

*Full Length Research Paper*

# Oxidative injury and enzymic antioxidant misbalance in schizophrenics with positive, negative and cognitive symptoms

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With its hallucinations, delusions, thought disorder, and cognitive deficits, schizophrenia affects the most basic human processes of perception, emotion, and judgment. Evidence increasingly suggests that schizophrenia is a subtle disorder of brain development and plasticity and oxidative injury contributes largely to pathophysiology of schizophrenia, indicated by the increased lipid peroxidation products in plasma and altered levels of enzymatic antioxidants in schizophrenic patients. However, the status of antioxidants and the extent of lipid peroxidation in erythrocytes have not been investigated so far in schizophrenia patients with different symptoms. In the present study, in order to examine the antioxidant status and lipid peroxidation in the schizophrenics with positive, negative and cognitive symptoms, the activities of three free radical scavenging enzymes glutathione transferase (GST), glucose-6-phosphate dehydrogenase (G6PD), ceruloplasmin ferroxidase (Cp) and the level of thiobarbituric acid-reactive substances (TBARS) as an index of lipid peroxidation were analyzed. Results showed that there was a significant increase in GST activity in all the schizophrenics when compared to normal and it was observed that there was a significant decrease in erythrocyte, G6PD and ceruloplasmin ferroxidase levels in patients with schizophrenia, when compared to controls. Schizophrenics with positive symptomology were found to have pronounced decrease in the activities of Cp ferroxidase and statistically more significant decrease in G6PD levels were found in patients with negative symptoms. Further a significant rise in oxidative stress and decreased secondary enzymic antioxidant status was observed in the chronic stage of schizophrenics as compared to those in acute condition. The study showed that the level of malondialdehyde was increased in schizophrenics with positive (163%), negative (137%) and cognitive (132%) symptoms compared to control groups. The increased activities of antioxidant enzymes may be a compensatory regulation in response to increased oxidative stress. The decreased concentrations of the antioxidants status support the hypothesis that lipid peroxidation is an important causative factor in the pathogenesis of schizophrenia. These data reveal that antioxidant defense mechanisms might be impaired in schizophrenic patients. Understanding these basic pathologic processes may yield novel targets for the development of more effective treatments.

**Keywords:** Schizophrenia, symptoms, secondary antioxidant enzymes, malondialdehyde (MDA), oxidative stress.

## INTRODUCTION

Schizophrenia is a debilitating, hereditary, mental disorder of the brain, resulting from abnormalities that

arise 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  $24 \pm 4.6$  years) in many cultures around the world (Sawa and Synder, 2002). In general, schizophrenia has symptoms that fall into three categories — negative, positive and cogni-

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tive (France, 2006). Signs and symptoms that occur continuously and progressively may indicate schizophrenia. The etiology of this psychiatric disorder is still remains elusive. In the last few decades, dopamine hyperactivity hypothesis predominates in the research field all the time. Recently more and more converging evidence indicates that oxidative mechanisms may play a role in schizophrenia (Lohr and Browning, 1995; Akyol et al., 2004). 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 symptoms (Yao et al., 2001).

Free radicals, primarily the reactive oxygen species, (ROS), super oxide and hydroxyl radicals, which are highly reactive, having an unpaired electron in an atomic or molecular orbit, are generated under physiological conditions during aerobic metabolism. As free radicals are potentially toxic, they are usually inactivated or scavenged by antioxidants before they can inflict damage to lipids, proteins or nucleic acids. Alteration in the oxidant-antioxidant profile is known to occur in Schizophrenia (Lohar, 1991; Hallowell, 1992). Moreover the body's defense mechanisms would play an important role in the form of antioxidants and try to minimize the damage, adapting itself to the above stressful situation. Antioxidants are compounds that dispose, scavenge and suppress the formation of free radicals, or oppose their actions (Sies, 1991). Normally, the ROS within the cells are neutralized by antioxidant defense mechanisms. Super oxide dismutase (SOD), catalase, and glutathione peroxidase (GSH-Px) are the primary enzymes involved in direct elimination of ROS, whereas glutathione transferase, glucose-6-phosphate dehydrogenase and copper-binding caeruloplasmin are secondary antioxidant enzymes, which help in maintaining a steady concentration of glutathione and NADPH necessary for optimal functioning of the primary antioxidant enzymes (Maehly and Chance, 1954; Gutteridge, 1977; Maddipati, 1987; Vendemiale, 1999). These enzymes require micronutrients as co-factors such as selenium, iron, copper, zinc, and manganese for optimal catalytic activity and effective anti-oxidative defense mechanism (Halliwell, 1994). These enzymes block the initiation of free-radical chain reactions (Mahadik and Scheffer, 1996). If a homeostasis between rate of formation of free radicals and the rate of their neutralization of free radicals is not maintained, an oxidative damage, known as oxidative stress, occurs (Sies, 1991).

The brain makes up about 2% of body mass but consumes 20% of metabolic oxygen. The vast majority of energy is used by the neurons (Shulman et al., 2004). Due to the lack of glutathione-producing capacity by neurons, 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. Lipid peroxidation is a chain reaction between polyunsaturated fatty acids and ROS. It produces lipid peroxides and hydrocarbon polymers that are both highly toxic to the cell (Horton and Fairhurst, 1987). Malonyldialdehyde (MDA) is an end product of peroxidation of polyunsaturated fatty acids and related esters, and is, therefore, used as a marker of lipid peroxidation (Jain, 1984). The plasma MDA contents measured by reaction with thiobarbituric acid (TBA) were higher in 13 of 15 (87%) of psychiatric subjects (Chauhan et al., 2004).

Recent reports (Herken et al., 2001; Akyol et al., 2004; Hui-chun et al., 2006) also indicate increased levels of other lipid peroxidation markers in psychiatric disorders, thus confirming an increased oxidative stress in schizophrenia. Though there is accumulating evidence of altered antioxidant capacity in schizophrenia, studies of antioxidant systems in schizophrenia has produced the usual medley of conflicting results. In the present study, we investigated the antioxidant activities of erythrocyte glutathione transferase, glucose-6-phosphate dehydrogenase and copper-binding caeruloplasmin (secondary antioxidant enzymes) and malondialdehydes as a sign of lipid peroxidation levels in schizophrenic patients with positive, negative and cognitive symptoms. The effects of acute and chronic phase of schizophrenia on the level of these secondary antioxidant enzymes were also analyzed. The present study was undertaken during the month of September 2004 to June 2007, in the Postgraduate and Research Department of Biochemistry, Dr. N.G.P Arts and Science College, with the collaboration of Kovai Medical Centre and Hospital (KMCH), a multi-specialty hospital with a separate division for Psychiatry.

## MATERIALS AND METHODS

### Patients

A total of 60 schizophrenic patients of age group 18 - 65 years of both sexes from good socio-economic background were selected from Udhayam Mananala kaapagam, a mental Health care center, Coimbatore, Tamilnadu, India. The patients were divided into three groups with 20 subjects each: (1) schizophrenics with positive symptoms, (2) schizophrenics with negative symptoms, and (3) schizophrenics with cognitive symptoms. They all met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) criteria (American Psychiatric Association, 2000) for schizophrenia.

The positive symptoms of schizophrenic patients ranged from 19 to 58 (average  $29.8 \pm 11.5$  years), the negative symptoms of schizophrenic patients from 20 to 59 ( $32.7 \pm 12.3$ ) years, and the cognitive symptoms of schizophrenic patients from 22 to 51 ( $36.9 \pm 8.9$ ) years. Sixty age and sex-matched healthy normal control subjects with no individual and familial history of mental illness were recruited to participate in this study.

### Inclusion and exclusion criteria

Both patients and controls were recruited during the same period

**Table 1.** Mean secondary antioxidant enzyme activities and TBARS levels of schizophrenics with different symptoms and P values among the study and control groups. Results were expressed as mean  $\pm$  standard deviation

Schizophrenia Groups	GST U/g of Hb	G6PD U/g of Hb	CpFerroxidase U/g of Hb	Lipid Peroxides nmol MDA*/g of Hb
I. Positive Symptoms	1692 $\pm$ 74a	8.98 $\pm$ 1.63ac	61.09 $\pm$ 21.79a*	10.7 $\pm$ 0.38a*
II . Negative symptoms	1651 $\pm$ 92a	7.14 $\pm$ 2.01a*d*	68.62 $\pm$ 23.24ab	9.62 $\pm$ 0.22a*
III. Cognitive symptoms	1673 $\pm$ 86a	12.31 $\pm$ 1.56ad	64.34 $\pm$ 22.97a	9.13 $\pm$ 0.65a*
IV. Control	1529 $\pm$ 92	18.97 $\pm$ 1.94	89.80 $\pm$ 22.73	7.29 $\pm$ 0.73

a b c d p<0.01

a\* b\*c\* p<0.001

a (statistical significance compared to control group).

b (statistical significance between positive and negative group),

c (statistical significance between positive and cognitive group),

d (statistical significance between negative and cognitive group)

from Coimbatore district. Matching between the patients and controls was done according to sex and age. Study subjects were currently within normal ranges in their routine blood, urine and feces tests, electrocardiograph and radiographs; disorders associated with heart, brain, lung, liver, kidney and other pivotal organs were excluded.

All subjects did not take any antioxidant supplements such as vitamin C, vitamin E, -carotene, any plant based ayurvedha or siddha medicines or other similar substances within one month prior to blood draw. A standard diet was given to all patients.

The design and the layout of this project was carried out with the approval the Chairman, Kovai Medical Center and Hospitals, and due permission was obtained from the board of institutional review Committee of the Kongu Mananala Arakkattalai, before the start of the work.

Informed and written consent was obtained from all subjects prior to examination. Patients with a history of drug abuse or dependence, serious medical conditions, severe head injury or seizure disorders were excluded from the study.

#### Determination of secondary antioxidants and TBARS levels

G6PD activities (EC 1.1.1.49) were assayed according to the procedure described by Beutler (1984). GST activity (EC 2.5.1.18) was determined according to the method of Habig et al. (1974). Cp ferroxidase activity (EC 1.16.3.1) was determined by the method of Gutteridge and Quinlan (2000). TBARS was estimated according to the method of Ohkawa et al. (1979) with minor changes adopted by Devasaghayam et al. (2003). All reagents used were of analytical reagent grade, obtained from Sigma Chemicals, St. Louis, MO, U.S.A and were used without further purification. All the operations accord with the guidelines of the apparatus; and samples were done in triplets. All the values were presented as a mean value  $\pm$  SD. Statistical analysis between control and patient groups were performed by students 't' test. The results were expressed as a difference between the two values. Statistical significance 1% (p<0.01) and 0.1% (p<0.001) protection levels were used for comparison. Statistical tool Sigma Stat v 3.5, Systat Software, Inc. USA was used.

#### RESULTS

Results in Table 1 summarize all analyzed biochemical parameters. Table 1 shows significant increase in erythrocyte antioxidant enzyme GST activities and TBARS levels in all the study groups compared to the control

group. However, there was no significant difference in GST activity among the study groups. The estimation of Cp ferroxidase activity suggests a statistically significant decrease in all groups of schizophrenic patients, which was more expressed in schizophrenics with positive symptoms (61.09  $\pm$  21.79, p< 0.01) in comparison to control values (88.80  $\pm$  22.73). The levels of erythrocyte G6PD were significantly decreased in schizophrenics, compared to controls, but the decrease is statistically more significant in schizophrenics with negative symptoms.

Among all schizophrenics the activity of all antioxidant enzymes more decreased in chronic patients as compared to acute ones (Table 2), and similarly the oxidative stress was found higher in chronic cases as compared to acute.

#### DISCUSSION

The brain contains both enzymatic and non-enzymatic antioxidants against free radical damage. As the intensity of lipid per oxidation and antioxidative defense in erythrocytes to a certain extent reflects the state of the cell membranes of different tissues, including brain tissue (Vilkov et al., 1991), in our present study, we investigated the status of secondary antioxidant enzymes in erythrocytes of schizophrenic patients with positive, negative and cognitive symptoms. Our results indicate that there is an increase in free radical generation and decrease in antioxidant defense mechanism in schizophrenic people when compared to normal subjects. Highly significant increase in MDA and decrease in antioxidants was observed in schizophrenics complicated with various symptoms.

The secondary antioxidant enzymes, that is, G6PD, caeruloplasmin ferroxidase activities have been decreased significantly and GST activity have been increased in schizophrenic patients with positive, negative and cognitive symptoms compared to controls.

G6PD activity was found to be highly decreased in patients with negative symptoms. The role of G6PD defi-

**Table 2.** MDA and Secondary antioxidant enzymic levels of acute and chronic Schizophrenics (Values are mean  $\pm$  SD).

Parameters	Acute Schizophrenics	Chronic Schizophrenics
<b>GST (U/g of Hb)</b>	1742 $\pm$ 84	1613 $\pm$ 67*
<b>G6PD (U/g of Hb)</b>	8.98 $\pm$ 1.63	6.79.21 $\pm$ 2.97*
<b>Caeruloplasmin Ferroxidase (U/g of Hb)</b>	74.97 $\pm$ 21.80	59.28 $\pm$ 21.55*
<b>Lipid Peroxides nmol MDA*/g of Hb</b>	7.26 $\pm$ 0.523	12.92 $\pm$ 0.791*

Statistical comparison was done between acute and chronic Schizophrenics \*p < 0.001

ciency in psychiatric disorders has not been definitely established, studies varying from reports of acute psychotic cases to surveys of enzyme activity in hospitalized populations (Dern et al., 1963; Bowman et al., 1965; Fieve et al., 1965; Nasr et al., 1982). The first study dates back to 1962, when Dern et al. (1963) reported that there was a decrease in the activity of G6PD who suffered with acute psychosis. Interestingly, the activity of the hexose monophosphate shunt, whose first step is catalyzed by G6PD, can be stimulated in the brain by monoamine transmitters, perhaps in relation with the detoxication of monoamine-oxidase-dependent metabolites (Maker et al., 1981; Hothersall et al., 1982).

With regard to catatonic features and negative symptoms, Dern et al. (1963) had already raised the hypothesis of a potential role of G6PD deficiency, even though the context was that of schizophrenia subtypes. Their hypothesis was based on results from a survey of 351 Afro-American patients hospitalized for schizophrenia for longer than 8 months in Illinois. According to our results, G6PD deficiency was significantly in excess in the negative symptoms, (where catatonic features are dominant) in comparison to positive (paranoid) and cognitive cases especially in early onset cases. Our results are consistent with Bocchetta (2003) who stated that G6PD deficiency is the most peculiar pattern of acute psychiatric manic episodes, mostly characterized by loosening of association, agitation, catatonic symptoms, and/or transient confusion, concurrent hyperbilirubinemia, positive psychiatric family history, and partial response to long term lithium treatment. G6PD-deficiency rates were in excess in catatonic compared with paranoid subtypes (Bowman et al., 1965). In view of such controversial reports the hypothesis of a role of G6PD deficiency in different symptoms of schizophrenia has to be concentrated more in future.

Human Caeruloplasmin (Cp) is officially known as ferroxidase or iron (II): oxygen oxidoreductase. Our results showed the decreased ferroxidase in all schizophrenics. Erythrocytes have been extensively studied as a susceptible target for oxidative damage, since they are long-lived cells and very rich in Fe<sup>2+</sup>-containing molecules, primarily Hb, that generates oxygen radicals (Fung and Zhang, 1990; Glen et al., 1994). Recently, Kim et al. (1998) observed that Cp can catalytically remove hydrogen peroxide in the presence of thiols. The glutathione

peroxidase-like activity of Cp together with its ferroxidase activity would completely remove the primary reactants required for both Fenton chemistry and lipid peroxidation in brain.

Human glutathione transferases (GSTs) were shown to catalyze the reductive glutathione conjugation of aminochrome (2-3 dihydroindole-5, 6-dione). Dopamine, like other catecholamines, can be oxidized to the corresponding o-quinone (Hawley et al., 1967; Graham, 1978; Segura and Lind, 1989). The formation of catecholamine o-quinones is followed by cyclization involving the amino group of their side chains. The reduction of aminochrome, dopachrome, noradrenochrome, and adrenochrome is accompanied by their subsequent reoxidation by oxygen, which gives rise to reactive chemical species (Baez et al., 1994; Baez and Segura-Aguilar, 1994; Linderson et al., 1994; Baez and Segura-Aguilar, 1995). The oxidative conversion of dopamine into aminochrome (2,3-dihydroindole- 5,6- dione) and its subsequent reduction and reoxidation by oxygen are believed to be the cause of neurodegenerative processes in the dopaminergic system (Baez et al,1995).and in the mesolimbic system in schizophrenia (Cadet and Kahler, 1994; Smythies, 1996). Increased GST activity in our results may reflect a preceding oxidation of catecholamines or serve as a compensatory mechanism.

Examination of oxidative stress and antioxidant status revealed that the MDA level an indicator of oxidative stress was found to be significantly raised (P<0.001) in schizophrenics with various symptoms especially positive symptoms as compared to control subjects ranging in age from 15 to 65 years. Increased TBARS levels in erythrocyte from our schizophrenia patients are consistent with the previous results (Horrobin et al., 1991; Keshavan et al., 1993; Herken et al., 2001, Hui-chun et al, 2006).

Taken together, the data suggest that changes in susceptibility of erythrocyte lipids to peroxidation observed in schizophrenics with positive, negative and cognitive symptomatology may be explained in part by changes in levels of saturated and unsaturated fatty acids in RBC membranes in various types of schizophrenic subjects. Glen et al. (1994) suggest that negative symptoms are associated with high levels of saturated fatty acids and low levels of long-chain unsaturated ones in RBC membranes, while positive symptom patients show

the opposite picture (Graf et al., 1984). On the basis of these findings, it may be concluded that schizophrenic patients with positive symptoms are faced with increased oxidative stress. The increase in the ROS in the RBC membrane through various mechanisms might be the reason for the increased TBARS levels. The other possible explanation for the increased TBARS levels in red blood cells from patients in schizophrenia sub-groups is increased catecholamine metabolism and a resultant overproduction of ROS following neuroleptic drug treatment (Mahadik and Scheffer, 1996).

Lipid peroxidation is an autocatalytic process, which ultimately results in cell death (D'Souza and D'Souza, 2002). Because of continuous generation of free radicals by the oxidation of hemoglobin, erythrocytes are exposed to continuous oxidative stress, which ends in insufficient neutralization of free radicals causes oxidation of cellular lipids (Afanas'ev, 2005). Therefore it is claimed that the long-term chronic complications of schizophrenics are related to the accumulation of increased free radicals and lipid peroxidation. Analyzing the above data, it is predicted that the antioxidant defense mechanisms might be highly impaired in schizophrenic patients and lipid peroxide metabolites were high in schizophrenics with positive symptoms and chronic schizophrenics.

Among all schizophrenics the activity of all the secondary antioxidant enzymes were more decreased in chronic patients as compared to acute ones and similarly the oxidative stress was found higher in chronic cases as compared to acute. Further on comparing the levels of these enzymes in acute and chronic patients, its level depleted significantly in chronic subjects due to the increased oxidative stress levels found in chronic patients. Results in Table 2 indicates that the GST, G6PD, and cp ferroxidase levels in chronic schizophrenics were decreased as compared to acute, attributed to the antioxidant deficit due to chronic phase of schizophrenia. Taken together, the above data reveal that antioxidant defense mechanisms might be impaired in schizophrenic patients. These findings also provide a theoretical basis for the development of novel therapeutic strategies, such as antioxidant supplementation. This may suggest the hope for use of antioxidants in clinical trials to prevent and treat schizophrenic patients.

## Conclusion

In this work, we analyzed the various disturbances of the antioxidant systems in schizophrenics with various symptoms. A fall of the activities of the secondary antioxidant enzymes (glutathione-S-transferase, glucose-6-phosphate dehydrogenase, and caeruloplasmin ferroxidase) as well as an increase in the peroxidation of the lipids was noted among schizophrenic patients. These disturbances are investigated with the severity of the positive, negative, and cognitive signs of the disease. These results show that positive symptomatic study sub-

jects and chronic schizophrenia patients have more oxidative stress.

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