stress mechanisms also have been tied to schizophrenia and bipolar disorder. Increased levels of plasma SOD activities were reported in chronic schizophrenic patients that were put on antipsychotic medication and SOD activities negatively correlated with positive symptoms of schizophrenics (Ranjekar et al., 2003). Other antioxidants including glutathione peroxidase (GSH-Px) levels also have been implicated (Altuntas et al., 2000; Stoklasova et al., 1986; Abdalla et al., 1986; Buckman et al., 1987). It has been suggested that low GSH-Px is a contributing factor to structural brain abnormalities (Buckman et al., 1990; Yao et al., 2011). Several studies have reported that patients with bipolar disorder have significant alterations in antioxidant enzymes, lipid peroxidation, and nitric oxide levels (Andreazza et al., 2008), suggesting role of free radicals and antioxidants in the pathophysiology of bipolar disorder (Magalhaes et al., 2011; Sarris et al., 2011; Berk et al., 2011). Accumulating evidence implicates free radical-mediated pathology, altered antioxidant capacity, neurotoxicity and inflammation in neuropsychiatric and neurodegenerative disorders.

Oxidative stress and the brain

Precise chain of events occurring within the CNS that potentially cause or lead to oxidative stress-induced behavioral and cognitive decline is an interesting topic and can be examined at multiple levels. Biochemically, it is evident that different neurons have different

levels of vulnerability to oxidative stress. For example, hippocampus, amygdala and cerebellar granule cells have been reported as the most susceptible to oxidative stress in some studies (Wang and Michaelis, 2010), and consequently are purported to be the first to undergo functional decline. Our own preclinical work has suggested that behavioral and cognitive deficits are attributed to three brain regions: the hippocampus, amygdala and the pre-frontal cortex (PFC) (Solanki et al., 2015; Salim et al., 2010a; 2010b; Salim et al., 2011; Patki et al., 2013a; 2013b; Masood et al., 2008). Hippocampus seems to be at the hot seat and it appears that this brain region undergoes major biochemical changes that ultimately determine neuronal connections and function. Within the hippocampus, it is well known that the dentate gyrus-CA3 system exhibits structural plasticity with regenerative/remodeling capacity (Popov and Bocharova, 1992; McEwen, 2008; Sousa et al., 2000). Furthermore, several studies have suggested that pyramidal cells of CA3 and granule cells of DG are oxidative stress prone areas while others have suggested that pyramidal cells of CA1 are more susceptible to oxidative damage (Cruz-Sánchez et al. 2010; Uysal et al. 2011; Chang et al. 2012; Bearden et al. 2009; Huang et al. 2011; Huang et al. 2013). Regardless, region specific elevation of oxidative stress within CA1, CA3 and DG is important and can have significant functional consequences. This is particularly significant as DG has a preferential role in learning and memory function, and ventral hippocampus is implicated in anxiety and depression.

Furthermore, amygdala and PFC might undergo dendritic alterations as evidenced in situations of chronic stress. Dendritic shrinking in medial PFC and dendritic growth in amygdalar neurons in response to stress also has been reported (Wellman, 2001; Vyas et al., 2002; Kreibich and Blendy 2004; Radley et al., 2006; Brown et al., 2005). Stressful stimuli are known to alter prefrontal dendritic architecture and neuronal connectivity within the PFC (Luethi

et al., 2008; Liston et al., 2009). Interestingly, higher vulnerability of the hippocampus and amygdala to oxidative stress and breakdown of antioxidant defense system is evident. Therefore, it seems highly plausible that oxidative stress in the brain compromises biochemical integrity of the hippocampus and the amygdala. It is well known that the hippocampal dentate gyrus-CA3 system regulates structural plasticity, regenerative/remodeling capacity as well as neurogenesis factors like brain derived neurotrophic factor (BDNF) (Wang and Michaelis 2010). It has also been suggested that the pyramidal cells of CA1 and CA3 and granule cells of DG are highly susceptible to oxidative damage. Thus, oxidative damage of DG-CA function may diminish cell proliferation, impair remodeling capacity, alter structural plasticity and disrupt neurogenesis, collectively disturbing normal synaptic neurotransmission. And, oxidative stress-initiated neuroendocrine alterations within the amygdala including amygdalar hyperactivity and dendritic shrinking (Wellman, 2001; Vyas et al., 2002; Kreibich and Blendy 2004; Radley et al., 2006; Brown et al., 2005; Wood et al., 2010) can further potentiate synaptic disturbances by disrupting the hippocampus-amygdala projections. Furthermore, free radicals are known to oxidize the extracellular sites of glutamatergic N-methyl-D-aspartate (NMDA) receptors leading to attenuation of LTP and synaptic neurotransmission (Haxaire et al., 2012; Lee et al., 2012; Rai et al., 2013). Collectively, these events offer an attractive explanation for oxidative stress-induced behavioral and cognitive impairment.

Perhaps, psychological stress disrupts oxidant-antioxidant balance within the brain causing impairment of antioxidant enzyme function. This leads to glutathione depletion and increases oxidative stress. Simultaneously occurring glutamate toxicity, calcium imbalance and mitochondrial impairment collectively intensify oxidative stress causing biochemical distress in the brain. This disrupts neurocircuitry weakening hippocampal, amygdalar and cortical

connections ultimately causing behavioral and cognitive deficits (**Figure 1**). It seems reasonable to suggest that perhaps, tight regulation of oxidative stress either by enhancing activity of enzymes of antioxidant defense or by directly quenching pro-oxidants, offers the potential to limit psychiatric symptoms. Thus, data discussed in this review provides a basis for a biologically plausible oxidative stress hypothesis, which might explain how oxidative damage might cause psychiatric symptoms.

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Authorship Contributions

Samina Salim is the corresponding author and wrote this mini review article.

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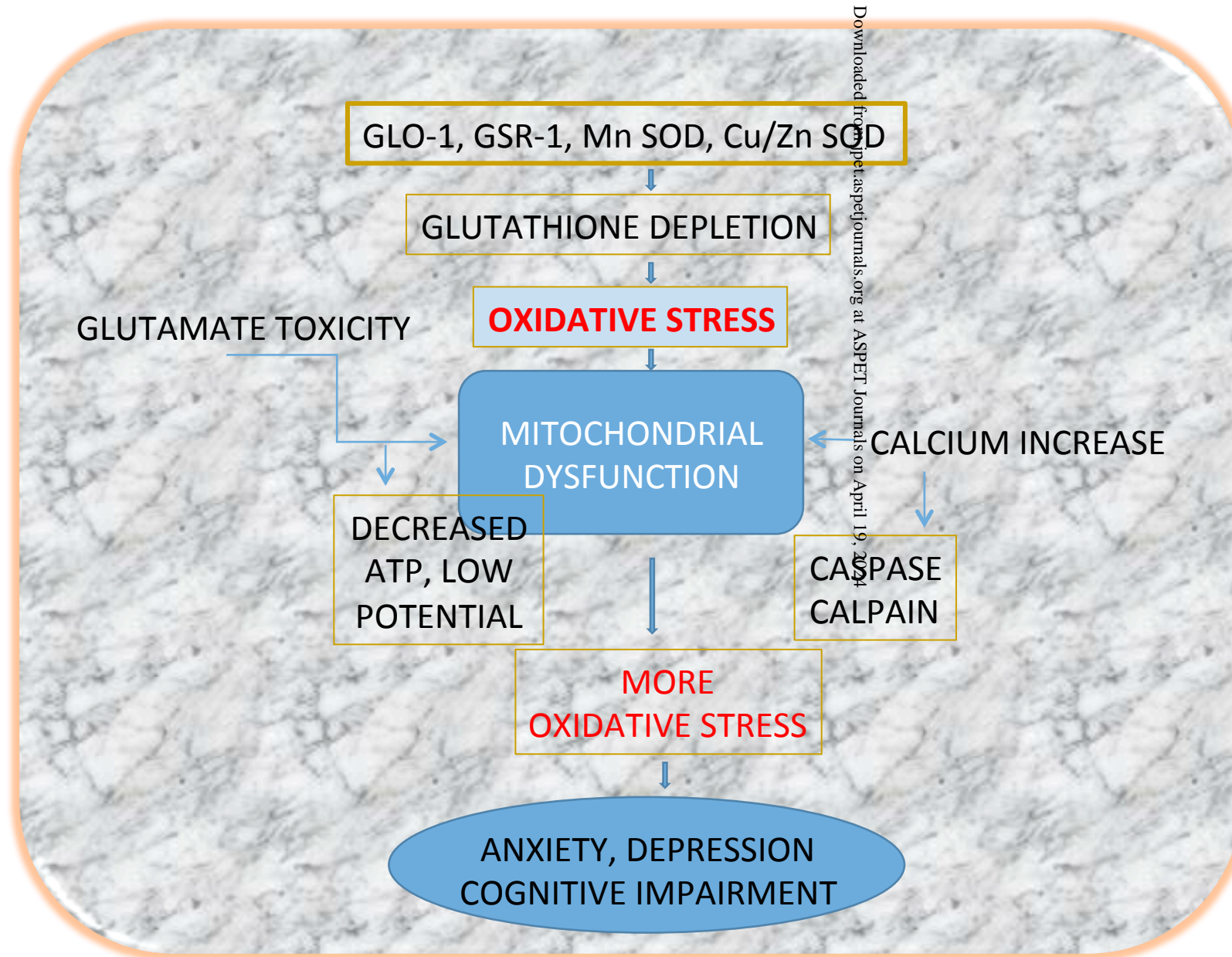
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Figure Legend

Figure 1: Schematic representation of how oxidative stress might lead to cognitive and behavioral deficits. Persistent psychological stress disrupts oxidant-antioxidant balance within the brain causing reduction in antioxidant enzyme function of glyoxalase (GLO)-1, glutathione reductase (GSR)-1, manganese superoxide dismutase (Mn SOD) and Cu/Zn SOD. This leads to glutathione depletion causing oxidative stress. Simultaneously occurring glutamate toxicity, calcium imbalance and mitochondrial impairment collectively intensify oxidative stress causing biochemical distress in the brain. This disrupts neurocircuitry weakening hippocampal, amygdalar and cortical connections ultimately causing behavioral and cognitive deficits.



Schematic representation of how oxidative stress might lead to cognitive and behavioral deficits