Altered Erythrocyte Deformability and Antioxidant Status in Patients with Schizophrenia

Şizofreni Hastalarında Değişen Eritrosit Deformabilitesi ve Antioksidan Enzim Düzeyleri

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Abstract

Objective: Schizophrenia is a major mental disorder whose etiology still remains unkown. There is   evidence that free radicals are involved in membrane pathology in the central nervous system and may play a role in the pathophysiology of schizophrenia. Red blood cells are also considered to be a peripheral marker in psychiatric illnesses. We aimed to provide further insight into the effects of changed antioxidant status and lipid peroxidation on the rheological behavior of red blood cells in schizophrenia.

Patients and Methods: Twenty patients with schizophrenia and 20 healthy subjects were included in the study. Antioxidant enzymes and lipid peroxidation were measured spectrophotometrically and red blood cell deformability was measured by shear stress diffractometer.

Results: Deformability of red blood cells was found to be decreased, lipid peroxidation was increased and antioxidant status was altered in the patients (p<0.05).

Conclusion: It is understood that erythrocyte deformability was impaired and antioxidant status was altered in patients with schizophrenia. *(Marmara Medical Journal 2012;25:133-7)*

Key Words: Antioxidant enzymes, Erythrocyte, Lipid peroxidation, Red blood cell deformability, Schizophrenia

Özet

Amaç: Şizofreni, etiyolojisi tam olarak açıklanamamış önemli mental hastalıklardan biridir. Serbest radikallerin merkezi sinir sisteminde membranlara hasar verebileceği ve bunun da şizofreninin fizyopatolojisinde rol oynayabileceğine dair veriler mevcuttur. Eritrositlerin de psikiyatrik hastalıklarda periferik bir gösterge olarak kullanılabileceği öngörülmektedir. Bizler bu çalışmada şizofrenli hastaların antioksidan kapasite ve lipid peroksidasyon düzeylerini ölçerek bu parametrelerin eritrositlerin deformabilite özellikleri üzerindeki etkilerini araştırmayı amaçladık.

Hastalar ve Yöntem: Yirmi şizofreni hastası ve 20 sağlıklı kontrol çalışmaya dahil edildi. Antioksidan enzimler ve lipid peroksidasyon düzeyleri spektrofotometrik olarak, eritrosit deformabilite düzeyleri ise shear stres difraktometresi aracılığıyla ölçülmüştür.

Bulgular: Hasta grubunda kontrol grubuna göre eritrosit deformabilite özelliklerinin azaldığı, lipid peroksidasyonu düzeylerinin arttığı, antioksidan enzim düzeylerinde ise değişiklikler olduğu gözlenmiştir (P<0,05).

Sonuç: Serbest radikallerin şizofrenide eritrosit deformabilitesi üzerinde olumsuz rol oynadığı ve şizofreni hastalarında antioksidan düzeylerinin değiştiği anlaşılmıştır. *(Marmara Üniversitesi Tıp Fakültesi Dergisi 2012;25:133-7)*

Anahtar Kelimeler: Antioksidan enzimler, Eritrosit, Lipid peroksidasyonu, Eritrosit deformabilitesi, Şizofreni

Introduction

Schizophrenia is a major mental disorder with a broad range of behavioural and biologial manifestations. Many hypotheses have been proposed that aim to dislose the pathophysiology of schizophrenia, but the etiology still remains unknown. There is abundant evidence that free radicals are involved in membrane pathology in the central nervous system and may play a role in a

number of neuropsychiatric disorders, including schizophrenia[1]. Findings to date suggest defects in phospholipid metabolism and cell signalling in schizophrenia; decreased polyunsaturated fatty acids (PUFAs) and altered phospholipids in plasma, skin fibroblasts[2] red blood cell (RBC)[3,4], platelets[5], and postmortem brain tissues[6]. Owing to their structure, which is rich in double bonds, PUFA render cellular membranes vulnerable to damage from free radicals, causing peroxidation.

Free radicals, primarily reactive oxygen species, superoxide and hydroxyl radicals, which are highly reactive having an unpaired electron in an atomic or molecular orbital, are generated under physiological conditions during aerobic metabolism[7]. Processes and in excess, can damage lipids, proteins and DNA. Regions of high oxygen consumption, lipid content and transition metals are at particular risk. Hence, neuronal membranes are uniquely vulnerable to radical- mediated damage . Antioxidants are molecules that can neutralize free radicals by accepting or donating an electron to eliminate the unpaired condition[8,9]. Oxidative stress is a state when there is imbalance between the generation of free radicals and defense capacity of the body. It is closely associated with a number of diseases including Parkinsons's disease, Alzheimer-type demantia and Huntington's Chorea[10].

Brain is particularly sensitive to oxidative damage. There are a lot of phospholipids and PUFAs in brain tissue under physiological conditions. They can cause the appearance of instabilities of neuron membranes, or even cell death owing to oxidative stress[11].

RBCs are not only involved in haemostasis, they are also considered to be a peripheral marker in psychiatric illnesses, such as schizophrenia. The results suggest that at least some of the schizophrenia disease process can be traced in peripheral tissue like plasma, blood cells or liver. The ability of the entire RBC to deform is of crucial importance for the maintenance of normal circulation. The damage induced by lipid peroxidation renders the RBC cell unstable, and therefore compromises fluidity, permeability and deformability[12,13].

The present study was designed to provide further insight into the effects of changed antioxidant status and lipid peroxidation on the rheological behavior of RBCs in schizophrenia.

Patients and Methods

This study was performed on 20 patients with schizophrenia (9 female, 11 male; between 18-46 ages; mean age ± SD: 34±8.9) and 20 healthy subjects (10 female, 10 male; mean age±SD: 33±9.3). There was no significant difference on the mean age and gender of the groups. Diagnosis of schizophrenia was made by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classification. 9 schizophrenic patients and 10 control subjects were smokers. Each participant's Body Mass Indexes were at average levels. There was no significant differences in these parameters between groups. None of the patients had any other significant psychiatric or somatic comorbidity. All subjects had normal nutritional habits without any supplements or antioxidants such as vitamin E, β-carotene, gingko biloba or other similar substances within one month prior to blood draw; they had no alcohol or drug abuse. The project was carried out with the approval of the local ethical committee and was in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants prior to examination.

10 mililiters of fasting venous blood were drawn from each subject at approximately 8.00 a.m. under fasting conditions. The samples were heparinized and centrifuged at 3000 rpm for 5 min. After plasma was taken to a separate eppendorf tube, RBCs were washed three times with phosphate buffer solution (PBS, pH 7.4) and erythrocyte packets were prepared. The separate plasma and erythrocytes were then kept at 4 °C in a thermostat immediately. Also 30 μl blood were taken from left hand middle finger of each subject with the help of micropipette and added to 2 ml of Dextran 60 solution.

Determination of RBC Deformability

Deformability of RBC was measured by shear stress diffractometer (Rheodyn SSD, Myrenne GmbH, Germany)[14]. Briefly 30 μl blood were added to 2 ml of Dextran 60 solution (viscosity 24 mPa s, osmolality 290 mOsm, pH 7.4), well-mixed and introduced to the device, where RBC suspension was shared. As a measure of deformability, RBC elongation index (EI) was measured at shear stresses from 0.3 to 60 Pa.

Determination of Lipid Peroxidation

The susceptibility of erythrocytes to lipid peroxidation was determined immediately by the method based on measuring the concentration of the pink chromogen compound- thiobarbituric acid reactive substances (TBARS) that forms when malondialdehyde (MDA) couples to thiobarbituric acid[15]. We use phosphate buffered saline (PBS)   (pH: 7.4), 30% tricloro acetic acid (TCA), 1% tiobarbituric acid (TBA) in 0.5 N NaOH, 0.001M, ethilen diamin tetra acetic acid (EDTA) and 5.848 M MDA (malondialdehyde standart) for TBARS determination.

0.4 ml erythrocyte suspension, 1.6 ml PBS and 1 ml 30% TCA mixed in a tube and centrifuged 15 minutes at 200 rpm. Supernatants were put in glass-tubes and 0.15 ml 0,1M EDTA and 0.5 ml 1% TBA added on these supernatants. These mixes were boiled in hot water for 15 minutes. After they cooled down, their optical density (OD) was measured at 532 nm at spectrophotometer. Standards were used in calculation. Basal TBARS levels of groups were expressed in nmol TBARS per gram of hemoglobin (nmol TBARS/gHb).

Determination of Antioxidant Enzymes

Measurement gluthatione peroxidase (GSH-Px) activity was performed by the coupled assay described by Paglia and Valentine using H_2O_2 substrate[16]. Briefly, erythrocyte suspensions were diluted with cold distilled water (1/15) and 3 times frozen and melted for 10 minutes. Erythrocyte lysate was   mixed with concentrated Drabkins solution and used in GSH-Px determination for 20 minutes. The result was presented in nmol/gHb.

Catalase (CAT) activities were determined as described by Beers and Sizer[17] and modified by Luck[18] in which the degradation of hydrogen peroxide was recorded spectrophotometrically at 240 nm. Erythrocyte packets were diluted 5 times with cold distilled water and centrifugated 20 minutes at 3000 rpm. This erythrocyte lysate was diluted in PBS (1/500) and used in CAT activity determination for 5 minutes. One unit of CAT was defined as the amount of enzyme that decomposes $1 \eta mol$ H_2O_2 /min under specific conditions.

Measurement of superoxide dismutase (SOD) activity was performed following the method by Sun et al[19]. Packed erythrocytes were lysed with 4 C 1/10 distilled water. 0.3 ml

chloroform and 0.5 ml ethanol were added to remove Hb and mixed for 1 minute. These mixtures were centrifuged for 1 hour at 13000 rpm and 4C. Supernatants were diluted with 0.001 M PBS and used in SOD determination. Eryhtrocyte SOD activity was expressed as U/gHb.

Statistical Analysis

The statistical Package for Social Sciences (SPSS 13.0) was used for statistical analysis. The data were expressed as the mean±SD. The data obtained were analyzed by the help of Student's t test and One-Way Anova test for the possible significant differences between the groups. We used One-Way Anova to analyze the EI values; and Student's t test to analyze lipid peroxidation and antioxidant levels. P< 0.05 was considered as statistically significant.

Results

RBC Deformability Indexes

Figure 1 shows the EI curve for erythrocytes from control and patient subjects at all shear stresses between 0.3 and 60 Pa. In all shear stress levels, schizophrenic patients' RBC deformability levels were found to be decreased when compared to the control values. The decrease is important statistically (p<0.05).

Antioxidant Enzyme and Lipid Peroxidation Values

Table I summarizes all analyzed biochemical parameters. The average levels of MDA in the patient group was higher (p<0.05) than that of the control group. In contrast, the mean levels of SOD, CAT and GSH-Px were found to be significantly lower (p<0.05) in patient group.
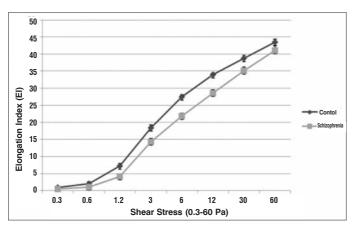

Figure 1. Elongation Index (EI) Values of Erythrocytes of Control and Schizophrenia Groups in different shear stresses (0.3-60 Pa)

Discussion

Schizophrenia is a devastating psychiatric disorder with a broad range of behavioural and biologic manifestations. Numerous studies suggest an association with genetic, endocrine, toxic-metabolic factors for the etiology of schizophrenia. A point of convergence for the theoretical models, occurs with regard to the neuronal membrane. The neuronal membrane contains a high proportion of PUFA and is the site for oxidative stress[10].

Free radicals are highly reactive chemical species generated during normal metabolic processes which in excess can lead to membrane damage. Oxidative stress is a state when there is imbalance between the generation of reactive oxygen species (ROS) and antioxidant defence capacity of the body. Neurons are mostmitotic cells. It is hard to refresh a neuron which has been damaged heavily by oxidative stress. Also the brain has a high oxygen consumption rate and these properties of the brain make it vulnerable to oxidative damage. Lipids are particularly susceptible to oxidative stress. There are a lot of phospholipids and PUFAs in brain tissue under physiological conditions. The changes in PUFAs metabolism, increased lipid peroxidation and the presence of oxidative stress are found in schizophrenia. They can change the neuron membrane stability or even cause cell death owing to oxidative stress. In various types of schizophrenia antipsychotic treatment affects the oxidative state of erythrocyte membranes in a different way[8,10,20].

In the present study, we determined significantly higher lipid peroxidation levels in schizophrenic patients than in the controls. Increased lipid peroxidation levels disable cellular membrane functions by stimulating phospholipase A2 and thus releasing interleukins by stimulating the immune system[21]. Our data support other studies that have shown an increased lipid peroxidation in schizophrenia[1,21-26]. TBARS is an end product of lipid peroxidation. In this study, antioxidant enzymes (SOD,GSH-Px and CAT) are found to be decreased statistically in schizophrenic patients. In the literature, decreased erythrocyte SOD, GSH-Px and CAT activities have been found in most studies[23,27,28]. On the other hand, there are also some contradictory results. In some studies, increased SOD, GSH-Px and CAT activities have been reported[21,29,30]. In the present study, increased TBARS levels may be due to insufficent antioxidant acitivity in schizoprenic patients. SOD dismutases superoxide radicals to form hydrogen peroxide which in turn is changed to water and oxygen by GSH-Px and catalase, thereby preventing the formation of hydroxyl radicals. Failure of this antioxidative system results in enhanced lipid peroxidation[25].

The damage induced by lipid peroxidation renders the cell unstable, and therefore compromises fluidity, permeability, signal transduction and causes receptor, mithocondrial DNA and nuclear

Table I. Antioxidant enzyme and lipid peroxidation levels of control and schizophrenia groups.

	MDA(nmol/gHb)	CAT (U/gHb)	GSH-Px(U/gHb)	SOD(U/gHb)
Control	77.2±18.4	194.4±37	27.2±12.6	1622±421
Schizophrenia	98±20.6*	158.2±32*	18.5±8.20*	1112±368*

*Significantly different from control group (p<0.05).

alterations. The existence of these products within cell membranes results in an unstable membrane structure, altered membrane fluidity and permeability and impaired signal transduction[9,10].

The ability of the RBC to deform is of crucial importance for performing its function of oxygen delivery and it is also a determinant of the cell survival time in the circulation[31,32]. Several factors may contribute to a shortened RBC life span, including reduced RBC deformability, which can lead to an increased splenic sequestration and erythrophagocytosis[33,34]. RBC deformability depends on the cell geometry (surface/volume ratio), cytoplasmic viscosity, and viscoelastic properties of the RBC membrane[35].

These hemorheological determinants can favour an increase in peripheral resistances and in arterial blood pressure, causing or worsening hypertension, a decrease in oxygen transport to tissue and peripheral perfusion, a decrease of the active exchange surface area in the microvasculature, especially in complicated hypertension[36].

Normally the RBCs must be deformed (they usually become parachuted) in order to pass through the microcirculation. Reduction of the RBCs deformability results in poor RBCs flow through the microcirculation and subsequently poor tissue oxygenation[37]. Increase of the blood viscosity results in global reduction of brain perfusion[38]. Although the brain represents only 2% of the body weight, it utilizes fully 25% of the body's total oxygen consumption. Decreased RBC deformability will also decrease oxygen utilization. Also RBC deformability is one of the main determinants of resistance against blood flow. Decreased RBC deformability may cause some important clinic implications such as ischemic brain, which may underlie the pathophysiologic mechanism of schizophrenia. Also, impaired RBC deformability may cause problems to schizophrenic patients vulnerable to cardiovascular disease, as one of the determinants of the blood fluidity is properties of RBC.

In the literature, there is a study supporting our results. Nakashima et al. found schizophrenic patients had significantly lower erythrocyte deformability than did the normal control[39]. All these results suggest that there is a disturbance of microcirculation and tissue oxygenation in schizophrenic patients.

Central nervous system cells are more vulnerable to the toxic effects of free radicals because they have a high rate of cathecholamine oxidative metabolic activity[10,40]. The results suggest that at least some of the schiophrenia disease process can be traced in peripheral tissue like plasma, blood cells or liver[41].

Specifically free radical mediated abnormalities may contribute to the development of a number of clinically significant consequenses, including prominent negative symptoms, tardive dyskinesia, neurological soft signs and Parkinsonian symptoms[3]. These findings provide a basis for the development of novel therapeutic models, including fatty acid and antioxidant supplemantation in the future.

Further elucidation of the role of free radical and antioxidants in schizophrenia and its treatment will require systematic investigation.

Acknowledgement

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