Epilepsi 2016;22(3):86-92 DOI: 10.14744/epilepsi.2016.86580

ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Evaluation of Dynamic Thiol-Disulphide Homeostasis in Patients with Epilepsy

Epilepsili Hastalarda Dinamik Tiyol-Disülfid Homeostazisinin Değerlendirilmesi

Dr. Şadiye GÜMÜŞYAYLA

Şadiye GÜMÜŞYAYLA,[1] Gönül VURAL,[1] Hesna BEKTAŞ,[2] Salim NEŞELİOĞLU,[3] Orhan DENİZ,[1] Özcan EREL[4]

[1]Department of Neurology, Yıldırım Beyazıt University Faculty of Medicine, Ankara, Turkey
[2]Department of Neurology, Ankara Atatürk Training and Research Hospital, Ankara, Turkey
[3]Department of Biochemistry, Ankara Atatürk Training and Research Hospital, Ankara, Turkey
[4]Department of Biochemistry, Yıldırım Beyazıt University Faculty of Medicine, Ankara, Turkey

Summary

Objectives: The aim of this study was to investigate dynamic thiol-disulphide homeostasis as a novel oxidative stress parameter in patients with epilepsy.

Methods: A total of 100 participants were included in the study. Of these, 50 participants were diagnosed with epilepsy and remaining 50 were healthy individuals. Total thiol (–SH+–S-S–) and native thiol (–SH) levels in serum were measured in all patients. Quantity of dynamic disulphide bond and (–S-S–) x 100 / (-SH), (–S-S-) x 100 / (–SH+–S-S–), and –SH x100 / (–SH+–S-S–) ratios were calculated from these values. Data obtained were compared between patients with epilepsy and healthy individuals.

Results: No statically significant difference was determined between patients with epilepsy and healthy individuals in terms of total thiol, native thiol, and dynamic disulphide bond levels and (–S-S–) x 100 / (-SH), (–S-S-) x 100 / (–SH+–S-S–), and –SH x 100 / (–SH+–S-S–) ratios. Neither was there significant correlation between total thiol, native thiol, and dynamic disulphide bond levels and (–S-S–), (–S-S–) x 100 / (-SH), (–S-S-) x 100 / (–SH+–S-S–) and –SH x 100 / (–SH+–S-S–) ratios of patients and seizure frequency or duration of illness.

Conclusion: Oxidative stress is considered to be one of the molecular changes that are the underlying causes of epileptogenesis. In this study, we investigated dynamic thiol-disulfide homeostasis in patients with epilepsy using a new method in the literature.

Keywords: Dynamic thiol-disulphide homeostasis; epilepsy; oxidative stress; thiol metabolism.

Özet

Amaç: Bu çalışmanın amacı epilepsili hastalarda yeni bir oksidatif stress parametresi olarak dinamik tiyol-disülfid homeostazisini araştırmaktır.

Gereç ve Yöntem: 50 tanesi epilepsi hastası, 50 tanesi de sağlıklı gönüllü olmak üzere toplam 100 katılımcı çalışmaya dahil edildi. Çalışmaya katılan tüm epilepsi hastaları ve sağlıklı gönüllülerin serumda total tiyol (–SH+–S-S–) ve nativ tiyol (–SH) düzeyleri ölçüldü. Dinamik disülfid bağ düzeyi (–S-S–) ve (–S-S–) x 100 / (-SH), (–S-S-) x 100 / (–SH+–S-S–) ve –SHx100 / (–SH+–S-S–) oranları bu değerlerden hesaplandı. Elde edilen veriler epilepsi hastaları ve sağlıklı gönüllüler arasında kıyaslandı.

Bulgular: Epilepsi hastaları ve sağlıklı gönüllüler arasında total tiyol, nativ tiyol miktarları, dinamik disülfid bağ düzeyi ve (–S-S–) x 100 / (-SH), (–S-S-) x 100 / (–SH+–S-S–) ve –SH x 100 / (–SH+–S-S–) oranları arasında istatistiksel olarak anlamlı bir farklılık bulunmadı. Ayrıca hasta grubunda total tiyol, nativ tiyol miktarları, dinamik disülfid bağ düzeyi ve (–S-S–) x 100 / (-SH), (–S-S-) x 100 / (–SH+–S-S–) ve –SH x 100 / (–SH+–S-S–) oranları ile nöbet sıklığı ve hastalık süresi arasında bir korelasyon bulunmadı.

Sonuç: Oksidatif stresin epileptogenezin altında yatan moleküler değişikliklerden biri olduğu düşünülür. Bu çalışmada, biz literatürde yeni geliştirilmiş bir metod ile epilepsi hastalarında dinamik tiyol-disülfid homeostazisini araştırdık.

Anahtar sözcükler: Dinamik tiyol-disülfid homeostazisi; epilepsi; oksidatif stress; tiyol metabolizması.

Submitted *(Geliş)*: 31.12.2015
Accepted (Kabul) **:** 25.07.2016
Available Online *(Çevrimiçi yayınlanma)*: 04.11.2016
***Correspondence (İletişim)*:** Şadiye GÜMÜŞYAYLA, M.D.
***e-mail (e-posta)*:** sadiyetemel@yahoo.com

Introduction

Epileptic seizures are clinical manifestations of an abnormal, excessive, hypersynchronous discharge of a population of cortical neurons in the central nervous system (CNS).[1] Epilepsy is a disorder of CNS characterized by recurrent seizures unprovoked by acute systemic or neurological insult.[2] Epileptogenesis refers to process of brain injury caused by triggering of molecular and cellular changes that lead to spontaneous seizures. Epileptogenesis may occur as result of various genetic and acquired mechanisms. In CNS, degradation of balance between excitatory and inhibitory mechanisms and increase in neuronal excitability stimulate mechanisms that lead to epileptogenesis. Final common pathway resulting in epileptogenesis brings increased excitability and synchronicity to the cells. Earlier studies in the literature have shown that oxidative stress plays a role in epileptogenesis.[3–5] Oxidative stress is cell and tissue damage to biological structures such as proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and carbohydrates caused by reactivity of free radicals in living organism.[6] This condition is characterized by balance between oxidative and anti-oxidative mechanisms of living organisms. Oxidative stress occurs as result of increased production of reactive oxygen species (ROS) or reduced defense mechanisms against reactive species. Since brain tissue consumes largest amount of oxygen, brain is very sensitive to oxidative stress. Development of oxidative stress in CNS is due to insufficiency of antioxidant defense systems and increased production of ROS. In addition, brain is rich in terms of polyunsaturated fatty acids and these acids cause oxidative stress.[7–9] As with epilepsy, oxidative stress affects a large group of other diseases and degenerative processes in CNS. Although underlying cellular mechanism of epileptogenesis is not fully understood, advanced information about role of oxidative stress in epilepsy has been obtained.[10,11]

There are many tests used to measure antioxidant and oxidant molecules in living organism that can illustrate oxidative stress. Thiols are a class of organic compound that contain sulfhydryl (-SH) group formed by combination of a hydrogen and a sulfur atom with a carbon atom. They are known as antioxidant molecules due to their reductant features. ROS formed in the organism transfer excessive electrons to thiols and oxidize them, forming disulphide bonds. However, these disulphide bonds are reversible; they can turn back into thiols, depending on organism's antioxidant-oxidant balance. Thus, thiol-disulphide homeostasis is dynamic.[12–14] Antioxidant protection of this dynamic thiol-disulphide homeostasis is of critical importance for detoxification, signal transduction, apoptosis, regulation of enzymatic activation, transcription factors, and cellular signaling mechanisms. In the disease processes caused by oxidative stress, dynamic thiol-disulphide homeostasis of organism is expected to be affected.[12,13] Oxidative stress is increasingly held responsible for epilepsy. Oxidative stress is considered to be one of the main mechanisms of increased risk of seizures and repeated seizures, which result in epileptogenesis by leading to abnormal structural changes to proteins, membrane lipids, DNA, and RNA.[6,7,11] Determination of changing thiol-disulphide homeostasis caused by oxidative stress provides valuable information for various abnormal biochemical processes.[12] It is quite possible that oxidative stress is responsible for epileptogenesis and that this balance has deteriorated in patients diagnosed with epilepsy.

The aim of this study was to investigate a novel, easily calculated, readily available, and relatively cheap oxidative stress parameter, thiol-disulphide homeostasis, in patients diagnosed with epilepsy and to compare the results with healthy controls. In this study, it was hypothesized that underlying mechanisms of epilepsy, a chronic, dynamic disease, affect thiol-disulphide homeostasis in the organism.

Materials and Methods

Participants

This study was conducted with a total of 50 patients (21 women and 29 men) aged between 18 and 60 years diagnosed with epilepsy according to International League Against Epilepsy (ILAE) 1989 criteria and 50 healthy volunteers (25 men and 25 women) aged between 19 and 60 years, who have no complaints or epileptic seizures, with their written, informed consent. Approval of the Yıldırım Beyazıt University Faculty of Medicine ethics committee was obtained prior to initiating the study. Further clinical evaluation of all participants in the study was performed by researchers in clinical and outpatient settings. Detailed data regarding medical history, neurological examination, age, sex, seizure type, seizure frequency, duration of disease, antiepileptic drug dose, duration of use, and information regarding whether epileptic seizures were under control were obtained for each participant. No volunteer participating in the study had a history of smoking, alcohol, or drug

use. Physical and neurological examinations of patients and healthy volunteers were normal. Patients who had a seizure within last 12 hours, were diagnosed with progressive brain disease, other chronic systemic disease, or with chronic use of drugs other than anti-epileptic treatment were excluded from the study. No malignancy, systemic disease, or neurological disease was detected in healthy individuals in control group, and none had any history of chronic drug use. There were no acute medical problems such as trauma or infection when blood samples were obtained. Lipid profile, blood glucose levels, complete blood count, kidney function tests, blood electrolyte levels, and iron profile of all patients were normal.

Blood sampling and analytic procedure

Venous blood samples from patient and control groups were collected from antecubital vein. Blood samples were taken in the morning after 12 hours of fasting in tubes with ethylenediaminetetraacetic acid. Blood samples were centrifuged at 1500 rpm for 10 minutes within 30 minutes after receiving them from participants in order to obtain serum samples. These serum samples were stored at -80° C until biochemical analyses were conducted.

Laboratory method

In this study, dynamic thiol-disulphide homeostasis in serum samples of epilepsy patients and healthy individuals was identified using an automated method newly developed by Erel et al.[12] Total thiol (–SH+–S–S–) and native thiol (–SH) concentrations in samples were measured using Ellmann and modified Ellmann reagent. -SH content was subtracted from –SH+–S–S– content and half of this difference was calculated; this value was amount of dynamic disulphide bonds (-S-S-). In addition, (–S-S–) x 100 / (-SH), (–S-S-) x 100 / (–SH+–S-S–) and –SH x 100 / (–SH+–S-S–) ratios were calculated using these parameters.

Statistical analysis

In the present study, compliance of variables such as total thiol, native thiol, dynamic disulphide bond, (–S-S–) x 100 / (-SH), (–S-S-) x 100 / (–SH+–S-S–), and –SH x 100 / (–SH+–S-S–) ratios with normal distribution was evaluated using Shapiro-Wilks test. Interquartile range (IQR) was used to present descriptive statistics of variables without normal distribution and for discrete variables. Average standard deviation (SD) values of variables with normal distribution are provided (mean±SD).

Mann-Whitney U test was used to evaluate difference between groups (patient-control) in terms of total thiol, native thiol, and dynamic disulphide bond level variables.

Independent samples t-test was used to compare (–S-S–) x 100 / (-SH), (–S-S-) x 100 / (–SH+–S-S–), and –SH x 100 / (–SH+–S-S–) variables within groups.

Variance analysis was used to see to difference between seizure type and total thiol, native thiol, and dynamic disulphide bond. R 3.1.2 for Windows software (The R Project for Statistical Computing, https://www.r-project.org/) was used for correlation analysis (polyserial correlation coefficient) between patient group and specified variables.

IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA) and MS-Excel 2007 were used for statistical analyses and calculations. Statistical significance level was $p<0.05$.

Results

Average age of patients with epilepsy was 41.66±15.39 years, whereas average age of healthy control individuals was 40.78±15.08 years (p=0.497). No statistically significant difference was found between patient and control groups in terms of age and gender variables (Table 1).

Median value of total thiol levels was 477.55 mmol/L (IQR=63.20) for group with epilepsy, and median value of total thiol levels was 472.55 mmol/L (IQR=55.72) for healthy control group. There was no statically significant difference between groups in terms of total thiol values (p=0.699). Median value of native thiol levels was found to be 440.75 mmol/L (IQR=56.45) for patients with epilepsy, whereas median value of native thiol level was 431.3 mmol/L (IQR=51.97) for healthy individuals. There was no statically significant difference between groups in terms of native thiol values (p=0.410). Median value of dynamic disulphide bond level was 21.45 mmol/L (IQR=6.40) for group with epilepsy, whereas median value of dynamic disulphide bond for control group was 18.55 mmol/L (IQR=5.10). There was no statically significant difference between the 2 groups in terms of dynamic disulphide bond (p=0.126) (Table 2).

Average –S-S x 100 / -SH value of individuals in the group with epilepsy was found to be 0.04%±0.01, whereas average –S-S x 100 / -SH value of control group was 0.04%±0.01. No statistically significant difference was found between pa-

Table 1. Descriptive statistics on the basis of age and gender between groups

	Group						Test statistic
	Patients			Controls			p
	n	%	Mean±SD	n	%	Mean±SD	
	50	50.0		50	50.0		
Age, years			41.66±15.39			40.78±15.08	=0.497
Gender							
Female	21	42		25	50		
Male	29	58		25	50		

SD: Standard deviation.

Table 2. Descriptive statistics and comparison of total thiol, native thiol, and dynamic disulfide bond variables between groups

	Patients (IQR)	Median Controls Median (IQR)	Z	p
Total thiol	477.55 mmol/L (63.20)	472.55 mmol/L (55.72)	0.386	0.699
Native thiol	440.75 mmol/L (56.45)	431.30 mmol/L (51.97)	0.824	0.410
Dynamic disulphide bond	21.45 mmol/L (6.40)	18.55 mmol/L (5.10)	1.531	0.126

IQR: Interquartile range.

Table 3. Descriptive statistics and comparison of –S-S- x 100 / -SH, –S-S- x 100 / -S-S+-SH, and –SH x 100 / -S-S+-SH variables by group

	Patients	Controls	t, Z*	p
	Median±SD	Median±SD		
–S-S- x 100 / -SH	0.04%±0.01	0.04%±0.01	0.343	0.732
–S-S- x 100 / -S-S+ -SH	0.04%±0.02	0.04%±0.01	0.124*	0.901
–SH x 100 / -S-S+-SH	0.91%±0.02	0.91%±0.02	0.341	0.734

-S-S-: Dynamic disulphide bond; -SH: Native thiol; -S-S-+-SH: Total thiol. SD: Standard deviation.

tient and control groups in terms of –S-S x 100 / -SH variable (p=0.732). Average –S-S x 100 / -S-S+-SH value of individuals in the group of patients with epilepsy was 0.04%±0.02, whereas average –S-S x 100 / -S-S+-SH value of control group was 0.04%±0.01. No statistically significant difference was found between patient and control groups in terms of –S-S x 100 / -S-S+-SH variable (p=0.901). Average SH x 100 / -S-S+-SH value of individuals in the group of patients with epilepsy was found to be 0.91%±0.02, whereas average –SH x 100 / -S-S+-SH value of individuals in the control group was 0.91%±0.02. No statistically significant difference was found between patient and control groups in terms of –SH x 100 / -S-S+-SH variable (p=0.734) (Table 3).

A weak positive relationship was found between total thiol, native thiol, and dynamic disulphide bond and disease duration, but this relationship did not reach statically significant level (polyserial correlation coefficients are 0.321, 0.299, and 0.200, respectively; p-values: 0.081, 0.121, and 0.273, respectively) (Table 4).

A weak positive relationship was also found between total thiol, native thiol and dynamic disulphide bond and seizure frequency, but relationship didn't reach level of statistical significance (polyserial correlation coefficients are 0.084, 0.044, and 0.154, respectively; p-values: 0.905, 0.612, and 0.728, respectively) (Table 4).

Discussion

Present study is the first to evaluate dynamic thiol-disulphide homeostasis in serum of patients with epilepsy us-

Table 4. Analysis of patient group in terms of correlation between total thiol, native thiol, and dynamic disulphide bond and duration of disease and seizure frequency

	Polyserial Correlation Coefficient	
		p
Native thiol – Duration of disease	0.299	0.121
Total thiol - Duration of disease	0.321	0.081
Dynamic disulphide bond- Duration of disease	0.200	0.273
Native thiol – Seizure frequency	0.044	0.612
Total thiol - Seizure frequency	0.084	0.905
Dynamic disulphide bond - Seizure frequency	0.154	0.728

ing new, automated, calorimetric method. In this study, quantity of total thiol, native thiol, and dynamic disulphide bond in serum of patients with epilepsy and healthy individuals were measured using new method that objectively demonstrates thiol-disulphide homeostasis mechanism, an important and dynamic redox system, and –S-S- x 100 / -SH, –S-S- x 100 / -S-S+ -SH, –SH x 100 / -S-S+-SH ratios were also investigated taking concept that oxidative stress is important in epilepsy pathogenesis into account.

Since oxidative stress plays an important role in pathogenesis of many diseases, thiol chemistry has become increasingly important. However, quantities of thiol and disulphide have previously been measured in thiol compounds with low molecular weight. It has now become possible to assess dynamic thiol-disulphide homeostasis using new method developed by Erel et al.[12] This new method will illustrate if thiol metabolism is affected in many disease pathogeneses and thereby demonstrate if oxidative stress is important in disease pathogenesis. Therefore, in the present study, dynamic thiol-disulphide homeostasis, which can be used as a marker of oxidative stress in patients with epilepsy, was investigated using this newly developed method.

Since determining role of ROS in pathogenesis of neurodegenerative diseases of CNS such as Parkinson's disease, stroke, and dementia, role of oxidative stress in epilepsy has become an increasingly important topic that has been investigated by many researchers.[2,10–12,15–18] Cell apoptosis, mitochondrial damage, and formation of reactive oxygen types in many brain regions, including especially hippocampus of experimental epilepsy models of rats, have been demonstrated. In these experimental models, it has been shown that acute damage caused by ROS lead to chronic epileptic diseases over time.[2,19–21] Various oxidant and antioxidant parameters have been investigated in patients diagnosed with epilepsy. In several studies, malonyl-dialdehyde (MDA) levels, the main degradation product of lipid peroxidation, are found to be significantly higher in patients with epilepsy.[7,22–24] In other studies, total antioxidant capacity was found to be significantly lower in group of patients with epilepsy.[25] As an antioxidant enzyme, paraoxonase -1 has been found to be reduced in patients with epilepsy.[7] In addition, nitric oxide level, an important ROS, has been found to be significantly higher in patients newly diagnosed and not yet treated.[2,26–28] Considering all these data, there is a ground causing oxidative stress in patients with epilepsy. There are, however, some studies that have conflicting results on this issue.[29,30] Patsoukis et al.[29] investigated thiol redox status and oxidative stress in an experimental epilepsy model. Although they identified significant decrease in some antioxidant molecules, they reported that there was no significant decrease in one of the most important non-protein thiols, glutathione and glutathione disulphide.[29] Keskin Guler et al.[30] found that an antioxidant enzyme, glutathione peroxidase, was significantly increased in patients with epilepsy compared to healthy controls.

Thiol, which is an important antioxidant molecule, and redox systems of this molecule have become increasingly important. Thiol metabolism is dynamic, playing a key role in physiology of many CNS functions. This dynamic process allows for features of transport and signal transduction in cells in a healthy way. In addition, this redox system provides structural and functional integrity of protein and normal enzyme activities. Some diseases, especially those with neurodegeneration, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis have been proven to be characterized by abnormal thiol-disulphide homeostasis.[12–14] Considering impacts of canal pathologies and

neurodegeneration, we have speculated that this homeostasis may be corrupted in epileptic patient group as well. Dynamic thiol-disulphide homeostasis in this group of patients was investigated using a new method developed by Erel et al. that has been proven to be reliable and able to measure dynamic thiol-disulphide homeostasis objectively.[12] When data obtained from patient group were compared with data of group of healthy individuals, there was no significant difference between groups in terms of total thiol, native thiol, dynamic disulphide bond values, or –S-S- x 100 / -SH, –S-S- x 100 / -S-S+ -SH, and –SH x 100 / -S-S+-SH ratios. In addition, total thiol, native thiol, and dynamic disulphide bond values were not correlated with seizure frequency or duration of disease. In the study conducted by Mudaraddi et al.,[31] plasma total thiol levels were found to be significantly lower in patients diagnosed with epilepsy. Murali et al.[32] also observed reduction in total thiol levels of rats that were made epileptic in experimental models. Survey of the literature revealed that thiols are mostly antioxidant molecules, but sometimes act as pro-oxidant molecules because they are affected by physiological status of organism.[33,34] Concentration of sulphur-containing amino acids may change antioxidative properties of proteins and enzymes that participate in structures such that they become pro-oxidative. Thus, thiols are both antioxidant and pro-oxidant molecules. Oxidative stress level of organism determines antioxidant and pro-oxidant effects of thiols. This balance has dynamic status and thiols are very active molecules in terms of bio chemistrical point. Thus, this balance represents an evaluation of current status of an organism at a given time.[12,33]

In this study, all patients with epilepsy used antiepileptic drugs as mono- or polytherapy. Some studies have shown that antiepileptic drugs can turn redox status of organism toward to favourable form in patient with epilepsy.[35–37] Thus, we may have found this balance unchanged in patient group for 2 reasons: 1) antiepileptic drugs may affect this balance favorably, or 2) serum samples were taken during seizure-free period.

This study is the first to assess dynamic thiol-disulphide homeostasis in patients with epilepsy in the literature. In this respect, this study is very important. However, this is a preliminary study. Evaluating this balance in prolonged seizures, in drug-naïve patients, and in larger sample may contribute to understanding disease pathology. Another limitation is that we could not correlate our results with other oxidative stress parameters, such as lipid hydroperoxide, total antioxidant status, total oxidant status, oxidative stress index, paraoxonase, or arylesterase. Further studies that take these factors into account are needed.

Acknowledgements

The authors would like to thank Özcan Erel's research asistants for their invaluable assistance. The authors also would like to acknowledge Meliz Vural for her professional translation and Blue Tower Educational Services for their professional editing. The statistical evaluation of this study was done by the Yıldırım Beyazıt University Statistical Consultancy Application and Research Center.

Financial support

This research received no financial support from public, commercial, or not-for-profit sectors.

Ethical standards

The authors assert that all procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Ethical approval for the study was granted by the ethics committee of Yıldırım Beyazıt University, Faculty of Medicine.

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