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REVIEW PAPER

Effects of Antiepileptic Drugs on Antioxidant and Oxidant Molecular Pathways: Focus on Trace Elements

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Abstract Current reports on trace elements, oxidative stress, and the effect of antiepileptic drugs are poor and controversial. We aimed to review effects of most common used antiepileptics on antioxidant, trace element, calcium ion (Ca^{2+}) influx, and oxidant systems in human and experimental animal models. Observations of lower blood or tissue antioxidant levels in epileptic patients and animals compared to controls in recent publications may commonly support the proposed crucial role of antioxidants in the pathogenesis of epilepsy. Effects of old and new antiepileptics on reactive oxygen species (ROS) production in epilepsy are controversial. The old antiepileptic drugs like valproic acid, phenytoin, and carbamazepine induced ROS overproduction, while new epileptic drugs (e.g., topiramate and zonisamide) induced scavenger effects on over production of ROS in human and animals. Antioxidant trace element levels such as selenium, copper, and zinc were generally low in the blood of epileptic patients, indicating trace element deficiencies in the pathogenesis of epilepsy. Recent papers indicate that selenium with/without topiramate administration in human and animals decreased seizure levels, although antioxidant values were increased. Recent studies also reported that sustained depolarization of mitochondrial membranes, enhanced ROS production and Ca^{2+} influx may be modulated by topiramate. In conclusion, there is a large number of recent studies about the role of antioxidants or neuroprotectants in clinical and experimental models of epilepsy. New antiepileptic drugs are more prone to restore antioxidant redox systems in brain and neurons.

Keywords Antiepileptic drugs · Antioxidants · Oxidative stress · Trace element · Seizures · Ca^{2+} signaling

Abbreviations

AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid
Cu	Copper
GSH	Glutathione
GSH-Px	Glutathione peroxidase
MDA	Malondialdehyde
NFkB	Nuclear factor kappa B
NMDA	*N*-methyl-D-aspartate
PTZ	Pentylenetetrazole
ROS	Reactive oxygen species
Se	Selenium
SOD	Superoxide dismutase

Introduction

Epilepsy is a common chronic neurological disorder with various etiological factors which affects about 2–3 % of the general population with approximately 50 million people worldwide (Azam et al. 2012). Epilepsy has been divided into idiopathic, symptomatic, and cryptogenic forms and the oxidative stress has important role on etiology of the epilepilectic forms (Hayashi 2009; Seven et al. 2012).

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

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peroxidation, is rich in iron, which can catalyze hydroxyl radical formation, and is low in catalase activity (Shin et al. 2011; Nazıroğlu 2012). Additionally it produces high amount of reactive oxygen species (ROS) such as superoxide, hydrogen peroxide, and hydroxyl radical, owing to high aerobic metabolism. Eventually these products make the brain most sensitive to oxidative injury (Nazıroglu 2007; Ozmen et al. 2007).

A number of experimental and clinical reports suggest the involvement of oxidative stress in pathophysiology of epilepsy (Nazıroğlu et al. 2009; Rowley and Patel 2013). Increased free radicals in membrane lipid peroxidation and decreased glutathione (GSH) concentrations in the epileptic focus (Jesberger and Richardson 1991) were reported. Further, the involvement of free radicals in seizures is also supported by reports which indicate that exogenously administered antioxidant protects the brain against seizures (Gupta et al. 2003). Growing evidence indicates that long-term antiepileptic drug treatment leads to an increase in oxidative stress which is similar to that observed during epileptogenesis although the topics on the antiepileptic drugs are conflicting (Table 1). For example, valproic acid has been found to increase lipid peroxidation in patients receiving it (Martinez-Ballesteros et al. 2004). Contrary to this observation some anti-epileptic agents like phenytoin have been shown to decrease oxidative stress demonstrated by increase in glutathione reductase activity in patients receiving it (Stanton and Moskal 1991).

Main antioxidant trace elements are copper, zinc, and selenium. For example, selenium, an essential trace element in humans, has antioxidant properties; and prevents neuronal cell bodies from oxidation and keeps them biologically healthy. To date, approximately 30 types of selenoproteins have been identified. Some of these selenoproteins have vital enzymatic functions (Rayman 2000). The importance of selenium is because of the 21-amino-acid selenocysteine, one of the selenoproteins (Martinez-Ballesteros et al. 2004). Brain contains a high quantity of selenium, especially in gray matter (Nazıroğlu et al. 2009). The most important function of GSH-Px, a selenium-dependent enzyme, is reducing hydrogen and organic peroxides in the presence of reduced GSH (Weber et al. 1991). There is direct relationship between antioxidant trace elements and epilepsy. For example, correlation between selenium or GSH-Px deficiency and epilepsy has been shown (Schweizer et al. 2004).

The aim of this review paper is to investigate the role of antiepileptic drugs in relationship with oxidative stress, antioxidant redox systems, and trace elements in epilepsy.

Oxidative Stress and Epilepsy

Initiation and progression of epilepsy are induced free oxygen radicals and, therapies aimed at reducing oxidative stress may ameliorate tissue damage and favorably alter the clinical course (Azam et al. 2012). At the cellular level, intense seizure activity typically initiates a massive influx of calcium ions via voltage-gated calcium channels and glutamate receptors, such as kainate, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA)-dependent cation channels. Elevated intracellular Ca^{2+} leads to biochemical cascades which trigger acute hippocampal cell death after epilepsy (Nazıroğlu et al. 2009). Additionally, high levels of intracellular Ca^{2+} can induce generation of ROS, uncoupling of mitochondria and activation of a wide range catabolic enzymes that are capable of interfering with cell function (Pariente et al. 2001; Patel 2004; González et al. 2006, 2007). On the other hand, exposure of mitochondria to high cytosolic-free Ca^{2+} was shown to increase formation of ROS through depolarization of mitochondria (Fig. 1). Sustained depolarization of mitochondrial membranes and enhanced ROS formation could impair production of nicotinamide adenine dinucleotide phosphate (NADPH) and ATP. Indeed, rises in NAD(P)H auto-fluorescence associated with single seizure-like events in slices, decline with time during *status epilepticus* (Schuchmann et al. 1999). Moreover, in vivo studies suggested a failure of ATP production after prolonged *status epilepticus* (Gupta et al. 2001). Today, free radicals are known to be both the cause and the consequence of epileptic seizures (Patel 2004). Transient receptor potential (TRP) cation channels have six subfamilies and some TRP channels such as TRPM2 and TRPV1 are activated by oxidative stress (Naziroglu 2011; Nazıroğlu et al. 2012). These channels may play a role in the etiology of epilepsy due to their oxidative stress-dependent mechanisms. The subject should be clarified by future studies.

Oxidative stress is defined as an imbalance between higher cellular levels and ROS such as superoxide radical, hydrogen peroxide, nitric oxide, and cellular antioxidant defense (Nazıroğlu 2012; Cardenas-Rodriguez et al. 2012; Espino et al. 2012). Neuronal cell death may be both a cause and consequence of epileptic seizures. Oxidative stress occurs when the productions of ROS exceed the removal capacity through the antioxidant redox system and results in excessive levels of free radical intermediates (Patel 2002). Liang and Patel (2004) have demonstrated oxidative damage to susceptible targets (protein, lipids, and DNA) caused by persistent seizures (*status epilepticus*). Neuronal cytosolic Ca^{2+} influx induces mitochondrial depolarization. Several studies have demonstrated an increase in mitochondrial oxidative stress and subsequent cell damage after persistent seizures (Weber et al. 1991; Pariente et al. 2001; González et al. 2006, 2007).

Antioxidant Trace Elements

There have been numerous reports on the association of trace elements and epilepsy. The cascade of neurotoxic

Table 1 Effects of antiepileptic drugs on oxidative stress and trace elements in humans and animals

Antiepileptic drug	Subject/material	Value/effect	References
Phenytoin	Rat/brain	MDA/increase	Reeta et al. (2009)
		GSH/decrease	
	Human/blood	MDA/increase	Liu et al. (1997)
		Cu, Zn–SOD/increase	
		Cu/increase	
		GSH/decrease	
Sodium valproate	Children/plasma	GSH-Px/increase	Kurekci et al. (1995)
	Children/erythrocyte	GSH-Px/increase	Yuksel et al. (2001)
		SOD/increase	
	Adult/blood	Se–GSH-Px/increase	Hamed et al. (2004)
	Children/blood	GSH-Px/no effect	Ashrafi et al. (2007a)
	Adult/blood	Se–GSH-Px/no effect	Verrotti et al. (2002)
	Adult/erythrocyte	GSH-Px/no effect	Yis et al. (2009)
		SOD/increased	
		MDA/increased	
Carbamazepine	Adult/plasma	Se–GSH-Px/no effect	Hamed et al. (2004)
	Children/erythrocyte	GSH-Px/no effect	Ashrafi et al. (2007b)
	Adult/blood	Se–GSH-Px/no effect	Verrotti et al. (2002)
	Children/erythrocyte	MDA/increase	Yuksel et al. (2001)
		SOD/increase	
Zonisamide	Mice brain/cultured neurons	GSH/increase	Asanuma et al. (2010)
	PC12 cells	GSH-Px/increase	Yürekli and Naziroglu (2013)
		GSH/increase	
		MDA/decrease	
		Caspase-3/decrease	
		Cytosolic Ca^{2+}/decrease	
Topiramate	Rat brain/microsomes	GSH-Px/increase	Nazıroğlu et al. (2008)
	Rat/erythrocytes	GSH-Px/increase	Nazıroğlu et al. (2009)
	Rat/hippocampus	GSH-Px/increase	Muriach et al. (2010)
	Rat/brain cortex	MDA/decrease	Nazıroğlu et al. (2008, 2009)
	Rat/erythrocyte and plasma	GSH-Px/increase	Nazıroğlu et al. (2009)
		GSH/increase	
		Vitamin C, vitamin E/increase	
	Mice/brain	GSH/decrease	Agarwal et al. (2011)
		MDA/increased	
	Human/blood	GSH, GSH-Px, vitamin A and vitamin C/increase	Yürekli and Naziroglu (2013)

Se selenium, *Cu* copper, *Se* selenium, *MDA* malondialdehyde, *GSH* glutahhione, *GSH-Px* glutathione peroxidase, *SOD* superoxide dismutase

events that lead to epileptic seizures is highly complex, but the main event involves the accumulation of ROS (Hayashi 2009). The ROS formation has been found to be both the cause and the result of epileptic seizures in human (Yuksel et al. 2001; Hamed et al. 2004). Selenium, zinc, and copper are three trace elements that are involved in the metabolism of ROS. For example, selenium is involved in the reduction of peroxide by participating in the structure of GSH-Px, which is a very important antioxidant enzyme (Hamed et al. 2004).

Selenium

The equilibrium of trace elements is essential for a healthy nervous system because most of them contribute to the activation of specific enzymes that play important roles in many pathways of the central nervous system. Antioxidant defense mechanisms are an important pathway involving trace elements. GSH-Px, which is a selenium-dependent enzyme that is involved in antioxidant defense mechanisms, controls the intracellular levels of hydrogen

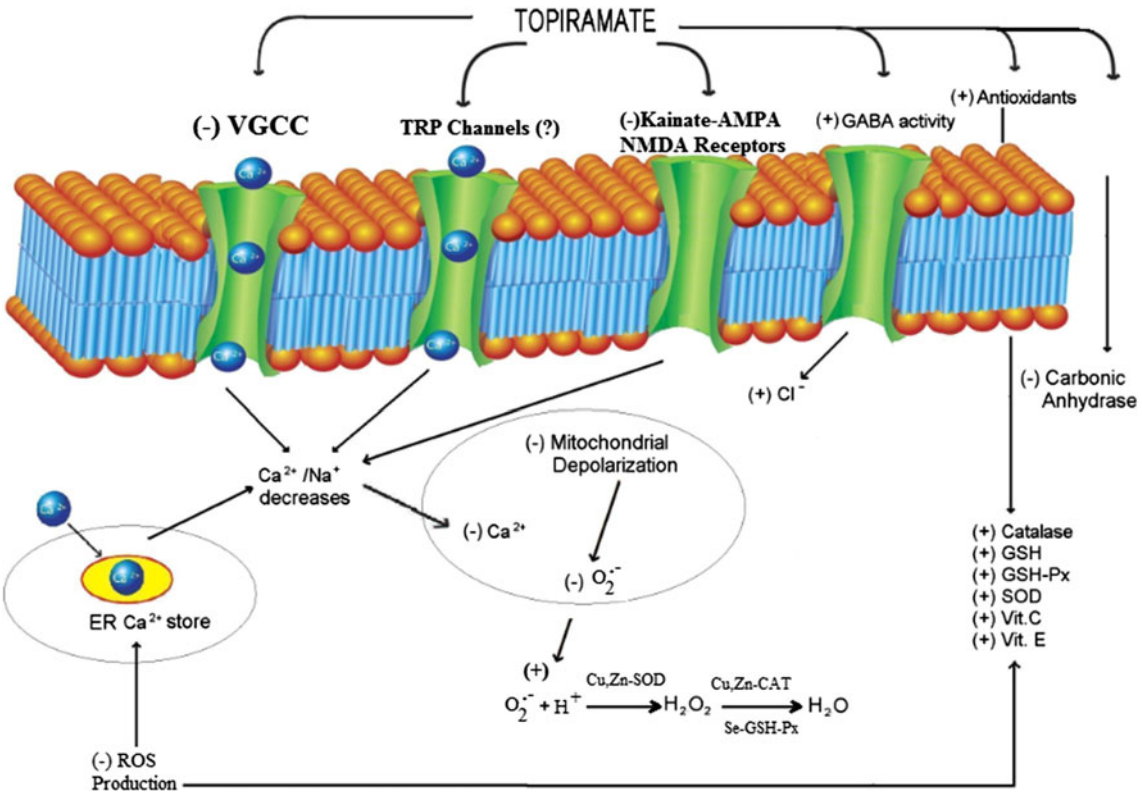

Fig. 1 Free radical generation and Ca^{2+} uptake induce seizure activity by direct activation of Ca^{2+} channels although topiramate-induced modulator role in Ca^{2+} influx through voltage-gated Ca^{2+} channels (VGGC) and glutamate receptors namely AMPA, kainate, and *N*-methyl-D-aspartate (NMDA). During the physiological process, superoxide radicals (O_2^-) produces and the radicals converted hydrogen peroxide (H_2O_2) by copper (Cu) and zinc (Zn) superoxide dismutase enzyme. The hydrogen peroxide (H_2O_2) is converted to water (H_2O) by Cu- and Zn-dependent catalase (CAT) and selenium (Se)-dependent glutathione peroxidase enzyme (GSH-Px) enzymes. Mitochondria were reported to accumulate Ca^{2+} provided cytosolic Ca^{2+} rises or provided mitochondrial uptake exceeds mitochondrial Ca^{2+} extrusion, thereby leading to depolarization of mitochondrial membranes. On the other hand, exposure of mitochondria to high free Ca^{2+} was shown to increase formation of ROS. The sustained depolarization of mitochondrial membranes and enhanced ROS production may be modulated by topiramate. Transient potential (TRP) or TRP melastatin 2 (TRPM2) channel activity-induced Ca^{2+} influx increases may be modulated by topiramate. The molecular pathway may be a cause of epileptic seizures and represents a fruitful subject of topiramate for further study. − Decrease, + increase

peroxide and hydroxyl radical (Nazıroğlu et al. 2009). It is well known that increased production of free radicals due to oxidative stress or the decreased functioning of antioxidant defense systems may lead to seizures or increase the risk of their recurrence (Savaskan et al. 2003; Hamed et al. 2004; Ashrafi et al. 2007a), because oxidative stress produces peroxidated membrane lipids and damages the cells (Hayashi 2009). Low levels of selenium and GSH-Px have been found in patients with epilepsy (Yuksel et al. 2001; Ashrafi et al. 2007b). Selenium-deficient rats have been found to be more susceptible to excitotoxicity (Savaskan et al. 2003).

The GSH-Px deficiency was reported in children with intractable epilepsy (Weber et al. 1991; Ramaekers et al. 1994). They found administration of selenium can help to treat the children following discontinuation of anticonvulsive drugs. Ashrafi et al. (2007a) reported that serum selenium level in intractable epilepsy patients was lower than that in healthy children, and they concluded that measurement of serum selenium in intractable epilepsy is helpful in recognizing the condition. In another study, Ashrafi et al. (2007b) found the patients affected by epilepsy have lower GSH-Px activity than the healthy children. Wirth et al. (2010) showed that cerebral selenium deficiency is associated with the incidence of seizure in mice through reduced activity of GSH-Px. Oztas et al. (2007) found that the damage to the blood–brain barrier in male rats due to seizure is increased if there is selenium and vitamin E deficiency; they concluded that management of seizure attacks with selenium has beneficial effects on reducing breakdown of the blood–brain barrier. Savaskan et al. (2003) observed a increased seizure rate in selenium-deficient rats due to greater susceptibility to kainate-induced excitotoxicity and the authors concluded that selenium has a fundamental role in neuronal susceptibility to excitotoxic lesions and seizure attacks. However, a study reported no significant change of serum selenium level in epilepsy patients as compared to healthy control patients

during seizure attacks (Hamed et al. 2004). Mahyar et al. (2010) reported lower selenium level in children with simple febrile seizures than in febrile children without seizure. Recently, Seven et al. (2012) reported a significant decrease in selenium levels in patients with idiopathic intractable epilepsy. It has been suggested that antiepileptic drug therapies deplete total body selenium stores and failure to give appropriate selenium supplementation, especially to patients receiving valproic acid during pregnancy may increase the risk of neural tube defects or other free radical-mediated damage (Arakawa and Ito 2007).

Febrile seizures are the most common brain-related disease in children (Castano et al. 1997). Although the pathophysiology of febrile seizures is still unknown, several studies have indicated that multiple factors can be involved in the pathogenesis of febrile seizures, including elements such as iron and zinc (Tütüncüoğlu et al. 2001; Daoud et al. 2002). The role of other elements in developing febrile seizures and brain disorders, including selenium, has been reported in some studies (Tütüncüoğlu et al. 2001; Schweizer et al. 2004). Ramaekers et al. (1994) and Weber et al. (1991) investigated GSH-Px activity in children with intractable and they found administration of selenium can help to treat the children following discontinuation of anticonvulsive drugs. Nazıroğlu et al. (2008) reported on use of selenium for control or inhibition of seizure caused by excitotoxic agents.

Copper and Zinc

Zinc is an essential trace metal in humans and animals. Zinc deficiency results in defects of the central nervous system as well as peripheral neuropathy (Oki et al. 2012). Some evidence has indicated a relationship between zinc and seizure activity, but the detailed significance of zinc in convulsive activity is not clear (Seven et al. 2012). Clinical manifestations of zinc deficiency, such as memory deficits, learning disorders, and alterations in emotional behavior suggest hippocampal dysfunction (Oki et al. 2012). Changes in levels of trace elements have been proposed to underlie febrile seizures. Particularly, low zinc levels have been proposed as related factor of febrile seizure. The mechanism underlying the role of zinc levels in seizures has been examined in studies on mouse models and in vitro studies. Numerous reports have suggested that zinc modulates specific GABA receptors, and this mechanism is known to contribute to seizure inhibition (Andre et al. 2010; Amiri et al. 2010).

Amiri et al. (2010) reported decreased serum selenium, zinc, and copper levels in the children with febrile convulsion and in the control group. Ganesh et al. (2011) compared serum zinc levels in children (22 with epileptic seizures, 23 with simple febrile seizures and 22 controls) and they showed decreased serum zinc levels in children with febrile seizures than in those with epileptic seizures and normal children. Recently, Wojciak et al. (2013) assessed the serum zinc and copper concentrations in 23 children with initial recognition of epilepsy before beginning of pharmacological therapy in comparison with a healthy control group of 25 children. They demonstrated that epilepsy decreased zinc level although it increased copper levels in the patients.

On the other hand, Verrotti et al. (2002) assessed whether epileptic children have abnormal values of serum copper, zinc, selenium, GSH-Px and superoxide dismutase (SOD). They evaluated the effect of long-term therapy with sodium valproate and carbamazepine on these parameters in 36 epileptic patients before the beginning of therapy and after 1 year of therapy with sodium valproate or carbamazepine. After 1 year of therapy, patients treated with sodium valproate and carbamazepine continued to show normal values. They demonstrated that epilepsy per se and treatment with sodium valproate and carbamazepine do not affect levels of copper, zinc, and SOD values (Verrotti et al. 2002). Similarly Kurekci et al. (1995) investigated the effect of long-term antiepileptic drugs therapy on copper, zinc, manganese, magnesium, and SOD in the plasma in children with epilepsy. They reported plasma copper, zinc, manganese, and magnesium concentrations of patients were not different from those of control subjects during treatment with valproate or carbamazepine monotherapy. However, they observed serum sodium valproate levels were correlated with the increase of plasma zinc level in the patients.

Oxidative Stress and Antiepileptic Drugs

As it was mentioned above, free oxygen radicals are physiological products of the cellular metabolism. For examples, phagocytes are producing free oxygen radicals for killing ingested bacteria and virus. However, when the production of free radicals increases or defense mechanism of the body decreases, they cause cellular dysfunction by attacking at the polyunsaturated sites of the biological membranes leading to lipid peroxidation (Naziroglu 2007). As it was mentioned above, antioxidant enzymes are SOD, catalase, and GSH-Px in the brain. SOD dismutases superoxide radical to hydrogen peroxide. Catalase is an enzyme responsible for detoxification of the hydrogen peroxide formed by the action of SOD. The catalase activity in the rodent brain is very low. The involvement of free radicals in seizures is also supported by reports which indicate that exogenously administered antioxidant protects the brain against seizures (Gupta et al. 2003). Some papers indicate that long-term treatment with old antiepileptic drugs leads to an increase in oxidative stress which is

similar to that observed during epileptogenesis (Chang and Abbott 2006). However, the idea was not further confirmed (Hamed et al. 2004; Ashrafi et al. 2007).

Hence, results on the subject are also conflicting. For example, sodium valproate has been found to increase lipid peroxidation in patients receiving it (Martinez-Ballesteros et al. 2004). Contrary to this observation some antiepileptic agents like phenytoin and topiramate have been shown to decrease oxidative stress, which were demonstrated to increase in glutathione reductase and GSH-Px activities in patients (Stanton and Moskal 1991; Nazıroğlu et al. 2009; Ganesh et al. 2011).

Topiramate

Topiramate, a sulfate-substituted monosaccharide, is a novel compound that has a broad spectrum against antiepileptic activity. Mechanisms that are likely to account for the anticonvulsant activity of topiramate include a negative modulatory effect on the a-amino-3-hydroxy-5-methyl-4-isoxazol propionic acid (AMPA)/kainate subtype of glutamate receptors, a positive modulatory effect on $GABA_A$ receptors, a use- and time-dependent blockade of voltage-activated Na^+-channels, a negative modulatory effect on a neuronal L-type high voltage-activated Ca^{2+}-channel and is also inhibitor of the carbonic anhydrases, particularly subtypes II and IV (White 2005). There are scarce report about interactions between oxidative stress and topiramate. Most of the papers indicated the antioxidant role of topiramate in brain and neurological cells. On the subject, Cardenas-Rodriguez et al. (2012) observed dose-dependent ROS scavenger effects of topiramate in different cell lines. The effect of introperitoneal topiramate was investigated by Kubera et al. (2004) (40 and 80 mg/kg) on the fully developed kainate (15 mg/kg)-induced *status epilepticus* in the rat. The topiramate at a dose of 80 mg/kg in frontal cortex of the rats reduced the kainate-induced lipid peroxidation (Kubera et al. 2004). Our group has also investigated the effects of selenium administration (0.3 mg/kg/day) on topiramate (50 mg/kg/day) and pentilentetrazol (60 mg/kg)-induced brain toxicity in rats. We have proved that topiramate administration with or without selenium caused decreased lipoperoxidation levels in the brain cortex (Nazıroğlu et al. 2008). Vitamin E (alpha tocopherol) is a lipid soluble strong antioxidant that interferes with the chain reaction of oxidative stress (Nazıroglu et al. 2004) although Vitamin C (ascorbic acid) is water soluble molecule that can scavenge several radicals (Ekmekcioğlu et al. 2008). Similarly, in another study of our group (Nazıroğlu et al. 2009) indicated that topiramate and vitamin E treatment caused a decrease in serum nitric oxide, erythrocyte and plasma lipoperoxidation levels and brain spike numbers, whereas GSH-Px, GSH, vitamin C and vitamin E levels and latency to the first spike of EEG were increased by the topiramate treatment.

Armagan et al. (2008) indicated that topiramate and vitamin E have protective effects on pentylenetetrazol-induced nephrotoxicity by inhibition of free radicals and support of the antioxidant redox system. In doses of 50 and 100 mg/kg/day topiramate and 150 mg/kg vitamin E caused an increase of kidney SOD and catalase enzyme activities in the same study.

We have previously investigated the effects of selenium and topiramate on pentylenetetrazole (PTZ)-induced blood toxicity in rats. We have found that selenium and topiramate induced protective effects on the PTZ-induced blood toxicity by inhibiting free radical supporting antioxidant redox system (Nazıroğlu et al. 2008).

Nuclear factor kappa B (NFkB) is known to respond to oxidative stress and to act as a regulator of apoptotic processes (Schreck et al. 1992). Muriach et al. (2010) investigated GSH, GSH-Px, and caspase 3 values for checking the influence of oxidative stress on NFkB response, and the possible induction of NFkB activation-related apoptosis in an experimental model of cocaine administration in rats. They concluded that topiramate had a modulatory role against necrosis NFkB activation in the frontal cortex and against NADPH positive cells in the hippocampus (Muriach et al. 2010).

Cardile et al. (2001) reported that topiramate (1–100 μg/ml) increased the oxidative stress in astrocytes. Agarwal et al. (2011) compared the effects of lamotrigine, oxcarbazepine, and topiramate on cognition during experimental epileptogenesis in mice. Topiramate administration (10 mg/kg) to kindled as well as non-kindled animals increased lipid peroxidation and malondialdehyde (MDA) production, and decreased GSH levels. It was reported that lamotrigine and oxcarbazepine did not show significant alteration in oxidative stress values (Agarwal et al. 2011).

Recently, our group investigated effects of topiramate and selenium supplementation on antioxidant and oxidant stems in patients with epilepsy and refractory epilepsy (Yürekli and Nazıroğlu 2013) and we observed a modulatory role of topiramate and selenium supplementation on GSH, GSH-Px, total antioxidant capacity, vitamins A and vitamin C in the blood of epileptic patients.

Sodium Valproate and Carbamazepine

Sodium valproate is an effective drug for treating simple and complex epileptic seizures as a monotherapy and as a component of polytherapy. The effects of sodium valproate on oxidant status are conflicting in different studies. Chang and Abbott (2006) showed that oxidative stress has a

potential role on sodium valproate-induced hepatotoxicity. Solowiej and Sobaniec (2003) reported insignificant elevations of MDA concentrations in patients treated with sodium valproate and carbamazepine. Michoulas et al. (2006) also reported higher urinary levels of 15-F2T-isoprostane, a marker of oxidative stress in epileptic children treated with sodium valproate. On the other hand, Verrotti et al. (2002) found that sodium valproate therapy does not appear to cause oxidative stress in epileptic children who remained non-obese during treatment. Yis et al. (2009) found that GSH-Px activity does not change during treatment with sodium valproate and they found elevated levels of superoxide dismutase in patients with newly diagnosed idiopathic epilepsy. They also showed a positive correlation between duration of treatment and SOD activities (Yis et al. 2009).

In another study, Cengiz et al. (2000) evaluated the effects of sodium valproate and carbamazepine therapy on erythrocyte GSH, GSH-Px, SOD, and lipid peroxidation in epileptic children. They found that GSH levels were reduced and GSH-Px increased in the sodium valproate and carbamazepine groups (Cengiz et al. 2000). Reduction in the GSH amount may result in an increase of organic hydroperoxides. Yuksel et al. (2001) determined changes in the antioxidant system in epileptic children receiving long-term antiepileptic drugs. In their study 16 patients were treated with sodium valproate and 14 with carbamazepine; 13 months later these parameters were retested. Their results showed that SOD and lipid peroxidation levels were increased but the GSH-Px levels were decreased in epileptic children on sodium valproate therapy compared with the control group and the results before treatment. No significant differences of these parameters were reported in epileptic children undergoing carbamazepine therapy compared with the control group, although lipid peroxidation level was slightly higher in epileptic patients before treatment. They concluded that antioxidant systems in epileptic children on carbamazepine therapy are better regulated in comparison with epileptic children on sodium valproate therapy (Yuksel et al. 2001).

Levetiracetam

Levetiracetam, the *S*-enantiomer of a-ethyl-2-oxo-1-pyrrolidine acetamide, is an antiepileptic drug that has broad-spectrum effects on partial and generalized seizures in several models of epilepsy. The clinical effectiveness of LEV has been reported in patients with partial refractory epilepsy (Oliveira et al. 2007). The therapeutic mechanism of levetiracetam remains unclear, some studies considering that is unrelated to any modulation of neuronal voltage-gated Na^+ or low-voltage-activated Ca^{2+} (T type) channels (Oliveira et al. 2007). Meanwhile, other in vitro and in vivo studies suggested a role of both calcium channels N-type and GABAergic in the activity of levetiracetam (Lukyanetz et al. 2002; Poulain and Margineanu 2002). Oliveira et al. (2007) study indicated that levetiracetam may alter pilocarpine-induced changes in catalase and reduced GSH levels, in lipid peroxidation level, and nitrite–nitrate formation in mice hippocampus and they observed that lipid peroxidation, nitrite/nitrate formation, and changes in antioxidant brain enzymes are involved in the pathophysiology of pilocarpine-induced seizures and *status epilepticus* (Oliveira et al. 2007). Except its antiepileptic potential, Stettner et al. (2011) indicated that levetiracetam may also act as a histone deacetylase inhibitor, suggesting that this drug exhibits both anti-inflammatory and anti-oxidative effects, and it may be potentially useful for treating oxidative stress and inflammation in the peripheral nerve (Stettner et al. 2011).

Zonisamide

Zonisamide is originally synthesized in Japan and has been used for over 10 years to treat intractable epilepsy. Zonisamide has significant effects on T type Ca^{2+} channels and oxidative stress (Murata 2004). To our knowledge, there is not enough study about the effects of zonisamide on oxidative stress, trace elements and epilepsy. Asanuma et al. (2010) investigated changes in GSH and GSH synthesis-related molecules, and the neuroprotective effects of zonisamide on dopaminergic neurodegeneration using 6-hydroxydopamine-injected hemiparkinsonian mice brain and cultured neurons or astrocytes. They observed protective effects of zonisamide on GSH levels in astroglial C6 cells by enhancing the astroglial cystine transport system and/or astroglial proliferation via S100beta production or secretion. Yurekli et al. (2012) investigated the effect of zonisamide on the oxidative stress, cell viability, Ca^{2+} signaling, and caspase activity that induced by the MPP^+ model of Parkinson's in neuronal PC12 cells. Lipid peroxidation and cytosolic-free Ca^{2+} concentrations were higher in the MPP^+ group than in control, although their levels were lower in zonisamide and the zonisamide plus MPP^+ groups than in control. Reduced GSH and glutathione GSH-Px were lower in the MPP^+ group, although they were higher in the zonisamide and the zonisamide plus MPP^+ groups than in control (Yurekli et al. 2012).

Phenytoin

Phenytoin was introduced nearly 60 years ago for use in epilepsy and is still widely prescribed for partial and

generalized seizures. Similar to carbamazepine, it blocks voltage-dependent neuronal sodium channels (Yaari et al. 1986). Other effects of phenytoin include diminishing synaptic transmission, limiting fluctuation of neuronal ionic gradients via sodium–potassium ATPase, and affecting second messenger systems by inhibiting Ca^{2+}-calmodulin protein phosphorylation (Delgado-Escueta and Horan 1980; Holland et al. 1993).

Phenytoin is effective in the treatment of both generalized tonic-colonic and focal onset seizures (Miller et al. 2004). However, phenytoin has a narrow margin of safety and its use in epileptic patients has occasionally been associated with disturbances in the blood antioxidant defense systems and increased lipid peroxidation (Herzog et al. 2005; Hirsch et al. 2008). Many authors have suggested that phenytoin initiates oxidative damage and cognitive impairment in experimental animals and epileptic patients taking phenytoin monotherapy or receiving multiple drugs (Reeta et al. 2009). Reeta et al. (2009) measured the levels of MDA and GSH in rat brain after phenytoin treatment. MDA levels in the rat brain were significantly increased and the GSH levels were significantly reduced in the phenytoin-treated rats (Reeta et al. 2009). Liu et al. (1997) measured the serum MDA, serum copper, serum zinc, copper/zinc SOD, and reduced GSH concentrations in 20 female epileptics with phenytoin monotherapy compared with 12 female epileptics without anticonvulsant therapy and 20 female healthy controls. For the female epileptics with phenytoin monotherapy, serum MDA concentration, copper/zinc SOD, and serum copper content in their study were increased whereas GSH level was significantly decreased. They observed also that the level of serum MDA was associated with the elevation of copper/zinc SOD activity and serum copper content in all the samples collected from epileptics and controls. They concluded that oxidative stress was enhanced in the female epileptics with phenytoin monotherapy (Liu et al. 1997).

Phenytoin is also known to deplete vital nutrients, such as calcium, folic acid, vitamin D, vitamin K, biotin, carnitine, copper, selenium, and zinc (Thaakur and Pushpakumari 2007). In the literature there is not enough information about selenium and phenytoin interaction. On the subject, Ozolins et al. (1996) suggested that selenium-dependent and -independent GSH-Px detoxifies hydrogen peroxide and lipid hydroperoxides may mediate the teratogenicity of phenytoin and related xenobiotics. They were the first to demonstrate selenium-dependent GSH-Px activities in embryonic tissues of CD-1 mice with dietary selenium-deprivation. Their results implicated ROS and lipid hydroperoxides in the mechanism of phenytoin teratogenicity and suggested that GSH-Px are important embryoprotective enzymes (Ozolins et al. 1996).

Lamotrigine

Lamotrigine is an antiepileptic drug, also known as a mood stabilizer, that inhibits presynaptic voltage-gated Na^{+} channels and reduces the presynaptic release of glutamate in pathological states (White 2005). Scarcely studies are in the literature about the effects of lamotrigine on oxidative stress. Arora et al. (2010) observed the effect of lamotrigine and carbamazepine on cognitive function and oxidative stress in brain during chemically induced epileptogenesis in rats. They indicated that lamotrigine treatment had no effect on oxidative stress parameters alone, while it significantly decreased oxidative stress in the PTZ-kindled group as compared to the PTZ-kindled carbamazepine-treated group (Arora et al. 2010). In a similar study as mentioned above Agarwal et al. (2011) assessed the effect of three anticonvulsants, lamotrigine, oxcarbazepine, and topiramate on cognitive function and oxidative stress during pentylenetetrazole kindling in mice. MDA, GSH levels, SOD, and catalase activity were measured as an indicator of oxidative stress. Lamotrigine and oxcarbazepine did not show significant alteration in oxidative stress parameters and cognitive functions tests (Agarwal et al. 2011). Neuroprotective effects of this drug have also been demonstrated in cerebral ischemia models (Tufan et al. 2008). Literature connecting lamotrigine and trace elements is scarce. In a traumatic brain injury model in rats, Hellmich et al. (2007) suggested that lamotrigine treatment inhibits presynaptic release of glutamate and reduces neurotoxic zinc levels after traumatic brain injury.

Conclusion and Future Directions

The existing knowledge about the impact of epilepsy and antiepileptic drugs on trace elements and free radical/antioxidant system is poor and controversial. There are four main future directions. (1) Information on trace element and new antiepileptic drugs, such as zonisamide and lamotrigine, is scarce. In addition, reports of old and new antiepileptic drugs are conflicting on antioxidant levels in human and animals relationships between old and new antiepileptic drugs. Hence, effects of the new drugs on the oxidant and antioxidant values such as MDA, GSH-Px, and SOD should be investigated by further experiments. (2) The second topic is calcium ion signaling and transient receptor potential (TRP) channels in epileptic hippocampal neurons. There is no report on the oxidative stress-dependent activation of TRP cation channels in epileptic patients and animals via over production of free oxygen radicals. Hence, these subjects should be clarified by future experiments.

Clinical reports suggest that both epilepsy and antiepileptic drugs, especially older generation antiepileptics, have negative effect on cognition which affects the life quality of epileptic patients. However, it is not clear whether it is epilepsy or oxidative stress or both which contribute to the decline of cognitive function. It is well known that older generation antiepileptic drugs cause cognitive impairment oxidative stress could be the triggering mechanism involved in cognitive impairment during experimental epileptogenesis as well as during drug treatment. Third, on new antiepileptic drugs, particularly topiramate and zonisamide, further, clinical and biochemical studies are required, to demonstrate a correlation between cognitive dysfunction and oxidative stress during epilepsy and antiepileptic drug therapy.

Fourth, in different studies low serum zinc levels were determined but there are poor evidences that zinc, copper, and selenium supplementations are able to reduce the incidence of febrile seizure, and further investigation is necessary. Present studies do not catch the full complexity trace elements deficiencies in epileptogenesis, and we believe that further studies will have a huge clinical contribution to in improving the life quality of of epileptic patients.

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