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Minireviews

Oxidative Stress and the Central Nervous System

Samina Salim

Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, Texas

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ABSTRACT

Biochemical integrity of the brain is vital for normal functioning of the central nervous system (CNS). One of the factors contributing to cerebral biochemical impairment is a chemical process called oxidative stress. Oxidative stress occurs upon excessive free radical production resulting from an insufficiency of the 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. Although oxidative stress has historically been considered to be involved mainly in neurodegenerative disorders such as Alzheimer disease, Huntington disease, and Parkinson disease, its involvement in neuropsychiatric disorders, including anxiety disorders and depression, is beginning to be recognized. This review is a discussion of the relevance of cerebral oxidative stress to impairment of emotional and mental well-being.

Introduction

Oxidative phosphorylation occurring in the mitochondria is a major source of ATP. As a by-product, this process produces free radicals or reactive oxygen species (ROS), reactive nitrogen species (RNS), and carbon- and sulfur-centered radicals (Pero et al., 1990). In moderate or low amounts ROS are considered essential for neuronal development and function, whereas excessive levels are hazardous. ROS-generated nitrous oxide and carbon monoxide promote important physiologic functions, such as long-term potentiation (LTP) via glutamate-dependent mechanisms (O'Dell et al., 1991; Stevens and Wang, 1993; Verma et al., 1993; Zhuo et al., 1993; Knapp and Klann, 2002). Under normal conditions, deleterious effects of ROS production during aerobic metabolism are neutralized by the 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 (O'Dell et al., 1991; Stevens and Wang, 1993; Verma et al., 1993; Zhuo et al., 1993; Knapp and Klann, 2002). 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 on the basis of observations that when oxidative stress–induced excessive ROS release triggers cellular damage, damaged macromolecules themselves may 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 mutations in the mitochondrial DNA (Gross et al., 1969; Chomyn and Attardi, 2003; Kraytsberg et al., 2003; Trifunovic et al., 2004). Therefore, ROS accumulation is a cellular threat that, 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 (Kohen et al., 1999, 2000). The antioxidant enzyme system includes superoxide dismutase (SOD), glyoxalase, glutathione reductase, glutathione peroxidase, and catalase (CAT) (Griendling et al., 2000). SOD enzymes, including Cu-Zn SOD and Mn-SOD, facilitate spontaneous dismutation of superoxide radicals to generate H_2O_2, which is further removed by CAT and glutathione peroxidase enzymes (Saso and Firuzi, 2014). The

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ABBREVIATIONS: CA, cornu ammonis; CAT, catalase; DG, dentate gyrus; GSH, glutathione; LTP, long-term potentiation; mHtt, mutant Huntington protein; Nrf2, nuclear factor erythroid 2–related factor; PD, Parkinson disease; PFC, prefrontal cortex; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase.

low-molecular-weight antioxidants include glutathione, uric acid, ascorbic acid, and melatonin, which offer neutralizing functions by causing chelation of transition metals (Chance et al., 1979). Glutathione, which occurs in reduced (GSH) and also in oxidized form (glutathione disulfide) is the most important nonenzymatic endogenous antioxidant and can be regenerated by glutathione reductase with the consumption of NADPH (Gul et al., 2000). In this manner optimum levels of reduced GSH are maintained (Kohen and Nyska, 2002; Halliwell, 2006). The endogenous ratio of GSH to glutathione disulfide is considered 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 that encode antioxidants and detoxification enzymes such as heme oxygenase 1 (HO-1), NAD(P)H dehydrogenase quinone 1, SOD1, glutathione peroxidase 1 (GPx1), and CAT (Itoh et al., 1997). Thus, Nrf2 pathway activation occurs to combat the accumulation of ROS and RNS species. Owing 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 defense mechanisms are saturated to the point they become ineffective (Anderson and Maes, 2014). Cytosolic enzymes such as glyoxalase I by detoxifying methylglyoxal offer protection from oxidative damage (Distler and Palmer, 2012). methylglyoxal generates highly oxidative advanced glycation end products 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 by which ROS cause cerebral tissue damage are not well understood but ROS are reported to trigger a variety of molecular cascades that increase blood-brain barrier permeability and alter brain morphology, thus causing neuroinflammation, and neuronal death (Gu et al., 2011). Involvement of hypothalamic-pituitary-adrenal axis–mediated glucocorticoid receptor signaling, glutamate toxicity, and *N*-methyl-D-aspartate receptor signaling systems also has been suggested (Makino et al., 1996; Okamoto et al., 1999; Tanaka et al., 1999; Albrecht et al., 2010; Nguyen et al., 2011). Thus, evidence of increased brain oxidative damage in the development of central nervous system pathologies has been reported for neurodegenerative diseases, including Alzheimer disease, Parkinson disease, and amyotrophic lateral sclerosis, cerebrovascular disorders, demyelinating diseases, and psychiatric disorders (Sorce 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 pathologic hallmarks of the disease (Kipps et al., 2005; Obeso et al., 2008; Gandhi and Abramov, 2012). Alzheimer disease, Parkinson disease (PD), and Huntington disease are commonly occurring neurodegenerative disorders that involve neurotoxic aggregation of specific proteins in the brain. Accumulation of misfolded tau and amyloid β proteins occurs in Alzheimer disease, and α-synuclein and mutant Huntington protein (mHtt) accumulate in PD and Huntington disease, respectively. Cause and effect relationship between oxidative stress and these protein aggregates has been theorized. Some studies have reported age-associated increase in oxidative stress–led ROS as a contributor to formation of neuronal plaque, α-synuclein, and mHtt (Li et al., 2013), and other studies have suggested a role for amyloid β protein formation in ROS production (Behl et al., 1997; Abramov and Duchen, 2005; Shelat et al., 2008). Likewise with regard to PD pathology, it is reported that oxidative stress promotes α-synuclein aggregation in dopaminergic neurons, and that α-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. Whereas accumulation of mHtt led to decrease in antioxidant protein peroxiredoxin Prx1, the overexpressed wild-type Prx1 significantly reduced mHtt-induced toxicity (Pitts et al., 2012). Amyloid β-mediated ROS production was reported to induce lipid peroxidation, causing impaired membrane permeability and activating excitotoxicity mechanisms because of increased calcium (Ca^{2+}) influx. This is believed to significantly alter neurotransmission and cognitive functions. In fact, several studies have implicated ROS in amyloid β-induced impairment in LTP, a cellular correlate of learning and memory (Dumont et al., 2009; Ma et al., 2011; Ma and Klann, 2012; Parajuli et al., 2013), 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 (Post, 1992; Kessler, 1997). Several pathophysiological mechanisms have been implicated in these orders, including genetic predisposition, monoamine deficiency, circadian disruptions, hypercortisolemia, and inflammation (Belmaker and Agam, 2008). The involvement of oxidative stress mechanisms have also been suggested in some psychiatric illnesses, including depression, anxiety disorders, schizophrenia, and autism spectrum disorders (Valko et al., 2007; Ng et al., 2008; Bouayed et al., 2009). Increased levels of ROS and RNS (Suzuki and Colasanti, 2001; Dhir and Kulkarni, 2011; Maes 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 samples from depressed subjects (Maes et al., 2011).

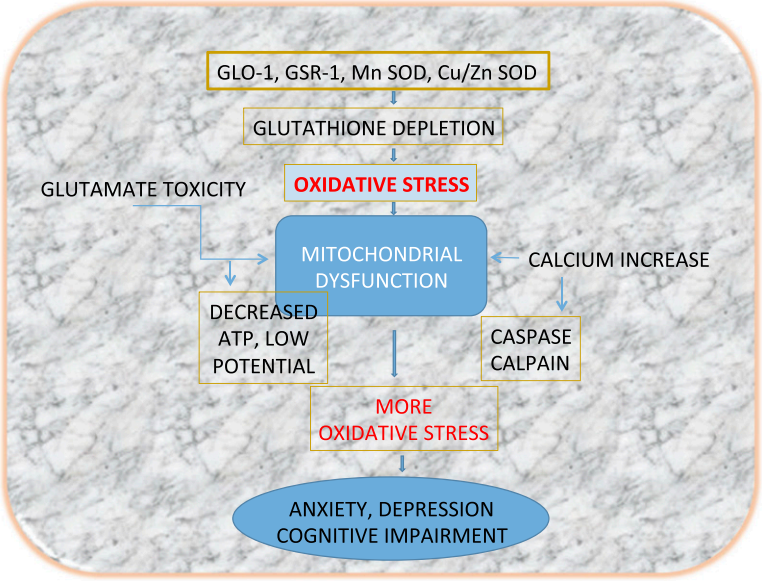
An association between depression and polymorphisms in SOD and CAT genes is also known (Maes et al., 2011). The hypothesis is that the antidepressants exert their therapeutic

effect by suppressing proinflammatory cytokines and ROS/RNS production or by 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 who were put on antipsychotic medication, and SOD activities were negatively correlated with positive symptoms of schizophrenics (Ranjekar et al., 2003). Levels of other antioxidants, including glutathione peroxidase (GSH-Px), also have been implicated (Abdalla et al., 1986; Stoklasová et al., 1986; Buckman et al., 1987; Altuntas et al., 2000). It has been suggested that low GSH-Px is a contributing factor to structural brain abnormalities (Buckman et al., 1990; Yao and Reddy, 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 the role of free radicals and antioxidants in the pathophysiology of bipolar disorder (Berk et al., 2011; Magalhães et al., 2011; Sarris 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

The precise chain of events occurring within the central nervous system that potentially causes or leads 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: hippocampus, amygdala, and prefrontal cortex (PFC) (Masood et al., 2008; Salim et al., 2010a,b, 2011a,b; Patki et al., 2013a; 2013b; Solanki et al., 2015). 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–cornu ammonis (CA)3 system exhibits structural plasticity with regenerative/remodeling capacity (Popov and Bocharova, 1992; Sousa et al., 2000; McEwen, 2008). Furthermore, several studies have suggested that pyramidal cells of CA3 and granule cells of the dentate gyrus (DG) are oxidative stress–prone areas, whereas others have suggested that pyramidal cells of CA1 are more susceptible to oxidative damage (Bearden et al., 2009; Cruz-Sánchez et al., 2010; Chang et al., 2012; Huang et al., 2012, 2013; Uysal et al., 2012). Regardless, region-specific elevation of oxidative stress within cornu ammonis areas CA1 and CA3, and DG is important and can have significant functional consequences. This is particularly significant as the 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; Brown et al., 2005; Radley et al., 2006). Stressful stimuli are known to alter prefrontal dendritic architecture and neuronal connectivity within the PFC (Liston et al., 2009; Luethi 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 DG-CA3 system regulates structural plasticity, regenerative/remodeling capacity, as well as neurogenesis factors like brain-derived



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

Fig. 1. Schematic representation of how oxidative stress might lead to cognitive and behavioral deficits. Persistent psychologic 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 and ultimately causing behavioral and cognitive deficits.

neurotrophic factor (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; Brown et al., 2005; Radley et al., 2006; 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 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, psychologic 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 and weakens hippocampal, amygdalar, and cortical connections, ultimately causing behavioral and cognitive deficits (Fig. 1). It seems reasonable to suggest that, perhaps, tight regulation of oxidative stress, either by enhancing the 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 that would explain how oxidative damage might cause psychiatric symptoms.

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Address correspondence to: Dr. Samina Salim, Department of Pharmacological and Pharmaceutical Sciences, University of Houston, Texas. E-mail: ssalim@uh.edu