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Cu, Zn- and Mn-superoxide dismutase levels in brains of patients with schizophrenic psychosis

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Summary. Impaired oxidative stress defense has been reported in blood of both drug-naïve and antipsychotic-treated patients suffering from schizophrenic psychosis, indicating the involvement of free radical metabolism in the pathogenetic processes of schizophrenia.

In this study, the concentrations of two isoenzymes of superoxide dismutase (SOD), Cu, Zn- and MnSOD, were determined with ELISA in various cortical (frontal, parietal, temporal and occipital cortex) and subcortical areas (putamen, caudate nucleus, thalamus, and substantia innominata) of post-mortem brain tissue from patients diagnosed with a schizophrenia spectrum disorder and compared with those of controls. Post-mortem brain tissue from individuals without neuropsychiatric disoders served for control.

Cu, Zn- and MnSOD levels were significantly increased in frontal cortex and substantia innominata of the index group, respectively. In all other areas both types of SOD remained virtually unchanged.

Detection of SOD changes in the brain supports previous reports of alterations of antioxidant indices in blood cells of patients with schizophrenia and suggests a specific neuroanatomical distribution pattern of oxidative stress processes possibly related to the pathophysiology of schizophrenia.

Keywords: Schizophrenia, psychosis, post-mortem, brain, free radicals, antipsychotic drugs.

Introduction

Schizophrenic psychoses affect ca 1% of the population. These devastating mental disorders are associated with hallucinations, delusions and thought disturbances. Furthermore, they represent an increased risk for suicide attempts and mortality is significantly increased in affected patients (Pinikahana et al., 2003). Many clinical and basic research groups around the world are focusing on the etiopathogenesis of schizophrenic psychoses. The great clinical diversity, however, probably reflects a considerable etiologic heterogeneity. Neuronal maldevelopment (Jakob et al., 1986; Thome et al., 1998), genetic factors (Kendler, 2003), viral infections (Pearce, 2001), and impaired neurotransmission (Carlsson et al., 1999; Kornhuber et al., 1994) have been suggested to be involved in the pathophysiology of this group of disoders. A rising body of evidence suggests that oxidative stress is implicated in the pathophysiology of schizophrenic psychoses (Yao et al., 2001). Rather than being a primary cause of psychotic disorders, oxidative injury is considered as an intermediate/final common pathogenetic process that contributes to deterioration of the disease course and poor outcome. In several studies, oxidative stress parameters have been determined in patients with schizophrenic psychosis. Total plasma antioxidant status as well as individual plasma levels of antioxidants such as albumin, bilirubin and uric acid were found to be decreased in drug-free patients or in subjects undergoing antipsychotic treatment (Yao et al., 1998), suggesting an increased risk for oxidative damage. Patients suffering from chronic schizophrenic psychoses exhibited lower levels of ascorbic acid in plasma and urine (Suboticanec et al., 1990) as well as lower ratios of alpha-tocopherol to cholesterol compared with those in healthy controls (McCreadie et al., 1995). These biochemical findings reflecting the oxidative stress status correlated with the severity of the disorder. Similarly, decreased alpha-tocopherol levels were shown in patients with tardive dyskinesia induced by chronic treatment with antipsychotic drugs (Brown et al., 1998). Scavenging antioxidant enzymes have been thoroughly studied in blood of patients with schizophrenic psychoses. However, results have been inconsistent. Increased erythrocyte SOD activity has been reported by some investigators but not by others (Yao et al., 2001). Enhanced glutathione peroxidase (gp) activity was found in erythrocytes of schizophrenia patients (Herken et al., 2001; Kuloglu et al., 2002). In contrast, lower gp activity was reported in erythrocytes (Altuntas et al., 2000) and plasma (Akyol et al., 2002) and unchanged gp activity was demonstrated in polymorphonuclear leucocytes of patients with schizophrenic psychoses (Srivastava et al., 2001). Furthermore, catalase activity was reported to be increased in erythrocytes of schizophrenia patients (Herken et al., 2001), whereas no alterations of the activity of this enzyme could be observed in leucocytes (Srivastava et al., 2001). Nonetheless, evidence of an altered lipid peroxidation has consistently been reported in patients with schizophrenia. Increased levels of malondialdehyde, pentane, and lipid peroxides were found in blood, breath and CSF, respectively (Altuntas et al., 2000; Pall et al., 1987; Phillips et al., 1993). Moreover, elevated lipid peroxides in plasma were reported at the onset of psychosis in drug-free, first-episode patients (Mahadik et al., 1998). Further, there is evidence of abnormalities in mitochondrial oxidative phosphorylation, a site of significant free radical production in schizophrenic

psychoses: Activity of cytochrome-c oxidase, a key enzyme in the mitochondrial electron transport chain, was found to be decreased in the frontal cortex and caudate nucleus of patients with schizophrenia (Cavelier et al., 1995) and reduced oxidative metabolism was evident by positron emission tomography (Buchsbaum et al., 1990).

Virtually all studies on oxidative stress in schizophrenic psychoses have been assessed in peripheral tissues with few reports concerning indexes of oxidative processes in CSF or brain. However, oxidative stress indices originate from various sources in the body and therefore, such peripheral findings may not accurately mirror the state of oxidative stress parameters in the brain. In the current study, we used post-mortem tissue from cortical and subcortical regions of patients with schizophrenic psychosis to determine concentrations of two isoenzymes of SOD: the dimeric, cytoplasmic Cu, ZnSOD and the tetrameric, mitochondrial MnSOD. Post-mortem brain tissue from individuals without neuropsychiatric disoders served as control.

Methods

Subjects

Post-mortem human brain specimens were obtained from 13 subjects (9 females, 4 males) who met the ICD-10 criteria for schizophrenia in clinical records (ICD-10 F20; World Health Organization, 1992) and 19 control subjects (10 females, 9 males) from the Gerontopsychiatric Hospital, Mauer, Austria and the Institute of Forensic Medicine, University of Würzburg, Germany. Post-mortem analysis was approved by the Ethic Committe of the University of Würzburg, Germany.

The control group consisted of individuals evaluated to be free of psychosis in a psychiatric assessment. None of them had received antipsychotic medication and none had exhibited any symptoms of other neuropsychiatric disorders (Table 1). All patients with schizophrenic psychosis were treated with antipsychotics (from 10.5 to 1000 mg chlorpromazine equivalents, CPZe) except subjects #6 and #9 who were free of antipsychotic treatment (Table 2). Further, patients #7, #8, #10, and #13 were additionally treated with anticholinergic substances to avoid extrapyramidal side effects. Subject #6 was reported to have been a heavy smoker, subjects #2 and #6 were alcoholics and subject #3 had oligophrenia and spastic paresis of legs from birth. Neuropathological examination of brain material conducted in control and index cases showed no evidence for any other neuropsychiatric disorders. Patients and controls came from a similar socio-cultural background, were of the same ethnic origins (Caucasian) and resided in the same geographical area.

Brain homogenates

Cortical regions (frontal, parietal, temporal and occipital cortex) as well as subcortical areas (putamen, caudate nucleus, thalamus, and substantia innominata) were dissected according to standardized procedures (Gsell et al., 1993). Subsequently, the tissue was homogenized in 20 volumes (w/v) of 5 mM phosphate-buffered saline (PBS, pH 7.4) containing 0.1% Tween-20 and aprotinine 500000 KIE using a homogenizer (Polytron, potter S, B. Brown, Melsungen, Germany, 1000 rpm, 30 sec) followed by sonification (40 pulsations, power 2, 20 sec) with a sonifier (250 Branson, Danbury, Connecticut, USA). The homogenates were centrifuged at 15000 rpm for 30 minutes to remove cellular debris. The supernatants were used for protein determination and Cu, Zn- and MnSOD analysis.

Cu, Zn and MnSOD ELISA

For the detection of Cu, Zn- and MnSOD levels, commercially available sandwich-type ELISA Kits (RPJ 302 and 301, Immunodiagnostics, Bensheim, Germany) were used, respectively, according to the instructions of the manufacturer.

Table 1. Control subjects

Age/Gender	Clinical diagnosis	Neuropsychiatric medication	Cause of death	Postmortem interval (hours)
#1 84/W	None	None	Pneumonia	53
#2 88/M	None	None	Cardiac failure	17
#3 77/W	None	None	Pulmonary embolism	
#4 80/W	None	None	Myelodysplastic syndrome	28
#5 73/W	None	None	Pankreatitis	10
#6 80/W	None	None	Cardiac failure, Pneumonia	72
#7 30/M	None	None	Cardiac failure	24
#8 84/M	None	None	Cardiac failure	5
#9 75/W	None	None	Pulmonary embolism	
#10 63/M	None	None	Cardiac failure	10.5
#11 90/W	None	None	Cardiac failure	24
#12 67/M	None	None	Cardiac failure	20
#13 61/M	None	None	Cardiac failure	18
#14 69/M	None	None	Cerebral insult	16
#15 80/W	None	None	Cardiac failure, Pneumonia	64
#16 66/W	None	None	Cardiac failure	35
#17 62/M	None	None	Pulmonary edema	7
#18 78/M	None	None	Cardiac failure	29
#19 71/W	None	None	Hepatic failure	29

Subject; mean age $\pm$ SD (73 ± 13); mean post-mortem time $\pm$ SD (27 ± 19)

Table 2. Subjects with schizophrenic psychosis

Age/Gender	Clinical diagnosis	Antipsychotic treatment (mg CPZe)	Cause of death	Postmortem interval (hours)
#1 72/W	ICD10:F20.0	Haloperidol (500)	Pneumonia	21
#2 51/M	ICD10:F20.5	Haloperidol (250)	Cardiac failure, Metastating lung carcinoma	8.5
#3 57/M	ICD10:F20.2	Thioridazine (50)	Pneumonia	4.1
#4 81/W	ICD10:F20.0	Thioridazine (50)	Pneumonia	35
#5 71/M	ICD10:F20.0	Haloperidol (500)	Cardiac failure, Pneumonia	4
#6 72/W	ICD10:F20.0	–	Cardiac failure	12
#7 65/W	ICD10:F20.2	Chlorprothixen (35)	Pulmonary embolism	25
#8 88/W	ICD10:F20.2	Chlorprothixen (10.5)	Pneumonia, Metastating lung carcinoma	26
#9 91/W	ICD10:F20	–	Pneumonia	52.5
#10 86/W	ICD10:F20	Haloperidol (1000)	Cardiomyopathy	
#11 51/W	ICD10:F20	Thioridazine (25)	Pulmonary embolism	4
#12 83/W	ICD10:F20.5	Thioridazine (50)	Pneumonia	17.5
#13 57/M	ICD10:F20.5	Fluphenazine (150)	Cardiac failure	10.5

ICD10:F20.0: Schizophrenia, paranoid type; ICD10:F20.5: Schizophrenia, residual type; ICD10:F20.2: Schizophrenia, Catatonia; ICD10:F20: Schizophrenia without classification. Numbers in parenthesis represent transformed medications into mg chlorpromazine equivalents (CPZe). # subject; mean age $\pm$ SD (71 ± 14); mean post-mortem $\pm$ SD (18.3 ± 14.6)

Protein determination

Protein quantification was performed by means of a commercial protein assay kit (Sigma Diagnostics Inc. St Louis, USA) according to (Lowry et al., 1951).

Statistical analysis

The non-parametric Spearman test was used to correlate SOD concentrations and possible confounding parameters, such as age and post-mortem time. The Mann-Whitney *U*-test for non-parametrically distributed values was further used to compare enzyme concentrations between females and males in the control group as well as effects of high *vs* low potency neuroleptics on SOD concentrations. The same test was used to compare SOD levels of the patient group with those of the control group. The level of significance was set at $P < 0.05$. All data analyses were performed with the statistical Graph-Pad-Prism software package (version 3.0a).

Results

SOD concentrations were independent of age and post-mortem delay, gender and neuroleptic potency (data not shown). Cu, ZnSOD concentration was

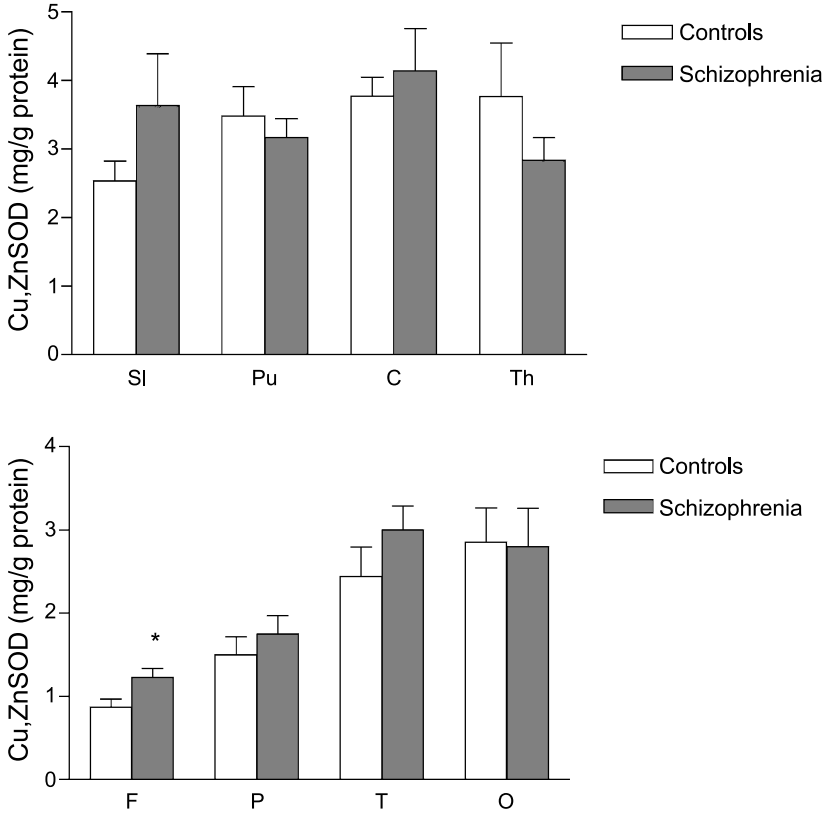

Fig. 1. Cu, ZnSOD levels in brains of patients with schizophrenic psychosis and controls. Upper panel: *SI* substantia innominata (n = 6); Pu: putamen (n = 7); *C* caudate nucleus (n = 7); *Th* thalamus (n = 5). Lower panel: *F* frontal cortex (n = 9); *P* parietal cortex (n = 13); *T* temporal cortex (n = 13); *O* occipital cortex (n = 11). Concentrations are represented in mg/g protein. *$P < 0.05$ significantly different from controls (Mann-Whitney *U*-test)

significantly increased in the frontal cortex of patients with schizophrenic psychosis compared to control subjects (1.23 ± 0.11 *vs* 0.87 ± 0.09 mg/g protein) (Fig. 1). In other areas Cu, ZnSOD remained virtually unchanged (parietal cortex: 1.75 ± 0.22 *vs* 1.50 ± 0.21; temporal cortex: 3.0 ± 0.29 *vs* 2.45 ± 0.35; occipital cortex: 2.80 ± 0.46 *vs* 2.83 ± 0.41; substantia innominata: 3.63 ± 0.76 *vs* 2.53 ± 0.29; caudate nucleus: 4.14 ± 0.62 *vs* 3.77 ± 0.27 mg/g protein). Levels of Cu, ZnSOD were slightly reduced in putamen and thalamus of the patients group compared with controls (3.16 ± 0.28 *vs* 3.48 ± 0.43 and 2.83 ± 0.33 *vs* 3.77 ± 0.77 mg/g protein), respectively. However, none of these differences reached statistical significance (Fig. 1).

A significant elevation of MnSOD concentration was evident in the substantia innominata of patients with schizophrenic psychoses compared to control subjects (4.64 ± 1.07 *vs* 1.54 ± 0.27 mg/g protein). MnSOD concentrations remained unchanged in the other subcortical areas (caudate nucleus: 2.27 ± 0.08 *vs* 1.93 ± 0.20; putamen: 2.17 ± 0.22 *vs* 2.09 ± 0.28; thalamus

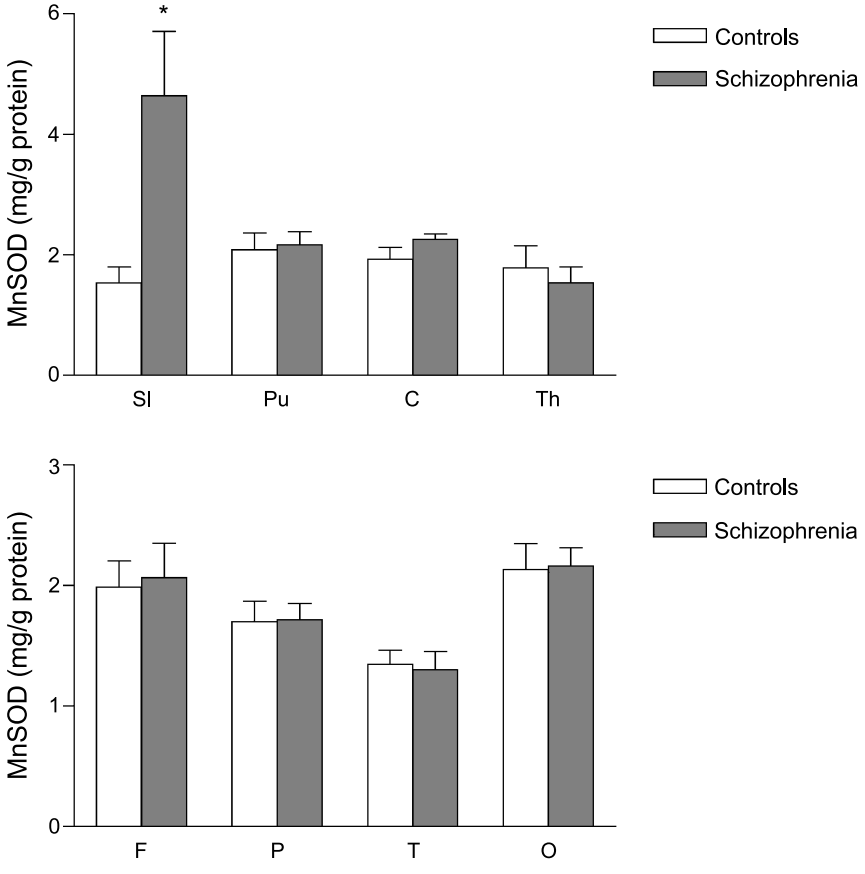

Fig. 2. MnSOD levels in brains of patients with schizophrenic psychosis and controls. Upper panel: *SI* substantia innominata (n = 6); *Pu* putamen (n = 7); *C* caudate nucleus (n = 7); *Th* thalamus (n = 5). Lower panel: *F* frontal cortex (n = 9); *P* parietal cortex (n = 13); *T* temporal cortex (n = 13); *O* occipital cortex (n = 11). Concentrations are represented in mg/g protein. *$P < 0.05$ significantly different from controls (Mann-Whitney *U*-test)

1.79 ± 0.37 *vs* 1.54 ± 0.26 mg/g protein), as well as in all other cortical areas investigated (frontal cortex: 2.06 ± 0.29 *vs* 1.98 ± 0.22 temporal cortex: 1.30 ± 0.15 *vs* 1.35 ± 0.12; occipital cortex: 2.16 ± 0.15 *vs* 2.13 ± 0.21; parietal cortex: 1.72 ± 0.14 *vs* 1.70 ± 0.17 mg/g protein) (Fig. 2).

Discussion

The present finding that SOD concentrations are increased in specific brain regions of patients with schizophrenia support previous results concerning SOD in the periphery: Blood SOD levels were significantly elevated in subjects with schizophrenic psychosis compared with controls and showed a positive relation to the brief psychiatric rating scale and the scale for the assessment of positive symptoms total score (Zhang et al., 2003a). Moreover, in an on-off haloperidol treatment design, investigating changes in the antioxidant enzyme activities in schizophrenia patients, drug-free condition resulted in SOD activity significantly higher compared with that in control subjects (Zhou et al., 1999). Finally, drug-naive patients with first-episode schizophrenia showed increased SOD activity (Khan et al., 1997). In contrast, in the study of (Ranjekar et al., 2003) levels of SOD were found to be lower in plasma of patients with schizophrenia compared to controls. It is reasonable to discuss increases in SOD activity or levels rather as compensatory processes to obtain homeostasis following oxidative stress and decreases as the endpoint of a long oxidative status. To our knowledge there is so far only one study that investigated SOD changes in post-mortem brain tissue of patients with schizophrenic psychosis (Loven et al., 1996). This group measured the activity of Cu, ZnSOD and MnSOD in the frontal and temporal cortex of four patients. In contrast to our report, Cu, ZnSOD activity remained unchanged in both regions whereas MnSOD activity was increased in both regions. It is known that SOD activity highly correlates with contents of SOD (Saito et al., 1982). Therefore, this controversy may be due to the causal heterogeneity in schizophrenia resulting in a profile of biochemical alterations determined by variable anatomical abnormalities rather than the different SOD parameters measured.

Our results concerning increase of Cu, ZnSOD and MnSOD in frontal cortex and substantia innominata of patients with schizophrenic psychosis add biochemical support to previously reported imaging and neurohistological studies performed in these regions of schizophrenia subjects (frontal cortex:) (Bogerts, 2002) and (substantia innominata) (Averback, 1981; Stevens, 1982).

The question of whether the changes in Cu, ZnSOD and MnSOD concentrations detected in our study are associated with primary causes of the psychiatric disorder or they represent secondary changes in response to increased oxidative stress remains open. Moreover, antipsychotics may influence oxidative status and consequently antioxidant defense at least by two ways: First, antipsychotics themselves may be a direct source of free radicals (Chignell et al., 1985). Second, blockade of D2-receptors by antipsychotic drugs increase the production and availability of dopamine, which can lead to enhanced formation of quinones as well as hydrogen peroxide both of which can further generate

free radicals (for review:) (Koutsilieri et al., 2002). The involvement of some antipsychotics in regulation of antioxidant indices has been evident in several studies (Khan et al., 2003; Parikh et al., 2003; Zhang et al., 2003b). However, two patients in this study were free of antipsychotic treatment and concentrations of SOD in their brains were similar with those in antipsychotic-treated subjects. Moreover, comparison of the effect of high and low affinity antipsychotics on the concentrations of SOD in our postmortem tissue did not reveal any statistical difference, indicating that the increase of SOD concentrations in our study seemed to be independent of antipsychotic treatment. Nonetheless, the small number of drug-free psychotic subjects in our study cannot exclude that changes in SOD levels may have been induced by antipsychotic treatment than by the psychosis itself. Another issue which deserves consideration is that antioxidant status may correlate with chronic antipsychotic treatment-associated disorders such as tardive dyskinesia (for review:) (Yao et al., 2001). None of our patients was reported to have suffered from this disorder although extrapyramidal complications were evident in four patients who therefore received anticholinergics, as mentioned above. It is noteworthy that regions which are important for both parkinsonian movements and tardive dyskinesia such as putamen and caudate nucleus did not exhibit any alterations in SOD concentrations in our index group.

Besides the superoxide scavenging function, SOD is also involved in other cellular processes. SOD is essential for the termination of cellular growth and differentiation (Mahadik et al., 1996a; Wang et al., 2002). Consequently, any impairment of the enzyme in the developing brain might contribute to alterations in neural plasticity potentially present until adulthood that can be relevant to the pathogenic cascade of schizophrenic psychoses (Bloom, 1993; Jakob et al., 1986; Weinberger, 1987). In the same line, delayed initial growth and rate of growth has been found in cultured skin fibroblasts from patients suffering chronic schizophrenic psychoses related with poor premorbid functioning (Mahadik et al., 1991; Mukherjee et al., 1994). Poor premorbid functioning was found to be associated with impaired SOD (Mahadik et al., 1996b). Of interest is also the interrelationship between SOD and neurotrophic factors. For example brain-derived neurotrophic factor (BDNF) increases SOD activity and expression (Gong et al., 1999; Ikeda et al., 2002) whereas nerve growth factor induces SOD mRNA (Li et al., 1998). This indicates that changes in concentrations of SOD may be mediated through altered regulation of neurotrophic substances. In this context it is striking that in the frontal cortex, where increased levels of SOD were measured in this study, increased levels of BDNF as well as reduced neurotrophin-3 can be detected (Durany et al., 2001), suggesting that alterations in the interaction between antioxidants and neurotrophic factors may be relevant to impaired neural plasticity processes possibly involved in the pathophysiology of schizophrenic psychoses.

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