



OXIDATIVE STRESS: A NOVEL TREATMENT TARGET IN PSYCHIATRIC DISORDER

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ABSTRACT

Growing evidences supporting the dysregulation of antioxidant defense mechanism and a parallel increase in oxidative load has been reported by several studies in schizophrenia. A fall of the activities of the secondary antioxidant enzymes (glutathione-S-transferase, glucose-6-phosphate dehydrogenase, caeruloplasmin, Ferroxidase) as well as an increase in the peroxidation of the lipid was also noted among schizophrenic patients. In addition, several studies have reported central and peripheral changes in the oxidative defenses, principally the glutathione system, mirrored by consequences of oxidative stress including protein carboxylation, DNA damage and apoptosis, which is congruent with the process of neuroprogression leading to structural brain changes. Further research is necessary to shed light on the mechanism and pathway underlying free radical generation and target these pathways in order to establish an additional approach for the management of schizophrenia. The essential consideration is to deliver the proper scavenger to the affected site within the time frame of or prior to maximal tissue damage. There are several natural and synthetic compounds already selected and extensively studied. Clearly, strategies aimed at limiting free radical production, oxidative stress and damage may slow the progression of neurodegeneration in psychiatric disorder. Since neurotransmitter pathology and oxidative stress are closely related in schizophrenia, hence, it might be possible that this imbalanced antioxidant defense may act as a initiator of this disease. However, the mechanism and involvement of oxidative stress in the pathogenesis of this neurological disease needs to be well understood, to design effective and targeted approaches to antioxidant therapy.

Keywords: Antioxidants, Oxidative stress, Serotonergic, Schizophrenia.

INTRODUCTION

Schizophrenia is a debilitating, hereditary, disorder of the brain, resulting from abnormalities that arises early in life and disrupt normal development of the brain and has a lifetime risk of 1% and affects at all age groups (average age at the onset 24±4.6 year) in many culture around the world. The onset usually occurs around 18-25 years of age and is often preceded by premorbid behavioural deviations, such as social withdrawal and affective changes^{1,2}. The World Health Organization found schizophrenia to be the world's fourth leading cause of disability^{3,4} that accounts for 1.1% of the total DALYs (Disability Adjusted Life Years) and 2.8% of YLDs (years of life lived with disability)⁴. In general, schizophrenia has symptoms that fall into three categories-that are negative, positive and cognitive symptoms. Positive symptoms (hallucination, delusion, thought disorganization) are known as psychotic symptoms. These are symptoms that appear, which people without schizophrenia do not have and involve an excess of normal bodily functions. In the cluster of Negative symptoms (loss of motivation, affective blunting, alogia, social withdrawal) of schizophrenia, social dysfunction is an important component, beginning in the premorbid stages and continuing on chronically throughout the entire course of illness. Cognitive disturbance in schizophrenia have similar pattern of emergence and deficits in attention, memory and executive function have been reported to be correlated with social functioning. The etiology of this psychiatric disorder is still unknown.

In the last few decades, dopamine hypothesis predominated in the research fields. This hypothesis of schizophrenia proposes that dysfunction in DA neurotransmission is the underlying cause of symptoms of schizophrenia^{5, 6}. The inability of dopaminergic abnormalities to explain a neuropathology of schizophrenia has led to the search for other error in neurotransmission and development of other hypothesis. The psychotomimetic effect of non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine and PCP in healthy humans and their ability to exacerbate several psychotic symptoms in schizophrenic patients have prompted a view of schizophrenia as being related to a hypofunctional state of glutaminergic neurotransmission. Glutamate may also be involved in schizophrenia through its interaction with dopamine or subtle forms of excitotoxicity⁷⁻¹⁰. The serotonergic (5-HT) system has also been frequently implicated in schizophrenia¹¹. The two major classes of psychedelic hallucinogenic drugs, lysergic acid diethylamide and mescaline are believed to mediate their effects through 5-HT_{2A} receptors¹²⁻¹⁴. Despite evidence for altered serotonergic markers in schizophrenia, there is comparatively little evidence of primary dysfunction of serotonergic system in schizophrenia. Alteration in γ -aminobutyric acid neurotransmission in the PFC of patients has also been proposed, on the basis of theory and experimental evidences¹⁵⁻¹⁸. Despite formulation of several hypotheses, the pathophysiology of schizophrenia remains also in large part unknown. Recently more and more converging evidences indicates that oxidative



mechanism may play role in schizophrenia^{1,2}. Specifically, free radical mediated abnormalities may contribute to the development of a number of clinically significant consequences in schizophrenia, including prominent negative symptoms, tardive dyskinesia, neurological soft signs and parkinsonian symptoms³. Free radical, primarily plasma nitric oxide (NO) was found to be higher⁴ or unchanged¹⁹ in whole chronic patients but lower in deficit patients¹⁹ and less in the cerebrospinal fluid²⁰ and more in the caudate region of postmortem brain²¹ from patients with schizophrenia, inversely the antioxidant level such as activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) will show lower. The total antioxidant capacity decreased in patients.

OXIDATIVE STRESS

Chemical compounds and reactions capable of generating potential toxic oxygen species/free radicals are referred to as Pro-oxidants. On the other hand compounds and reactions that dispose of these species, scavenge ring them, suppressing their formation or opposing their actions are called antioxidants. In normal cell, there is an appropriate pro-oxidant-antioxidant balance. However, this balance can be shifted towards the prooxidants when production of oxygen species is increased or when levels of antioxidants are diminished. This state is called oxidative state and can result in serious cellular damage if the stress is prolonged or massive. Oxidative stress is implicated in the etiopathogenesis of a variety of human diseases. Common element in such diverse human disorders as ageing, neurodegeneration, cancer, arthritis and many others is the involvement of partially reduced forms of oxygen.

Oxidative stress induced by free radicals disrupts the equilibrium of biological systems by damaging the major constituent molecules, including proteins, lipids and DNA, leading eventually to cell death. Polyunsaturated fatty acids (PUFA) within the cell membrane and lipoprotein are particularly susceptible to oxidative attack (lipid peroxidation), often as result of metal ion- dependent hydroxyl radical formation. Following initiation by a single radical, if oxygen is present, long chain of lipid peroxides may be formed by a rapid free radical chain reaction causing serious disruption of cell membrane function²².

Protein exposed to free radical attack may get fragmented, cross-linked or aggregated. The consequences include interference with ion channels, failure of cell receptor function and failure of oxidative phosphorylation. Free radical-induced damage to DNA may cause destruction of bases and deoxyribose sugars or single and double strand breaks.

The brain, under conditions of stress is in a high state of metabolic activity. The "leakage" of high-energy electrons along the mitochondrial electron transport chain causes the formation of O₂ and H₂O₂. The production of mitochondrial superoxide radicals occurs primarily at two discrete points in the electron transport chain, namely at

complex I (NADH dehydrogenase) and at complex III (ubiquinone-cytochrome c reductase). Under normal metabolic conditions complex III is the main site of ROS production.

ANTIOXIDANTS

Antioxidants can be defined as substances whose presence in relatively low concentrations compared to that of utilizable substances, significantly inhibit or delay the oxidation of that substrate (e.g. Lipid/Protein/DNA). Primarily they function as blockers of radical processes. Antioxidants may be enzymes that catalyze the breakdown of free radicals, those that prevent the participation of transition metal ions in free radical generation and free radical scavengers.

The antioxidant enzymes superoxide dismutase, catalase and glutathione peroxides exist to catalyze the reduction of oxidants primarily in the intracellular environment. These enzymes are present in mitochondria and cytosol. The enzyme superoxide dismutase (SOD) catalyzes the conversion of O₂ into H₂O₂. Catalases remove hydrogen peroxide, are found in peroxisomes in most of the tissues, and probably serve to remove peroxide generated by peroxisomal oxidase enzymes. Glutathione peroxidases are major enzymes that remove hydrogen peroxide generated by SOD in cytosol and mitochondria, by oxidizing the tripeptide bearing a thiol group, glutathione (GSH) into its oxidized form (GSSG). Glutathione is the brain's dominant free radical scavenger and it is a tripeptide composed of glutamate, cysteine and glycine. It shuttle between reduced monomeric form (GSH) and oxidized dimeric form (GSSG) in the scavenging process. The source of oxidative stress and consequences of oxidative stress are reviewed in Berk *et al*²³ and summarized in Figure 1.

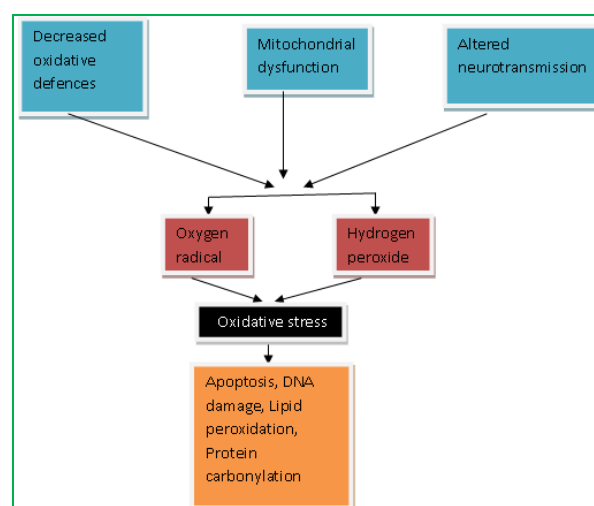


Figure 1: Sources of oxidative stress and its further implication

The central nervous system shows increased susceptibility to oxidative stress because of its high oxygen consumption rate (20% of the total oxygen inhaled by the body) that accounts for the increased generation of oxygen free radicals and reactive oxygen substrates like

superoxide radical (O_2^-), singlet oxygen (1O_2), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH \cdot). Brain has a low level of anti oxidative defense system. The concentration of various anti oxidative enzymes like SOD, GPX, GRd, and catalase is low in brain. The Glutathione (GSH), concentration is also very much reduced in the brain when compared to other various organs in the body. In addition to these factors, brain has high concentration of ascorbate and iron in certain regions, which provide favorable environment for the generation of oxygen free radicals. Brain is also enriched with polyunsaturated fatty acids (PUFA) that render them susceptible to oxidative attack. This burden is increased by a number of factors, including the oxidative potential of monoamines such as glutamate, as well as Generation of secondary oxidative cellular insults through the neurotoxic effects of released excitatory amines (particularly dopamine and dopamine) and secondary inflammatory responses. Due to lack of glutathione-producing capacity by neuron, the brain has a limited capacity to detoxify ROS. Therefore, neurons are the first cells to be affected by the increase in ROS and shortage of antioxidants and as a result, are most susceptible to oxidative stress. This burden is increased by a number of factors, including the oxidative potential of monoamines such as glutamate, as well as the vulnerability of the brain's lipid components to oxidation.

Factor that enhance brain's susceptibility to oxidative damage:

1. High Oxygen utilization (Thus generating higher amounts of free radical by-products).
2. Biochemical environment conducive to oxidation.
 - a. High lipid content.
 - b. Reducing potential of neurotransmitter.
 - c. Presence of redox-catalytic metals e.g iron and copper.
3. Relatively limited antioxidant defenses.
4. Generation of secondary oxidative cellular insults through the neurotoxic effects of released excitatory amines (particularly dopamine and dopamine) and secondary inflammatory responses.

Although production of free radical is a part of normal physiological function but excess of it has potential to damage most of content of the cell, including DNA damage, Lipid peroxidation.

ROLE OF OXIDATIVE STRESS IN PSYCHIATRIC DISORDER

The greatest volume of oxidation biology data are present in schizophrenia. Demonstration of the antioxidative effects of established therapeutic agents and clinical trials of antioxidant therapies complete the evidence base. Such manifold evidences strengthen the hypothesis, that oxidative stress is a common pathophysiological process in major psychiatric disorder. As the direct measurement

of free radical concentration is not possible because of their short half life and low concentration, oxidative status was estimated by assay of reactive species metabolites (e.g nitric acid metabolites), Antioxidant enzyme (e.g superoxide dismutase, catalase, glutathione peroxidase), antioxidants (e.g GSH, vitamin C and E, albumin and bilirubin) and oxidation products (e.g lipid peroxidation products). In the essence these studies have demonstrated reduced concentration of antioxidants such as albumin and bilirubin in schizophrenia, GSH dysregulation and increased lipid peroxidation products.

Several theories based on brain neurotransmitter imbalances like dopamine, serotonin, glutamate, adrenergic and GABergic etc have predominated the schizophrenia research. Multiple lines of evidence suggest that a dysfunction in the glutamatergic neurotransmission via the N-methyl-D-aspartate (NMDA) receptors contributes to the pathophysiology of schizophrenia²⁴.

The hypothesis that some deficiency in NMDA function might play a role in the pathophysiology of schizophrenia is supported by observations that administration of NMDA glutamate receptor antagonists such as phencyclidine (PCP) or ketamine induces psychosis in rodents²⁵ as well as in humans²⁶. Since it was found in many studies that NMDA receptor antagonist like ketamine induce perceptual abnormalities, psychosis like symptoms and mood change in healthy human and patients with schizophrenia. Glutamate level was also found to be increased in these patients. This raised glutamate may cause excitotoxic damage by binding to non-NMDA receptors, increasing calcium input, enhancing the neuronal NOS activity and thereby increasing NO production.

NO generation may have several deleterious effects on cells. It can produce hydroxyl as well as nitrogen dioxide radicals and reacts with superoxide radicals produced elsewhere in cell (e.g mitochondria or the NADPH oxidase), or can be produced by nNOS itself particularly in conditions of low arginine or high oxygen; to form peroxynitrite, which kills the neuron by activating mitochondrial permeability transition. The effects was prevented by L-arginine or by nNOS inhibitor and peroxynitrite and superoxide scavenger in cultured neurons²⁷.

As NO or peroxynitrite inhibit cytochrome oxidase which increases ROS production. Since a bidirectional relationship exist between neurotransmitter activity and oxidative stress and places the relevance of oxidative stress mechanism within the more familiar context of neurotransmitter pathogenesis theories²⁸. As an example, hyperdopaminergic state associated with psychosis and mania might increases oxidative stress, whereas oxidative stress might impinge on neurotransmitter metabolism, leading to dopamine auto-oxidation and impaired glutamatergic neurotransmission. Illness also has been associated with oxidative stress together with decreased level of brain –derived neurotrophic factor, implicating



oxidative stress in the pathway leading to neurostructural and neurofunctional changes in schizophrenia. Several factor might contributing to mitochondrial dysfunction and ROS production are summarized in Figure 2, which ultimately leads to cellular dysfunction.

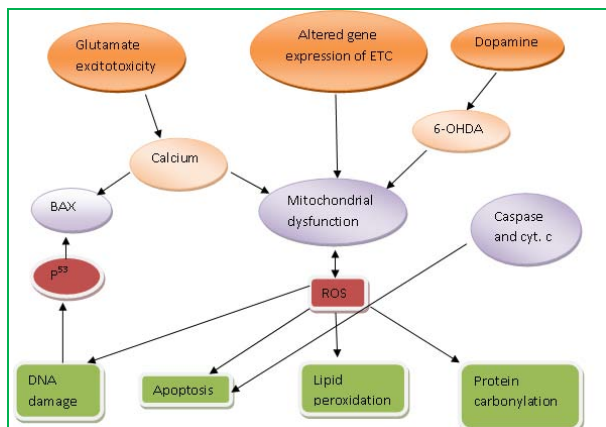


Figure 2: Factor contributes to ROS Production and its further consequences.

Level of nitric oxide metabolites and antioxidant enzymes has been reported to altered in these disorder, but the results have been less consistent, perhaps reflecting differences in tissue specimen, diagnosis, illness phase^{13,14,15,28,31}. There are evidences of increased NO production in the postmortem brain tissue of patients with schizophrenia and increased concentration of NOS in the cerebellum region. Taken together these finding further supports the theory that the theory that NO is involved in the free radical pathology of schizophrenia.

In addition to superoxide and hydroxyl radicals, a pathway to excess free radical generation and subsequent oxidative stress is the formation of peroxynitrite by a reaction of nitric oxide and superoxide radical (Figure 3).

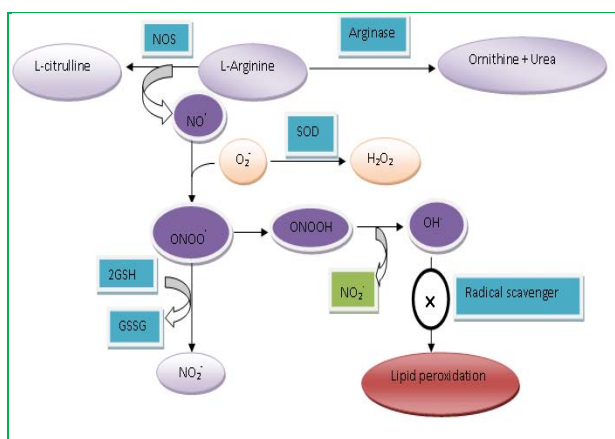


Figure 3: Production of nitric oxide radicals and fate of peroxynitrite pathways

Some studies has been reported that high level of NO induces neuronal cell death by causing inhibition of mitochondrial cytochrome oxidase in neuron^{32,33}. NO inhibition of neuronal respiration caused neuronal depolarization and glutamate release and followed by excitotoxicity by glutamate receptor³²⁻³⁶. This

excitotoxicity may be potentiated by second mechanism, as NO from iNOS results in glutamate release from astrocytes via calcium release from intracellular stores stimulating exocytosis of vesicular glutamate release³⁷. Thus inflammatory – activated astrocytes maintained a higher extracellular glutamate level, which is probably not sufficient to induce excitotoxicity alone, but may well be sufficient if in addition neuronal respiration is inhibited so that NMDA receptors is activated by both depolarization and glutamate. This irreversible damage to respiratory complexes may be mediated by:

1. Oxidation or nitration of the respiratory complex by peroxynitrite.
2. NO - induced glutamate release and excitotoxicity, as it is blocked by NMDA receptor antagonists.
3. NO or Peroxynitrite inhibition of cytochrome oxidase causing ROS production resulting in secondary damage of other respiratory complexes (possibly by peroxynitrite).

Since it was found in many studies that NMDA receptor antagonist like ketamine induce perceptual abnormalities, psychosis like symptoms and mood change in healthy human and patients with schizophrenia. Glutamate level was found also to be increased in these patients and glutamate induced excitotoxicity is reason behind neuronal cell death in schizophrenia. It might be due to the reason as in schizophrenia there is hypofunctional state of NMDA receptor and for experiment purpose which is produced by NMDA receptor antagonist. To compensate this hypofunction glutamate level get increased in synaptic cleft, at least partially, have been attributed to the blockade of NMDA receptor located on inhibitory GABAergic neuron^{38,39}. This disinhibitory action has been reported to increase the neuronal activity and excessive glutamate release in limbic striatal regions^{40,41}. This process has been summarized in Figure.4

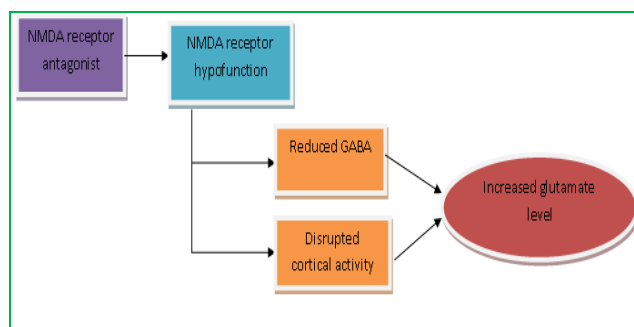


Figure 4: Conceptual relationship between NMDA receptor antagonist model of psychosis and schizophrenia.

Glutamate has close relation to neuron cell death, as glutamate is fastest excitatory neurotransmitter in the human brain. Since glutamate is a NMDA receptor agonist and nNOS in neuron is partly bound close to the NMDA receptor and is activated by calcium entering via the receptor gated ion channel. Binding of glutamate to NMDA receptor open receptor gated ion channel which also activate nNOS. This increases formation of NO, which by feedback mechanism further regulate release of

glutamate. In this way nNOS synthetase inhibitor might be reduce glutamate mediated excitotoxicity in schizophrenia. Extracellular glutamate activates neuronal NMDA receptor (NMDAR) and AMPA receptors (AMPA), which decrease plasma membrane potential, which increases cytosolic calcium and activate NMDAR, which also increases calcium. Calcium elevation may:

1. Stimulate nNOS production of NO and peroxynitrite, which activates mitochondrial permeability transition (MPT) and activate poly ADP-ribose polymerase(PARPP), which induces death by energy depletion and induces AIF release from mitochondria.
2. Activate MPT, which induces death by energy depletion or AIF release, which induces DNA strand breaks.
3. Activates calpain, which induces AIF release and BID cleavage, which may itself induce AIF release and cytochrome C release, which activate caspases. Caspases cause neuron cell death. This all mechanism has been explained in Figure 5.

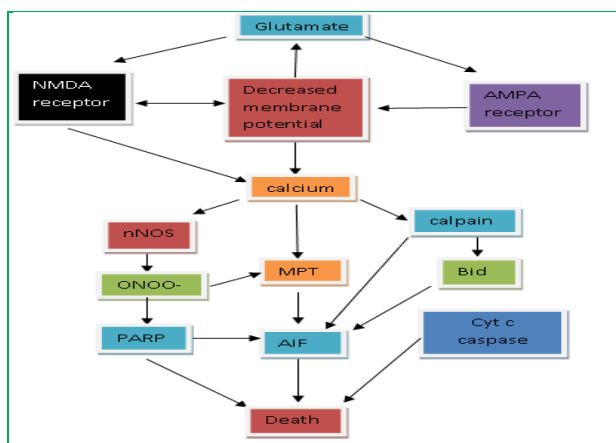


Figure 5: Mechanism of glutamate- induced neuronal death

As NO or peroxynitrite inhibit cytochrome oxidase which increases ROS production. Since a bidirectional relationship exist between neurotransmitter activity and oxidative stress and places the relevance of oxidative stress mechanism within the more familiar context of neurotransmitter pathogenesis theories⁴². As an example, hyperdopaminergic state associated with psychosis and mania might increases oxidative stress, whereas oxidative stress might impinge on neurotransmitter metabolism, leading to dopamine auto-oxidation and impaired glutaminergic neurotransmission. Illness also has been associated with oxidative stress together with decreased level of brain derived neurotrophic factor, implicating oxidative stress in the pathway leading to neurostructural and neurofunctional changes in schizophrenia.

Under physiological condition, free radical damage can be balanced by the antioxidant defense mechanism (Figure 6), compromised of a series of enzymatic and non-enzymatic components i.e SOD, CAT, GSH-Px as well as vitamin C and E. These enzymes act cooperatively at different site in the metabolic pathway of free redicals. Superoxide dismutase catalyzes the conversion of

superoxide radical to hydrogen peroxide. Catalase and glutathione peroxidase convert hydrogen peroxide to water. Glutathione peroxidase (GSH-Px) use glutathione (GSH) to yield oxidized form of glutathione, which is converted back to glutathione by glutathione reductase. Hydrogen peroxide is susceptible to auto-oxidation to form hydroxyl radicals, particularly in the presence of metal catalysts such as iron. Produced free radical induce metabolism enzyme activity to a certain degree, while excess free radical such as superoxide and hydroxyl radicals will, in turn, injure enzyme, so that more free radical are accumulated. Some studies reported that there is increase in free radical generation in schizophrenia and antioxidant defense is impaired⁴³. The free radical plays an important role in the genesis of neuronal membrane that could be responsible for the beginning and aggravation of the basic disease^{44,45}. The brain and nervous system possess high potential of the initiation of free radical reaction, which relative to other tissue can cause more damage in brain and nervous system due to insufficient antioxidant protection and existing intensive aerobic metabolism accompanies with oxygen radical production⁴⁶. There are several mechanism by which free radical may be generated in the brain.

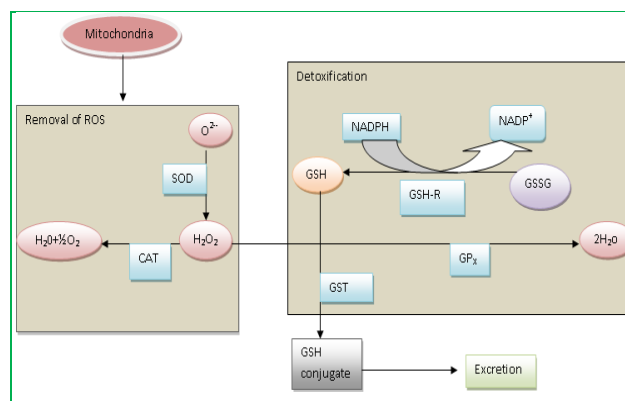


Figure 6: Oxidative defense mechanism. Mitochondrial respiration leads to the production of ROS including superoxide O_2^- and H_2O_2 Removal of the ROSs might be via superoxide Dismutase (SOD) and subsequently by catalase or through glutathione pathway. GSH reduce H_2O_2 to water catalysed by glutathione peroxidase (GPx). GSSG is then reduced by glutathione reductase (GSH-R).

The metabolism of catecholamine such as dopamine and norepinephrine is probably associated with free radical production and condition associated with increased catecholamine metabolism may increase the free radical burden. Of the different brain regions the basal ganglia may be particularly at risk for radical induce damage because they contain large amount of iron (which can associated with increased free radical production through the fenton reaction). Increased erythrocyte superoxide dismutase activity was found in patients with schizophrenia, which could be an adaptive response of these enzymes to increased production of oxygen following oxidative decomposition of catecholamines⁴³. It is likely that sustained oxidative stress may increase SOD and CAT activity. Decreased antioxidant defense probably

exist later in patients under chronic treatment with neuroleptics^{21,47}. The changes in activity of antioxidant enzyme might offer some important clue to explain pathologic mechanism of abnormal free radical metabolism. The free radical produced during the metabolism of catecholamines may result in neurotransmission abnormalities at dopamine terminals. The brain has certain attributes that make it exceptionally vulnerable to free radical attack. It has highly oxygenated structures responsible for almost one-fifth of the body's total oxygen. Endogenous antioxidant glutathione have a close relation to NMDA receptor. The NMDA receptor possesses an extracellular redox site which modulates the NMDA response⁴⁸. In the absence of glutathione, the glutamate-induced depolarization is minimal, while in presence (100Um-mM range) this response is maximally increased³³. As glutathione is released by cell depolarization⁴⁹ and assuming that an intracellular glutathione deficits reflects itself by an extracellular one (the exact synaptic concentration of it being difficult to estimate), it can be hypothesized that in case of a pathological glutathione deficit this potentiation would be perturbed, leading to an under activation of NMDA receptor. Endogenous antioxidant Glutathione, the major intracellular non-protein thiol, is known as a nucleophilic scavenger and an enzyme catalysed antioxidant, and plays an important role in protecting the brain against oxidative stress and harmful xenobiotics^{50,51}. On other hand, Glutathione is known to potentiate the NMDA receptor response to glutamate⁴⁸. Glutathione is released into the extra cellular space, predominantly in the cortex⁴⁹ and glutathione has been proposed to play a neuromodulator/ neurotransmitter role (Figure 7).

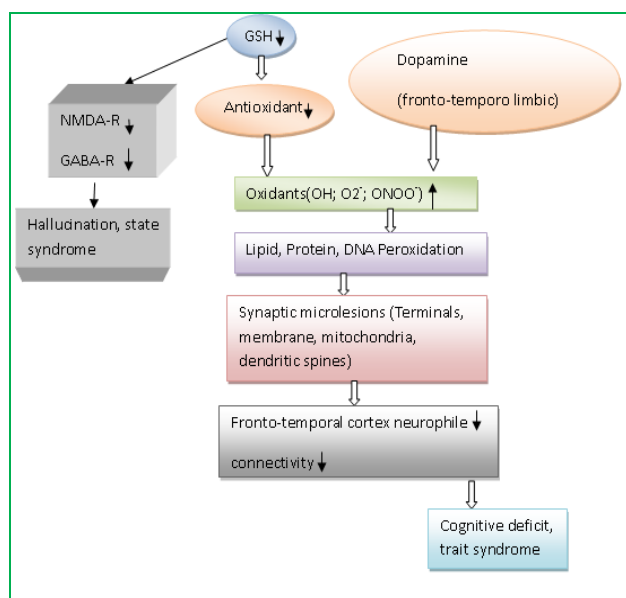


Figure 7: Flow diagram describing the relation of glutathione to schizophrenia

A glutathione deficit could affect dopaminergic and glutaminergic signaling mechanisms, thus indirectly decreasing the efficacy of NMDA-receptor activation when dopamine receptors are stimulated. This idea is

supported by the fact that glutathione is known to contribute to enzymatic phosphorylation/dephosphorylation which are potentially important for functional modification of receptors. Such a mechanism would be of particular interest in view of the fact that most antipsychotic drugs are antagonist of the dopamine receptor as GSH was found to be decreased in schizophrenia, along with decreasing antioxidant defence it also affect affinity of glutamate to NMDA receptor. This phenomena leads to hypofunctional state of NMDA receptor. So in schizophrenia oxidative stress plays important role in initiation and further progression of disease⁵²⁻⁵⁴.

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