

## Review Article

# Modulation of Antioxidant Enzymatic Activities by Certain Antiepileptic Drugs (Valproic Acid, Oxcarbazepine, and Topiramate): Evidence in Humans and Experimental Models

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It is estimated that at least 100 million people worldwide will suffer from epilepsy at some point in their lives. This neurological disorder induces brain death due to the excessive liberation of glutamate, which activates the postsynaptic N-methyl-D-aspartic acid (NMDA) receptors, which in turn cause the reuptake of intracellular calcium (excitotoxicity). This excitotoxicity elicits a series of events leading to nitric oxide synthase (NOS) activation and the generation of reactive oxygen species (ROS). Several studies in experimental models and in humans have demonstrated that certain antiepileptic drugs (AEDs) exhibit antioxidant effects by modulating the activity of various enzymes associated with this type of stress. Considering the above-mentioned data, we aimed to compile evidence elucidating how AEDs such as valproic acid (VPA), oxcarbazepine (OXC), and topiramate (TPM) modulate oxidative stress.

*Dedicated to Dr. Bernardino Huerta-Gertrudis (in memoriam)*

## 1. Introduction

Neurological diseases are a major cause of health concerns at different life stages and lead to considerable utilization of medical resources [1]. Epilepsy is one of the most common neurological disorders in both children and adults [2, 3]. The term epilepsy describes a group of disorders characterized by the presence of chronic, recurrent, and paroxysmal alterations of the motor and sensory neurological functions secondary to a disorder in the electrical activity of a neuron population [4]. The term epileptic syndrome

refers to various disorders characterized by a group of signs and symptoms that occur simultaneously. These signs include the type of crisis, causes, anatomic aspects, precipitating factors, age of onset, severity, prognostics, chronicity, and electroencephalographic activity, and the clinical characteristics are identified based on the patient's age [2, 5].

Epileptic seizures and syndromes are classified according to the International League Against Epilepsy (ILAE), using genetic studies and electroclinical, neuropsychological, and neuroimaging research. Epilepsy can be divided, based on its

etiology, into idiopathic disease or disease associated with a hereditary predisposition, as symptomatic or associated with any event that damages the brain, and as cryptogenic or of unknown cause [6, 7].

Currently, the epilepsy prevalence is reported to be five to 10 cases per 1,000 individuals. It is estimated that at least 100 million people worldwide will present with epilepsy at a certain life stage [4, 8]. The ILAE reports that the disease prevalence lies between four and 10 cases per 1,000 individuals, and the incidence lies between 20 and 70 cases per 100,000 individuals per year. The prevalence rate in Latin-American countries is the highest, in the range of 14 to 57 per 1,000 individuals [6, 7].

Epilepsy control using antiepileptic drugs (AEDs) depends on several factors: efficacy, side effects of the hormonal alteration, teratogenicity, pharmacokinetics, interactions between AEDs or other drugs, serum levels, cost, and the neurologist's experience with AED use [9]. The patient may respond in three different manners: remitting seizures spontaneously (without AED use), responding adequately to AED administration, or presenting refractoriness to the treatment drug. The most commonly used AEDs are valproic acid (VPA), oxcarbazepine (OXC), and topiramate (TPM), which are considered the first-option treatments for the diverse manifestations of this pathology.

A wide variety of AEDs have been divided into generations according to their date of introduction to clinical use. These agents are categorized as first- (1857–1978), second- (1993–2009), and third- (2009 to date) generation AEDs. The second- and third-generation drugs are described in Table 1 [10, 11].

## 2. Overview of Valproic Acid, Oxcarbazepine, and Topiramate

VPA is a carboxylic acid composed of eight carbons and is used to treat several types of epilepsy due to its broad action spectrum and efficiency [12] (Figure 1(a)). The mechanism of action, similarly to that of other AEDs, is not fully known; however, it has been reviewed in various articles. These reports can be divided into two groups: studies suggesting that VPA increases gamma aminobutyric acid (GABA) transmission and research indicating that this AED may directly interact with the neuronal membrane. Löscher [12] studied VPA interference with GABAergic transmission in 1993. This report is based on the observation that VPA increases the levels of the inhibitory neurotransmitter GABA [12]. Other researchers have confirmed Löscher's studies [13–15]. This effect can be produced either by glutamate decarboxylase activation [16, 17]; by the inhibition of GABA-degrading enzymes such as GABA aminotransferase [17], succinic semialdehyde dehydrogenase [18], aldehyde reductase [19], and  $\alpha$ -ketoglutarate dehydrogenase [17]; or by an increase in glutaminase activity [20]. Alternative mechanisms involve potentiation of the postsynaptic response of GABA, GABA<sub>A</sub> receptor modulation, and depolarization induced by N-methyl-D-aspartic acid (NMDA) [21–23].

With respect to the mechanism of VPA interactions with the neuronal membrane, it has been reported that this

TABLE 1: Primary second- and third-generation AEDs (listed in chronological order). Modified from Shorvon (2009) and Löscher and Schmidt (2011) [10, 11].

| Second generation | Third generation    |
|-------------------|---------------------|
|                   | Vigabatrin          |
|                   | Zonisamide          |
| Chlordiazepoxide  | Lamotrigine         |
| Sulthiame         | Oxcarbazepine       |
|                   | Felbamate           |
| Diazepam          | Gabapentin          |
|                   | Topiramate          |
| Carbamazepine     | Tiagabine           |
| Valproate         | Levetiracetam       |
|                   | Pregabalin          |
| Clonazepam        | Rufinamide          |
|                   | Lacosamide          |
| Clobazam          | Ethyl carbamazepine |
|                   | Retigabine          |

AED decreases the excitatory synaptic potential necessary for the synchronization network and the neuronal firing in the substantia nigra [24–26]. VPA also activates conductance in the potassium channels and interferes with other biochemical pathways related to energy metabolism in the brain. However, to date, this activity has not been proven to be an additional mechanism of AED action [27].

OXC was developed as a carbamazepine analog (Figure 1(b)) [28], and its pharmaceutical activity occurs mainly through its active metabolite, 10,11-dihydro-10-hydroxy-carbamazepine (Figure 2). The mechanisms of action have not been clarified, but it is reported that the principal mechanism involves a blockade of voltage-dependent sodium [29]. *In vitro* electrophysiological and animal studies have demonstrated that this AED activity is based on the interference with transmembranal sodium, calcium, and potassium (i.e., voltage-dependent) ionic currents. These agents also modify the release of certain neurotransmitters, such as glutamate [29, 30].

TPM is a monosaccharide substituted with sulfate groups [2,3:4,5-bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate] (Figure 1(c)). Five mechanisms that reportedly contribute to its antiepileptic action are as follows: blockage of the sodium channels, which reduces the duration and frequency of the action potentials [31]; a positive modulating effect of the GABA<sub>A</sub> receptors [32, 33]; inhibition of the ionotropic glutamate receptors alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)/kainate; a negative modulatory effect of the calcium channels activated by L-type voltage; and inhibition of carbonic anhydrase subtypes II and IV [32].

## 3. Oxidative Stress and Its Role in Epilepsy

In the last two decades, the study of ROS and reactive nitrogen species (RNS) has sparked great interest in clinical

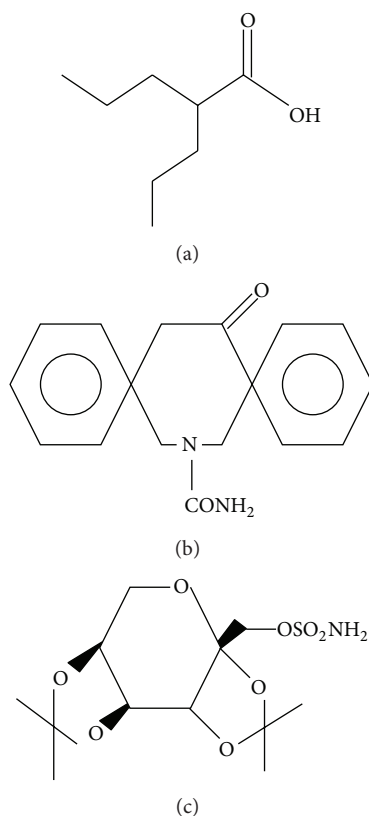


FIGURE 1: Chemical structures of (a) VPA, (b) OXC, and (c) TPM.

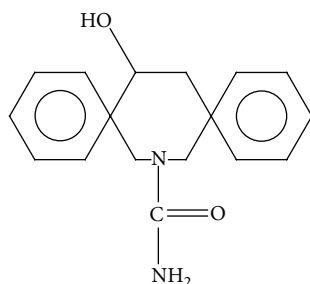


FIGURE 2: Chemical structure of 10,11-dihydro-10-hydroxycarbazepine, main active metabolite of OXC.

and experimental medicine. Both species are (a) generated during the irradiation of ultraviolet (UV) light, X-rays, and gamma rays, (b) products of reactions catalyzed by metals, (c) present in air pollutants; (d) produced by neutrophils and macrophages during inflammation, and (e) byproducts of reactions catalyzed by the electron carriers in the mitochondria [34].

ROS and RNS are known for their dual role in biological systems, as they can be beneficial or harmful. The beneficial effects of ROS can be observed in their physiological role in numerous cellular responses and cell signaling systems. By contrast, at high concentrations, ROS can be important mediators of cell damage to various structures such as lipids, proteins, and nucleic acids. The beneficial effects of ROS are supplemented by the action of nonenzymatic antioxidants

and by the antioxidant enzyme system. Despite the presence of the antioxidant defense system to combat oxidative damage caused by ROS, this damage accumulates throughout life [34].

The imbalance between the ROS and RNS levels (such as superoxide, radical  $O_2^{\bullet-}$ ; hydrogen peroxide,  $H_2O_2$ ; hydroxyl radical,  $HO^{\bullet}$ ; and nitric oxide,  $NO^{\bullet}$ ) and the cellular antioxidant defense system (superoxide dismutase, SOD; catalase, CAT; glutathione peroxidase, GPx; glutathione reductase, GR; and glutathione-S-transferase, GST) is defined as “oxidative stress” [34]. Because this disequilibrium can appear at the cellular level (involving the mitochondria, cytochrome P450 system, peroxisomes, and activation of inflammatory cells [35]), it is involved in the development of several diseases such as cancer, atherosclerosis, and arthritis and in neurodegenerative disorders such as epilepsy [34, 36].

The participation of oxidative stress in diseases of the central nervous system (CNS) is well established [37, 38]. The brain is highly sensitive to oxidative damage because this organ contains a large number of easily oxidized fatty acids (20:4 and 20:6) and a limited antioxidant system [37].

Oxidative stress is strongly implicated during seizures induced by excitotoxicity, due to mitochondrial ROS generation. Since the beginning of the 1990s, oxidative stress has been associated with neuronal hyperexcitation caused by CNS diseases [39]. Dalton, in 1995, was the first to identify brain damage induced by the presence of oxidative stress in an animal experimental model [40].

The presence of  $NO^{\bullet}$  is known to be a cause of seizures [41].  $NO^{\bullet}$  is formed from high concentrations of inducible nitric oxide synthase (iNOS). The role of oxidative stress in pentylene-tetrazole-induced epilepsy has been proven in rodents [42–44]. The increased activity of glutamatergic systems induces status epilepticus and causes an energy imbalance, increasing ROS formation [45]. Several studies have linked seizures and cell damage to the excitotoxicity induced by pentylene-tetrazole [46]. Seizures are linked to the increased release of glutamate and NMDA receptor activation. In fact, during epileptic seizures induced by different models, there is an extracellular  $Ca^{2+}$  concentration decrease and a cytosolic  $Ca^{2+}$  concentration increase [47].

The effects mediated by  $Ca^{2+}$  during excessive glutamate receptor activation (excitotoxicity) lead to neuronal degeneration and give rise to oxidative stress. The phospholipase  $A_2$ -dependent activity of  $Ca^{2+}$  mediated by glutamatergic receptors liberates arachidonic acid (AA), which generates  $O_2^{\bullet-}$  through its metabolism by lipoxygenases and cyclooxygenases for eicosanoid formation [48].

The constant formation of  $NO^{\bullet}$  by the glia is neurotoxic because it increases the neuronal sensitivity to this reactive species. The neurotoxic action of  $NO^{\bullet}$  is likely caused by the formation of peroxynitrite ( $ONOO^-$ ), which is rapidly formed by the reaction of  $NO^{\bullet}$  with  $O_2^{\bullet-}$ . Under conditions of energy deficit and elevated intracellular  $Ca^{2+}$  concentration, xanthine oxidase generates  $O_2^{\bullet-}$ . In this environment, lactic acid is generated, which promotes the release of  $Fe^{2+}$ , the Haber-Weiss reaction, and the production of  $HO^{\bullet}$  [49]. Furthermore,  $ONOO^-$  can react with tyrosine in proteins to form 3-nitrotyrosine (3-NT) [50].

TABLE 2: Effect of AEDs on the activity of antioxidant enzymes or oxidative stress markers in epileptic patients.

| AEDs                  | Antioxidant enzymatic activity/oxidative stress markers | Findings   | Ref      |
|-----------------------|---|--|----------|
| VPA                   | GPx   | Kurekci et al., in 1995, found a significant increase in GPx activity in children diagnosed with epilepsy.   | [51]     |
| VPA and carbamazepine | GSH, GPx, SOD, and malonaldehyde (MDA)                  | Cengiz et al., in 2000, evaluated the effect of VPA and carbamazepine on the levels of GSH, GPx, SOD, and lipid peroxidation in the erythrocytes of 30 children diagnosed with epilepsy and compared with 25 healthy children. The authors found that during a one-year treatment with VPA (in 16 children) or carbamazepine (in 14 children), the GPx levels were significantly increased, but the GSH levels were significantly decreased. With combined drugs, they were no significant differences in the SOD activity and lipid peroxidation levels.  | [52]     |
| VPA and carbamazepine | GPx, SOD, and MDA                                       | Yüksel et al., in 2001 and 2000, found a significant increase in the levels of lipid peroxidation and decreased GPx activity in the serum of 14 children treated with VPA for two years compared with that found in 27 healthy children. The SOD serum levels increased significantly during the first year. In 13 children diagnosed with epilepsy and then treated with carbamazepine for two years, lipid peroxidation increased significantly in the serum, compared with the control group. During the second year of treatment with carbamazepine, the serum SOD levels were significantly higher, compared with the control group and with the same group before treatment.   | [53, 54] |
| VPA and carbamazepine | Se, GPx, and Cu/Zn-SOD                                  | Verrotti et al., in 2002, found that 36 children with epilepsy and no treatment exhibited no significant differences in the serum levels of Se, GPx, and Cu/Zn-SOD, compared with the control group (14 children). One year after beginning therapy with VPA (in 22 patients) or carbamazepine (in 14 patients), the values of these parameters were unchanged.  | [55]     |
| VPA and carbamazepine | SOD, GPx, and MDA                                       | Solowiej and Sobaniec, in 2003, found that 25 children treated with VPA, 16 children treated with carbamazepine, and 27 children treated with polytherapy (carbamazepine + VPA) exhibited a significant decrease in the serum SOD activity, compared with 61 healthy children. The serum GPx activity was significantly increased in all patient groups except in those receiving combination therapy, compared with the control group. The lipid peroxidation levels in the serum were significantly increased in all patients.   | [56]     |
| VPA                   | GPx   | Hamed et al., in 2004, found that 14 adult patients without treatment exhibited no significant decrease in GPx activity but exhibited a significant reduction in the total antioxidant capacity in the serum. Fifty-five patients with epilepsy treated using VPA exhibited a significant increase in their serum GPx levels and total antioxidant capacity.   | [57]     |
| OXC                   | GPx, SOD, and MDA                                       | Bolayir et al., in 2004, found that the GPx activity, SOD activity, and lipid peroxidation levels in erythrocytes were significantly different after one year of therapy with oxcarbazepine. This study was performed in 13 adult patients, and the results were compared with the results obtained from 15 healthy adults and from the same patients before monotherapy.  | [58]     |
| VPA                   | MDA   | Martínez-Ballesteros et al., in 2004, found a significant increase in lipid peroxidation in 76 patients compared with the control group.   | [59]     |
| VPA and Carbamazepine | SOD, GPx, GR, and MDA                                   | Sobaniec et al., in 2006, evaluated the effect of therapy with AEDs and how these drugs changed the SOD, GPx, and GR activity and the lipid peroxidation levels in the erythrocytes of 90 pediatric patients and 61 healthy children. The activity of the antioxidant enzymes was significantly higher. The lipid peroxidation levels were significantly lower in children treated only with carbamazepine. In children treated with VPA, the activity of all antioxidant enzymes was lower. Higher levels of lipid peroxidation were concurrently demonstrated. In patients treated with combination therapy, the SOD activity was lower, whereas the activity of GPx and GR was higher. In addition, lower lipid peroxidation levels were displayed. | [60]     |



TABLE 2: Continued.

| AEDs                                  | Antioxidant enzymatic activity/oxidative stress markers | Findings  | Ref  |
|---------------------------------------|---|---|------|
| VPA                                   | NO <sup>•</sup> , SOD, CAT, and MDA                     | Peker et al., in 2009, investigated the effect of VPA on the serum levels of NO <sup>•</sup> , lipid peroxidation, and certain antioxidant enzymes (SOD and CAT) in 21 children treated with VPA for one year and in 26 healthy children. We observed a significant increase of 10% in the levels of NO <sup>•</sup> in children treated with VPA, compared with healthy children. There were no significant differences in the levels of lipid peroxidation and antioxidant enzymes. | [61] |
| —                                     | GPX and MDA   | Güneş et al., in 2009, analyzed the erythrocyte antioxidant status of 31 children with febrile seizures and 30 febrile children without seizures. The levels of lipid peroxidation were significantly higher, and the GPx and SOD levels were significantly lower in the group of children with febrile seizures compared with the group that did not present with seizures.  | [62] |
| VPA, carbamazepine, and levetiracetam | 8-OHG   | Varoglu et al., in 2010, determined in 32 patients treated with VPA, 17 treated with carbamazepine, 8 with levetiracetam, and 11 with polytherapy that the levels of low-density lipoprotein (LDL) and 8-OHG were significantly higher in all patients, compared with the control group. Comparing the monotherapy versus the polytherapy, only the valproate + levetiracetam combination yielded a significant increase in 8-OHG.  | [63] |
| OXC                                   | NO <sup>•</sup> and MDA                                 | Arhan et al., in 2011, found a significant decrease in the serum levels of NO <sup>•</sup> and lipid peroxidation in 16 children diagnosed with idiopathic epilepsy and treated for three months with OXC.  | [64] |
| VPA                                   | SOD, CAT, MPO, and MDA                                  | Y.J. Zhang et al., in 2011, reported a significant decrease in the antioxidant activity of SOD and CAT. They also found a significant increase in the MPO activity and lipid peroxidation levels. This study was performed in 26 epileptic children treated for six and 12 months with VPA, compared with 30 healthy children.  | [65] |

#### 4. Antioxidant Enzymes Induced by VPA, OXC, and TPM: Evidence in Humans and Experimental Models

It is established that VPA, OXC, and TPM are capable of modulating the oxidant-antioxidant system. Particularly, enzyme antioxidant activity studies have demonstrated that the administration of certain AEDs causes decrease in enzyme activity, increase in the antioxidant system, or even the absence of an effect upon the antioxidant system.

VPA can modulate negatively or positively the enzymatic activity. Chaudhary and Parvez, in 2012, found a significant reduction of GST, GR, GPx, SOD, and CAT activity. They also observed significantly increased xanthine oxidase activity and lipid peroxidation levels in the cerebellum and cerebral cortex of rats [66]. Zhang et al., in 2011, observed a significant decrease in the antioxidant activity of SOD and CAT, a significant increase in the myeloperoxidase (MPO) activity, and increased levels of lipid peroxidation in epileptic children [65]. Varoglu et al., in 2010, observed significantly increased 8-hydroxyguanosine (8-OHG) levels in the serum of epileptic patients [63]; Peker et al., in 2009, found a significant increase of NO<sup>•</sup> in the serum of epileptic children [61]. Martínez-Ballesteros et al., in 2004, observed significantly increased lipid peroxidation in epileptic patients treated with VPA [59]. Other studies have revealed a positive regulatory effect on the antioxidant activity of certain proteins [56, 67–69].

A few *in vivo* and *in vitro* studies have reported the effect of the OXC and TPM AEDs on the antioxidant defense system, the lipid peroxidation levels, and the ROS levels. Positive regulation of the antioxidant system by OXC has not been reported to date. Cardile et al. in 2001 and Pavone and Carile, in 2003, demonstrated increased ROS levels in cultured astrocytes, which caused negative regulation [70, 71]. Agarwal et al., in 2011, found significantly increased lipid peroxidation levels and significantly decreased levels of reduced glutathione (GSH) in rats with pentylentetrazole-induced epilepsy [72].

Cardile et al., in 2001, and Agarwal et al., in 2011, reported a negative regulatory effect of TPM. With respect to the positive regulatory effect of TPM on the antioxidant system, a significant increase in SOD, CAT, GPx, and neuronal nitric oxide synthase (nNOS) activities, as well as in GSH levels, has been observed. Significantly decreased lipid peroxidation levels have also been observed in experimental epilepsy models [43, 73–76]. Our research group has demonstrated for the first time that TPM has direct antioxidant activity *in vitro* against O<sub>2</sub><sup>•-</sup>, H<sub>2</sub>O<sub>2</sub>, HO<sup>•</sup>, and hypochlorous acid (HOCl) in a concentration-dependent manner. In this study, we demonstrated that the scavenging activity of TPM might explain its neuroprotective properties [77]. Human studies have evaluated the effects of AEDs on the antioxidant system; see Table 2.

Although there is evidence in humans and experimental models that these AEDs (VPA, OXC, and TPM) modulate the activity of antioxidant enzymes, this evidence is not conclusive. It is necessary to study further how AEDs induce effects in antioxidant capacities in different types of epilepsy. In particular, our research group is interested in determining the activity of the antioxidant enzymes and their modulation by AEDs in epileptic pediatric patients.

## 5. Therapeutic Relevance

To date, the mechanisms involved in the etiopathogenesis of epilepsy remain unclear; however, the evidence showed that oxidative stress is involved in the epilepsy development. Therefore, the knowledge that current AEDs can modulate other systems opens a new therapeutic window for the population suffering from epilepsy and other chronic and degenerative CNS diseases, in which oxidative stress is one of the mechanisms underlying these pathologies.

## Conflict of Interests

The authors of this work have no conflict of interests to declare.

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