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Oxidative Stress in Schizophrenia: An Integrated Approach

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Abstract

Oxidative stress has been suggested to contribute to the pathophysiology of schizophrenia. In particular, oxidative damage to lipids, proteins, and DNA as observed in schizophrenia is known to impair cell viability and function, which may subsequently account for the deteriorating course of the illness. Currently available evidence points towards an alteration in the activities of enzymatic and nonenzymatic antioxidant systems in schizophrenia. In fact, experimental models have demonstrated that oxidative stress induces behavioural and molecular anomalies strikingly similar to those observed in schizophrenia. These findings suggest that oxidative stress is intimately linked to a variety of pathophysiological processes, such as inflammation, oligodendrocyte abnormalities, mitochondrial dysfunction, hypoactive *N*-methyl-D-aspartate receptors and the impairment of fast-spiking gamma-aminobutyric acid interneurons.[BKYB1] Such self-sustaining mechanisms may progressively worsen producing the functional and structural consequences associated with schizophrenia. Recent clinical studies have shown antioxidant treatment to be effective in ameliorating schizophrenic symptoms. Hence, identifying viable therapeutic strategies to tackle oxidative stress and the resulting physiological disturbances provide an exciting opportunity for the treatment and ultimately prevention of schizophrenia.

Keywords

Schizophrenia; Oxidative Stress; Antioxidant; Immune Response; Parvalbumin; *N*-methyl-D-aspartate Receptor

1. Introduction

Schizophrenia is a chronic, severe and disabling psychiatric illness that affects about 1% of the population worldwide (Jackobson, 2000; Perala *et al*., 2007). The symptoms of the

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disorder can be divided into three main categories: positive symptoms (e.g. delusions and hallucinations), negative symptoms (e.g. flat affect, lack of motivation and deficits in social function) and cognitive deficits (Carpenter, 1994; Tamminga and Holcomb, 2005). Although the symptoms that establish the diagnosis are usually not present until young adulthood, prodromal symptoms and endophenotypic features of cognitive and social deficits can precede psychotic illness and manifest in unaffected relatives.

The prevailing hypothesis for the etiology of schizophrenia is that variations in multiple risk genes, each contributing a subtle effect, interact with each other and with environmental stimuli to impact both early and late brain development (Weinberger, 1987; Lewis and Lieberman, 2000; McDonald & Murray, 2000; Lewis and Levitt, 2002; Sawa and Snyder, 2002; Mueser and McGurk, 2004; Harrison and Weinberger, 2005; Jaaro-Peled *et al.*, 2009). Although a clear mechanism underlying the pathogenesis of schizophrenia remains unknown, oxidative stress as a consequence of aberrant reduction-oxidation (redox) control has become an attractive hypothesis for explaining, at least in part, the pathophysiology of schizophrenia (Cadet and Kahler, 1994; Reddy and Yao, 1996; Fendri *et al.*, 2006; Ng *et al.*, 2008; Behrens and Sejnowski, 2009; Dean *et al.*, 2009a; Do *et al.*, 2009, [2010]; Wood *et al.*, 2009a; Yao *et al.*, 2001, [2004], 2006, 2009; Matsuzawa and Hashimoto, 2010; Zhang *et al.*, 2010).

The last four decades have witnessed a great increase in our knowledge of the basic molecular mechanisms underlying oxidative stress. Most remarkably, functional genetic analysis has identified molecular mechanisms that are conserved in yeast, nematodes, flies and mammals. Analysis of these model systems suggests that redox mechanisms are not fixed but are reversible. Similarly, cognitive dysfunction associated with an imbalance in the generation and clearance of reactive oxygen species (ROS) and reactive nitrogen species (RNS) also seems to be variable and possibly open to modification [BKYB2](Kamsler and Segal, 2003; Calabrese *et al.*, 2006). Recent studies have implicated these mechanisms in the control of brain pathology, raising the possibility that altered regulation of fundamental mechanisms of oxidative stress may contribute to the pathogenesis of schizophrenia and related disorders (Floyd, 1999; Chauhan and Chauhan, 2006; Ng *et al.*, 2008; Do *et al.*, 2009; Wood *et al.*, 2009a).

In this review, we explore the basic molecular mechanisms of redox regulation in the brain. We begin with a brief description of oxidative stress and its regulation. Then we turn to a discussion of clinical and pre-clinical findings of redox impairment that induce brain pathology in schizophrenia, through mechanisms that likely involve aberrant inflammatory responses, mitochondrial dysfunction, oligodendrocyte abnormalities, epigenetic changes, hypoactive *N*-methyl-D-aspartate (NMDA) glutamate receptors and the impairment of fast-spiking gamma-aminobutyric acid (GABA) interneurons (**see** Figure 1). There is hope that our growing understanding of the molecular basis of oxidative stress mechanisms within the brain will allow us to rise to the challenge of treating and preventing the clinical symptoms and cognitive deficits associated with schizophrenia.

2. What is Oxidative Stress?

Oxidative stress occurs when cellular antioxidant defense mechanisms fail to counterbalance and control endogenous ROS and RNS generated from normal oxidative metabolism or from pro-oxidant environmental exposures (Kohen and Nyska, 2002; Berg *et al.*, 2004). The link between oxidative stress and the pathophysiology of disease can be explained by the physiological phenomenon commonly referred to as the ‘oxygen paradox’ (Davies, 1995). This concept states that oxygen plays contradictory roles, one essential for life and the other as a toxic substance (Davies, 1995; Kohen and Nyska, 2002). The deleterious effects of

oxygen relate directly to the fact that atomic oxygen is a free radical and molecular oxygen is a biradical (Davies, 1995). The biradical property of oxygen dictates that full reduction of oxygen to water as a terminal event in the electron transport chain requires 4 electrons. The sequential donation of electrons to oxygen during this process can generate ROS as intermediates, and "electron leakage" can also contribute to the formation of ROS [BKYB3] (Davies, 1995; Miwa and Brand, 2003; Genova *et al.*, 2003). The most important ROS in humans are hydrogen peroxide (H_2O_2), superoxide radical (O_2•−), and hydroxyl radical (OH•). Reactive nitrogen species include nitric oxide (NO) and peroxinitrite (ONOO•). Fortunately, several cellular antioxidant defense mechanisms exist to counterbalance the production of ROS and RNS, including enzymatic and nonenzymatic pathways (Nordberg and Arner, 2001).

Because the redox status of cells is involved in regulating various transcription factors/activators (e.g., activator protein- and modulating signaling pathways, appropriate ROS/RNS levels are necessary for normal physiological function of living organisms (Sun and Oberley, 1996). Nuclear factor κB, for example, becomes more transcriptionally active in response to the contribution of ROS to the degradation of IκB, the inhibitory partner of nuclear factor κB that sequesters it in the cytosol (Hayden and Ghosh, 2004). Thus ROS can play an important role in modulating inflammation. Excessive ROS may, however, have detrimental effects including modification of macromolecules such as nucleic acids, proteins and lipids (Kohen and Nyska, 2002). Lipid peroxidation is a well-characterized effect of ROS that results in damage to the cell membrane as well as to the membranes of cellular organelles (Rathore *et al.*, 1998). In addition, ROS can contribute to mutagenesis of DNA by inducing strand breaks, purine oxidation, and protein-DNA cross-linking, and other ROS mediated alterations in chromatin structure may significantly affect gene expression (i.e. epigenetic changes) (Konat, 2003). Modification of proteins by ROS/RNS can induce denaturation that renders proteins nonfunctional (Lockwood, 2000; Stadtman and Levine, 2003). Similarly, an overabundance of ROS/RNS can cause inactivation of critical enzymes and induce cell death through activation of kinases and caspase cascades (Cai *et al.*, 1998; Evans *et al.*, 2004; Scherz-Shouval and Elazar, 2007).

The brain is particularly vulnerable to oxidative damage (Rougemont *et al.*, 2002; McQuillen and Ferriero, 2004), given its relatively low content of anti-oxidant defenses in addition to its high metal content (e.g. iron, zinc, copper and manganese), which can catalyze the formation of ROS/RNS. The brain utilizes more than 20% of oxygen consumed by the body yet comprises only 2% of the total body weight (Dringen, 2000; Berg *et al.*, 2004). The high energy demand from oxidative glucose metabolism plus a high concentration of polyunsaturated fatty acids and relatively low levels of antioxidants are therefore thought to render the brain more vulnerable to oxidative insult than most organs (Bains and Shaw, 1997; Dringen, 2000) (**see** Figure 2**)**.

3. Antioxidant Systems

The potential toxicity of ROS/RNS in the brain is counteracted by a number of antioxidants that can protect the brain against oxidative damage in several ways, including: (1) removal of ROS/RNS (Ozturk *et al.*, 2005), (2) inhibition of ROS/RNS formation, and (3) binding metal ions needed for catalysis of ROS/RNS generation. Glutathione peroxidase and glutathione reductase are well-known intracellular antioxidant enzymes. Glutathione peroxidase converts peroxides and hydroxyl radicals into nontoxic forms, often with the concomitant oxidation of reduced glutathione (GSH) into the oxidized form glutathione disulfide (GSSG), and glutathione reductase recycles GSSG to GSH. Other enzymes and pathways are also involved in the management of cellular defense against oxidative stress. Notably, catalase and superoxide dismutase, acting in concert with glutathione peroxidase

constitute the major defense or primary antioxidant enzymes against superoxide radicals (DeKosky *et al.*, 2004; Dringen *et al.*, 2005). In addition, glutathione-*S*-transferase and glucose-6-phosphate dehydrogenase help in the detoxification of ROS by decreasing peroxide levels or maintaining a steady supply of metabolic intermediates like GSH and nicotinamide adenine dinucleotide-phosphate (NADPH) necessary for optimum functioning of the primary antioxidant enzymes (Vendemiale *et al.*, 1999). Similarly, thioredoxin and thioredoxin reductase can catalyze the regeneration of many antioxidant molecules, including ubiquinone, lipoic acid, and ascorbic acid (vitamin C), and as such constitute an important antioxidant defense against ROS/RNS. Other notable defense mechanisms against free radical-induced oxidative and nitrosative stress include α-tocopherol (vitamin E), bilurubin, albumin, uric acid, niacin, carotenoids and flavonoids (Nordberg and Arner, 2001; Cho *et al.*, 2009).

Another key antioxidant within biological systems is NO. Nitric oxide is an important messenger molecule involved in many physiological and pathological processes within the mammalian body, both beneficial and detrimental (Mustafa *et al.*, 2009; Shahani and Sawa, 2010). Being a free radical, NO has both pro-and antioxidant properties. Nitric oxide can be protective against oxidative injury, depending on the specific conditions (Kanner *et al.*, 1991). The NO radical can both stimulate lipid oxidation and mediate oxidant-protective reactions in membranes (Radi *et al.*, 1991). Nitric oxide reacts rapidly with peroxyl radicals as a sacrificial chain-terminating antioxidant. However, if left unchecked NO free radical can react with superoxide radical to form highly toxic peroxynitrite. Table 1 shows a list of neutralising antioxidants against ROS/RNS and additional physiological antioxidants.

4. Alterations in Antioxidant Defense Systems in Schizophrenia

Clinical and preclinical investigations of the actions of antioxidative defense systems in the brain suggest several ways in which ongoing oxidative stress might impact the occurrence and course of schizophrenia. In this section, we describe clinical and preclinical studies that may shed light on the role that oxidative stress plays in schizophrenia.

4.1. Clinical studies

Several studies have documented alterations in antioxidant enzymes in schizophrenia, but this is not always consistent. While reduced levels of the antioxidant enzymes are generally reported in patients with schizophrenia compared with controls (Dadheech *et al.*, 2008; Singh *et al.*, 2008; Raffa *et al.*, 2009), other studies have reported either no change (Srivastava *et al.*, 2001) or a strengthening of antioxidant status in schizophrenia (Kuloglu *et al.*, 2002; Dakhale *et al.*, 2004; Kunz *et al.*, 2008). A recent meta-analysis indicated that there is an increase in the levels of lipid peroxidation products and NO (discussed in further detail below) in schizophrenia, while superoxide dismutase activity was found to be significantly decreased in the disorder (Zhang *et al.*, 2010). This study also showed that the activities of glutathione peroxidase and catalase were not affected in patients with schizophrenia (Zhang *et al.*, 2010). Nonetheless, various reports from different research groups have indicated lower (Reddy *et al.*, 1991), elevated (Herken *et al.*, 2001) or normal (Yao *et al.*,1998a) catalase levels in schizophrenia patients. The levels of glutathione peroxidase have also been reported to be inconsistent in patients with schizophrenia (Herken *et al.*, 2001; Ranjekar *et al.*, 2003; Gawryluk *et al.*, 2010). The results in the measure of superoxide dismutase are also contradictory, with an increase (Reddy *et al.*,1991; Zhang *et al.*, 2003), decrease (Mukerjee *et al.*, 1996; Ranjekar *et al.*, 2003) or no change (Yao *et al.*, 1998a) in enzyme activity in patients with schizophrenia. Interestingly, the levels of superoxide dismutase have been found to be high in chronic schizophrenic patients (Reddy *et al.*, 1991; Yao *et al.*, 1998a,b; Zhang *et al.*, 2003) or to be low in neuroleptic-naïve first-episode schizophrenic patients (Raffa *et al.*, 2009), suggesting that the efficacy of

neuroleptics may in part be mediated by promoting an endogenous antioxidative mechanism (Padurariu *et al.*, 2010). [BKYB4]

Post-mortem studies have reported a 40% depletion of GSH in the caudate nucleus of schizophrenia patients (Yao *et al.*, 2006). Similarly, Gawryluk and colleagues have recently reported reduced levels of GSH in postmortem prefrontal cortex of patients with schizophrenia (Gawryluk *et al.*, 2010). In addition, magnetic resonance spectroscopy studies have shown that levels of GSH were reduced by 52% in the prefrontal cortex and by 27% in cerebrospinal fluid of drug-naïve schizophrenia patients (Do *et al.*, 2000). However, other spectroscopy studies have failed to detect a decrease in the levels of GSH in the anterior cingulated cortex (Terpstra *et al.*, 2005), posterior medial frontal cortex (Matsuzawa *et al.*, 2008) or the medial temporal lobe (Wood *et al.*, 2009b). In the latter studies, patients were receiving neuroleptic treatment and some of the variability of the results may therefore be related to medication status (drug-naïve versus patients on medication), sample source, ethnicity or the region of the brain investigated.

To examine a novel cell model based on patient-derived cells from the human olfactory neuroepithelium, an elegant study assessed gene and protein expression and cell function from healthy controls, patients with schizophrenia or Parkinson's disease (Matigian *et al.*, 2010). The olfactory neuroepithelium is the only neural tissue in the human body that is easily accessible (Féron *et al.*, 1998) and demonstrates disease-dependant alterations in cell biology in schizophrenia (McCurdy *et al.*, 2006), amongst other neurological disorders. In their study, Matigian and colleagues identified several pathways already implicated in schizophrenia including Reelin, Il-8 and Erb signaling in addition to GSH metabolism (Matigian *et al.*, 2010). The findings that molecular profiles from human olfactory neuronal cells are similar to that of post-mortem brain tissue from patients with schizophrenia support the use of this cell model for studying cellular and molecular bases of neurological conditions such as schizophrenia.

The levels of plasma antioxidants (uric acid, albumin and bilirubin) have been reported to be significantly lower in schizophrenia (Yao *et al.*, 1998c; 2000; Reddy *et al.*, 2003). These findings were found to be independent of smoking status (Reddy *et al.*, 2003). Plasma levels of α-tocopherol (McCreadie *et al.*, 1995) and ascorbic acid (Suboticanec *et al.*, 1990) have also been reported to be lower in schizophrenic patients. In contrast, thioredoxin has been shown to be increased during the acute phase of schizophrenia (Zhang *et al.*, 2009), but becomes normalized in chronic schizophrenic patients on long-term antipsychotic pharmacotherapy (Zhang *et al.*, 2009). Serum thioredoxin was also found to be positively correlated with positive symptoms of schizophrenia (Zhang *et al.*, 2009). Other studies have shown the levels of lipid peroxidation products (e.g. malondialdehyde and thiobarbiturate reactive substances) to be increased in plasma, serum (McCreadie *et al.*, 1995; Zhang *et al.*, 2006; Dietrich—Muszalska and Olas, 2009) and red blood cells (Mahadik *et al.*, 1998; Herken *et al.*, 2001) of schizophrenic patients. These observations strengthen the evidence for a defective antioxidant system as an early pathophysiological change associated with the disease, rather than a sequela of drug effects, chronic disease and smoking (Reddy *et al.*, 2003).

4.2. Preclinical studies

Various studies have shown that alterations in antioxidant systems cause cognitive impairment and biochemical changes relevant to schizophrenia. Dean and colleagues have shown that treatment of Sprague-Dawley rats and C57BL/6 mice with 2-cyclohexene-1-one (CHX), a compound that reduces brain GSH levels by conjugating to GSH via glutathione transferase (Masukawa *et al.*, 1989), dose-dependently reduced striatal and frontal cortical GSH levels to levels similar to those observed in patients with schizophrenia (Dean *et al.*,

2009b). In both species, GSH depletion resulted in disruption of short-term spatial recognition memory in a Y-maze test. Because GSH has been shown to modulate glutamatergic activity (Janaky *et al.*, 1994; Oja *et al.*, 2000), it has been suggested that a GSH deficit may contribute to a dysfunction in glutamatergic pathways responsible for long-term potentiation (LTP) (Steullet *et al.*, 2006), a phenomenon critical for learning and required to encode memories (Martin *et al.*, 2000). Treatment with CHX, however, did not affect sensory motor gating as indexed by prepulse inhibition (PPI), a preattentive process that is considered an endophenotype of schizophrenia, in both species following treatment with MK-801 or dizocilipine, an NMDA receptor antagonist, and amphetamine, which increases synaptic dopamine release (Dean *et al.*, 2010). Although in rats treated with CHX, the effect of amphetamine to disrupt PPI was reversed, potentially suggesting a decrease in pre-synaptic dopamine release or dopamine receptor function.Therefore, acutely reduced GSH levels may not be directly involved in the disruption of PPI observed in schizophrenia (Dean *et al.*, 2010).

Experimental evidence from rats exposed to early postnatal (days 5-16) treatment with l-buthionine-(S,R)-sulfoximine (BSO), an accepted rodent model of oxidative stress which induces a transitory deficit in GSH, have shown that GSH deficiency leads to long-lasting behavioral aberrations (Cabungcal *et al.*, 2007). For example, BSO treatment leads to impaired spatial learning and memory (viz. worse performance in the homing hole board task) (Cabungcal *et al.*, 2007). These findings highlight the role of oxidative changes during development in cognitive processes associated with schizophrenia. Specifically, oxidative stress during early development may lead to a dysfunction in integrating sensory information relevant for spatial representation. Such a deficit may arise from a misconnectivity in specific brain regions involved in modulating distinct cognitive processes (Cabungcal *et al.*, 2007).

A recent study demonstrated the importance of altered oxidative stress state in inducing anomalies of brain neural oscillations and neuronal pathology underlying cerebral integration and cognitive functioning (Steullet *et al.*, 2010). The study used a mouse model in which disrupted expression of the modifier (GCLM) subunit of glutamate cysteine ligase (GCL), the rate-limiting enzyme of GSH synthesis, elicits elevated oxidative stress (Yang *et al.*, 2002). These mice exhibited altered behavior during an object recognition task, increased novelty-induced exploration in addition to altered emotion and stress-related behaviors (Steullet *et al.*, 2010). Furthermore, the GSH deficit within these mice resulted in a specific reduction in parvalbumin (PV) containing inhibitory interneurons and a concomitant reduction in β/γ oscillations in the hippocampus of young adult mice (Steullet *et al.*, 2010). The fast-spiking basket and chandelier cells that contain PV are known to play a critical role in regulating synchronous neuronal discharges in multiple frequency bands (e.g., theta, gamma, ripple) via both chemical and electrical synapses (Freund, 2003; Klausberger *et al.*, 2003; Whittington and Traub, 2003; Buzsaki and Draguhn, 2004; Freund and Katona, 2007). These findings therefore highlight the role of oxidative changes in electrophysiological, behavioral and cognitive deficits associated with schizophrenia.

5. Nitric Oxide in Schizophrenia

Evidence is accumulating that NO may be involved in the pathophysiology of schizophrenia given the various roles that NO plays in the brain, such as regulating synaptic plasticity (Holscher and Rose, 1992), neurotransmitter release (Lonart *et al.*, 1992), and neurodevelopment (Truman *et al.*, 1996; Hindley *et al.*, 1997; Downen *et al.*, 1999; Contestabile, 2000; Gibbs, 2003). Nitric oxide is especially important as the second messenger of NMDA receptor activation, which interacts with both dopaminergic and serotonergic pathways (Lorrain and Hull, 1993; Brenman and Bredt, 1997). Abnormal

functioning of these pathways has been suggested to be involved in the pathophysiology of schizophrenia. Perhaps relevant to the previous connection are the findings suggesting that nitric oxide synthase (NOS, an enzyme widely expressed throughout the brain and which is responsible for NO production in the central nervous system) inhibitors protect against phencyclidine (PCP) induced schizophrenia-mimicing phenotypes such as PPI deficits and cognitive inflexibility in animals (Johansson *et al.*, 1997; Klamer *et al.*, 2001, 2004; Wass *et al.*, 2008, 2009). Interestingly, postmortem studies have reported elevated levels of NO and NOS in brain tissue of subjects with schizophrenia and have suggested that NOS may be activated in the illness (Baba *et al.*, 2004; Yao *et al.*, 2004; Xu *et al.*, 2005). Similarly, it was shown that NO levels in red blood cells are significantly increased in patients with schizophrenia (Herken *et al.*, 2001). However, the evidence surrounding NO metabolites in schizophrenia has been inconsistent with studies reporting both increased (Zoroglu *et al.*, 2002; Suzuki *et al.*, 2003; Yilmaz *et al.*, 2007) and decreased (Suzuki *et al.*, 2003; Lee and Kim, 2008; Nakano *et al.*, 2010) levels. A negative correlation was observed between NO metabolite levels and positive and negative syndrome scale (PANNS) scores in schizophrenia subjects, indicating that reduced plasma NO metabolites maybe related to the severity of negative symptoms in schizophrenia (Nakano *et al.*, 2010).

Altered populations or distribution of NOS-containing neurons have been reported in frontal (Akbarian *et al.*, 1993a) and temporal (Akbarian *et al.*, 1993b) cortices, hypothalamus (Bernstein *et al.*, 1998), and cerebellum (Karson *et al.*, 1996; Bernstein *et al.*, 2001) in schizophrenia. Consistent with a role of NOS in schizophrenia, a number of genetic association studies have reported that single nucleotide polymorphisms in the NOS gene are associated with schizophrenia (Shinkai *et al.*, 2002; Brzustowicz *et al.*, 2004; Fallin *et al.*, 2005; Reif *et al.*, 2006; Tang *et al.*, 2008; Wratten *et al.*, 2009; Cui *et al.*, 2010), although some results are inconsistent with such associations (Okumura *et al.*, 2009). Genetic and functional data for NOS revealed an association between a putative cis-acting polymorphism in the NOS gene and decreased protein NOS expression in the prefrontal cortex of patients with schizophrenia (Cui *et al.*, 2010). The same study also showed that the age of schizophrenia onset was earlier in patients carrying the cis-acting polymorphism in the NOS gene (Cui *et al.*, 2010).

Decreased activity of receptors sensitive to NO has also been reported in schizophrenia. The cholinergic receptors (e.g. α7 nicotinic acetylcholine receptor) known to be sensitive to NO toxicity were decreased in both blood and cortex of patients with schizophrenia (Perl *et al.*, 2003; Matthew *et al.*, 2007). Patients with schizophrenia frequently smoke cigarettes and often smoke heavier than the normal population (Matterson and O'shea, 1984; Goff *et al.*, 1992; Lasser *et al.*, 2000). The high level of smoking has been proposed as a form of self-medication to alleviate symptoms of their illness including depression, anxiety, anhedonia or amotivation (Glassman, 1993; Olincy *et al.*, 1997). In this context, a series of studies in humans has implicated the α7 nicotinic acetylcholine receptor in the physiology of P50 auditory gating (a measure of preattentive auditory processing). Nicotine gum and physostigmine were found to improve gating in the relatives of persons with schizophrenia who also had impaired auditory gating (Adler *et al.*, 1992). Thus, NO appears to influence neurotransmission (e.g. cholinergic transmission) and may play a role in some of the endophenotypes associated with schizophrenia.

6. Imbalance in Homocysteine Metabolism and Epigenetic Changes in Schizophrenia

Hyperhomocysteinaemia (a medical condition characterized by an abnormally elevated level of homocysteine in the blood) can cause oxidative stress via a number of mechanisms such as auto-oxidation of homocysteine to form ROS (Heinecke *et al.*, 1987), increased lipid

peroxidation (Jones *et al.*, 1994) and reduced production of glutathione peroxidase (Upchurch *et al.*, 1997). A recent study by Brown and colleagues reported that higher maternal homocysteine levels may be a risk factor for schizophrenia (Brown *et al.*, 2007). Specifically, mothers that have elevated third-trimester homocysteine levels may elevate schizophrenia risk through developmental effects on brain structure and function and/or through subtle damage to the placental vasculature that compromises oxygen delivery to the fetus (Brown *et al.*, 2007). In this context, it has been shown that high levels of homocysteine are negatively correlated with glutathione peroxidase activity (Pasca *et al.*, 2006), suggesting that high levels of homocysteine may also be associated with oxidative stress in schizophrenia.

Because oxidative damage to specific gene promoters results in gene silencing (Lu *et al.*, 2004), it may be that irreplaceable post-mitotic cells, such as neurons, respond to unrepaired DNA damage by silencing expression of the affected genomic region, rather than by undergoing apoptosis. The mechanism of silencing is likely epigenetic; specifically, it may be mediated through dysregulation of DNA methylation. High homocysteine levels have been shown to be accompanied by high *S*-adenosyl-homocysteine levels with the elevation of *S*-adenosyl-homocysteine suggested to be associated with DNA hypomethylation and alterations in gene expression (James *et al.*, 2002). Altered gene expression has been shown to be associated with the pathogenesis of schizophrenia (Tsankova *et al.*, 2007; van Vliet *et al.*, 2007; Jiang *et al.*, 2008). *S*-Adenosyl-homocysteine and its analogs have been reported to be a non-competitive inhibitor of catechol-*O*-methyltransferase (COMT), an enzyme that catalyses the first step in the degradation of monoamine neurotransmitters such as dopamine, epinephrine and norepinephrine (Coward and Sweet, 1972; Coward *et al.*, 1972, 1973). The more active allele of COMT is reported to be associated with schizophrenia (Egan *et al.*, 2001) and although not immediately intuitive, it might be that elevated levels of homocysteine may play some aggravating role in the pathogenesis of schizophrenia through an indirect effect on COMT (Applebaum *et al.*, 2004).

7. Genetic Susceptibility to Schizophrenia

Genetic factors may also contribute in modulating the threshold for vulnerability to oxidative stress in schizophrenia (for a review see Kodavali *et al.*, 2010). Recent evidence has shown manganese superoxide dismutase (Akyol *et al.*, 2005) and glutathione *S*-transferase T1 (Saadat *et al.*, 2007) to be associated with schizophrenia. A functional polymorphism in the glutathione *S*-transferase p1 gene has been reported to be associated with vulnerability to develop psychosis in the setting of methamphetamine abuse (Hashimoto *et al.*, 2005), which may have some bearing on schizophrenia. A mitochondrial DNA sequence variation affecting a subunit of NADPH-ubiquinone reductase (complex 1), a component of the electron transport chain responsible for generating superoxide, has also been associated with schizophrenia patients and with increased superoxide levels in post-mortem brain samples (Marchbanks *et al.*, 2003). In another study, the GCLM subunit of the GCL enzyme has been suggested as a susceptibility gene in schizophrenia (Tosic *et al.*, 2006). Similarly, genetic analysis of the trinucleotide (GAG) repeat polymorphism in the GCL catalytic subunit (GCLC) gene showed a significant association with schizophrenia in two independent case-control studies (Swiss and Danish) (Gysin *et al.*, 2007). The same study revealed an association between disease-associated GCLC GAG trinucleotide repeat genotypes and decreased GCLC protein expression (Gysin *et al.*, 2007). Do and colleagues have recently gone on to demonstrate that patients with the trinucleotide repeat GAG susceptibility polymorphism also show reduced plasma total cysteine levels, and an increase of the oxidized form of cysteine, namely cystine, content (Do *et al.*, 2010). These patients also exhibit increased levels of plasma free serine, glutamine, citrulline, and arginine. These data suggest that schizophrenia patients exhibit alterations of plasma thiols levels in addition

to a decreased capacity to synthesize GSH that most likely reflects a dysregulation of redox control and an increased susceptibility to oxidative stress that is most likely of a genetic origin (Gysin *et al.*, 2007, 2009; Do *et al.*, 2010). Taken together, these studies provide additional support for the involvement of oxidative stress in the etiology of schizophrenia.

8. Neurotransmitter Metabolism and Oxidative Stress in Schizophrenia

The biological effects of neurotransmitters are linked to their chemical properties. It has been shown that metabolism of serotonin (Yao *et al.*, 2009), glutamate (Smythies, 1999) and dopamine (Smythies, 1999) play important roles in mediating redox balance within biological systems. These neurotransmitters have generated a great deal of research in a variety of mental disorders, including schizophrenia (Grima *et al.*, 2003; Smythies, 1999; Yao *et al.*, 2009). In this section, we specifically focus on how abnormal metabolism of dopamine and glutamate may play a pathological role in schizophrenia.

8.1 *Dopamine*

The classical dopamine hypothesis of schizophrenia postulates a hyperactivity of dopaminergic transmission at the D2 receptor. It is of interest that enzymatic metabolism of dopamine leads to hydrogen peroxide generation, which, via autooxidation of dopamine, leads to the production of ROS such as dopamine quinones and superoxide (Hastings, 1995; Fleckenstein *et al.*, 2007). These ROS may then interact with superoxide dismutase and GSH, leading to a reduction in the available levels of these antioxidants.

Do and colleagues have studied the effect of dopamine in cultured cortical neurons with a low level of GSH. This study suggests that dopamine alone decreased GSH by 40% (Grima *et al.*, 2003). This effect appears to result from the direct conjugation of dopamine semiquinone/quinone with GSH. Furthermore ethacrynic acid, a potent inhibitor of glutathione-*S*-transferase, decreased GSH in a concentration-dependent manner. When added to ethacrynic acid, dopamine further lowered GSH levels. As this additional decrease is blocked by superoxide dismutase or D1/D2 receptor antagonists, it likely involves the generation of superoxide via activation of dopamine receptors. It also reduces the mitochondrial membrane potential (Grima *et al.*, 2003). Most interestingly, a significant decrease in the number of neuronal processes was induced by a 24-hour application of dopamine with ethacrynic acid, which also reduced the levels of GSH. The underlying mechanism of this effect of reduced GSH level on neuronal morphology may include ROS-evoked lipid peroxidation, leading to membrane alterations, and cytoskeleton modification (Halliwell and Gutteridge, 1998; Valko *et al.*, 2007). These findings are consistent with the reported reduction of neuropil and dendritic spines in regions rich in dopamine innervation (Selemon *et al.*, 1995, 1998; Garey *et al.*, 1998; Glantz and Lewis, 2000; Selemon, 2001) and with the postulated retrograde degeneration of the mediodorsal nucleus of the thalamus projecting to those regions (Pakkenberg, 1990; Popken *et al.*, 2000) in patients with schizophrenia. The degeneration of spines with their synaptic contacts would lead to abnormal cortico-cortical and thalamo-cortical connectivity (Weinberger, 1987; Parnas *et al.*, 1996; Lewis and Lieberman, 2000; Andreasen, 2000). This may in turn be responsible for part of the symptoms of schizophrenia, particularly those involving cognitive and perceptive functions (Goldman-Rakic, 1991; Grima *et al.*, 2003).

8.2 Glutamate

The glutamate hypothesis of schizophrenia posits that the function of the NMDA receptor is compromised in this disease (Coyle, 1996, 2006). This postulate is largely based on the observations that PCP and other NMDA antagonists can induce psychosis that is diagnostically difficult to differentiate from schizophrenia (Javitt and Zukin, 1991; Krystal

et al., 1994, 2002; Newcomer and Krystal, 2001). While glutamate serves as the major excitatory neurotransmitter in the central nervous system via ionotropic and metabotropic receptors, it is also known to be excitotoxic at high levels (Platt, 2007). The toxic effects of glutamate on cell viability ensue from two major factors: Firstly, an influx of calcium ions may trigger an osmotic entry of isotonic fluid that renders the cells vulnerable to mechanical stress. Secondly, a cycle of excitation caused by increased calcium entry into cells results in the further release of glutamate. The latter may result in ROS production due to the accumulation of glutamate and calcium related oxidative events (Olney, 1989; Hirose and Chan, 1993).

Whereas the hypofunction of the NMDA receptor results in reduced calcium flow through these channels, the resultant effect is an increased level of free intracellular calcium in large neuronal populations (Olney *et al.*, 1999; Schwartz *et al.*, 1994). This is because deactivation of NMDA receptors on GABAergic interneurons removes the inhibition of major excitatory pathways that innervate primary neurons of cerebrocortical and limbic brain regions (Olney and Farber, 1995; Olney *et al.*, 1999). These pathways are, then, able to induce an abnormal increase in free intracellular calcium in their targets by activating non-NMDA glutamate gated ion channels as well as G protein-coupled receptors, which are capable of mobilizing calcium from internal stores (Sharp *et al.*, 1994) and subsequently triggering oxidative damage (Lidow, 2003).

A recent study has revealed that perinatal PCP administration to rats results in region-specific changes in the levels of GSH and the activities of the enzymes involved in its metabolism (i.e. glutathione peroxidase and glutathione reductase) (Radonjic *et al.*, 2009). Alterations in superoxide dismutase activity and the level of lipid peroxides were also reported (Radonjic *et al.*, 2009). Interestingly, the activity of catalase was not changed in any of the investigated brain structures (Radonjic *et al.*, 2009). Within the prefrontal cortex, GSH, superoxide dismutase and glutathione reductase levels were all reduced whereas an increase in glutathione peroxidase level was observed. In the hippocampus, reduced GSH, glutathione peroxidase and glutathione reductase levels were accompanied with an increased level of lipid peroxides (Radonjic *et al.*, 2009). In addition, GSH content was decreased in the caudate nucleus, while the major findings in the thalamus were, increased levels of lipid peroxides and glutathione reductase activity (Radonjic *et al.*, 2009). These findings suggest that NMDA receptor malfunction might be related to the redox status of patients with schizophrenia.

9. Abnormal Iron Metabolism as a Mechanism for Oxidative Stress

Several studies have implicated imbalances of trace elements, including manganese, zinc, copper, and iron in schizophrenia (Yanik *et al.*, 2004; Rahman *et al.*, 2008). A disruption in the homeostasis of the latter two redox-active metals is particularly significant in light of the increases in oxidative stress parameters such as lipid peroxidation, and the oxidative damage to proteins and nucleic acids. Because free iron has been implicated in undergoing redox transitions in vivo (via superoxide-driven Fenton chemistry: $Fe^{2+} + H_2O_2 \dashrightarrow Fe^{3+} + \bullet OH + OH^-$) with the consequent generation of oxygen free radicals more than any other transition metal (Winterbourn, 1995), the focus of this section will be on abnormalities of brain iron metabolism and its involvement in schizophrenia.

Iron plays an important role in the human body. Almost two thirds of the total amount of iron is located in hemoglobin (Yuan *et al.*, 1995). Most of the remaining iron is located in the liver, spleen, heart and brain. Iron is adept at catalyzing redox reactions within biological systems (Wright and Bacarelli, 2007). Transferrin and ferritin are iron-transporting proteins which also possess antioxidant properties (Loeffler *et al.*, 1995; Nappi and Vass, 2000;

Fisher *et al.*, 2007; Madsen and Gitlin, 2007). Both proteins are synthesized in several tissues, including brain (Loeffler *et al.*, 1995; Fisher *et al.*, 2007; Madsen and Gitlin, 2007) and act as antioxidants by reducing the concentration of free ferrous ion (Loeffler *et al.*, 1995). Several authors have reported that the levels of iron, ferritin and transferrin are reduced in the serum of patients with schizophrenia as compared to normal controls (Weiser *et al.*, 1994; Kuloglu *et al.*, 2003; Yanik *et al.*, 2004). Other studies have reported no change in levels of iron in postmortem brains of schizophrenic patients (Casanova *et al.*, 1990; Kornhuber *et al.*, 1994).

A deficiency of maternal iron as a risk factor for schizophrenia spectrum disorders (SSDs) was recently evaluated (Insel *et al.*, 2008). It was postulated that maternal iron deficiency during pregnancy, assessed via maternal hemoglobin concentration, may disrupt essential pathways and iron-dependent processes involving dopaminergic neurotransmission, myelination, and energy metabolism. Disturbances of these pathways during fetal development might heighten the susceptibility to schizophrenia in adulthood. This study showed that reduced maternal hemoglobin concentration was associated with a nearly 4-fold statistically significant increased rate of SSDs (Insel *et al.*, 2008), hence suggesting that maternal iron deficiency may be a risk factor for SSDs among offspring.

In keeping with this notion, a recent study demonstrated the importance of hypoferremia (viz. a cytokine induced reduction of serum non-heme iron) in inducing behavioural and biochemical changes relevant to schizophrenia (Aguilar-Valles *et al.*, 2010). The study used a rat model of localized injury induced by turpentine, which triggers the innate immune response and inflammation, in order to investigate the effects of maternal iron supplementation on the offspring's dopamine function. Offspring of turpentine-treated mothers exhibited an enhanced behavioral sensitization to amphetamine following repeated exposure to this drug, when compared to control offspring. These behavioral changes were accompanied by increased baseline levels of tyrosine hydroxylase, dopamine and its metabolites, selectively in the nucleus accumbens (Aguilar-Valles *et al.*, 2010). Interestingly, the behavioral and neurochemical changes were prevented by maternal iron supplementation. Given that schizophrenia is associated with increased subcortical dopamine, it is probable that abnormalities in fetal/maternal iron homeostasis may play a role in developmental processes that render the offspring more susceptible to schizophrenia.

Taken together, these results suggest that reduced iron levels may be associated with schizophrenia in a subset of patients. Because oxidative stress can be induced under situations of iron deficiency (Knutson *et al.*, 2000; Casanueva and Viteri, 2003), free radical formation resulting from iron deficiency may lead to functional disturbances and foster genetic alterations that could in turn contribute to the development of schizophrenia.

10. Mitochondrial Dysfunction and Abnormal Energy Metabolism in Schizophrenia

Oxidative phosphorylation in the mitochondria generates superoxide anion. Furthermore, enzymatic oxidation of biogenic amines by monoamine oxidase in the mitochondrial outer membrane produces hydrogen peroxide. Damaged mitochondria not only produce more oxidants, but mitochondria are also vulnerable to oxidative stress (Kowlatowski and Vercesi, 1999). Notably, peroxidation of membrane lipids yields toxic aldehydes (Keller *et al.*, 1997), which impair critical mitochondrial enzymes (Humphries and Szweda, 1998; Ben-Shachar and Laifenfeld, 2004; Martins-de-Souza *et al.*, 2010). Other essential proteins are directly oxidized, yielding carbonyl and nitrated derivatives (Andreazza *et al.*, 2010). Subsequently, increases in membrane permeability to calcium, other ionic imbalances, and impaired glucose metabolism (Hazlett *et al.*, 2004) aggravate the energy imbalance.

Several studies have demonstrated that mitochondrial malfunction can lead to cellular degeneration (Calabrese *et al.*, 2001; Martins-de-Souza *et al.*, 2009, 2010) as a result of the formation of ROS/RNS (Lenaz, 2001). A disturbance of energy metabolism in mitochondria may play a role in the pathophysiology of schizophrenia (Prabakaran *et al.*, 2004; Martins-de-Souza *et al.*, 2009). Notably, a study using a combined transcriptomic, proteomic, metabolomic approach in addition to hierarchial clustering on human prefrontal cortex tissue in order to detect molecular signatures associated with schizophrenia found alterations in proteins associated with mitochondrial function and oxidative stress responses (Prabakaran *et al.*, 2004). Other studies have also suggested increased lactate levels (Prabakaran *et al.*, 2004), and mitochondrial dysfunction with concomitant defects in neuronal oxidative phosphorylation in schizophrenia (Ben-Shachar *et al.*, 1999; Ben-Scachar and Laifenfeld, 2004; Karry *et al.*, 2004; Prabakaran *et al.*, 2004; Martins-de-Souza *et al.*, 2009). Finally, abnormal mitochondrial morphology, size and density have also been reported in the brains of schizophrenic individuals (Ben-Shachar, 2002).

11. Inflammatory Response Induces Oxidative Stress in Schizophrenia

Maternal exposure to infection during pregnancy has been associated with an increased risk of offspring developing schizophrenia (Brown and Susser, 2002; Brown and Derkits, 2010). Although the epidemiological relationship between in utero infections and schizophrenia remain unclear, the maternal cytokine-associated inflammatory response to infection may be a crucial link, as the identity of the pathogen seems irrelevant (Gilmore and Jarskog, 1997; Buka *et al.*, 2001; Pearce, 2001; Brown *et al.*, 2004; Deverman and Patterson, 2009; Meyer *et al.*, 2009; Patterson, 2009; Watanabe *et al.*, 2010). The mechanism linking maternal immune infection to schizophrenia is suspected to occur as follows: maternally infected cells may promote an increased production of inflammatory cytokines that cross the placenta and then increase interleukin (IL)1β, IL-6, (Tumor necrosis factor) TNF-α and (Interferon) IFN-β among others, by fetal cells (Ohyama *et al.*, 2004). DNA fragmentation may then be induced by free radical production associated with the increase in these cytokines, especially interferon-β. The impact of this damage on nuclear and mitochondrial DNA damage in the neuron could be even more severe due to the high neuronal energy consumption rate and the lack of cell turnover. Due to the positive feed-back loops formed in such a mechanism, the disease state could self-sustain and persist resulting in the progressive development of pathological features and clinical symptoms associated with schizophrenia.

In keeping with this notion, inflammatory responses induced by proinflammatory T cells provide a source of free radicals with the capacity to modify proteins, lipids, and nucleic acids that are potentially toxic for neurons. Important work has therefore been directed towards understanding the consequences and the mechanisms linked to T cell dysfunction in patients with schizophrenia (Henneberg *et al.*, 1990; Sperner-Unterweger *et al.*, 1999; Mazzarello *et al.*, 2004; Rudolf *et al.*, 2004; Maxeiner *et al.*, 2009). Craddock and colleagues have recently shown a decreased activation of helper T cells in both unmedicated and minimally medicated schizophrenia patients as compared with controls (Craddock *et al.*, 2007). To follow up on this indication that patients with schizophrenia exhibit physiological differences in T cell responses, Craddock and colleagues undertook a more systematic investigation of T cell proliferative responses by conducting a microarray analysis of differentially expressed genes in isolated T cells from schizophrenia patients and controls. Functional profiling revealed prominent transcript changes in categories pertaining to cell cycle machinery, intracellular signaling, metabolism and oxidative stress (Craddock *et al.*, 2007). These results suggest that altered T cell response may correspond with oxidative stress in some patients with schizophrenia.

The effects of bacterial infections on triggering oxidative stress during fetal brain development have been evaluated by Lanté and colleagues who administered a lipopolysaccharide injection during pregnancy to rats 2 days before delivery (Lanté *et al.*, 2007). This treatment triggered an oxidative stress response in the hippocampus of male fetuses, evidenced by damage to proteins (as indexed by a rapid rise in protein carbonylation) and by decreases in α-tocopherol levels and in the ratio of reduced/oxidized forms of glutathione (GSH/GSSG). In contrast, none of the biochemical changes observed in males were observed in female fetuses. The authors also showed that NMDA synaptic currents and LTP in addition to spatial recognition in the water maze, were impaired in male but not in female offspring exposed to immune activation by lipopolysaccharide in utero. The sex-dependent effects of lipopolysaccharide treatment are consistent with the impression that male schizophrenic patients seem to exhibit greater structural brain abnormalities (Flaum *et al.*, 1990; Nopoulos *et al.*, 1997) in addition to a more severe clinical profile compared to female patients (Flor-Henry, 1990; Aleman *et al.*, 2003), especially in terms of cognitive deficits (Roy *et al.*, 2001).

Interestingly, pretreatment with the antioxidant *N*-acetyl cysteine (NAC), a precursor of GSH, prevented the lipopolysaccharide induced changes in the biochemical markers of oxidative stress in male fetuses, and the delayed detrimental effects in male offspring, completely restoring both LTP in the hippocampus and spatial recognition performance (Lanté *et al.*, 2007). Together these findings suggest that the antioxidant properties of NAC may provide an efficient supplement for the treatment of symptoms associated with schizophrenia.

12. Oligodendrocyte Dysfunction in Schizophrenia

Schizophrenia has long been considered a disorder consisting of a disconnection between different cortical areas (Friston and Frith, 1995; Stephan *et al.*, 2006). Given that white matter constitutes the anatomical infrastructure for neural connectivity, it has been hypothesized that aberrant connectivity of brain regions may explain altered processing patterns documented by functional neuroimaging and electrophysiology studies in patients with schizophrenia (Bartzokis, 2002; Hulsoff *et al.*, 2004). Consistent with this notion, a reduced density and compromised morphology of oligodendrocytes as well as signs of deviant myelination have been observed in patients suffering from schizophrenia (Uranova *et al.*, 2004, 2007). Oligodendrocytes are the predominant iron-containing cells of the brain (Connor, 1994, 1995). They also contain reduced level of GSH, glutathione peroxidase and mitochondrial manganese superoxide dismutase (Juurlink *et al.*, 1998). In addition, oligodendrocytes are vulnerable to intracellular GSH depletion (Back *et al.*, 1998; Cammer *et al.*, 2002a), which may result in cell death (Oka *et al.*, 1993). This sensitivity to GSH depletion is ameliorated by free radical scavengers such as α-tocopherol (Cammer *et al.*, 2002a,b). Also, cell death can be prevented by NAC (Cammer *et al.*, 2002b). Taken together, oligodendrocytes appear to be highly susceptible to oxidative stress-induced damage, which may lead to myelin deficiency.

Instead of compromising oligodendrocyte functions, oxidative stress may also directly damage myelin. For instance, peroxide and hydroxyl radical can react with the polyunsaturated fatty acids that are present in myelin sheaths, directly triggering demyelination (Halliwell, 1992). It has recently been reported that free radical-related molecules such as NO and peroxynitrite generated by activated microglia (Merrill *et al.*, 1993; Li *et al.*, 2005) in addition to inflammatory cytokines such as TNF-α and IFN-γ (Buntinx *et al.*, 2004) result in cytotoxicity toward oligodendroctyes. Furthermore, TNF-α has been shown to compromise the growth of oligodendrocytes and the expression of mRNA for myelin basic protein in cultures (Cammer and Zhang., 1999). The same study

showed that TNF-α also inhibited the survival and proliferation of the oligodendrocyte progenitors and their subsequent differentiation into mature myelinating phenotypes. In summary, impaired redox function and inflammatory induction, in combination with previously described deficits in the expression of oligodendrocyte-related genes (Hakak *et al.*, 2001; McCullumsmith *et al.*, 2007; Iwamoto *et al.*, 2008), suggest a multifactorial pathway linking oxidative stress to the abnormalities of myelination observed in schizophrenia.

13. Redox Dysregulation of NMDA-Receptor Mediated Transmission in Parvalbumin-Containing Interneurons

Although the evidence from experimental studies and from postmortem investigation shows that NMDA receptor dysfunction has relevance to schizophrenia, it is still debatable as to which specific NMDA receptor subunits are involved in the cascade of molecular events leading to the neuronal deficits and dysfunction associated with schizophrenia.

Postmortem evidence from human brain has shown that the expression of the NR2A subunit is reduced in subjects with schizophrenia (Beneyto and Meador-Woodruff, 2008). In fact, NR2A expression levels have been shown to be reduced in glutamic acid decarboxylase (GAD) 67 positive neurons in subjects with schizophrenia (Woo *et al.*, 2004, 2008). The reduced NR2A expression is possibly due to a reduced NMDA receptor activity at the affected interneurons because it has been shown in other studies that NR2A expression seems to be down-regulated by reduced glutamatergic input and vice versa (Kinney *et al.*, 2006; Behrens *et al.*, 2007; Xi *et al.*, 2009).

Receptors that contain the NR2A subunit are tightly regulated by redox-active agents including GSH (Kohr *et al.*, 1994; Choi and Lipton, 2000; Lipton *et al.*, 2002) and play a pivotal role in the maintenance of the function of PV interneurons (Kinney *et al.*, 2006). In line with these observations, treatment of intermediate duration with the NMDA receptor antagonist MK-801 has been shown to almost completely down-regulate the expression of NMDA receptor subunits and PV in microdissected PV-positive interneurons in the rat frontal cortex (Xi *et al.*, 2009). In this context, we have recently found that, in schizophrenia, the expression of the mRNA for the NR2A subunit of the NMDA receptor in PV neurons also appears to be decreased (Bitanihirwe *et al.*, 2009). This latter finding supports the notion that reduced glutamatergic inputs to PV neurons via the NMDA receptor contributes to the down-regulation of PV and GAD67 messenger RNA transcripts (Kinney *et al.*, 2006; Behrens *et al.*, 2007) and hence plays a central role in the functional disturbances of PV neurons in schizophrenia (Olney and Farber 1995; Lisman *et al.*, 2008; Gonzalez-Burgos *et al.*, 2010; Woo *et al.*, 2010).

Behrens and colleagues have recently shown that prolonged exposure to ketamine, an NMDA receptor antagonist, induces the release of the pro-inflammatory cytokine IL-6, which results in a subsequent induction and activation of the electron transporter and ROS-generating NADPH oxidase (Nox) enzyme (Behrens *et al.*, 2007). Superoxide overproduction as a result of NOX activation could result in the chain of events that initiates processes resulting in reduced expression of GABAergic markers and the consequent loss of inhibitory capacity in PV interneurons (Behrens *et al.*, 2007, 2008; Dugan *et al.*, 2009). Given that ketamine augmented NOX expression in the mouse brain, and that both apocynin (an inhibitor of NOX activity) pretreatment and NOX deficiency prevented ROS generation and the decrease of PV expressing interneurons, NOX activation was indicated as a major contributor to the pathogenesis of ketamine-induced psychosis and possibly also to schizophrenia (Behrens *et al.*, 2007, 2008; Sorce *et al.*, 2010). Together these findings provide evidence for a potential pathological link between NMDA hypofunction, enhanced

neuronal production of IL-6 and oxidative stress, which may in turn be associated with the GABAergic dysfunction often observed in the brain of patients with schizophrenia (Behrens *et al.*, 2007, 2008; Behrens and Sejnowski, 2009; Dugan *et al.*, 2009).

14. Current Therapeutic Modalities

Therapy using antioxidants has the potential to prevent, delay, or ameliorate many neurologic disorders including schizophrenia (Delanty and Dichter, 2000, Moosmann and Behl, 2002, Ng *et al.*, 2008, Dodd *et al.*, 2008; Seybolt, 2010). For example, supplementation of omega-3 poly unsaturated fatty acids in combination with ascorbic acid and α-tocopherol is effective in improving psychopathology (viz. increased scores on the Brief Psychiatric Rating and the PANNS) in chronic-medicated schizophrenic patients (Arvindakshan *et al.*, 2003). Similarly, it has been reported that treatment with Ginkgo biloba extract (a powerful flavonoid antioxidant) and haloperidol results in better PANNS scores (Zhang *et al.*, 2001a), enhances the effectiveness of the antipsychotic and reduces some extrapyramidal side effects (Zhang *et al.*, 2001b). Atypical antipsychotic medication with ascorbic acid (Michael *et al.*, 2002; Dakhale *et al.*, 2005), α-tocopherol (Michael *et al.*, 2002), and lipoic acid (Kim *et al.*, 2008) have also been shown to improve the clinical outcome of patients with schizophrenia.

Moreover, treatment with NAC the rate limiting factor in the synthesis of GSH (Dodd *et al.*, 2008), has been shown to improve core symptoms of schizophrenia (Berk *et al.*, 2008; Lavoie *et al.*, 2008; Bulut *et al.*, 2009). Specifically, administration of NAC has been shown to improve cognitive functioning as indexed by mismatch negativity (MMN) (Lavoie *et al.*, 2008). Mismatch negativity is an auditory event related potential component that is elicited when a sequence of repetitive standard sounds is interrupted infrequently by physically deviant (e.g. pitch, intensity, location, duration), “oddball” stimuli. The MMN occurs rapidly following deviant stimuli; the response begins 50 ms following the onset of the deviation and peaks after an additional 100–150 ms. Physiologically, the MMN is the first measurable brain response component that differentiates between usual and unusual auditory stimuli and shares many of the properties of an automatic, memory-based comparison process (Naatanen *et al.*, 1989). Using this task, a differential response to deviant stimuli compared to distracters (i.e. infrequent tones of a higher pitch) presented in an auditory oddball paradigm, has been shown to be impaired in schizophrenia (Shelley *et al.*, 1991; Javitt *et al.*,1993; Catts *et al.*, 1995; Shutara *et al.*, 1996; *et al.*, 1998). This impairment may in part be mediated by NMDA receptor hypofunction (Javitt and Zukin, 1991; Umbricht *et al.*, 2000; Coyle, 2006), which, in turn, may result from GSH deficit (Light and Braff, 2005; Steullet *et al.*, 2006). In this context, it has been suggested that NAC treatment could increase GSH levels in schizophrenia patients (Lavoie *et al.*, 2008), restoring normal GSH levels and thus improving NMDA reception functioning, which is thought to be reflected by the amplitude of the MMN (Javitt *et al*, 1998). Treatment with antioxidants may therefore serve as an effective therapeutic strategy in schizophrenia.

15. Conclusion

There is growing evidence supporting increased oxidative stress in schizophrenia with likely contributions from environment, genetic and immunological factors. However, the exact molecular mechanisms are yet to be determined. Indeed, the maintenance of redox balance within cells is a primary component of homeostasis underlying neuronal survival. It may not be too surprising therefore that any process that leads to a disruption of the redox balance can drastically interfere with a range of other biochemical processes and result in neuronal deficits and dysfunction.

Compared to other organs in the body, brain tissue is more vulnerable to oxidative stress due to its high oxygen consumption, high content of polyunsaturated fatty acids and low levels of antioxidant enzymes. Even so, neuronal cells are endowed with a range of protective mechanisms. The difficulty is that these may be overwhelmed by additional oxidative load and that a failure of protective mechanisms may allow endogenous oxidative processes to damage cells and result in the pathophysiology of neurological disease. Pathways and mechanisms that control oxidative stress such as GSH metabolism, can modulate pathology and cognitive deficits in rodent models of schizophrenia (Cabuncgal *et al*., 2007; Dean *et al.*, 2000b, Steullet *et al.*, 2010). However, the role of these conserved pathways in the onset and progression of schizophrenia in humans is still unclear. The resolution of this basic issue will depend on future clinical interventions that target these pathways to ascertain their role in cognitive dysfunction and neuropathogenesis. Tackling of the oxidative stress involvement offers a novel therapeutic target for schizophrenia. However, only when the mechanisms and involvement of oxidative stress in the pathogenesis of schizophrenia are understood, will approaches to antioxidant therapy be designed effectively and targeted. It is thus noteworthy that preliminary results of some clinical trials have suggested improved cognitive functioning in individuals with schizophrenia who receive antioxidant therapy, particularly NAC (Berk *et al.*, 2008; Lavoie *et al.*, 2008; Bulut *et al.*, 2009). Hence, identifying viable therapeutic strategies to restore redox balance and the physiological disturbances that result from oxidative stress provide an exciting opportunity for the treatment and ultimately prevention of schizophrenia.

Research highlights

- Evidence of oxidative stress in schizophrenia.
- Redox dysregulation during neurodevelopment may play a role in schizophrenia.
- Antioxidants may prove to be a useful adjunctive treatment for schizophrenia.

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Figure 1.
Schematic illustration of the involvement of oxidative stress in schizophrenia.

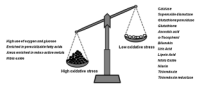

Figure 2.
The Brain is susceptible to oxidative damage

Table 1

Redox-active species and their corresponding neutralizing antioxidants. Direct role = direct redox-active species scavenging activity; Indirect Role = prevent the accumulation of toxic species rather than acting directly on ROS/RNS

ROS	Anti Oxidants (endogenous)		Antioxidants (Exogenous)
	Direct Role	***Indirect Role***	
Hydroxyl Radical	Glutathione Peroxidase Glucose-6-Phosphate Dehydrogenase Thioredoxin	-	Ascorbate Flavonoids Lipoic Acid
Lipid Peroxide	Glutathione Peroxidase Glutathione-*S*-Transferase Glucose-6-Phosphate Dehydrogenase Nitric Oxide	-	α-Tocopherol Carotenoids Flavonoids Ubiquinone Niacin
Superoxide Radical	Superoxide Dismutase (cofactor copper/zinc/ manganese) Glutathione Glucose-6-Phosphate Dehydrogenase Thioredoxin	Albumin	Ascorbate Flavonoids
Hydrogen Peroxide	Catalase Glutathione-*S*-Transferase Glutathione Nitric Oxide Thioredoxin Reductase	Ferritin Transferrin Hemoglobin	Ascorbate, Carotenoids Lipoic Acid Glucose-6-Phosphate Dehydrogenase
Pro-Oxidant/antioxidant equilibrium	Thiols (Glutathione, N-acetyl cysteine) NADPH, Thioredoxin	Bilurubin Uric Acid	Flavonoids