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Impaired antioxidant defense at the onset of psychosis

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Abstract

Previous studies found peripheral activities of antioxidant enzymes to be abnormal in schizophrenic patients. It is not understood whether this is integral to the disease process or a result of long-term treatment with neuroleptics. Red blood cell activities of three antioxidant enzymes – superoxide dismutase, glutathione peroxidase, and catalase – were therefore examined in 14 drug-naive, first episode patients with a diagnosis of schizophrenia or schizophreniform disorder and 10 normal subjects. The patients had an average duration of psychosis of 4.46 days (SD 2.5). Superoxide dismutase activity was significantly lower in patients than in normal controls, with no difference between the groups in activities of the other two enzymes. Lower superoxide dismutase activity was associated with deterioration of school functioning from childhood to early adolescence and a history of poorer school functioning during early adolescence. These findings indicate a compromised antioxidant defense at the onset of psychosis, and suggest that oxidative injury might contribute to adverse developmental events in the pathogenic cascade of schizophrenia.

Keywords: Oxyradical; Superoxide dismutase; Glutathione peroxidase; Catalase; (Schizophrenia)

1. Introduction

Free radicals are chemical species with an unpaired electron in one of their orbits. Production of oxygen free radicals (oxyradicals) is a ubiquitous event during cellular aerobic metabolism. If produced in excess, or not removed effectively, oxyradicals result in cellular damage, such as peroxidation of membrane lipids, oxidation of proteins, and damage to DNA. The physiology of free radical metabolism has been extensively reviewed (e.g., Halliwell and Gutteridge, 1989; Miguel et al., 1989), and only a few salient features are mentioned here. Under physiological conditions, damage from oxyradicals is prevented by a complex cellular antioxidant defense. A critical components of this comprise the antioxidant enzymes superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), which work in a sequential and concerted manner. SOD dismutates superoxide ($\cdot O_2^-$) to yield hydrogen peroxide (H_2O_2) and oxygen [$2\cdot O_2^- + 2H^+ = H_2O2 + O_2$]. H_2O_2 is also formed during the oxidation of amino acids by amino acid oxidase, mono-

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amine oxidase, and xanthine oxidase. H_2O_2 is not an oxyradical because it does not have an unpaired electron, but it must be promptly removed by either GPx or CAT. Otherwise, in the presence of transition metals, it is converted to hydroxyl ion (·OH) [$Fe^2 + H_2O_2 = Fe^{3+} + \cdot OH + OH^-$], the most toxic radical known. In the presence of transition metals, $\cdot O_2^-$ can also be directly converted to ·OH. Further, $\cdot O_2^-$ reacts with nitric oxide (NO) to form the oxyradical peroxynitrite (·ONOO). Thus, high SOD activity, which results in increased H_2O_2 production, must be accompanied by increased GPx and/or CAT activity to limit injury by ·OH radicals. On the other hand, low SOD activity will result in inefficient removal of $\cdot O_2^-$ and increased oxidative injury to cellular elements by ·OH and ·ONOO.

Oxidative tone refers to the amount of oxyradicals produced and, in humans, this cannot be directly measured in vivo. Oxidative stress is determined by the balance between oxidative tone and adequacy of the antioxidant defense. Thus, an inefficient antioxidant defense could result in oxidative stress and injury even when oxidative tone is not increased. This provides a rationale for examining elements of the antioxidant defense system in disease states.

Red blood cell (RBC) activities of antioxidant enzymes have been found to be altered in chronic schizophrenic patients. SOD activity has consistently been found to be high (Michelson et al., 1977; Golse et al., 1978; Abdalla et al., 1986), with one exception (Sinet et al., 1983). GPx activity has been found to be either normal or low (Stoklasova et al., 1985; Abdalla et al., 1986), and lower GPx activity has been found to be associated with greater cortical sulcal prominence on CT scan (Buckman et al., 1987). CAT activity has been found to be low (Glazov and Mamzev, 1976). Only one published study examined RBC activities of all three antioxidant enzymes (Reddy et al., 1991). In that study, relative to normal controls, medicated chronic schizophrenic patients had higher SOD activity, which indicates increased oxidative tone, normal GPx activity, and lower CAT activity. This profile indicates a decreased protection against oxidative injury, particularly by ·OH, which could result in peroxidation of membrane lipids. This is consonant with reports of high levels of membrane lipid peroxidation products in plasma (Prilipko, 1984; Peet et al., 1993; Mahadik et al., 1995) and cerebrospinal fluid of schizophrenic patients and neuroleptic treated patients, particularly those with movement disorders (Pall et al., 1987; Lohr et al., 1990).

It is unclear from the above findings whether there is a fundamental deregulation of antioxidant defense in schizophrenia or whether these reflect effects of long-term neuroleptic treatment. Studies in humans (Reddy et al., 1992; 1993), animals (Szabo et al., 1983; Roy et al., 1984; Murthy et al., 1989; Cadet and Perumal, 1990), and in vitro (Yamamoto et al., 1960), indicate that neuroleptics can alter antioxidant enzyme activities in both peripheral tissues and brain. To determine whether schizophrenia is associated with an abnormal antioxidant defense, we examined RBC activities of antioxidant enzymes in drug-naive patients during a first episode of psychosis.

2. Subjects and methods

The sample comprised 14 patients with schizophrenia ($n = 10$) or schizophreniform disorder ($n = 4$) and 10 normal controls. The patients were active duty service personnel admitted at the D.D. Eisenhower Army Medical Center at Fort Gordon, GA, for a first episode of psychosis. Normal controls were volunteers recruited from the Medical College of Georgia or the community. The research was approved by institutional review boards of both institutions. DSM-IIIR diagnoses were based on a clinical interview using the Structured Clinical Interview for DSM-IIIR Diagnoses (SCID) at baseline and clinical evaluations over the first six months of illness. Normal controls were screened using the SCID: Nonpatient Version. Four patients, who at six month follow-up did not meet DSM-IIIR criteria for either schizophrenia or schizophreniform disorder, and one schizophrenic patient who had received 11 doses of a neuroleptic at the time of admission to the protocol, were not included in this study. All subjects were medically healthy, and none had a history of seizures or severe head injury with loss

of consciousness, or a history of substance abuse within the last year. Additionally, normal controls had a negative history of psychosis, major mood disorder, dementia, and mental retardation in their first degree relatives. All patients had a negative urinary drug screen and laboratory values (SMA 18) were in the normal range.

The clinical state of the patients was evaluated independently by two of the authors (E.E.C. and R.S.) at baseline and findings recorded on an anchored Brief Psychiatric Rating Scale. Only the pretreatment baseline BPRS total scores, positive symptom scores (sum of scores on items of conceptual disorganization, hallucinatory behavior, unusual thought content, and suspiciousness), and negative symptom scores (emotional withdrawal, blunted affect, and motor retardation) are examined in this report. Interrater reliability was satisfactory for all three variables (intraclass correlations >0.85). Premorbid adjustment during childhood (upto age 11 years) and early adolescence (ages 11–14 years) was evaluated using the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982), with information from the patient, as well as a parent. For each period, data were analyzed separately for items reflecting social functioning (peer relationships and sociability–withdrawal) and those reflecting instrumental functioning (scholastic performance and adaptation to school). The rationale for this approach has been discussed elsewhere (Mukherjee et al., 1991).

At the time of blood drawing, 11 patients had never been treated with an antipsychotic drug, and three had received a single dose of neuroleptic. The latter underwent a 4 day washout before blood drawing. Venous blood samples were drawn in the morning, placed in polyethylene tubes containing 0.1 ml EDTA, and transferred to the laboratory at the VA Medical Center where they were immediately processed. The blood was centrifuged at 2500 rpm for 10 minutes at 4°C. The RBC pellet was washed twice with equal volume of saline, and centrifuged at 2500 rpm for 3 min. Washed RBCs were stored at −70°C until assay. Samples were identified only by code numbers, and all assays were conducted blind to the diagnostic status of donors. Enzyme assays were done in triplicate and the average used to calculate specific activity.

Hemolysate was prepared by diluting with 10 volumes of distilled water, and membranes were removed by centrifugation at 10,000 rpm for 15 minutes at 4°C. SOD activity was determined using a spectrophotometric method (Nikishimi et al., 1972; Fried et al., 1975) and comparing with standard human SOD (Sigma Chemical Corp). GPx activity was determined using the method of Flohe and Gunzler (1984). CAT activity was determined using the method of Aebi (1984). All enzyme activities are expressed as units per gram of hemoglobin.

Data were analyzed using nonparametric statistics. Mann-Whitney tests were used for between group comparisons on continuous measures, and Spearman rank correlation co-efficients (r) were used for bivariate comparisons. All values were corrected for ties, and two-tailed significance values were used throughout.

3. Results

The characteristics of the subjects and their RBC activities of antioxidant enzyme are shown in Table 1. Normal controls were significantly older than the patients, but all subjects were between the ages of 18 and 40 years and there was no significant correlation between age and antioxidant enzyme activities in either normal controls or patients ($r<0.10$, $p>0.50$ for both comparisons). Activities of antioxidant enzymes are not known to be affected by age within such a truncated range (Stevens et al., 1975). There was no effect of gender on antioxidant enzyme activities. RBC SOD activity was significantly lower in the patients than in normal controls, but the groups did not differ in their respective GPx or CAT activities (see Table 1). However, four patients had RBC CAT activities that were well below the normal range.

There was a significant inverse correlation between RBC SOD activity and PAS instrumental (school) functioning score for early adolescence ($r=-0.75$; $p<0.005$), but not for childhood. A measure of deterioration was derived by subtract-

Table 1
Sample characteristics and red blood cell activities of antioxidant enzymes

	First episode psychosis patients ($n=14$)	Normal controls ($n=10$)
Age (years)*	22.82 (4.2)	28.61 (7.3)
Men: Women ratio	11:3	6:4
Duration of psychosis (days)	4.46 (2.5)	
Superoxide dismutase activity**	1453.36 (451.9)	2132.30 (221.6)
Glutathione peroxidase activity	36.97 (4.4)	35.48 (3.8)
Catalase activity	223.52 (32.0)	234.51 (25.5)

Figures in parentheses are standard deviations of the means. All enzyme activities are expressed as units per Gm Hb.
Mann–Whitney test: *$p=0.04$; **$p=0.006$.

ing the childhood instrumental functioning score from the corresponding early adolescence score. SOD activity was significantly and inversely correlated with this measure of deterioration ($r=-0.78$; $p<0.005$). There was no significant correlation between SOD activity and PAS measures of social adaptation for either period.

CAT and GPx activities were not significantly correlated with premorbid functioning scores. Antioxidant enzyme activities were not correlated with age at onset (which corresponded to age), baseline BPRS total score, positive symptom score, or negative symptom score.

4. Discussion

This study indicates that nonaffective psychosis is associated with an impaired antioxidant defense. Specifically, RBC SOD activity was significantly lower than normal in patients, indicating that the first line of defense against oxidative injury is impaired at the onset of psychosis. Low SOD was associated with greater deterioration of school functioning from childhood to early adolescence and, consequently, a history of poorer school functioning during early adolescence. GPx activity was normal. While, on the average, RBC CAT activity did not differ between patients and normal controls, four patients had CAT activity below the normal range.

Considering the very short duration of psychosis at the time of blood sampling (4.46 days on average), and the associations with history of premorbid functioning, it is likely that oxidative injury owing to an impaired antioxidant defense precedes the onset of psychosis. Further, because of their impaired antioxidant defense, some patients might be vulnerable to oxidative injury even if oxyradical production is normal. There is no condition where low SOD is not associated with oxidative injury, and we have found increased plasma levels of membrane lipid peroxidation products in these patients (Mahadik et al., 1995).

Low RBC SOD activity has also been found in association with non-insulin-dependent diabetes mellitus (NIDDM) (Collier et al., 1990) and familial amyotrophic lateral sclerosis (Rosen et al., 1993). In the latter, it appears to be owing to a gene mutation. Schizophrenia is associated with a high prevalence of NIDDM (Balter, 1961; Tabata et al., 1987; Mukherjee 1995; Mukherjee et al., 1996) as well as a high prevalence of family history of NIDDM (Mukherjee et al., 1989), and a 155-fold increase in ALS has been found in the relatives of schizophrenic patients of Ashkenazi descent (Goodman, 1994). It remains to be determined whether low SOD activity in schizophrenic patients is a trait or state related phenomenon. One study examined SOD activity in skin fibroblasts from schizophrenic patients and psychiatric controls that comprised mostly of patients with mood disorders, and found no difference between the groups (Cohen et al., 1987). Since they did not include normal subjects, it is unclear whether SOD

activity was normal in schizophrenic patients or low in both groups.

It is well known that cigarette smoking is highly prevalent among schizophrenic patients. Smoking is associated with increased oxyradical production. However, in normal individuals, this is accompanied by increased activities of antioxidant enzymes to cope with the increased oxidative tone (Toth et al., 1986). Thus, differences in smoking behavior between patients and normal subjects cannot account for our findings.

A more critical issue is the relevance of altered peripheral activities of antioxidant enzymes for brain pathology. Basal activities of antioxidant enzymes are regulated constitutively and not in a tissue specific manner, and are systemically induced in response to increased oxidative tone (Allen, 1991). In an animal model, SOD activity has been shown to increase in both brain and RBC shortly after focal ischemic stroke (Kramer et al., 1987). We have found SOD activity to be low in both brain and RBC of prediabetic db/db mice (Mahadik et al. 1992). Brain SOD activity and RBC SOD activity have been shown to be positively correlated in Down's syndrome (Sinet, 1982), and alterations in similar directions occur in both peripheral and central antioxidant enzymes in Alzheimer's disease (Anneren et al., 1986; Delacourte et al., 1988; Zelman et al., 1989). While activities of antioxidant enzymes need to examined in brains from schizophrenic patients, such data will be confounded by the effects of many years of illness and its pharmacological treatment and cannot provide insight on oxidative stress at the onset of psychosis.

The findings of this study are in contrast to the high RBC SOD activity (Michelson et al., 1977; Golse et al., 1978; Abdalla et al., 1986; Reddy et al., 1991) and low CAT activity (Glazov and Mamzev, 1976; Reddy et al., 1991) found in chronic schizophrenic patients. In a within-subject repeated-measures study, we found neuroleptic withdrawal in chronic schizophrenic patients to be associated with a lowering of RBC SOD activity, as well as CAT activity (Reddy et al., 1992; 1993). Thus, given sufficient time off neuroleptics, SOD activity might be found to be subnormal also in chronic schizophrenic patients. The evidence suggests that treatment with conventional neuroleptics might be associated with increased oxidative tone, and increased SOD activity occurs in response to this stress. Whether high SOD in neuroleptic treated schizophrenic patients compensates fully for the increased oxidative tone is not known. In a preliminary study, we found that lower RBC SOD activity was associated with more severe neurological signs in chronic schizophrenic patients (Reddy et al., 1994). Thus, elevated SOD activity, presumably a response to increased oxidative stress, may not confer adequate protection in all patients.

Neuroleptic treatment has been found to decrease CAT activity both in vitro (Yamamoto et al., 1960) and in the brain (Cadet and Perumal, 1990). We earlier found low RBC CAT activity in poor outcome chronic schizophrenic patients at a long-term care institution (Reddy et al., 1991). In this study, although on average CAT activity did not differ between patients and normal controls, four patients had CAT activity below the normal range. Initial findings suggest that low CAT activity is associated with a less favorable course of illness and early recurrence of psychosis after initial recovery (Mukherjee et al., 1995). These suggest that, in some schizophrenic patients, low RBC CAT activity might be integral to the illness and not secondary to neuroleptic treatment. Low CAT activity can have serious adverse consequences, especially if SOD activity is high, as seems to occur with neuroleptic treatment, with a resultant increased production of H_2O_2 that can be converted to ·OH, and there is no compensatory increase in GPx activity.

It is not understood at present why, in the presence of increased SOD activity, activities of CAT and GPx are not increased to protect against oxidative injury from ·OH ions. It is even more perplexing why RBC SOD activity increases with neuroleptic treatment, but is subnormal in drug naive first episode psychotic patients in whom we have found increased plasma levels of membrane lipid peroxidation products (Mahadik et al., 1995). No study has examined as yet mitochondrial SOD (Mn-SOD) activity in schizophrenic patients. This is an important issue because of the possibility of oxidative injury to mitochondrial DNA.

Considering the therapeutical implications, these are important avenues for future research.

If not removed efficiently and promptly, as might occur with low SOD activity, $\cdot O_2^-$ can be converted to ·OH. This, in turn, will result in a cascade of membrane lipid peroxidation and loss of long chain polyunsaturated essential fatty acid (PUFA) derivatives from cell membranes. Recent studies in chronic schizophrenic patients have found increased levels of membrane lipid peroxidation products (Lohr et al., 1990; Peet et al., 1993) and decreased RBC membrane levels of arachidonic acid and docosahexanoic acid, which are PUFAs highly enriched in the brain (Vaddadi et al., 1990; Glen et al., 1994; Yao et al., 1994). Animal studies have found that deficiency of PUFAs during early development, especially the n-3 PUFA docosahexanoic acid, results in impaired learning (Neuringer et al., 1986; Yamamoto et al., 1987; Bourre et al., 1989; Wainwright, 1992; Crawford, 1993).

On the other hand, $\cdot O_2^-$ can react with ·NO to form the oxyradical ·ONOO. There is evidence for a role of ·NO in neurotransmission, especially at NMDA glutamatergic receptors. Excessive removal of ·NO by $\cdot O_2^-$ could result in deficient glutamatergic activity and impairment of long term potentiation and learning. It has been shown that the concentration of $\cdot O_2^-$ influences the biological behavior of ·NO (Hogg et al., 1993). When ·NO is in excess over $\cdot O_2^-$, it can have an antioxidant role. However, if $\cdot O_2^-$ is present in excess, ·NO exhibits pro-oxidant behavior, likely through the production of ·ONOO. Glutamatergic activity might also be involved in synaptic pruning (Mattson et al., 1989), a critical event in brain maturation. It is of interest that, in this study, low SOD activity was associated with deterioration of school functioning from childhood to early adolescence, the period when synaptic pruning is starting to peak. We earlier suggested that, where premorbid functioning in adolescence is concerned, it might be important to recognize the distinction between continuity of impaired functioning from childhood onward and deterioration of functioning from childhood to adolescence (Mukherjee et al., 1991). The findings of this study add further evidence in support of such a distinction.

Until now, a role of oxidative injury in schizophrenia has been considered mainly in the context of neuroleptic effects and tardive dyskinesia (TD) (Cadet et al., 1986; Cadet and Lohr, 1987). This has led to therapeutic trials with α-tocopherol in patients with TD, with some positive results reported (Lohr et al., 1987; Elkashef et al., 1990; Scapicchio et al., 1991; Adler et al., 1993; Peet et al., 1993). These were based on a presumed increase of oxyradical production as a consequence of increased catecholamine turnover. The findings of this study indicate that some patients with schizophrenia may be poorly equipped to deal with oxidative stress owing to an impaired antioxidant defense. That, in some cases, oxidative stress might play a role in brain developmental and maturational processes in the pathogenic cascade of schizophrenia has not been previously considered. The findings reported above suggest such a possibility and call for more systematic research on the role of oxidative stress in schizophrenia.

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