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Effects of antiepileptic drugs on dynamic thiol/disulphide homeostasis in children with idiopathic epilepsy

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ABSTRACT

Purpose: Anti-epileptic drugs have been widely used in children with epilepsy. Although several studies have investigated the role of oxidative stress and the effects of antiepileptic drugs on several oxidative markers in epilepsy, adequate information is not available on this issue. This study aimed to investigate the changes in thiol disulphide homeostasis in children with epilepsy under two commonly prescribed AED monotherapies, carbamazepine and valproic acid.

Methods: A hundred and one children with epilepsy using valproic acid or carbamazepine and 58 healthy children were included in this study. Of the 101 patients with idiopathic epilepsy, 58 were on valproic acid monotherapy and 43 patients were on carbamazepine monotherapy. The total thiol, native thiol, and disulphide levels were measured and the disulphide/native thiol, disulphide/total thiol and native thiol/total thiol ratios were calculated in both groups.

Results: The total thiol and native thiol levels of the valproic acid treated group were significantly lower than the control group ($p < 0.05$). The native thiol level of carbamazepine treated group was lower than the control group without a significance ($p = 0.123$). Disulphide level, disulphide/native thiol and disulphide/total thiol ratios were significantly higher and native thiol/total thiol ratio was significantly lower in both valproic acid and carbamazepine treated group compared with the control group.

Conclusion: Thiol/disulphide homeostasis is impaired in children with idiopathic epilepsy using valproic acid or carbamazepine. Valproic acid which is frequently used in childhood epilepsy may modify this balance more than carbamazepine monotherapy. More importantly, the new method used in our study proposes a promising, practical and daily applicable test for evaluating oxidative stress in these patien

1. Introduction

Epilepsy is a common chronic, neurological disorder and childhood epilepsies represent about 25% of the whole epilepsy population [1]. Modern advances in diagnostic technology, particularly in neuroimaging and molecular genetics, now permit better understanding of the pathophysiology of epilepsy. Defective ion transportor ion channel structure in the neuronal membrane, inhibitory–excitatory mechanisms, and regulatory modulator systems have been implicated in the pathogenesis of epilepsy [2–4]. Nowadays, increasing evidence suggest that oxidative stress is implicated in the underlying mechanism of epilepsy. In its simplest definition, oxidative stress refers to the inbalance in oxidant and antioxidant homeostasis leading to the production of toxic reactive oxygen and nitrogen species [5]. Excess reactive oxygen species can cause oxidative damage in vulnerable targets such as polyunsturated fatty acids, thiol groups and DNA. Several biomarkers have been evaluated to show the biochemical alterations to oxidative stress in patients with epilepsy [6,7]. However, clinical studies evaluating oxidant status in children with epilepsy under drug treatment are scarce. While some found increased lipid peroxidation, others found no change in oxidant markers in epileptic patients under drug treatment. Growing evidence indicates that antiepileptic drug treatment leads to an increase in oxidative stress which is similar to that observed during epileptogenesis

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Table 1
Age and sex distribution of groups, showing no difference between neither of the groups.

	Carbamazepine treated group (*n*:43)	Valproate treated group (*n*:58)	Control group (*n*:58)	*p*-Value
Distribution of sexes (male/female)	21/22	25/33	27/31	0.74
Age (years)	7.6 ± 2.8 (3–16)	8.8 ± 2.2 (3–12)	8.2 ± 2.7 (4–17)	0.72

Thiols are sulfhydryl group containing organic compounds found in albumin and cysteine derived molecules such as glutathione, homocysteine, and γ-glutamylcysteine. Thiols are good reductants. Thiols can undergo oxidation reaction via oxidant molecules and form disulphide bonds [8]. Under normal conditions, these disulphide bonds can again be reduced into thiol groups; so that the dynamic thiol–disulphide homeostasis is preserved [9]. However, under the conditions of oxidative stress, the oxidation of cysteine residues can lead to the reversible formation of mixed disulphides between protein thiol groups and low-molecular-mass thiols. Thiol/disulphide homeostasis has critical roles in maintaining the oxidative balance, antioxidant protection, detoxification, signal transduction, apoptosis, the regulation of enzymatic activity and transcription factors, and cellular signaling mechanisms transduction and programmed cell death [10]. Recent researches has focused on the possible impairment of dynamic thiol–disulphide homeostasis concept developed by Erel et al. [10] in neurological diseases such as stroke, migraine, febrile convulsion [11–13].

In this study, we evaluated dynamic thiol/disulphide homeostasis of children with idiopathic epilepsy receiving antiepileptic drugs and compare with age and gender matched healthy children using a novel automatic and spectrophotometric method developed by Erel and Neşelioğlu. The aim of this study was to determine the effects of antiepileptic drugs on disulphide stress. To the best of our knowledge, this is the first study to assess the dynamic thiol/disulphide homeostasis of pediatric patients with idiopathic epilepsy using antiepileptic drugs. This untargeted method has the potential to identify the relationship between oxidative stress and antiepileptic drug use in pediatric epileptic patients.

2. Material method

The study was approved by the local ethical committee of Gazi University School of Medicine. The total thiol content, native thiol and disulphide levels, disulphide/native thiol, disulphide/total thiol and native thiol/total thiol ratios were evaluated in the serum plasma of 101 (46 male,55 female) patients with idiopathic epilepsy receiving valproate or carbamazepine monotherapy and 58 (27 male, 31 female) healthy children. Of the 101 patients with idiopathic epilepsy, 58 were on valproic acid monotherapy and 43 patients were on carbamazepine monotherapy. No significant difference was observed between the groups in terms of age (p:0.72) and gender (p:0,74). Patients with symptomatic and syndromic epilepsy, mental motor retardation and underlying a chronic disorder were not included in the study. The patients were not taking previous medication trials prior to valproic acid or carbamazepine use. The patients were not taking other medications at the time of study. There were no acute medical conditions such as infection, physical exertion and trauma at the time of blood drawn. All of the patients were receiving valproic acid or carbamazepine treatment for at least six months and all patients were seizure-free after valproic acid or carbamazepine monotherapy. Drug level in plasma was at the therapeutic concentration (valproic acid, 50–100 μg/ml, carbamazepine, 4–10 μg/ml).

Blood samples were obtained from the patients in the interictal period. Fasting samples were obtained from the patients and from healthy controls. The blood samples were then centrifuged at 1500 cycles for 10 min. Thereafter, serum samples were separated and kept at −80 °C until the investigation time. Serum native thiol and total thiol levels were measured with novel and fully automated tests described by Erel and Neselioglu [10]. After serum extraction, the test takes about 12 min to measure these values with the automated system. Disulphide concentrations were calculated as the half of the difference between levels of the total thiol and native thiol. Then, disulphide/total thiol percent ratio, disulphide/native thiol percent ratio, and native thiol/total thiol percent ratio were calculated.

Statistical Package for Social Sciences 21.0 (SPSS Inc.; Chicago, IL, USA) software was used for statistical analysis. Measured values were evaluated and reported as means ± standard deviation (SD). Kolmogorov-Smirnov test was used to determine the normal distribution of variables. Independent samples *t*-test was used to determine the differences in variables between the patients and control group. The chi-Square test was used in the evaluation of the gender distribution of the groups. A p-value less than 0.05 was considered as significant.

3. Results

A total of 101 subjects were included in the study. The mean age of patients and distribution of sexes did not differ between the groups (Table 1).

The total thiol and native thiol levels of the valproic acid treated group were significantly lower than the control group ($p < 0.05$)). The native thiol level of carbamazepine treated group was lower than the control group without a statistical significance ($p = 0.123$) (Fig. 1) Disulphide level, Disulphide/Native thiol and Disulphide/Total thiol ratios were significantly higher and native thiol/ total thiol ratio was significantly lower in both valproic acid and carbamazepine treated group compared with the control group (Table 2).

The mean duration of carbamazepine treatment was 16.51 ± 8.12 months [6–33] and the mean duration of valproic acid treatment was 14.58 ± 8.70 months [6–36]. There was no difference between each group. Next, we have examined correlation of duration of treatment and total thiol, native thiol and disulphide levels and no significant correlation was found in either of the drugs.

4. Discussion

In this study, we investigated -for the first time- thiol disulphide homeostasis in children treated with valproic acid or carbamazepine for idiopathic epilepsy in the literature. The major findings were that (a) Total thiol, and native thiol levels were lower in the patients than controls and (b) Disulphide levels were higher in the patients than controls (c) native thiol/ total thiol ratio was lower in patients than controls. Despite the fast-growing literature about the effect of antiepileptic drug therapy with several different oxidant markers, they have not reached the level of evidence for widespread utilization [14–17].

Brain injury resulting from seizures is a dynamic process that comprises multiple factors contributing to neuronal cell death. These may involve genetic factors, excitotoxicity- induced mitochondrial dysfunction, altered cytokine levels, and oxidative stress [18]. Seizure-like activity at the cellular level initiates significant influx of calcium via voltage-gated and *N*-methyl-D-aspartate (NMDA)-dependent ion channels [5]. The brain is particularly susceptible to oxidative stress because it utilizes the highest amount of oxygen compared with other bodily organs. The brain also contains high concentrations of polyunsaturated fatty acids that are prone to lipid peroxidation, is rich in iron, which can catalyze hydroxyl radical formation, and is low in CAT activity [19]. Oxidative stress results in functional cellular disruption

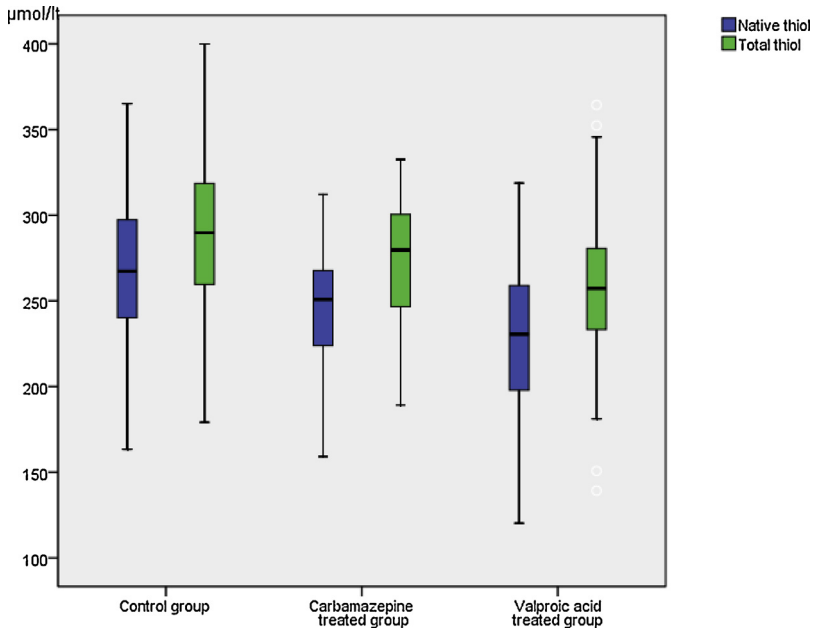

Fig. 1. Native thiol and total thiol levels in epileptic children using valproic acid or carbamazepine and the control group, showing significantly lower total thiol and native thiol levels of the valproic acid treated group and lower native thiol level of carbamazepine treated group without a statistical significance.

and cellular damage and may cause subsequent cell death via oxidation of biomolecules such as proteins, lipids, and nucleotides. Protein oxidation leads to functional changes or deactivation of various enzymes [20]. Lipid peroxidation causes membrane structure alterations that affect membrane fluidity and permeability and membrane protein activity [21].

Dynamic thiol disulphide homeostasis status has critical roles in antioxidant protection, detoxification, signal transduction, apoptosis, regulation of enzymatic activity and transcription factors and cellular signalling mechanisms [10]. Moreover, dynamic thiol/disulphide homeostasis is being increasingly implicated in many disorders. There is also a growing body of evidence demonstrating that an abnormal thiol disulphide homeostasis state is involved in the pathogenesis of a variety of diseases, including diabetes [22], cardiovascular disease [23], cancer [24], rheumatoid arthritis [25], chronic kidney disease [26], acquired immunodeficiency syndrome (AIDS) [27], Parkinson's disease, Alzheimer's disease, Friedreich's ataxia (FRDA), multiple sclerosis and amyotrophic lateral sclerosis [28–30] and liver disorder [31]. There are no studies on the effect of antiepileptic drugs on thiol disulphide homeostasis. Therefore, determination of dynamic thiol/disulphide homeostasis can provide valuable information on various normal or abnormal biochemical processes in epileptic patients using antiepileptic drugs. Some papers indicate that long-term treatment with antiepileptic drugs leads to an increase in oxidative stress which is similar to that observed during epileptogenesis [32–37]. Several first-choice drugs for various epileptic syndromes, such as valproic acid, carbamazepine, phenytoin, or phenobarbital, increase lipid peroxidation and nucleic acid oxidation in blood or blood cells [33–36]. However, the idea was not further confirmed.

Seizure generation may be related to the homeostatic imbalance of antioxidants and oxidants. To date, various experimental seizure models have been developed to investigate the role of endogenous antioxidants in response to excitotoxic oxidative stress. Impairment of endogenous antioxidant factors against oxidative stress is involved in seizure generation. Antiepileptic drugs, at least in part, impair antioxidant systems.

Valproic acid is an effective drug for treating simple and complex epileptic seizures as a monotherapy and as a component of polytherapy. The effects of valproic acid on oxidant status in children with epilepsy are conflicting in different studies [37–40]. Chang et al showed that oxidative stress has a potential role on valproic acid induced hepatotoxicity [41]. Verrotti et al reported no change in oxidative status in children with epilepsy during VPA treatment [39]. We previously found no significant difference in nitric oxide, malondialdehyde and xanthine oxidase levels in children with epilepsy using valproic acid [14]. Yuksel et al. found increased serum lipid peroxidation in children with epilepsy receiving VPA for 13 months when compared to control group and the pretreatment levels [37]. Michoulas et al. also reported higher urinary levels of 15-F2T-isoprostane, a marker of oxidative stress in children with epilepsy treated with VPA [38]. Yiş et al found an increase not

Table 2
The values of thiol and disulphide levels of the epileptic children and the control group ;showing statistically significant higher Disulphide level, Disulphide/Native thiol and Disulphide/Total thiol ratios and significantly lower native thiol/ total thiol ratio in both valproic acid and carbamazepine treated group compared with the control group.

Variables	Carbamazepine treated group (*n*:58) (mean ± SD)	Valproate treated group (*n*:43) (mean ± SD)	Control group (n:58) (mean ± SD)	$p < 0.05$
Native thiol, µmol/L	245,05 ± 36,21	227,17 ± 42,41	266,65 ± 43,24	**b-c**
Total thiol, µmol/L	273,80 ± 35,27	256,99 ± 44,31	288,75 ± 48,77	**b-c**
Disulphide, µmol/L	14,37 ± 4,44	14,90 ± 6,36	11,04 ± 4,92	**a-c, b-c**
Disulphide /Native thiol (%)	6,07 ± 2,38	6,85 ± 3,51	4,10 ± 1,55	**a-c, b-c**
Disulphide/Total thiol (%)	5,34 ± 1,82	5,87 ± 2,48	3,75 ± 1,31	**a-c, b-c**
Native thiol/Total thiol (%)	89,31 ± 3,65	88,24 ± 4,96	92,49 ± 2,63	**a-c, b-c**

reaching a pathological level in lipid peroxidation during valproic acid treatment [17]. In this study, the seizures of the patients were under control with valproic acid monotherapy and none of them had symptomatic epilepsy. In this study, we found that the total thiol and native thiol levels of the patients under valproic acid treatment were significantly lower than the control group group. Disulphide level, disulphide/native thiol and disulphide/total thiol ratios were significantly higher, native thiol/ total thiol ratio was significantly lower in children with epilepsy using valproic acid. The oxidation of cellular thiol-containing compounds, such as glutathione and protein cysteine residues, is considered to play an important role in many biological processes. Depending on the oxidant-antioxidant balance of the organism, the reversible disulphide bonds can be reduced to thiol. Thiols are affected by oxidation and converted to disulphides. As an oxygen scavenger during oxidative stress, thiols maintain the redox balance. The decreased levels of thiol groups of proteins are associated with decreased serum antioxidant power.

Taken together, this situation suggests that valproate treatment may significantly effect thiol disulphide homeostasis and induce oxidative injury in children with epilepsy. This may represent an altered capacity to prevent various nonspecific forms of injury that occur through drug metabolism. Changes in this homeostasis may also be expressed as an indicator of risk for toxicity in diverse clinical applications of valproate. Therefore, in the light of this new knowledge, a prospective study could be performed to sensitize clinicians towards this effect.

Carbamazepine is among the most commonly used and earliest drug licensed for the treatment of focal epileptic seizures. The effects of carbamazepine on oxidative stress have been investigated only in a few studies. Carbamazepine has been shown to induce disturbances in enzymatic antioxidant status and lipid peroxidation to a lesser extent than valproic acid or phenytoin [33,34,40,42]. Cengiz et al. evaluated the effects of sodium valproate and carbamazepine therapy on erythrocyte GSH, GSH-Px, SOD, and lipid peroxidation in children with epilepsy. They found that GSH levels were reduced and GSH-Px increased in the sodium valproate and carbamazepine groups [43]. Yuksel et al. investigated changes in the antioxidant system in children with epilepsy receiving long-term valproic acid and carbamazepine treatment. They didn't find any significant difference in SOD and GSH-Px levels, but a slight increase in lipid peroxidation levels in children receiving carbamazepine, concluding that antioxidant systems in children with epilepsy on carbamazepine therapy are better regulated in comparison with children with epilepsy on sodium valproate therapy [37]. Similar to these previous reports, our report revelaed lower levels of native thiol levels without a statistical significance. Disulphide level, disulphide/native thiol and disulphide/total thiol ratios were higher and native thiol/ total thiol ratio was also lower in patients using carbamazepine. We used a novel method for evaluation and our findings were in aggreement with previous reports. Review of the results suggested a better regulation of oxidant antioxidant system in children receiving carbamazepine and it may be concluded that the treatment had mild effects on the antioxidant system. Thus, further biochemical evidence should be considered and certainly, this novel method; thiol/ disulphide homeostasis; might be one of the considerations.

We have failed to demonstrate a significant effect in favour of either valproic acid or carbamazepine for the duration of the treatment. This result is surprising given the strong impression that antiepileptic drugs cause an increase in oxidative stress similar to epileptogenesis process. This outcome may be influenced by both the short duration of drug use, as well as the failure of the analysis to detect an interaction. The longest duration of drug treatment was 36 months in our groups. It may well be that an interaction does not exist. To better comment on this finding, it will be better to examine these both in the pretreatment and post-treatment period. However, we are aware that in studies of long duration, the assumption of these values over time is unlikely to be appropriate, so if more data can be made available to us for updates of this study, we would like to perform a more appropiate time follow up which allow for treatment effects to vary over time.

The most obvious limitation to the current study is the cross sectional design of this study. Therefore, prospective randomized controlled studies are needed to confirm our findings. Future studies should be directed in determining how different antiepileptic drugs play a role in thiol homeostasis. Nevertheless, the novelty of our study is that it is the first study to investigate the thiol/disulphide homeostasis in antiepileptic drug using children as there are very limited data on this system

In conclusion, the evidence from this study indicate impaired thiol disulphide homeostasis in children with epilepsy using antiepileptic drugs. This system is better regulated in children on carbamazepine monotherapy compared with children with epilepsy on valproate monotherapy. Therefore, antioxidant replacement like vitamin or food supplementation may be helpful for these patients. We think that these findings enhance our understanding of the relationship between oxidative stress and antiepileptic drugs.

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