Chapter 1

Epilepsy Treatment and Nutritional Intervention

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1. Introduction

1.1. Epilepsy

Epilepsy is the most common chronic brain condition with epileptiform neuronal discharges, characterized by recurrent unproved seizures with at least two and at least 24 hrs apart. Epileptiform patterns in electroencephalogram (EEG) should confirm the diagnosis. It is the most expensive chronic neurological brain disorder in Europe (Andlin-Sobocki et al. 2005; Majkowski and Majkowska-Zwolińska, 2010). According to the World Health Organisation and the World Bank, the costs of epilepsy constitutes 0.5% of all diseases (Leonardi and Ustrun, 2002).

The incidence of epilepsy in the whole population is estimated as about 50-60 cases per 100.000 persons per year, and it is aged depending. In elderly, above 65 yrs old, it is increasing and about 80 yrs old is about 200 cases /100.000/year and in young preschool age children 100-150 / 100.000/year (Forsgeren, 2004). Worldwide prevalence of epilepsy is about 1% (in whole world about 50 millions of persons). However, according to Poter (1988), 45 to 100 million people worldwide were estimated to have epilepsy. Prevalence, like incidence, is age related; in age above 70 yrs it is highest (about 2%), and a little lower in infants. Extremes of life in humans are associated with increased incidence of epilepsy and increased susceptibility to oxygen stress in the developing immature brain (Lafemina et al., 2006) and in aged animals (Liang and Patel, 2004; Avramovic et al., 2012). It is an open question if there is a causal relation between these two events.

Occurrence of the first seizure, at any age, does not necessary mean epilepsy and a need for antiepileptic drug (AED) administration. It may be symptomatic and diagnostic procedure should be implemented to exclude or confirm an etiological cause. In the whole life of a person, from birth to death, at least one epileptic seizure may occur − including febrile convulsions − in about 8% of otherwise healthy population. In about one of them epilepsy will develop.

Once diagnosis of epilepsy, as defined, is established AED treatment should be started, and in majority of seizure free patients should be continued for several years after the last seizure. In at least 1/3 of epileptic patients with pharmaco-resistant epilepsy, their seizures tend to recur despite of using more than one AED. This group of patients may require life long administration of AEDs. However, a patient's drug resistancy does not imply that the patient will never become seizure-free on further adjustment of AED therapy or other treatment intervention (Kwan et al., 2010; Fröscher, 2012). Introduction of so called new generation of AEDs, while substantially better tolerated, as far as adverse events are concerned, did not make breakthrough in control of pharmaco-resistant form of epilepsy.

All AEDs, with various mechanisms of actions, can to some extent control frequency and severity of epileptic seizures, but not to prevent epileptogenesis (will be discussed in some detail later in this text) which may start after any kind of inborn or acquired brain pathology. However, AEDs may to some extent prevent secondarily cortical epileptization due to epileptic seizures and epileptiform patterns in EEG by reducing or inhibiting occurrence of seizures and/or epileptiform discharges and their spreading to various parts or whole brain structures. On the other hand some AEDs can produce oxygen stress.

In patients with AED therapy resistance, other treatment e.g. neurosurgery may be beneficial in the patients with epileptogenic focus which is precisely localized and is not in eloquent cortical areas. Vagus nerve stimulation is used in addition to AEDs in patients if their seizures are not adequately controlled and there is no possibility to perform neurosurgery (e.g. diffuse brain pathology). Ketogenic diet (KD) may be helpful in some infants and young children with severe epilepsy. Protective modulation of oxidative stress and mitochondrial function by the KD was recently reviewed (Milder and Patel, 2012). The authors highlighted potential mechanism of the KD which can ultimately result in increased production of anti-oxidants and detoxification enzymes with the protective effects of the KD. The diet in Wistar rats revealed an increase in anti-oxidant activity in hippocampus (glutathione peroxidase (GSH-Px) about 4 times) and no changes in lipoperoxidation levels (Ziegler et al., 2003). Cerebral cortex was not affected by the KD, and in cerebellum was a decrease in anti-oxidant capacity. The authors conclude that KD might contribute to protect the hippocampus from neurodegenerative sequelae of seizures. Using organotypic hippocampal slice cultures, it was shown that ketone bodies abolished hippocampal network hyperexcitability following metabolic insult (hypoxia) (Samoilova et al., 2010). The study demonstrated a direct link between metabolic resistance and better control of excessive synchronous abnormal electrical activity. Chronic in vitro ketosis has neuroprotective but not anticonvulsant activity.

However, both methods neurosurgery and KD − are used in rather small percentage of drug resistant epilepsy patients. There is a number of intervention procedures which are at experimental level, still.

In short, currently, AED administration in great majority of patients is the most successfully used symptomatic treatment of seizures but not epilepsy itself. However, long-term treatment, in particular, when polytherapy is used, may result in adverse events including cognitive function impairments, and in turn in decrease the patients' quality of life. Thus, continuous search and trials are needed to find compounds of antiepileptogenesis prevention, to improve

seizure control and prevent adverse events, in particular, long term ones affecting cognitive functions. Ideas of various brain disorders, including epilepsy, are teleologicaly explicitly associated with the oxygen toxicity paradigm (Atroshi et al., 2007). Consequently, anti-oxidant interventions are logical procedure with a hope for better health care for these groups of patients. Rational for use of these essential compounds to stay healthy is that they cannot be synthesized in human body. Thus, anti-oxidant supplements could have a potential role in preventing diseases. However, in a normal diet, in high-income countries, sufficient amounts of anti-oxidants may be provided Despite of that more than one third of adults regularly take anti-oxidant supplements (Bjelakovic et al., 2013). The authors assessed whether different doses of beta-carotene, vitamin A and vitamin E affect mortality in primary or secondary prevention randomized clinical trials low risk of bias (53 trials, 241,883 persons aged 18-103 years, 44% women). The study was based on Cochrane systematic review analyzing beneficial and harmful effect of the anti-oxidant supplements in adult. Meta-regression analysis showed that the dose of vitamin A was significantly positively associated with all cause mortality. Vitamin A in a dose above recommended daily allowance (RDA) (>800 μg) did not significantly influence mortality. Beta-carotene in dose above 9.6 mg, and vitamin E in dose above the RDA (>15 mg) significantly increased mortality.

1.2. Oxygen stress

Within the last three decades interest in oxygen stress and its role in the development of oxygen pathology has been considerably increasing and the importance of this phenomenon − increasingly recognized not only in the brain disorders e.g. epilepsy (Azam et al., 2012), headache (Vurucu et al., 2013) but also in other organ function e.g. heart, vascular disorders, diabetes, nasal polyps (Bozkus et al., 2013; Büyükkaya et al., 2013; Chalghoum et al., 2012; Kim et al., 2013; Madmani et al., 2013). Moreover, for the first time the pathophysiological consequences of L-ferritin deficiency in a human helped to define the concept for new disease entity − halmarked by idiopatic generalized seizures and atypical restless leg syndrome − in 23 yrs old female (Cozzi et al., 2013). The syndrome was accompanied with diminished levels of cytosolic catalase, superoxide dismutase (SOD) 1 protein levels, enhanced reactive oxygen species (ROS) production and higher level of oxidized proteins.

Oxygen stress means that the production of free radicals and ROS has exceded physiological the anti-oxidant defence mechanism capacity (Sies, 1985; Mahle and Desgupta, 1997). In Bartosz (2006) opinion, oxygen stress research may be the key to better understanding of certain biochemical, physiological and pathological aspects of living organisms and suggests that such understanding could be applied in clinical practice. Free radicals, the product of oxygen stress, may play an important role as physiological markers which control cell process signals. However, when produced in excess, or when anti-oxidant defense system is not efficient, the free radicals may lead to cell damage. Under physiologic circumstances, the brain has sufficient anti-oxidant defense mechanisms, including GSH-Px which converts potentially harmful H_2O_2 to oxygen and water at the expense of reduced glutathione (GSH) (Wang et al., 2003).

Excessive free radical production is related to various physiological and pathological states, including aging, epileptic seizures or the use of xenobiotics, including fat-soluble drugs (Nikietic et al., 1995; Martinez-Bellesteros et al., 2004; Patel, 2004); this also applies to old and to some new AEDs (Hamed and Abdellah, 2004; Kaipainen et al., 2004; Sobaniec et al., 2006; Atroshi et al, 2007; Avcicek and Iscan, 2007; Płonka-Półtorak et al., 2011). A number of non-specific factors as well as dietary habits affect the state of anti-oxidants in the healthy elderly (Anlasik at al., 2005). This suggests that at the current level of understanding, oxidation and anti-oxidation processes are rather ubiquitous and hence non-specific for particular disorder.

In epilepsy, when the number of free radicals in the brain neurons increases, this interferes with respiratory chain in the mitochondria, destabilizes the lysosomal membranes, and lowers the convulsion threshold (Tayarani et al., 1987; Frantseva et al., 1998; Frantseva et al., 2000; Patel 2002; Waldbaum and Patel, 2010a). Neuronal firing associated with prolonged epileptic discharges and seizures may lead to a number of neurochemical changes and cascades of events at the cellular and molecular level. This in turn, results in mitochondrial dysfunction, increased ROS and nitric oxide (NO) which precede neuronal degeneration and death with possible subsequent epileptogenesis and cortical epileptization − secondary epileptogenesis − which may result in cognitive function impairments and with chronic intractable epilepsy.

Experimental data indicate that NO may be involved in various way in pathophysiology of epileptic seizures. One of interesting mechanism was suggested by Cupello et al. (1997). The authors studied the effects of NO donors and L-arginine (NO precursor) on the up-take of GABA in synaptosomes of the rat brain. They found that NO decreases synaptosomal GABA up-take and it could result in a reduced availability of GABA at the synapses – leading to an increase of neuronal firing.

Mitochondria are emerging as key participants in cell death because their association with an over-growing list o apoptosis-related problems (Chang, 2010). Peroxydation of neuronal membranes modifies their electrophysiological properties and leads to abnormal bioelectric discharges of neurones. Among diseases involving dysfunction in the mitochondrial structures, epilepsy is prominent; it is a sign of energetic anomalies in ATP synthesis due to ADP phosphorylation (Patel, 2002). Mitochondria have important vital functions such as energy production, cellular harm control, neurotransmitter synthesis and free radical production. It is still not clear which of these functions is affected in epileptic seizures (Rowley and Patel, 2013).

Bilateral intracerebra-venticular infusion of all-homocysteic acid in immature rats, resulting in seizures, demonstrated that the marked decrease (approximately 60%) of mitochondrial complex I activity persisted during up to 5 weeks of survival following these seizures (Folbergova et al., 2010). This period of survival corresponds the development of spontaneous seizures (epileptogenesis) in this model. The authors assumed that the persisting inhibition of mitochondrial complex I may lead to the enhanced production of ROS and/or nitrogen species. In this way may contribute not only to neural injury in this model of seizures but also to epileptogenesis.

An increase in spontaneous and evoked epileptic seizures in a subgroup of mice with partial inherent mitochondrial manganese superoxide dismutnase (MnSOD or SOD2) deficit and

lipophylic metalloporphyrin catalytic anti-oxidant was reported (Liang and Patel, 2004; Liang et al., 2012). This effect correlated with chronic mitochondrial oxygen stress (aconitase enzyme deactivation) and reduced oxygen use. According to the authors, oxygen stress caused by free radical peroxides increases seizure susceptibility in this subgroup of mice. This susceptibility increases with age (corresponding to high incidence of epilepsy in elderly) and also with increased environmental stimulation and use of stimulants. It is interesting and worthwile to emphesize that **oxygen stress and mitochondrial dysfunction may both cause and be caused by epileptic attacks** (Heinemann et al., 2002; Patel, 2004; Sullivan et al., 2004; Waldbaum and Patel, 2010b). At present, an increasing attention is paid to the possible interaction between oxidative stress, resulting in disturbance of physiological signaling roles of calcium and free radicals in neurones, and mitochondrial dysfunction, cell damage and epilepsy (Martinc et al., 2012)

According to Dubenko and Litovchenko (2002), application of energy metabolism activators improves the clinical and electroencephalographic course of epilepsy. This has been demonstrated experimentally by positive histological changes. According to these authors, this treatment prevents neuronal harm and development of encephalopathy with its cognitive function impairments. Relation between epileptiform discharges and serious cognitive function impairments was shown in kindling animal model of epilepsy (Majkowski, 1981, 1990) and in young children without seizures but with continous spike and wave during sleep – so called electrical status epilepticus described by S.A. Tussinari (Patry et al., 1971). Thus, it was also shown that **not only epileptic seizures but also EEG discharges may cause complex metabolic neuronal lesions and oxidant/anti-oxidant disequilibrium** (Freitas et al., 2004; Ilhan et al., 2005a; Sok et al., 2006; Barros et al., 2007).

A number of experimental studies on animal models and humans have shown that all old and some new AEDs can also produce free radicals and significantly increase the peroxidation of neuronal membrane lipids and reduce the protective effects of anti-oxidants. These changes may lead to increased seizure and idiosyncratic drug effect frequency (Kurekci et al., 1995; Sudha et al., 2001; Hung-Ming et al., 2002; Hamed and Abdellach, 2009; Hamed et al., 2009; Dostalek et al., 2007).

Oxidation stress and resistance to AED effects triggers adaptive mechanisms i.e. production of endogenous anti-oxidants scavengers, which prevent the harmful effects of oxidation (Kawakami et al., 2006). These authors studied NO and endogenous anti-oxidant GSH scavengers, GSH-Px, complete (T) and superoxide dismutase (T-SOD), Mn –SOD and catalase in cerebrospinal fluid of children with various neurological disorders. All the anti-oxidant parameters were highest in children with bacterial meningitis compared with other groups. In the group of epilepsy NO, GSH and GSH-Px were higher than in the group with aseptic meningitis and the control group. In the authors' opinion oxygen stress may be related to seizure pathology and its reduction may lead to better prognosis for the course of epilepsy. Akarsu et al. (2007) came to similar conclusions. The authors studied the state of oxidation in 21 children with febrile convulsion and 21 children without febrile convulsions, assessing the level of arginase and catalase in their red blood cells, malondialdehyde (MDA) – an indicator of lipid peroxidation and NO in the plasma and cerebrospinal fluid. The control group

consisted of 41 children divided into two subgroups: 1-with fever without convulsions and 2 – without fever and without convulsions. Both fever and convulsions had a significant effect on the oxidation mechanisms. Febrile and afebrile convulsions differed in their generation of oxygen stress. According to the authors, in afebrile convulsion higher levels of oxygen stress might affect prognosis adversely. This is interpreted in terms of fever as a protective factor preventing neuronal lesion during convulsions. Recently, relation between febrile convulsion and oxygen stress was studied in 32 pediatric patients who within the preceding 8 hrs had experienced respiratory tract infection and had been diagnosed with simple febrile convulsions (Abuhandan et al., 2013). Total oxidant level (TOL) and total anti-oxidant level (TAL) were measured 8 hrs after seizure. The TOL and oxidative stress index were found to be significantly high ($p<0.01$ and $p<0.01$, respectively), and TAL was significantly lower ($p< 0.03$) compared to control group 30 healthy children. The authors conclude that increased oxidative stress may increase the risk of occurrence febrile seizures.

Since oxygen stress worsen the course of epilepsy, consistently with those observations, use of anticonvulsants in conventional epilepsy therapy and hence attenuation of oxygen stress could have a positive effect on the course of epilepsy (Costello and Delanty, 2004). Many authors share this opinion. However, these results are not used to inform and guide everyday epilepsy medication.

1.3. Objective

The chapter is intended to present and discuss current state of knowledge in various animal experimental models of seizures and human epilepsy research related to epileptogenesis and complex interaction between epilepsy, AEDs, and oxygen stress. The effects of various nutritional factors which restore balance in the oxidant/anti-oxidant system, and prevent epileptic attacks and AEDs from causing brain neuronal damages in experimental and human epilepsies will be up-dated.

1.4. Search method

A literature review was conduced to November 2013. The following search terms were used: oxygen stress, oxidants and antioxidants, animal seizure models, epilepsy and AEDs. It was searched data bases PubMed-line, the Cochrane Epilepsy Group's Specialized Register, indexed and non-indexed citation and relevant papers related to beneficial of antioxidants, and possible harmful effects AEDs and epileptic seizures in animal models and in epileptic patients.

2. Research review and discussion

2.1. Epileptogenesis

Epileptogenesis is the main challenge for contemporary epileptology, still. Any nonspecific brain damage may result in process of epileptogenesis which leads to seizure occurrence and

eventually to chronic epilepsy. Brain damage may be followed by immediate (with latency seconds to 1 hr) and/or early (minutes to 1 week) seizure and late (week to dozen of years) recurring seizures. Possible pathomechanism of these seizures, triggering factors, risk factors for development of epilepsy, onset after brain damage, age depending, type of clinical course of seizures, and responsiveness to AEDs are different in these groups (Majkowski, 1990).

Epileptogenic process can be arbitrarily divided into two – overlapping to some extent – stages: cascade of biochemical processes followed by better known electrophysiological stage which precedes epilepsy occurrence. Brain damage initiates a series of non-specific, complex biochemical changes at the neural, synaptic and molecular levels. Among these biochemical changes, oxygen stress resulting in disequilibrium between oxidants and antio-xidants has been postulated in pathogenesis of seizures by many authors (Ueda et al., 1998; Jacobson et al., 1999; Dal-Pizzol et al., 2000, Patel, 2002). Role of oxygen stress has been shown and discussed in experimental animal model of epileptic seizures (Mori et al., 1990; Dakin and Weaver, 1993; de la Pena and Porta-Etessam, 1998; Majkowski, 2007; Rowley and Patel, 2013; Ryan et al., 2012). The latter provided evidence for the occurrence of specific and irreversible oxidative modification of an important mitochondrial enzyme of a protein complex I. The complex is critical for cellular bioenergetics during the process of epileptogenesis. Mechanism of epileptogenesis is not known. However, data from animal models and from patients with temporal lobe epilepsy suggest that steady-state mitochondrial ROS and resulting oxidative damage of neurons occurs during different phases of epileptogenesis (Rowley and Patel, 2013). Epileptogenic substances produce, before seizure occurrence, an increase of free radicals, lipid peroxidation and decrease of GSH-Px – the most important anti-oxidant in brain. Lipid peroxidase correlates with an increase of seizure susceptibility. In turn, occurs dysfunction of the mitochondria, neuronal membrane permeability, disturbance of the balance between excessive neuronal activation and inhibition of neuronal transmission which may be due to an increase of glutaminergic or decrease of gabaergic transmitters (Murashima et al., 2005; Narkilati and Pitkanen 2005; Lasoń, 2006). These biochemical changes decrease seizure threshold and lead to epileptic neuronal discharges which may initiate kindling process (electro-epileptogenesis) leading to epileptic attacks (Tayarani et al., 1987; Majkowski, 1993; Frantseva et al., 1998; Frantseva et al., 2000; Liang and Patel, 2004; Waldbaum and Patel; 2010a). These biochemical study, indicating formation of specific protein in process of epileptogenesis, corresponds well with long-lasting synaptic plasticity which is seen in brain modification of sensory evoked potentials and epileptiform potentials development during kindling process of epileptogenesis (Majkowski and Kwast, 1981; Majkowski, 1989). Electrical kindling with its gradual development of epileptiform discharges is the most elegant model of chronic epilepsy which allows to study electrophysiological stage of epileptogenesis. Kindling phenomenon − produced by weak repeated electrical stimulation − described by Goddard et al., (1969), is characterized by widespread and long-lasting neuronal plasticity changes which can be seen in modification of behavior (seizure) and sensory evoked potential changes expressing long-lasting synaptic modification (Majkowski, 1989; 1993). This evoked potentals' modification is of the same kind as during learning processes (Majkowski and Kwast, 1981), what suggests new protein formation in the neurons is involved in epileptogenesis (Hyden, 1980).

It seems that oxygen stress may play essential role in the earliest biochemical stage of epileptogenesis − understood as formation of epileptogenic focus resulting in focal onset seizures. However, antiepileptogenic effects of various anti-oxidants used in different animal acute models of seizures is equivocal; the same anti-oxidant, and its dose, may have different effect in different models. Prevention or inhibition of epileptogenesis in different animal models, at best, shows delayed seizure occurrence in some seizure models (Zhao et at., 2006) and in some animals (Mori et al., 1990; Willmore et al., 1986; Suzer et al., 2000) but not prevention of epileptogenesis. A delay in seizure occurrence is understood as antiepileptogenic effects. In fact, it is not antiepileptogenic but anti-ictal effect. AEDs which increase seizure threshold, in the animal models and humans, may delay the first seizure occurrence e.g. in prevention of epileptogenesis of posttraumatic epilepsy, but not have antiepileptogenic effect. This delayed or diminished severity of seizures due to anticovulsants or anti-oxidants is also seen in chronic animal model of epilepsy (like kindling) with developed epileptiform neuronal discharges. This misunderstanding was shown in elegant hippocampal slice cultures as a model of traumatic brain injury, during acute and chronic (8 weeks) electrical recordings (Berdichevsky et al., 2011) Characteristic evolution of spontaneous epileptiform discharges, interictal spikes, seizure activity and electrical status epileptious was recorded. Peak cell death occurred immediately following slicing, and later secondary peak was associated with the peak of seizure-like activity. The secondary peak in neural death was abolished by either blockade of glutaminergic transmission by kynurenic acid or by elimination of ictal activity and status epilepticus by PHT. Withdrawal of these inhibitors was followed by spontaneous seizure activity recurrence. PHT anticonvulsant and neuroprotective effect disapeared after four weeks of continous administration. These interesting results show that AED may prevent seizures but not epileptogenesis. The authors conclude that in this vitro model secondary neuronal death is correlated with ictal but not interictal electrical activity.

Epilepsies in humans and in animal models of seizures or epilepsy are extremely heterogenous in their etiology, pathomechanisms and diversity of their behavioural menifestations. This heterogeneity corresponds to diversities of results in using anti-oxidants, various seizure models and animals. At present, there are no well documented − on evidence base medicine − studies with anti-oxidants in prophylaxis of epileptogenesis. The same may be said about AEDs (Beghi, 2003). The prophylactic use of AEDs should be short lasting and may be effective in immediate and early seizures. Recently, prophylatic effect for post-craniotomy seizures in patients without epilepsy was reported (Pulman et al., 2013). The authors reviewed the relevant literature and found that there is little evidence to suggest that PHT, CBZ, PB, VPA or ZNS administered prophylactically is effective or not effective.

The well documented beneficial effects of anti-oxidants are related to diminishing neurodegeneration produced by induced seizures and epileptic discharges. However, research on the role of oxygen stress opens a new chapter in epileptology with a hope of prevention biochemical processes leading to epileptiform neuronal discharges, epileptogenesis and cognitive function impairments in epileptic patients.

2.2. Preventing oxygen stress due to epileptic seizures in animal models

Research on animal experimental models (and clinical observation) has shown that epileptic seizures lead to a number of harmful activities in the brain: disturbed blood circulation, increased cerebrospinal fluid pressure, brain oedema, hypoxia, all of which lead to the sudden reduction of energy carriers (ADP, ATP, phosphocreatinine) and neuronal pH reduction. During seizures, arachidonic acid is released in the postsynaptic membranes. This has an activating effect on the presynaptic neuronal endings and leads to increased glutamate release. Arachidonic acid also increases the production of free oxygen radicals, leading to increased lipid peroxidation. These in turn may activate phospholipase C and then lead to the release of arachidonic acid from the cellular membranes, setting a vicious circle in motion (Bartosz, 2006).

2.2.1. DL-homocysteic acid-induced seizures in immature rats

Homocysteine (Hcy) is an exscitatory amino acid which markedly enhances the vulnerability of neuronal cells to excitatory and oxidative injury. Recently, it has been shown that oxidative stress, occurring in the brain of immature 12-day-old rats during and following the seizures, induced by *DL-homocysteic acid*, is apparently due to the increased free radicals production (SOD, CuZn SOD, MnSOD and GPX) and the limited anti-oxidant defense (catalase activity decrease). The pronounced and selective upregulation of SOD2 (MnSOD) indicates to increased ROS in the mitochondrial matrix. This may be associated with inhibiton of respiratory chain complex I (Folbergrová et al., 2013). The authors suggest that in addition to AED, substances with anti-oxidant properties might provide beneficial effects in treatment of epilepsy in children. Protective role of astrocytes in neuronal survival in response to the damage induced by Hcy was studied (Loureiro et al., 2010). The authors found that the cytoskeleton of cortical astrocytes (but not of neurons in culture) is a target to Hcy and effects are mediated by redox signaling. Astrocytes were able to respond to Hcy reorganizing their cytoskeleton, surviving and protecting neurons from Hcy damage.

2.2.2. Lithium-pilocarpine (Li-PIL) model of seizures

The modulatory effect of *dexamethasone (DEX)* using 5, 10, 20 mg/kg body mass of male Wistar rats was studied in Li-PIL epilepsy model (Al-Shorbagy et al., 2012). The authors found that effective anticonvulsant activity was only observed with 10 mg DEX/kg which reduced seizure production and incidence, as well as neuronal cell loss in the CA3 region of the hippocampus. It was associated with enhancements in the anti-oxidant system and interleukin as well as suppression of altered inflammatory markers. Dose 20 mg/kg DEX showed a tendency to shorten seizure latency, and neither affected seizure incidences nor CA3 neuronal loss. There was a lack of protection at 5 mg DEX/kg. The study indicates that there is an optimal dose of DEX for preventing the induction of seizures

2.2.3. The pentylenetetrazol seizure model (PTZ) and anti-oxidants

Astragalus mongholicus. The root extract of Astragalus mongholicus (AM), a traditional medicinal herbas, has powerful anticonvulsant effects in the mouse PTZ-induced seizure

model (Aldarmaa et al., 2010). Moreover, this effect was associated with an inhibition of PTZ-induced increase of lipid and protein peroxidation and ROS. The authors suggest that anticonvulsant effect of AM may be mediated by its protective actions against oxidative damage and amelioration of mitochondrial dysfunction.

Erdosteine. Prior administration of erdosteine (mucoliticum), which acts as an antioxidant, attenuated OS and delayed onset of PTZ-induced seizures in mice ($p<0.05$) (Ilhan et al., 2005b). The erdosteine pretreated mice had lower levels of MDA and xanthine oxidase (oxidisers) and a higher level of SOD than control animals ($p<0.001$). Thus, administration of erdosteine reduces convulsion-induced oxygen stress and therefore may protect neurons.

Mexidol, novel original Russian synthetic anti-oxidant (2-ethylo-6-methyl-3-oxypiridine succinate) and effects of AEDs (PB, LTG, phenazepam) and alpha-tocopherol were studied in PTZ-induced seizure model in Wistar rats (Beshkatova et al., 2003). Fivefold elevation of NO production was found in the induced seizures. Also, the level of secondary products of lipid peroxydation (LPO) and thiobarbituric acid reactive substances was significantly increased in the cortex. The authors found that mexidol and PB were to be the most effective in preventing of PTZ-induced seizures among all the studied substances. The authors suppose that supression of seizure-induced NO generation and LPO increase may be involved in the mechanism of AEDs action.

Nigella sativa oil. Nigella sativa oil, a powerful antioxidant which has been used in folk medicine and the kitchen for thousands of years, prevented PTZ-induced kindling in mice much more effectively than that of valproic acid (Ilhan et al., 2005a).

Polyphenols (grape juice). Epileptic seizures and AEDs may cause oxidative damage in hepatocytes. Wistar rats received organic grap juice or conventional grape juice (rich in phenols) and saline for 17 days before PTZ-induced seizures (Rodrigues et al., 2012). The results showed that both juices conferred protection against lipid and protein oxidative damage of liver, and limited the increase in PTZ-induced NO metabolite content in liver and serum. Moreover, both juices inhibited the PTZ-induced reduction in enzymatic anti-oxidant defenses (SOD, CAT) and sulfhydryl protein in the liver and serum. These results indicate that grape juices can provide an insight into natural neuroprotective compounds and may lead to the development of new therapeutic strategies for epileptic patients (Rodrigues et al., 2012).

Polyphenols (walnut kernels). Walnuts have high concentration of phenols. Its supplementation was associated with increased seizure threshold and reduced mortality in PTZ seizure model in Wistar adult male rats (Asadi-Shekaari et al., 2012). Moreover, there was prevention of neurodegeneration. The authors suggest that this effect may be due to high concentration in walnuts of phenols, which have anticonvulsant properties. Recently, antiepileptic effects of phenols were updated by Lasoń (2013) with notion that phenols can have clinical relevance for novel approach to treatment of epilepsy.

Physical activity. It has been found that swimming training (6 weeks) protects against the increase of neural excitability and oxidative neuronal damage in PTZ-induced seizures in rats (Souza et al., 2009). EEG recordings showed that the spikes' amplitude in rats was decreased after PTZ administration in all doses following swimming.

Topiramate (TPM) and selenium. TPM and selenium had protective effects on PTZ-induced brain damage in rats by inhibiting free radical production, regulating calcium-dependent processes, and supporting the antioxidant redox system (Naziroglu et al., 2008). Recent studies indicate that selenium with/without topiramate administration in human and animals decreased seizure levels, although anti-oxidant values were increased (Naziroglu and Yürekli, 2013).

Vitamin E and selenium. Intraperitoneal administration of PTZ – an antagonist of the GABA A-receptor – induced seizures and ruptured the blood-brain barrier in rats. This has been demonstrated by means of Evans dye, used to mark the permeability of this barrier (Oztas et al., 2001). It has been suggested that free radicals are involved in the permeability of the blood-brain barrier; this permeability leads to albumin extravasation to the thalamic nuclei, brain stem, frontal cortex and occipital cortex. Animals that have been given vitamin E or selenium (Se) prior to seizure induction, had less extravasation in these structures. It has also been demonstrated that in young rats and in normotermic conditions, barrier permeability was greater in males that in females ($p<0.05$) (Oztas et al., 2007).

2.2.4. The kainic acid model (KA) and anti-oxidants

The KA model is used as a model substance in the assessment of neurotoxicity. It leads to excessive ROS production due to reduced antioxidant activity. When KA was administered to rats, lipid peroxidation of the neuronal membrane increased in proportion to seizure progression (Ueda et al., 1997). In the same model, SOD and catalase activity increased significantly on day 5 following KA administration and returned to base level three weeks later; GSH-Px activity also increased significantly on day 5 but was still high three weeks later (Bruce and Baudry, 1995). Lipid and protein peroxidation, assessed by MDA concentration, increased significantly 8 and 16 hours later, then decreased on day 2 and day 5 following KA administration. The authors attribute the rapid increase in MDA and protein peroxidation to free radicals produced in this phase of the pathological KA effect; they conclude that the changes in enzymatic scavenger activity and the reduced MDA concentration may have been caused by glia proliferation due to neuronal death.

Gastrodia elata B1 (GE). Hsieh et al. (2001) tested a traditional Chinese herb GE, used to treat epilepsy, in a controlled study using the rat KA seizure model. They found that prior administration of GE significantly reduced in vitro lipid peroxidation in the brain, an effect analogous to the effect of phenytoin (PHT) – 20 mg/kg. In the authors' opiniont GE has an antiepileptic effect and is a free radical scavenger. This antiepileptic effect may be, at least, partly attributable to the GE's vanilla component (Hsieh et al., 2000).

Melatonin. In the mouse KA model, prior or simultaneous administration of melatonin (a powerful hydroxyl radical scavenger) (20 mg/kg i.p.) had an anti-oxidising effect and prevented lipid peroxidation, cerebral mitochondria DNA damage and seizures (Mohanan and Yamamoto, 2002).

Since oxidative stress is thought to play a role in pathogenesis of hypertention and epileptogenesis, it could be used as a tool for studying co-morbidity of both conditions (Atanasova et al., 2013). The authors studied efficacy of chronic pretreatment with *melatonin*, infused via

subcutaneous osmotic mini pump for 14 days, on KA-induced status epilepticus, oxidative stress and expression of heat shock protein (HSP) 72 in spontaneously hypertensive rats (SHRs) and normotensive Wistar rats. SHRs showed increase in the level of LP in frontal cortex and hippocampus and decreased cytosolic superoxide dismutase (SOD/CuZn) production in the frontal cortex compared to normotensive Wistar rats. Status epilepticus induced by KA was associated with increased LP and expression of HSP 72 in the hippocampus in the two strains, and increased SOD/CuZn production in frontal cortex of SHRs. Melatonin failed to suppress seizure incidence and intensity. However, latency was significantly increased in SHRs. Increased activity in SOD/CuZn and mitochondrial SOD Mn as well and reduced expression of HSP 72 in hippocampus was observed in Wistar rats pretreated with melatonin. **The observed strain differences in the efficacy of chronic melatonin expression before status epilepticus suggests a lack of direct link between the seizure activity and markers of oxygen stress and neurotoxicity.**

Petasites japonicum (BMP). Sok et al. (2006), studied the anticonvulsive effects of the plant grown in East Asia and used for both culinary purposes and in folk medicine. Its root extracts are still used for treating headaches and asthma. Prolonged administration of BMP, prior to KA administration, reduced mortality in mice by one half. Administration of the BMP-I subfraction reduced convulsive seizures and also significantly reduced neuronal loss in parts CA1 and CA3 of the hippocampus. The authors suggest that BMP-I is the factor responsible for prevention of oxidisation lesion in mouse brain.

SCH 58261 – a selective adenosine A(2A) receptor (A(2A)R) antagonist. KA induced seizures in young rats (21-day-old) were pretreated with SCH 58261 before (i.p.) KA administration (Bortolatto et al., 2012). It resulted in prolonged latency for the onset of the first clonic seizure and at the highest dose decreased the appearance of clonic seizures and mortality rate. The adenosine antagonist was also effective in protecting against alteration in oxidative stress parameters (ROS, CAT, GPx, and GST (glutathione S-tansferaze)) activities. Thus, SCH 58261 was protective against the induced neurotoxicity, and might represent a novel approach for the treatment of seizures.

Sesame seeds. Sesamin is a well-known antioxidant from sesame seeds and it scavenges free radicals. In KA–induced status epilepticus in mice and rats sesamin significantly decreased ROS, MDA and the mortality was decreased from 22% to 0% in rats (Hsieh et al., 2011).

Vineatrol. In the rat KA model, prior administration of vineatrol significantly reduced brain MDA levels but had no effect on the GSH levels (Gupta and Briyal, 2006). Doses exceeding 20 and 40 mg/kg lengthened the latency time to the first seizures. Additional administration of vineatrol 30 and 60 minutes after KA administration significantly reduced seizure incidence. The authors suggest that vineatrol could potentially be useful in status epilepticus.

2.2.5. The pilocarpine model of seizures, status epilepticus, oxidants and anti-oxidants

Pilocarpine, an imidasole alkaloid extracted from the leaves of the Pilocarpus jaborandi shrub, is a parasympathomimetic, a cholinergic agonist which acts similarly to acetylcholine. It is often used to evoke epileptic convulsions and status epilepticus in animal models. The

mechanisms leading to seizures or status epilepticus are unknown. It is thought that oxygen stress plays an important role but it is still unknown which brain structures are more sensitive.

The pilocarpine-induced status epilepticus had differential effects on catalase level in discrete brain structures (Freitas et al., 2004; Freitas et al., 2005). The highest elevation of the enzyme level was found in the hippocampus (36%), striatum (31%) and frontal cortex (15%); no changes were found in the cerebellum. According to the authors, the endogenous increase in catalase activity, responsible for removal of free oxygen radicals which are produced during convulsions, may be an auto-regulatory compensating defence mechanism which counteracts the negative effects of oxygen stress in the status epilepticus. In this model of epilepsy, results show that oxidative stress, lipid peroxidation and nitric oxide could be responsible for neuronal damage in the hippocampus (Freitas, 2009).Other researchers have come to similar conclusions (Kawakami et al., 2006; Tejada et al., 2007). The later authors investigated pilocarpine-evoked status epilepticus and found that MDA levels increased significantly in the brain cortex (64%), suggesting oxygen injury. They found a simultaneous increase in the anti-oxidising activity of catalase enzymes (28%), GSH-Px (28%) and SOD (21%). On the other hand, vitamin E concentration in the cerebral cortex was reduced (15%) due to increased lipid peroxydation following pilocarpine administration. The amount of lipid peroxydation product in cortical neurons of the cerebral hemispheres decreased by 30% at the peak of convulsions observed 10-15 min. after i.p. picrotoxin injection. In neuroglial cells of control animals the intensity of lipid peroxydation was 1.7-2.0 times lower (Flerov et al., 2004).

Apocynin. In pilocarpine-induced status epilepticus in rats, ROS generation was increased in CA1, CA3 and dentate gyrus of dorsal hippocampus (Pestana et al., 2010). The authors found that administration of apocynin (NADPH oxidase inhibitor) for 7 days prior to pilocarpine-induced status epilepticus had protective activity: ROS production and neurodegeneration in the studied structures were decreased by an average of 20% and 61%, respectively.

Lipoic acid. In pilocarpine-induced seizures in rats there was significant increase in lipid peroxidation, nitrite level and GPx, however, no alterations were found in SOD and catalase activities (Militão et al., 2010). Administration of lipoic acid significantly reduced the lipid peroxidation level and nitrite content, and increased the SOD, catalase and GPx activities in striatum after seizures. The study supports hypothesis that brain damage induced by the oxidative process plays a crucial role in seizures pathogenic consequences, and a protective effect could be achieved using lipoic acid.

Vitamin C. In the same model in rats, prior administration of vitamin C (250 mg/kg i.p.) reduced the negative effects of oxygen stress and neuronal lesion (Santos et al., 2008). The latency time to convulsion onset following pilocarpine administration was longer and mortality in the status epilepticus was reduced compared with the group which did not receive vitamin C or received physiological saline. This study also found that in the group which only received vitamin C the level of lipid peroxidation was lower than in the group which a) received pilocarpine and b) received pilocarpine and vitamin C. In all the experimental groups, catalase activity in the hippocampus increased compared with the control group which only received physiological saline. In the authors' opinion, the neuroprotective function of vitamin C in adult

rats may be due to reduced lipid peroxidation and increased catalase activity following convulsions and status epilepticus.

Vitamin E and status epilepticus. Barros et al. (2007) applied the same model and found that administration of vitamin E (200 mg/kg i.p.) 30 minutes prior to the administration of pilocarpine (400 mg/kg s.c.) leads to increased (214%) catalase activity in the hippocampus compared with rats which were only given policarpine (67%) or physiological saline. The authors conclude that increased catalase activity may be responsible for the regulation of free radicals evoked by the status epilepticus.

In pilocarpine-induced status epilepticus in rats autophagy – a process of bulk degeneration of cellular constituents through autophagosome-lysosomal pathways was studied (Cao et al., 2009). Status epilepticus induces an excess production of ROS resulting in an increase of autophagy which was a partially inhibited by pretreatment with vitamin E. The strong protective effect of vitamin E could be achieved in the same pilocarpine seizure model (Tome et al., 2010) The authors confirmed that oxidative stress occurs in rat hippocampus resulting in the brain damage and this plays a crucial role in seizure pathogenic consequences.

2.2.6. The audiogenic seizure model

Melatonin and valproic acid. Prolonged melatonin administration in rats congenitally predisposed to audiogenic convulsions (the Krushinsky-Molodkina model) had no effect on seizures evoked by a 20 times more powerful auditory stimulus (Savina et al., 2006). VPA administration significantly reduced convulsions but VPA and melatonin combination had a significantly larger anti-seizure effect: it lengthened latency time and reduced seizure severity. However, combined treatment led to much more rapid onset of myoclonia than in groups receiving either VPA or melatonin.

3. Oxygen stress and AEDs in animal models

3.1. Acetazolamide (AZM)

AZM or saline was given i.p. to Sprague Dawley rats before exposing to *hyperbaric oxygen model* – the pressure of 6 ATA of pure oxygen (Huang et al., 2004). There was a significant difference in the latency of hyperbaric oxygen-induced convulsions between AZM (200 mg/kg and 20 mg/kg) groups and saline controls ($p < 0.01$) and there was no significant difference between AZM (2 mg/kg) and saline group ($p > 0.05$). GSH-Px and MDA was increased in homogenized cortex, hippocampus and striatum in different ways and depending on the time of exposure to AZM. The results, according to the authors, suggest that AZM, which dilates the brain arteriolae, increases the supply of the oxygen breaking into the brain structures and aggravates the oxidation with its consequences.

3.2. Carbamazepine

Short term CBZ administration to roinbout trout and a low level of oxidative stress could induce adaptive responses of antioxidant enzymes, however, long-term exposure to CBZ could lead to serious oxidative damage of *fish brain* (Li et al., 2010).

3.3. Lamotrigine

LTG does not lead to detectable increases in lipid peroxidation in rats in vivo (Lu and Uetrecht, 2007). The anti-epileptic effectiveness of LTG in the *partial complex epilepsy model* (stimulation of the dentate gyrus) in rats was in reverse proportion to the level of nitric oxide (Sardo and Ferraro, 2007).

3.4. Levetiracetam

LEV (2000 mg/kg i.p.) administered prior to *pilocarpine administration* (400 mg/kg s.c.) in mice prevented lipid peroxidation increase in the hippocampus (but did not increase nitrate level or reduce catalase activity in the hippocampus or cortical glutathione) (Oliveira et al., 2007). Perhaps the anti-oxidising, neuroprotective effect of LEV and the consequent reduction of oxygen stress can be attributed to a different mechanism than the one which is active in the case of other AEDs.

3.5. Phenobarbital (PB)

Male Sprague – Dawley rats were pretreated with PB – a well known cytochrome P450 inducer (Dostalek et al., 2007). The markers of in vivo oxygen stress were influenced by PB resulting in significantly increased malondialdehyde, H_2O_2 generation and NADPH oxidation in vitro and significantly enhanced formation in vivo in liver and plasma.

3.6. Phenytoin (PHT)

PHT is known to produce ROS, which are involved in mechanism of the PHT-evoked teratogenesis and developmental toxicity. PHT initiates the oxidation damage to proteins and fats in the *maternal and embryonic liver tissue* organelle in murine rodents (Mahle and Dasgupta, 1997).

Gallagher and Sheehy (2010) used *cultured human prenatal liver slices* to study the effects of the human teratogen PHT on cell toxicity. Their findings in a relevant human model system are supportive of a protective role of GSH and alpha class glutathione S – transferases izoenzymes A1 against PHT toxicity and teratogenesis.

Using mutant catalase deficient mice and transgenic mice expressing human catalase, Abramov and Wells (2011) investigated protective importance of *embryonic catalase* against endogenous ROS and the ROS-imitating teratogen PHT in embryo culture. They provided evidence that the low level of embryonic catalase protects from developmental and xenobiotic-enhanced oxygen stress and that embryonic variations of this enzyme affect development.

3.7. Topiramate

TPM with its many mechanisms of action has undoubted effectiveness in the treatment of epilepsy in children. However, TPM administered to rat stomach for 3 months may lead to such adverse effects as toxic liver dysfunction (Huang et al., 2007). In a study of young rats it was found that small doses of TPM (40 mg/kg a day) may reduce total antioxidant capacity in the organism and lead to minor liver pathology. Large doses of TPM (80 mg/kg a day) or a combination of TPM (40 mg/kg) and VPA (300 mg/kg a day) significantly increased the risk of such adverse effects. GSH levels in the liver were significantly lower in the group taking large doses of TPM and the TPM+VPA group compared with the group taking small doses of TPM and the control group which was only given distilled water. Histopathological examination also revealed disseminated punctual necrosis, and as well lipid and degenerative changes in some hepatocytes.

TPM (40 and 80 mg/kg i.p.) had no effect on either rats' KA-induced status epilepticus or mortality but larger doses significantly reduced KA-produced lipid peroxidation (Kubera et al., 2004).

Treatment of diabetic mice with TPM, a potent mitochondrial carbonic anhydrazes (CA) inhibitor, prevented the oxidative stress caused by diabetes (Price et al., 2012). The authors studied the effects of pharmacological inhibition of mitochondrial CA activity on *streptozotocin induced-oxidative stress* and pericytes loss in the mouse brain. Pericytes are in immediate contact with endothelial cells and are vital for blood-brain barier integrity. These results provide for the first time evidence that inhibition of mitochondrial CA activity reduces diabetes-reduced oxidative stress in the mouse brain and rescuses cerebral policytes dropout. Mitochondrial CA may provide a new therapeutic targed for oxidative stress related impairments of the brain.

Anti-oxidant activity of TPM was shown also in vitro study (Cardenas-Rodrigues et al., 2013a). The results show that TPM displays scavenging capacity of superoxide, hydroxyl radical, hypochlorus acid, hydrogen peroxide, signled oxygen but not to peroxynitrite. Although TPM was less efficient than *nordihydroguaiaretic acid*, *dimethylthiourea, ascorbic acid, sodium pyruvate and glutathione* in its scavenging capacity. The authors conclude that anti-oxidant properties of TPM could explain it's the neuroprotective effect.

3.8. Valproic acid

In model of rat *cortical cell culture*, VPA was found to protect against the negative effects of oxygen stress (Wang et al., 2003). Administration of VPA for 7 days prevented lipid and protein oxidization anomalies and accumulation of free radicals. Short-term administration of VPA affects one or more of the neuroprotective processes.

Several mechanisms were suggested for VPA hepatotoxicity, however, most of them are associated with oxygen stress resulting in mitochondrial dysfunction. Rat liver mitochondria were obtained by differential ultra centrifugation and then incubated with different concentration of VPA (25-200μM) (Jafarian et al., 2013). The results showed that VPA could induce oxidative stress via rising in mitochondrial ROS, lipid peroxidation, mitochondrial membrane potential collapse, mitochondrial swelling and release of Cytochrome C. The authors found

that these effects were well inhibited by pretreatment of isolated mitochondria with *cyclosporin A* and *butylated hydroxytoluene.* The data show that VPA exerts mitochondrial toxicity by impairing mitochondrial functions leading to oxidative stress and Cytochrome C expulsion which starts cell death signaling (Jafarian et al., 2013).

3.9. Zonisamide (ZNS)

The major mechanisms of antiepileptic ZNS are inhibition of voltage-gated Na(+) channel, T-type voltage sensitive Ca(2+)channel, Ca(2+) relasing system and neuronal depolarization-induced glutamate release, and increased release of inhibitory neurotransmitters.

In the KA convulsion model in rats, pretreatment with ZNS led to increased anti-oxidant level in the hippocampus (Ueda et al., 2005). The study was performed in freely moving rats using in vivo microanalysis and electron paramagenetic resonance spectroscopy. In the authors' opinion, ZNS has neuroprotective properties against free radicals.

Neuroprotective properties of ZNS also have been shown *in iron-induced epileptogenic foci* in the rat brain (Komatsu et al., 2000). The authors found that the level of 8-hydroxy-2. deoksy-guanosine (8-OHdG), which is used as a marker for oxidative DNA damage, increased 15 min after ferric chloride solution injections reaching maximum after 30 min. ZNS prevented the increase of the 8-OHdG within 30 min after iron solution injection. This effect may be due to the ZNS antioxidant activity and might be interesting to use it in prevention of posttraumatic epilepsy development due to blood extravasation and epileptogenic affect of free ferrum.

3.10. Old and new AEDs

Pavone and Cardile (2003) studied effects of AEDs on oxygen stress in an *astrocyte culture from rats.* Selected list of studied variables includes: lactate dehydrogenase (LDH) and glutamine synthtase (GS) levels, ROS production, lipid peroxidation and DNA fragmentation. Drugs such as CBZ, TPM and OXC caused oxygen stress whatever their dose. Gabapentin (GBP), LEV, LTG, tiagabine (TGB) and ZNS on the other hand, caused no significant metabolic changes in large or small doses. Cortical astrocytes seem to tolerate this latter group of AEDs better than the former ones.

Animal models of seizures, in particular, epilepsy and oxidative processes are useful for developing antiepileptic drugs (Majkowski et al., 2011; Rowles and Olsen, 2012). However, one of the main problems in transferring animal-based data to humans is to define effectiveness of a dose.

4. Aging and anti-oxidants of omega-3 fatty acid

Omaga-3 fatty acids supplementation was added to standard laboratory food for 6 weeks to aged 24 months old Wistar rats (Avramovic et al., 2012). The results showed befeneficial effects of omega-3 fatty acid on the brain cortex with increased SOD activity and decreased lipid peroxidation in contrast to the control grup. The changes in oxidative/antioxidative balance

are due to effects of eicosapentanoic acid (EPA) and decosahexanoic (DHA) on lipids and enzyme of anti-oxidative system. Aging as a biophysiological process could be influeced by EPA and DHA.

5. Course of seizures and oxygen stress

An interesting effect of *prolonged seizures* (PS) versus *repeated-seizures* (RS) in one day old chicken *in pilocarpine-induced status epilepticus* has been reported (Tsai et al., 2010). In the PS group excessive levels of ROS and MDA, and lower activities of SOD and catalase were found when compared to the RS group ($p< 0.05$). This was associated with neuronal death in the PS group ($p < 0.01$). ROS, mitochondrial dysfunction and DNA damage played important roles in pathophysiology of the immature brain to PS-induced damage. The authors suggest that replenishment of SOD and catalase activities might be useful in protecting neurons against seizure-induced damage.

6. Sleep deprivation and oxygen stress

It is well known that *sleep deprivation* in epileptic patients may provoke seizures. The mechanism underlying this relation is unknown. Hirotsu et al. (2013) investigated changes in gene expression related to reactive oxygen species and NO production in the frontal cortex of a rodent model of temporal lobe epilepsy (PILO) in rats with *pilocarpine-induced status epilepticus* after paradoxidal sleep deprivation (PSD 24h) and total sleep deprivation (TSD 6h). The data show that PILO rats had increased NOX-2 expression and decreased SOD expression independent of sleep. Higher NOX-2 expression was observed only in PILO rats subjected to the control condition and TSD 6h. CAT expression in the frontal cortex of PILO rats submitted to PSD 24 h was reduced compared to that of PILO rats that were not sleep-deprived. In the authors opinion, the molecular changes in the frontal cortex following sleep deprivation suggest a machanism via oxidative stress.

7. Oxygen stress and AEDs in human epilepsy

AEDs have various and equivocal effects on the oxidization processes (Hamed and Abdellach, 2004; Hamed et al., 2004; Devi et al., 2008; Ounjaijean et al., 2011; Rowles and Olsen, 2012; Azam et al., 2012; Naziroglu and Yürekli, 2013;Rodriguez et al., 2013). Generally, epilepsy and prolonged AED treatment (CBZ, PHT and VPA) results in increased Zn, Ca, Na, MDA and GSH-Px. Usually, anti-oxidant trace elements' levels such as Se, Cu, Zn, Mg, and total antioxidant capacity and ceruloplasmine are low in the blood of epileptic patients. New AEDs are more prone to restore anti-oxidant system in brain. In untreated patients with epilepsy, uric acid (a powerful free oxygen radical scavenger) was elevated but the total anti-oxidant capacity

in the serum was reduced, suggesting that different anti-oxidants have different activities in this epileptic group. It was found that some nutrients may have a positive effect on the reduction of seizure frequency and may improve cognitive functioning in patients with epilepsy (vitamin B_1, B_6, vitamin E, Mg, Mn, taurine, glycine, omega-3 fatty acids). In order to prevent the negative effects of AEDs, prophylactic or therapeutic replenishment of folic acid, vitamin B6, vitamin D, and L-carnitine may be advisable. In some cases melatonin may reduce seizure frequency. However, supplementation can very seldom substitute AEDs completely (Gaby, 2007). Casuistic reports may be observed e.g. in pyridoxine (vitamin B6) deficiency seizures, usually, in neonates and infants.

7.1. Carbamazepine

It has been shown CBZ-induced toxic effects in erythrocytes in epilepsy treated patients (Ficcara et al, 2013). However, some beneficial effects of CBZ has been evident as an increased release of ATP and NO derived metabolites from erythrocytes to lumen, leading to an increased NO pool in the vasculature.

7.2. Oxcarbazepine

Bolayir et al. (2004) studied the effect of OXC on anti-oxidative processes in 13 adult patients with epilepsy prior to monotherapy and after 1 year of OXC monotherapy; 15 healthy controls were included in the study. Lipid peroxidation activity, SOD, GSH-Px and catalase in the red blood cells were measured. The patients had significant differences in level of GSH-Px and SOD after 1 year of treatment compared with pre-treatment levels. MDA level was also significantly different compared with the control group and the pre-treatment assessment. These findings suggest that the anti-oxidation systems in patients treated with OXC were negatively affected after 1 year of treatment.

7.3. Phenytoin

Mahle and Dasgupta (1997) found a significant increase in blood serum concentration of lipid hydroperoxydase in PHT monotherapy compared with the control group. Total blood serum anti-oxidant capacity was lower in patients than in healthy controls. These authors found a weak correlation between lipid hydroperoxidase concentration, triglyceridemia and cholesterol levels in the serum of patients with epilepsy.

The negative consequences of oxygen stress in serum were significantly larger in women with epilepsy treated with PHT monotherapy (N=20), than in healthy women (N=20) and women with untreated epilepsy (N=12) (Liu et al., 1997). For PHT treated epileptic woman, the MDA serum level was significantly increased ($p< 0.05$), and GSH level – significantly decreased ($p< 0.005$). This was not observed in untreated epilepsy and in healthy control women. The abnormal metabolism of S-Cu, CuZn-SOD, and GSH was highly involved in the PHT-mediated toxicity. According to the authors, addition of glutathione to PHT treatment – resulting in modification of the activity of CuZn-SOD enzymes and reduction of copper absorption during pregnancy, may prevent the incidence of the foetal phenytoin syndrome.

7.4. Phenytoin and carbamazepine

Comparative studies of the effects of PHT and CBZ monotherapies found a significant increase in the blood serum level of MDA and CuZn-SOD, and a significant reduction of glutathione in a patients treated with PHT compared with a healthy control group and a group with untreated epilepsy (Liu et al., 1998). No differences were found for CBZ except for a slight increase in CuZn-SOD activity. All in all, CBZ caused fewer interferences with antioxidant activity, lipid peroxidation and the level of trace elements (Cu, Zn).

7.5. Topiramate and Selenium

Neuroprotective effects of TPM and Se deficiency play a important role in pathophysiology of seizures in epileptic patients. Demirci et al., (2013) studied effect of Se and TPM in neural PC 12 cell by evaluating Ca(2+) mobilization, lipid peroxidation and anticonvulsant levels. The results showed that Se induced protective effects on oxidative stress in PC12 cells by modulating cytosolic Ca(2+) influx and anti-oxidant levels. TPM modulated also lipid peroxidation and glutathione and vitamin C concentrations in the cell system.

7.6. Valproic acid

VPA is frequently used in epileptic patients, mainly, in young children. In some forms of idiopathic epilepsy (myoclonic and absences) is the most effective drug, however, its use is limited due to adverse events related to dose and duration of treatment. Recently, Zhang et al. (2011) studied the VPA influence on neutrophils' oxidative metabolism and oxidant status. The study were performed on 26 newly diagnosed epileptic children with idiopathic epilepsy and 30 healthy children were included as control group. The authors performed the study before, after 6 and 12 months of VPA treatment. MDA, superoxide dismutase, catalase and glutathione peroxidase were measured in plasma. The results showed that VPA may activate neutrophils and cause oxidative stress, moreover, prolonged treatment may aggravate it. Multiple regression analysis showed that the time of treatment and the activation rates of neutrophils were indicator which has positive correlation with the levels of plasma MDA and that SOD activities were inversely correlated with MDA levels.

VPA can sometimes be related to allergic idiosyncratic hepatopathy, a rare condition but more frequent in children under 2 years of age taking more than one AED. The mechanism of toxic hepatopathy is unknown but it has been suggested that it is caused by oxygen stress which leads to excessive ROS production and reduction of total anti-oxidant capacity (Chang and Abbott, 2006; Sabayan et al., 2007). Therefore, specifics which reduce oxygen stress may protect against toxic hepatopathy in patients taking VPA. Sabayan et al. (2007) have hypothesized that garlic (allium) preparations may prevent this liver damage by removing free radicals and preventing the reduction of glutathione activity which accompanies treatment with VPA.

VPA used in monotherapy for 60 days in 50 children with epilepsy (mean age 8.5 ± 3.6 years) led to liver dysfunction and free radicals which seems to produce DNA oxidation injury in the liver cells not excluding neurons (Schulpis et al., 2006). The general oxidation state, measured by the level of 8-OHdG, depended on the VPA dose. A linear relation was found between VPA serum level and degree of lipid peroxidation. In a group of children with a mean VPA

concentration of 114 ± 9.7 μg/ml, peroxidation was significantly higher than in a control group of children with a mean VPA concentration of 81.0 ± 8 μg/ml. Free radicals caused DNA oxygen injury due to significant increase in the serum level of 8-OHdG. In the authors' opinions, 8-OHdG may be a good biological indicator of increased risk of VPA-related cell degeneration.

Other authors have also found a linear relation between lipid peroxidation and VPA levels in the plasma of patients with epilepsy (Martinez-Ballesteros et al., 2004). They measured lipid peroxidation spectrofluorometrically, before and after Fenton reaction evocation, in 76 patients and 4 healthy controls. Interestingly, lipid peroxidation was higher in patients with partial epilepsy than in patients with generalized epilepsy, and higher in women than in men. *The same sex-related differences in oxygen stress effects were found in PHT-treated epilepsy (Liu et al., 1997), in hyppocampal slices in patients (Li et al., 2005), in the mouse PTZ-seizure model (Oztas et al., 2007). In PTZ-seizure model in Wistar rats, seizure were more severe in females; moreover pretreatment by a nitric oxide syntase (NOS) inhibitor N-omega-nitro-L-arginine-methylester, completely prevented seizures in male rats, whereus increased severity frequency and duration in female rats, on the other hand, pretreatment by NO precursor sodium-nitroprusside increased seizure severity in male, and decreased in females (Uzum et al., 2005).*

The alteration of iron homeostasis and oxygen stress in 24 young adult epileptic patients treated with VPA monotherapy revealed a significant decrease of serum anti-oxidant levels while anti-oxidant enzyme activities increased (Ounjaijean et al., 2011). An interesting association was found between the daily dose of VPA and the concentration of non-transferrin bound iron (NTBI) ($p=0.009$), MDA ($p=0.022$) and Zn ($p=0.009$). Thus, the study has shown that VPA treatment in epilepsy patients contributes to the metabolism of iron, leading to the formation of NTBI and increase of oxidative stress. The alteration of iron homeostasis and oxygen stress product were not observed in the control group comprising of 24 sex and age-matched healthy volunteers.

In a recent study, Plonka-Półtorak et al. (2011) found that in long-term VPA monotherapy in adult young epileptic patients (and 21 healthy controls) frequency of seizures and duration of VPA therapy (7-14 years) were associated with changes of oxidative/antioxidative balance. The activity of erythrocyte SOD was higher in patients treated for a longer period (7-14 years) in comparison to controls ($p=0.001$) and patients with a short period of time ($p < 0.001$). Patients with uncontrolled epilepsy exhibited higher serum Zn than seizure-free patients ($p=0.041$). The most relevant parameters for anti-oxidative defence mechanism were plasma SOD, ferric reducing ability of plasma, uric acid and Zn.

It is interesting that commonly reported VPA oxidative stress effect occurs in overweight children (Verrotti et al., 2008). The study was performed on 31 epileptic children before and after 1 year of therapy with VPA. The control group consisted of 31 sex-, age-and BMI-matched healthy controls. In the authors' opinion, increase in the levels of oxidant markers (MDA) ($p < 0.001$) and lower level of antioxidant (vit. E, $p< 0.001$), probably caused by obesity, might contribute to endothelial dysfunction and arteriosclerosis in later life.

Very interesting effect of the mood stabilizing VPA on decrease of ROS in schizophrenic patient was reported (Paulsen Bda et al., 2012). Studies on schizophrenia have shown altered cell respiration and oxidative stress response, however this knowledge is acquired mainly from

postmortem brain analyses or from nonneuronal cells. The authors reported very interesting results that neural cells – derived from induced pluripotent stem cell generated from skin fibroblasts of a schizopherenic patient – presented a twofold increase in extra-mitochondrial oxygen consumption as well as ROS elevated levels compared to controls. The difference *in ROS levels was reverted by the mood stabilizer valproic acid.*

7.7. Valproic acid and carbamazepine

A comparative study of the effect of two-year VPA and CBZ monotherapies on changes in the antioxidant system in children with epilepsy found significant differences in the effects of both AEDs (Yuksel et al., 2001). The levels of GSH, GSH-Px, red blood cell SOD and serum lipid peroxidation were measured. They studied two groups: 1) 25 healthy children and 2) 27 children with epilepsy untreated prior to the study onset, 14 of whom were treated with VPA and 13 with CBZ. Treatment lasted for 2 years. Laboratory tests were conducted in treatment months 13 and 24. The anti-oxidant systems in children taking VPA for 2 years were more altered than the anti-oxidant systems of children taking CBZ.

Another comparative study of CBZ and VPA in children found no differences in the serum concentrations of Cu, Zn, Mn, Se and Mg (Kurekci et al., 1995). The only difference was found for GSH-Px activity which was significantly higher in the VPA group. No differences were found in SOD levels.

7.8. Valproic acid, carbamazepine and phenobarbital

A more recent comparative study yielded slightly different results of the effect of VPA, CBZ and PB monotherapies on the oxidation and anti-oxidation systems in 122 children – including healthy controls, untreated epileptic patients and epileptic patients treated with VPA, PHT, PB (Avcicek and Iscan, 2007). The authors found that the level of total anti-oxidant capacity in serum was significantly reduced in the group with untreated epilepsy compared with the healthy group. Level of peroxidation was significantly elevated in both the untreated group with epilepsy and the CBZ treatment group compared with healthy controls. The pattern of results was similar for the children treated with PB and the control group. According to the authors, children with epilepsy are at risk of oxygen stress due to seizures and AEDs. Their oxidation and anti-oxidation processes are unbalanced. VPA restores this balance more effectively than CBZ or PB.

8. Preventing oxygen stress in human AED treated epilepsy

8.1. Melatonin

Numerous studies of melatonin conducted over the last 30 years have confirmed that this neurohormone is susceptible to circadian rhythms, has anti-oxidant properties and modulates immunological activity (Harderland et al., 2006). Melatonin affects the blood platelets and prolongs their life. It is transported by the platelets to all the body tissues. Thanks to its

lipophilic function, it crosses the cell membranes easily, regulates blood-tissue exchange and interacts with the endothelial cells. Platelets can behave like mobile and wandering serotonergic and/or melatonergic elements, comparable with cerebral neurotransmitter release (Di Bella and Gualano, 2006). Melatonin is a free radical scavenger devoided of pro-oxidative activity (Tan et al., 2002) and therefore it reduces oxygen stress and prevents excessive excitotoxic effects arousal from injured neurones in various animal and human models.

In epilepsy patients melatonin is reduced compared with controls and is increased threefold following seizures (Bazil et al., 2000) Single evening dose of 5-10 mg melantion can exert a positive effect on the frequency of epileptic seizures in children with sleep disturbances (Fauteck et al., 1999).

The neuroprotective effect of melatonin has been confirmed in a randomized, double blind trial of children with epilepsy receiving VPA monotherapy (Gupta et al., 2004). The authors administered VPA+melatonin to 15 children and VPA+placebo to 14 children for 14 days. Post-test glutathione reductase (GSSG-Rd) levels were significantly higher ($p=0.05$) in the VPA +melatonin group and the percentile difference in the values of this enzyme was also significant ($p=0.005$). Thus, melatonin possesses anti-oxidant, antiexcitotoxic and free radical scavenging properties in the central nervous system.

Gupta et al. (2006) found that CBZ or VPA administered in monotherapy to 22 children with epilepsy had differential effects on melatonin serum levels. In both groups the endogenous and exogenous melatonin was measured 30 minutes after administration. The serum median level of melatonin was higher in the CBZ group 165 pg/ml (range 50-350) than in the VPA group, it was 78 pg/ml (range 13-260). In the authors' opinion these range differences in level of melatonin could be attributed to the different effects of these two AEDs, additive increase in ROS due to disease combined with CBZ, or possibly to differences in melatonin kinetics in conditions of oxidative stress.

8.2. Selenium

The neuroprotective effect of selenium in epilepsy is related to selenoproteins which are antioxidants (Atroshi et al., 2007; Naziroglu, 2009). Selenium insufficiency has been found in young children with severe mental retardation and drug-resistant epilepsy (Ramaekers et al., 1994). Oral administration of selenium (3-5 μg/kg m.c.) reduced seizure frequency, improved EEG recordings and normalized liver activity.

In another study, serum level of selenium in 30 patients with intractable epilepsy was also lower (66.88 ng/ml ± 17.58) than in healthy controls matched for age, socio-economic status and place of residence (85.93 ng/ml ± 13.93) ($p<0.05$) (Ashrafi et al., 2007). However, low selenium levels in serum did not correlate with the measured risk factors for drug-resistant epilepsy: with age of onset, infant seizures, neurological disorder or etiology of epilepsy.

It is suggested that blood GSH-Px activities could be a reliable indicator of selenium deficiency in patients with epilepsy (Naziroglu, 2009).

8.3. Plants

Assuming that AEDs can trigger free radical production and lipid peroxidation, Hung-Ming et al. (2002) studied TW970, a modified version of the Chinese herbal specific chaihu-longu-muli-tang which has antiepileptic and antioxidant properties. The TW 970 was administered for 4 months to 3 groups of adults: 1) 20 patients with drug-resistant epilepsy (at least 4 seizures a month); 2) 20 patients with mild epilepsy (fewer than 4 seizures a month), and 3) a control group of 20 healthy adults matched for age. The patients were tested prior to the introduction of TW970 and four months after introduction. In the resistant group, seizure frequency dropped from 13.4 ± 3.4 to 10.7 ± 2.5 a month but the difference was not significant ($p=0.084$). Prior to TW970 introduction, the resistant epilepsy group had significantly higher lipid peroxidation, increased MDA and CuZn-SOD activity, including reduced GSH, compared with the healthy control group. After 4 months of TW970 treatment, levels of MDA and CuZn-SOD normalized in the resistant epilepsy group whereas no significant changes in parameters were found in the mild epilepsy group, either prior to or following TW970 therapy. The authors suggest that TW970 may reduce seizure frequency in resistant epilepsy and that anti-oxidants may be responsible for this effect.

Japanise kampo (TJ-960) traditional herbal medicine was used for treatment of epilepsy (Hamada et al., 1993). The authors identified baicalein as one of the several components the most potent scavenger for radicals in $FeCl_3$ induced epilepsy model in rats. It is suggested that baicalein action is based upon radical quenching and anti-oxidant effects.

Many Native American plants are valued by local medical practitioners for their positive effects on health and a number of diseases, including epilepsy. *Celastrus paniculatus L.* (CP), *Picrorhiza kurroa (PK)* and *Withania somnifera L. (WS)* were investigated for their free radical scavenging capacity (Russo et al., 2001). It has been observed that methanolic extracts of these plants are dose-dependent free radical scavengers, and that they prevent DNA injury due to oxygen stress. PK extract had a more powerful effect than CP or WS. These favourable biological properties, reported in clinical and animal studies, have been attributed, at least in part, to their anti-stress, immune-modulating, anti-inflammatory and anti-aging effects. A similar anti-oxidant effect was observed using another plant in Ayurvedic medicine, *Bacopa monniera L.* (BM), which has free radical scavenging capacity (Russo et al., 2003).

8.4. Nootropics and anti-oxidants

It was reported that nootropics (phenotropil) and antioxidants (mexidol) potentiate AEDs in posttraumatic epilepsy treatment (Savenkov et al., 2013).The authors observed in 75 patients significant reduction of epileptic seizure frequency, decrease of epileptic changes in the EEG, improvement of cognitive function and quality of life. Coherent indicators of slow wave-activity were observed after treatment. The authors recommended to use mexidol and phenotropil with AEDs for complex treatment of posttraumatic epilepsy.

When interpreting clinically, these and the highlighted earlier results, one needs to be careful because the relationships in disease as heterogeneous as epilepsy are complex and multifac-

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torial. Moreover, the results, usually are not conducted according to rules of evidence based medicine.

9. Drug-resistant epilepsy and polytherapy

Drug-resistant seizures force physicians to use polytherapy with various AEDs. Polytherapy increases the production of free radicals and disturbs mineral balance to a greater extent than monotherapy, leading to increased oxygen stress. Both, increased free radical production and inhibition of the enzymes which remove scavengers, lead to adverse reactions and aggravation of the morbid process (Maertens et al., 1995; Hamed et al., 2004).

Patients with chronic epilepsy and long-term AED therapy are at greater risk of atherosclerotic changes in the arteries through complex molecular mechanisms that promote atherogenesis (Hamed and Nabeshima, 2005). Metabolic dysfunctions in these patients have been attributed to altered homocysteine, lipid and lipoprotein metabolism and uric acid.

In relevant study, relationship between the carotid artery intima-media thickness (CA-IMT) and lipid profile (MDA, oxidised LDL, total anti-oxidant capacity, GSH-Px and uric acid) were assessed in 225 adult patients with epilepsy (and 60 control subjects) (Hamed et al., 2007). Compared to the control group, the CA-IMT of treated and untreated patients common carotid artery, bifurcation area and internal carotid arteries were significantly thickened in 51.1%, 73.3% and 43.6% of patients, respectively. The study supports the opinion that in patients with epilepsy, various risk factors and CA-IMT become worse, which could be attributed to epilepsy itself and/or AEDs. According to the authors, these dysfunctions are indications for routine anti-oxidant multivitamin supplementation (folic acid, vitamins B12, B6, C, E, and beta-carotene). The protective, anti-atheromatic effect of vitamins is based on their anti-oxidant and anti-inflammatory properties. Tupeev et al. (1993) found a positive effect of prolonged vitamin E treatment (600 mg/day) in patients with generalized seizures: seizure frequency was reduced, EEG improved and anti-oxidant activity increased.

In other research highlighted earlier, increased lipid hydroperoxidase concentrations were weakly correlated with the risk factors for vascular changes (triglyceridemia, cholesterolemia) (Mahle and Dasgupta, 1997).

10. The effects of surgery on oxygen stress in AED-resistant temporal lobe epilepsy

López et al. (2007) studied the activity of anti-oxidant enzymes (SOD, catalase and GSH-Px) and markers of oxygen stress induced molecular neuronal injury (MDA and ROS) before and at various times after epileptic focus resection in 9 therapy resistant patients; a control group consisted of 32 healthy individuals. All the studied variables normalized postoperatively except SOD activity.

Several earlier interesting observations seem to be related to these findings to a certain extent. Turkdogan et al. (2002) found that increased lipid peroxidation in plasma may be causally related to the presence of abnormal structural changes as assessed by brain magnetic resonance (MR), rather, than to the treatment of epilepsy with focal or generalized epileptic discharges in the EEG, duration of epilepsy, or seizure frequency (more or fewer than 1 seizure a month). The authors found an increase in plasma lipid peroxidation in 52 children with epilepsy, treated with one or more AEDs and abnormal brain MR, compared with 16 healthy children (the difference was significant, $p<0.05$). No significant differences in anti-oxidant enzymes were found in either group. Patients with well-controlled seizures and children with drug-resistant seizures but normal MRs had a higher SOD activity than children in the control group ($p<0.05$). GSH-Px (an antioxidant) activity was not significantly different in the children with epilepsy compared to the control group.

This interesting and heterogeneous picture of enzymatic activity in children with epilepsy and control children suggests that the relationship between various laboratory tests and numerous variables associated with the heterogeneity and treatment of epilepsy are very complex. Although the authors took seizure frequency into consideration, they did not state when blood tests were undertaken relative to seizure occurrence or to an imminent seizure, nor do they report EEG epileptic activity prior to the blood test. This makes it very difficult to monitor the causal relationships between the results of the various tests and their epileptic correlates.

Study of oxygen stress markers in the neocortex of drug-resistant epilepsy patients submitted to epilepsy surgery, supported human findings being in agreement with those found in animal models (Rumia et al., 2013). The concurrent increase in catalase ($p<0.01$) and decrease in GPx ($p<0.05$) together with unchanged SOD levels, suggests catalase as the main anti-oxidant enzyme in human epileptic cortex. The substantial increase in the levels of oxidants – 0_2 (-) and 8-oxo-dG in epileptic patients – in comparison with non-epileptic cortex samples – supports a connection between chronic seizures and ROS-mediated neuronal damage.

11. Conclusions

1. It seems that oxygen stress and its products may play an essential role in earliest stage of epileptogenesis. However, antioxidants as well as antiepiletic drugs do not prevent epileptogenesis. In seizure or epilepsy animal models, at best, both antioxidants or antepileptic drugs can delay the first seizure occurrence and diminish seizures' severity.

2. Research on animal models and patients with epilepsy suggests that epileptic seizures, epileptiform discharges and some AEDs (especially polytherapy) may produce oxygen stress and have a negative effect on the oxidation – anti-oxidation balance.

3. AEDs and the drug dosages have differential effects on oxygen stress. In epileptic patients (and in animal models of seizures) CBZ, OXC, PB, PHT and VPA produce oxygen stress. In experimental models of seizures, the majority of new generation AEDs has no or minor effects on oxygen stress; usually they have a more favourable effect on the oxidation and

anti-oxidation enzyme balance, trace elements and electrolytic homeostasis than the odler AEDs.

4. Neuroprotectors (trace elements, vitamins and other antioxidants) help to reduce seizure-induced oxygen stress and therefore it is suggested that they should supplement AED treatment. It may be expected that the long-term AED adverse events will be diminished by combination of AED with antioxidants. However, one of the main problems is to find appropriate effective dose and kind of antioxidants restoring equilibrium between oxidative and anti-oxidative processes.

5. Since some AEDs, seizures and epileptiform discharges can lead to oxidation – anti-oxidation imbalance, it seems reasonable to develop new strategies that diminish negative effects of oxygen stress properties in current epilepsy treatment. New AED synthesis, without oxidative effects, would provide better quality of epilepsy medication.

6. Further studies of oxygen stress effects are needed to understand better the mechanisms of protective effects of anti-oxidants.

7. Research on the role of oxygen stress opens a new chapter in epileptology with a hope of prevention of biochemical proceses leading to epileptogenesis, better seizure control and diminish cognitive function impaiment.

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