



Age-related changes of superoxide dismutase activity in patients with schizophrenia

Promene aktivnosti superoksid dizmutaze kod bolesnika sa shizofrenijom zavisno od starosti

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Abstract

Background/Aim. Superoxide dismutase (SOD) is the critical enzyme in the detoxification of superoxide radicals because those are the first species produced in the majority of biological free radical producing reactions. Inconsistent data are present about SOD activity in patients with schizophrenia. Numerous studies show that SOD is elevated in chronic schizophrenic patients. However, decreased SOD activity is found in neuroleptic naive, first episode schizophrenic patients, in chronic-medicated patients and in chronic-unmedicated patients. The aim of this study was to examine the influence of age, gender, age at disease onset, the duration of the disease, the number of episodes, heredity, psychopathologic symptoms and drug treatment on erythrocyte SOD activity in patients with schizophrenia. **Methods.** This study included 68 consecutive patients with schizophrenia (29 males and 39 females) ranging in age from 18 to 61 years, divided into two age groups (< 34 years and > 34 years). SOD activity was measured in erythrocyte hemolyzates by commercially available Ransod test. **Results.** In the group of patients younger than 34 years SOD levels were significantly higher ($1,381 \pm 273$ U/gHb, $p = 0.038$) compared to the levels in the older patients ($1,231 \pm 206$ U/gHb). Gender and heredity did not induce any significant difference in SOD activity between the groups. A significant difference in enzyme activity was found between the younger and older patient groups having the onset of the disease

after 24 years of age ($1,408 \pm 217$ U/gHb *vs* $1,252 \pm 213$ U/gHb, $p = 0.031$, respectively). The patients in the younger group with more than one psychotic episodes had significantly higher SOD activity ($1,492 \pm 298$ U/gHb; $p = 0.009$) than those with only one episode ($1,256 \pm 177$ U/gHb), as well as than the older patients with more than one episode ($1,253 \pm 231$ U/gHb; $p = 0.014$). Although the duration of the disease did not induce any significant difference in enzyme activity between the younger and older patient groups, a significant negative correlation was obtained between SOD activity and the duration of the disease ($r = -0.511$, $p < 0.01$). No significant differences were found in SOD activity between the groups with the different positive and negative syndrome scale (PANSS) scores. First generation antipsychotics were associated with elevated enzyme activity in both groups. Simultaneous treatment of patients with first generation antipsychotics and second generation antipsychotics induced a significant decrease in SOD activity in the younger patient group. **Conclusion.** Our results show that erythrocyte SOD activity is increased in the early phase of schizophrenia, depending on age at the onset of the disease, the number of psychotic episodes, the duration of the disease and medical treatment.

Key words: schizophrenia; superoxide dismutase; erythrocytes; age factors; antipsychotic agents.

Apstrakt

Uvod/Cilj. Superoksid dizmutaza (SOD) je važan enzim u detoksikaciji superoksid radikala, primarne reaktivne vrste u većini bioloških procesa u kojima se stvaraju slobodni radikali. Podaci o aktivnosti SOD kod bolesnika sa shizofrenijom su nekonzistentni. Mnogobrojne studije pokazale su da je SOD povećana kod bolesnika sa hroničnom formom shizofrenije. S

druge strane, snižena aktivnost SOD nađena je kod bolesnika u prvoj epizodi bolesti, kod obolelih koji nikada nisu bili na terapiji antipsihoticima i kod hroničnih, lečenih i nelečenih bolesnika. Cilj rada bio je da se ispita uticaj pola, životnog doba, vremena pojave bolesti, trajanja bolesti, broja psihotičnih epizoda, herediteta, predominantne simptomatologije i klase primenjenih antipsihotika na aktivnost eritrocitne SOD kod bolesnika sa shizofrenijom. **Metode.** Ispitano je 68 bolesnika sa

shizofrenijom (29 muškaraca i 39 žena) starosti od 18 do 61 godine, podeljenih u dve grupe (< 34 godine i > 34 godine). Aktivnost SOD merena je u hemolizatu eritrocita komercijalnim testom Ransod. **Rezultati.** U grupi bolesnika mlađih od 34 godine aktivnost SOD bila je značajno viša ($1\,381 \pm 273$ U/gHb; $p = 0.038$) nego aktivnost SOD u grupi starijih bolesnika ($1\,231 \pm 206$ U/gHb). Nije utvrđena značajna razlika u aktivnosti SOD među grupama u pogledu pola i herediteta. Značajna razlika u aktivnosti enzima nađena je između mlađih i starijih bolesnika kod kojih je bolest počela posle 24. godine starosti ($1\,408 \pm 217$ U/gHb prema $1\,252 \pm 213$ U/gHb; $p = 0.031$). Bolesnici mlađe grupe koji su imali više od jedne psihotične epizode imali su značajno višu aktivnost SOD ($1\,492 \pm 298$ U/gHb; $p = 0.009$) od onih koji su imali samo jednu epizodu ($1\,256 \pm 177$ U/gHb) i od bolesnika starije grupe koja je imala više od jedne epizode ($1\,253 \pm 231$ U/gHb, $p = 0.014$). Mada dužina trajanja bolesti nije pokazala statistički

značajnu razliku u aktivnosti enzima među grupama, značajna negativna korelacija uočena je između trajanja bolesti i aktivnosti SOD ($r = -0.511$; $p < 0.01$). Nije nađena značajna razlika u aktivnosti enzima između grupa sa različitim skorovima skale pozitivnih i negativnih simptoma (PANSS). Antipsihotici prve generacije bili su udruženi sa povišenom aktivnošću enzima u obe grupe. Simultano lečenje bolesnika antipsihoticima prve i druge generacije izazivalo je značajan pad aktivnosti SOD u grupi mlađih bolesnika. **Zaključak.** Dobijeni rezultati pokazuju da je aktivnost eritrocitne SOD povišena u ranoj fazi shizofrenije i da zavisi od godina života bolesnika na početku bolesti, broja psihotičnih epizoda, trajanja bolesti i klase primenjenih antipsihotika.

Ključne reči:
shizofrenija; superoksid dismutaza; eritrociti; životno doba, faktori; antipsihotici.

Introduction

Superoxide dismutase (SOD), EC 1.15.1.1 is an enzyme that catalyzes the dismutation of the toxic superoxide radical, a by-product of oxygen metabolism, into either molecular oxygen or hydrogen peroxide¹. Hydrogen peroxide is further chemically converted by either glutathione peroxidase (GPx) or catalase into water^{2, 3}. Although cells contain a large number of antioxidants to prevent or repair the damage caused by reactive oxygen species (ROS) by maintaining these species in physiologically acceptable level, SOD is primary, critical enzyme in the detoxification of superoxide radicals because these are the main ROS, primarily generated in the most biological free radical producing reactions.

Three forms of SOD are present in humans and protect the cells from superoxide toxicity: copper- and zinc-containing SOD (CuZnSOD/SOD1) localized predominantly in cytoplasmic and nuclear compartments, manganese SOD (MnSOD/SOD2) localized within the mitochondrial matrix, and copper- and zinc containing SOD predominantly found in extracellular compartments (EC SOD/SOD3). Impaired activities of these isoforms can lead to a variety of cell damage from oxidant stress to the cell death⁴⁻⁶. Meta-analysis of oxidant stress in schizophrenia shows abnormalities in first episode psychosis, suggesting that it might be independent of antipsychotic medications and erythrocyte SOD might be a trait marker for schizophrenia⁷. However, impaired oxidant stress defense has been reported in blood of both drug-naïve and antipsychotic-treated patients, suffering from schizophrenic psychosis⁸. Plasma and erythrocyte SOD activities were found increased⁸⁻¹⁰ or decreased^{11, 12}, but total SOD (CuZn, Mn, and FeSOD) decreased¹³ in patients with schizophrenia. Both MnSOD and CuZnSOD were found lower in patients with tardive dyskinesia (TD) than those without TD¹⁴⁻¹⁶. These data show that some controversy still exists regarding the level of SOD activity in schizophrenia. A significant reason for this discrepancy might be a large scale of patient age (18–60 years)¹² tested as a whole group.

In relation to biological variability of antioxidant enzymes, it was shown that plasma and erythrocyte SOD activity was rather stable in adults below 65 years, and did not show any significant variation according to gender¹⁷. Later, Inal et al.¹⁸ noted significantly lower erythrocyte SOD activity in subjects aged 41–69 years than in younger ones, and a negative correlation between SOD activity and age. SOD levels in blood donors aged 58–65 years from the rural environment were significantly lower than those in their urban counterparts¹⁹. No significant differences were found in mitochondrial SOD and GPx activities in rats between 12 and 24 months of age, but age- and gender-related differences were observed in MnSOD expression²⁰.

The present study was designed to examine the relationship between SOD activity and a variety of demographic and clinical characteristics of patients with schizophrenia including age, gender, the onset of the disease, the duration, the number of episodes, heredity, psychopathological symptoms and drug treatment.

Methods

This study included 68 consecutive patients with schizophrenia (29 males and 39 females), mean age 32.7 ± 9.4 years, divided into two groups: the younger patient group (< 34 years, $n = 44$) and the older patient group (> 34 years, $n = 24$). They were recruited, screened and diagnosed for schizophrenia at the Clinic of Psychiatry of the Clinical Center Niš, using the diagnostic criteria of the International Classification of Mental and Behavioral Disorders (ICD-10). The patients were clinically observed, their personal history recorded, and the psychopathological evaluation and clinical management assessed using the Positive and Negative Syndrome Scale (PANSS). The groups were marked as PANSS positive score predominance – PANSS (+), PANSS negative score predominance – PANSS (-), as well as the group showing almost equally positive and negative symptoms – PANSS (+/-). The demographic and clinical characteristic of patients including age, gender, age at the onset of the disease

se, the disease duration, the number of episodes and heredity were collected using medical documentation, as well as autoanamnestic and heteroanamnestic data obtained from the patient family members. Heredity was assessed by the presence or absence of schizophrenia and bipolar affective disorder among the first and the second degree relatives. According to drug treatment the patients of both groups (younger and older) were divided into three subgroups: the patients treated with the first generation antipsychotic (FGA) – haloperidol, the patients treated with the second generation antipsychotics (SGA) – clozapine or olanzapine, and the patients receiving haloperidol and one of the second generation antipsychotics (FGA and SGA). The exclusion criteria were: coincidental immune, inflammatory, vascular and liver diseases, any substance (except tobacco) abuse, history or present symptoms of any other psychiatric or neurological disorder.

The patients' consent to participate in the study was obtained from each patient. The study was approved by the Human Ethics Committee of the Clinical Center Niš.

Venous blood was collected in tubes with EDTA. Plasma was separated by centrifugation at 3,000 rpm for 10 min and the buffy coat was removed, and packed cells washed three times with physiological saline. Erythrocyte suspension was used for hemolysate preparation in which the enzyme activity was measured.

SOD activity was measured by Ransod commercially available test (Randox Lab., Crumlin, UK) on the autoanalyzer AU-680 (Beckman Coulter International SA, Nyon, Switzerland) according to the instructions of the ma-

nufacturer. This method is based on superoxide inhibition to react with 2-(4-iodophenyl)-3/4nitrophenol)-5-feniltetrazolium chloride and form colored formazan in a xanthine/xanthine oxidase system. Enzyme activity was calculated according to SOD standards and expressed in units *per* gram (g) of hemoglobin (Hb). The reference range of Ransod method is 1,092–1,817 U/gHb.

Statistical analysis

Data analysis was performed using the SigmaStat computer program. The results are reported as $\bar{x} \pm SD$ and as median (interquartile range). The difference between the groups was tested by the One Way Analysis of Variance followed by Tukey or Dunn's post-hoc tests, respectively, as appropriate. $p < 0.05$ was considered to indicate statistical significance. Correlations between enzyme activity and demographic, clinical and drug treatment characteristics of patients were assessed using Spearman's coefficient.

Results

Table 1 shows demographic and clinical characteristics of the patients with schizophrenia. There was a statistically significant difference in age ($p < 0.001$) and duration of psychiatric disease ($p < 0.001$) between the two age groups (below 34 and above 34 years).

As shown in Table 2, in the group of patients younger than 34 years, SOD levels were significantly higher

Table 1

Characteristics	Groups of patients	
	< 34 years	> 34 years
Male/Female, n	19/25	10/14
Age (years), $\bar{x} \pm SD$	26.6 \pm 5.1***	41.4 \pm 7.0
Heredity (+/-), n	12/32	12/12
Age of disease manifestation (before/after 24 years), n	29/15	8/16
Duration of psychiatric disease (years), \bar{x} (range)	3(1-4.75)***	6(4.5-12.5)
Number of episodes (one/more than one), n	21/23	5/19
PANSS positive scores predominant (> 3), $\bar{x} \pm SD$	9.7 \pm 4.2	11.2 \pm 5.7
PANSS negative scores predominant (< -8), $\bar{x} \pm SD$	13.9 \pm 4.9	12.3 \pm 3.5
PANSS positive and negative scores almost equally expressed (>-8< 3), $\bar{x} \pm SD$	2.6 \pm 3.8	4.5 \pm 3.3
PANSS general psychopathology, $\bar{x} \pm SD$	49.3 \pm 8.5	47.5 \pm 9.5
FGA (haloperidol treated), n	14	8
SGA (clozapine or olanzapine treated), n	14	6
FGA and SGA treated, n	16	10

*** $-p < 0.001$ vs older patient group.

PANSS – positive and negative syndrome scale; FGA – first generation antipsychotics; SGA – second generation antipsychotics.

Table 2

Erythrocyte superoxide dismutase (SOD) activity in the patients with schizophrenia grouped by age	
Groups of patients	SOD (U/gHb)
Whole group (n = 68), \bar{x} (min-max)	1,255 (1,136–1,457)
patients < 34 years (n = 44), $\bar{x} \pm SD$	1,381 \pm 273***
patients > 34 years (n = 24), $\bar{x} \pm SD$	1,231 \pm 206

* $p = 0.038$ vs older patient group (> 34 years);

** $p = 0.001698$ vs whole group.

(1,381 ± 273 U/gHb, $p = 0.001698$) compared to the values of the patients of the whole group [1,255 (1,136–1,457) U/gHb], as well as to the values of the older patient group (1,231 ± 206 U/gHb, $p = 0.038$).

Related to gender SOD activity was insignificantly higher in the female patients than in the male ones in the younger patients group (Table 3).

Erythrocyte SOD activity in the heredity positive and heredity negative patients of the younger patient group was not significantly different compared to the corresponding older patient groups (Table 3).

SOD activity in the patients younger than 34 years was higher than in patients older than 34 year, regardless the age of patients at the disease onset (Table 3), but statistically significant difference in the enzyme activity was found only between subgroups of patients developing the disease after 24 years of age ($p = 0.031$).

In the younger patients group, the patients who had more than one psychotic episode had significantly higher SOD activity ($p = 0.009$) than those who had only one episode, as well as than the older patients with more than one psychotic episode ($p = 0.014$) (Table 3).

In the patients younger than 34 years, suffering more than five years, SOD activity was insignificantly higher ($p =$

0.078) in comparison with the SOD activities of the patients older than 34 years (Table 3). A significantly negative correlation coefficient was found between the duration of the disease and SOD activity ($r = -0.511$, $p < 0.01$). None of other studied factors significantly correlated with the enzyme activity.

No significant differences in SOD activity were found in different PANSS scores between the two age groups (Table 4).

Neither haloperidol, nor second-generation antipsychotic drugs used in the treatment of patients, caused significant differences in SOD activity between the groups. However, significantly higher enzyme activity was found in the younger patient group between those treated with FGA and those treated with FGA and SGA ($p = 0.010$) (Table 4).

Discussion

The major finding of this study is that erythrocyte SOD activity is significantly higher in the early phase of schizophrenia than in the later one which was confirmed by a significant negative correlation between the duration of the disease and SOD activity. Contrary to our findings Wu et al.⁸ observed that neither age nor duration of the illness were associated with SOD activity in the first-episode or chronic patients.

Table 3

Erythrocyte SOD activity and clinical features of schizophrenia in patients grouped by age

Characteristics	SOD (U/gHb)				<i>p</i>
	n	patients < 34 years	n	patients > 34 years	
Male	19	1,367 ± 289	10	1,310 ± 127	0.591
Female	25	1,415 ± 236	14	1,329 ± 355	0.517
Heredity (+)	12	1,288 (1,202–1,434)	12	1,305 (1,175–1,425)	0.926
Heredity (-)	32	1,361 ± 310	12	1,203 ± 174	0.122
Patient's age at the disease onset					
before 24 years	29	1,368 ± 297	8	1,209 ± 202	0.359
after 24 years	15	1,408 ± 217	16	1,252 ± 213	0.031
Number of episodes					
one	21	1,256 ± 177	9	1,206 ± 96	0.558
more than one	23	1,492 ± 298**	19	1,253 ± 231	0.014
Disease duration					
to one year	12	1,319 ± 188	-	-	-
less than 5 years	19	1,341 ± 230	7	1,378 ± 526	0.827
more than 5 years	13	1,474 ± 394	17	1,255 ± 214	0.078

** $p = 0.009$ vs younger patients having one episode; SOD – superoxide dismutase.

The data are presented as mean ± standard deviation or range (min–max).

Table 4

Erythrocyte superoxide dismutase (SOD) activity in patients with schizophrenia related to the predominant symptomatology and drug treatment.

Variables	SOD (U/gHb)				<i>p</i>
	n	patients < 34 years	n	patients > 34 years	
PANSS (+)	15	1,385 (1,187–1,481)	10	1,409 ± 329	0.756
PANSS (-)	15	1,399 ± 282	6	1,171 ± 238	0.234
PANSS (+/-)	14	1,219 ± 225	8	1,208 ± 183	0.914
FGA	14	1,500 ± 277**	8	1,406 ± 352	0.486
SGA	14	1,362 (1,073–1,709)	6	1,054 (980–1,129)	0.167
FGA and SGA	16	1,210 (1,181–1,292)	10	1,283 (1,121–1,412)	0.598

** $p = 0.010$ vs FGA and SGA of the younger patient group.

For abbreviations see under Table 1.

The data are presented as mean ± standard deviation or range (min–max).

In 1986 Abdalla et al.²¹ showed about 60% higher SOD activity in neuroleptic-treated and untreated patients with schizophrenia than those found in normal individuals. High erythrocyte SOD activity in schizophrenia have been reported in many previous studies^{10,22} which negatively correlated with malondialdehyde (MDA) concentration²³, while some other studies noted low SOD activity in patients with schizophrenia^{24,25}. Significantly lower levels of SOD and GPx with an increased oxidative stress as indicated by high blood MDA levels were found by Dadheech et al.¹² and Zhang et al.²⁵. Similar to our findings, Rukmini et al.²³ noted higher SOD activity in patients with schizophrenia in parallel with the increased catalase activity and MDA level. The increased erythrocyte SOD activity and decreased GPx activity were also found in patients with acute and chronic schizophrenia associated with lower erythrocyte reduced glutathione (GSH)¹⁰. In addition, a significant increase in cytosolic and mitochondrial isoenzymes of SOD were shown in frontal cortex and substantia innominata of postmortem brain tissue²⁶. This discrepancy may be in part explained by our results showing increased SOD activity in younger patients, *ie* in the early phase of schizophrenic disease. This high SOD activity may be induced in response to oxidant stress and increased production of ROS²⁷, as confirmed by the presence of carbonyl stress²⁸ and other markers of oxidative cellular damage²⁹. These findings indicate that oxidative stress is a primary event and that SOD activity abnormalities are its consequence. That is recently confirmed by Cabungcal et al.³⁰ who have shown that juvenile antioxidant treatment prevents adult deficits in the developmental model of schizophrenia. Higher conversion of superoxide might elevate hydrogen peroxide level which, in turn, could inactivate SOD³¹, leading to the inhibition of the enzyme activity in the later stage of the disease.

In attempt to explain the divergency of findings related to SOD in schizophrenia, some authors have studied SOD polymorphism. Hitzeroth et al.³² investigated the functional polymorphism (Ala-9Val) in the MnSOD gene in the Xhosa population and did not find any significant difference in either genotype or allele frequency between the schizophrenic and the control group, nor between the polymorphism and symptom severity. Another study³³ reported similar results related to the patients with schizophrenia, but it found a decrease in -9Ala (mutant) allele among patients with TD, suggesting that the -9Ala (high activity) MnSOD allele may play a role in protecting against susceptibility to TD in patients with schizophrenia.

Contrary to our results related to the SOD activity between PANSS subgroups in both groups, plasma SOD activities were found negatively correlated with positive symptoms of schizophrenia in first-episode patients⁸, and Yang et al.³⁴ noted a significantly positive relationship between the change in SOD at pretreatment and posttreatment and the reduction in the PANSS negative subscore. There is also an assumption that the positive symptoms of

schizophrenia are associated with hyperactivity of dopaminergic system and the increased production of ROS, due to auto-oxidation of catecholamines, which leads to increased oxidant stress in PANSS (+) patients³⁵.

Inconsistent data are present about the effects of antipsychotics on antioxidant enzymes and oxidant stress. In 2006 Zhang et al.²⁵ showed that the activities of SOD and GPx were decreased but the levels of MDA elevated in patients with the chronic form of schizophrenia as compared with the healthy controls. No significant differences were found in any parameters measured among all three subgroups treated with clozapine, risperidone or typical antipsychotics. Six years later, the same authors²² showed that blood levels of SOD and plasma nitric oxide were significantly increased in patients with schizophrenia and that both risperidone and haloperidol equivalently reduced the elevated blood SOD levels. There is also evidence that chronic haloperidol treatment for both 45 and 90 days significantly decreased MnSOD, CuZn SOD and catalase activities in the rat brain, whilst risperidone, clozapine or olanzapine treatments did not produce any alterations in the activity of antioxidant enzymes³⁶. These results are compatible with the study of Yao et al.³⁷ who observed that both SOD and GPx activities were higher in drug-free conditions than in patients treated with haloperidol. However, we found elevated SOD activity in the group of younger patients treated with FGA in comparison with the group of younger patients treated with FGA and SGA. SGA did not change SOD activity in both studied groups. In addition, Qing et al.³⁸ showed that atypical antipsychotics slightly up-regulated the expression of CuZn-SOD whereas haloperidol strongly increased the expression of this enzyme. These findings indicate that haloperidol could have not just a stimulatory effect on SOD activity, but could be an inducer of oxidant stress, and SGA have a potential to normalize the activity of the enzyme. The lowest activity of SOD observed in our patients simultaneously treated with FGA and SGA could be a consequence of dopamine D2 receptor antagonism and excessive dopamine auto-oxidation followed by the inhibition of enzyme activity due to overproduction of hydrogen peroxide, or could be the result of unknown biochemical mechanism.

Conclusion

Our results show that erythrocyte SOD activity is increased in the early phase of schizophrenia and that it depends on the onset of the disease, the number of psychotic episodes, the duration of the disease, and medical treatment. These findings suggest the use of antioxidants as adjuvant therapy in the prodromal and early phase of schizophrenia. Also, these data indicate that patients with schizophrenia should not be studied as the general population, but separately classified according to each factor that affects enzyme activity in a longitudinally designed study.

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