ejpmr, 2016,3(10), 416-423.

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

OXIDATIVE STRESS AND EPILEPSY: A REVIEW

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Article Received on 21/08/2016 **Article Revised on 11/09/2016** **Article Accepted on 01/10/2016**

ABSTRACT

Epilepsy is a serious neurological disorder which involves the abnormal discharges of electrical activity in the brain cells, giving rise to abnormal behaviours such as involuntary muscle movements, unusual perceptions or a disturbed level of consciousness. Epilepsy has been considered as a relatively common condition that can affect anyone at any age. The oxidative stress resulting from excessive free-radical generation is likely implicated in the initiation, development and progression of epilepsy. The present review article discusses about the probable role of oxidative stress in epilepsy. Moreover, strategies to prevent the development and progression of epilepsy have been conferred in the review.

KEYWORDS: Epilepsy, Oxidative Stress.

INTRODUCTION

Epilepsy has been considered as one of the most common serious neurologic disorders worldwide. About 50 million people have epilepsy worldwide and 90% of them are from developing countries.[1-2] The word "epilepsy" is derived from Latin and Greek words meaning "seizure" or "to seize upon" and hence epilepsy is generally defined as a tendency to the recurrent seizures.[3] The pathogenesis of epileptic seizures involves altered brain excitability due to the blemish in mitochondrial respiratory chain complexes, synapses and neurotransmitter receptors.[4-5] Epilepsy is a highly prevalent brain disorder in which oxidative stress is regarded as a possible mechanism involved in the development and progression of epilepsy in the patients presented with it.[6] Various causes have been reported which leads to oxidative stress in epilepsy like impairment of antioxidant systems, mitochondrial dysfunction, redox metals and arachidonic acid pathway.[6-8] Also, various experimental models have been designed for the study of the evolution, propagation and pathological consequences of epileptic discharge like kainic acid (KA)-induced seizures model, pilocarpine-induced seizure model, pentylentetrazole (PTZ)-induced seizure model and trimethyltin (TMT)-induced seizure models.[9-10] These experimental animal models have investigated for the evaluating the role of various antioxidant drugs in modulating the oxidative stress markers. A number of antiepileptic drugs and chemicals have been investigated to substantiate their probable effect on epilepsy like Neuropeptide S, curcumin, berberine, montelukast, melatonin, lycopene and sodium valproate.[11-13] The present review has been designed to highlight the probable role of oxidative stress in epilepsy and the strategies to prevent the development and progression of epilepsy.

EPILEPSY: ETIOLOGY AND CLASSIFICATION

Epilepsy is referred to as a common, sometimes chronic condition with physical risks alongwith psychological and socio economic consequences that impair the quality of life. Epilepsy can be regarded as idiopathic or symptomatic.[6] It has been estimated that around 50% of epileptic cases are symptomatic or acquired and thus, is associated with a previous neurological insult.[14] Also, the acquired form of epilepsy does not have a genetic link and progresses with age. However, the idiopathic epilepsy is mainly due to genetic causes and developmental brain disorders, mainly affecting mitochondrial and ion channel function. A number of genetic factors have been reported to contribute to epileptic seizures in idiopathic epilepsies by increasing neuronal excitability. The pathogenesis of epileptic seizures may be attributed to the altered brain excitability due to defect in mitochondrial respiratory chain complexes, synapses, and neurotransmitter receptors. Epilepsy has been documented to arise by a number of genetic and acquired factors. However, the etiology of epileptic seizures varies among various age groups, patient groups and geographical locations. Surprisingly, the congenital and perinatal conditions have been the most common causes of early childhood epilepsy onset; whereas epilepsy is found to be due to external non-genetic causes in adults.[7]

The epilepsy has been known to possess phases that can be studied under three main headings which include the acute phase or injury phase; the latency phase or epileptogenesis; and spontaneous recurrent seizures phase or chronic epilepsy.[11,15] In acute phase, many types of brain lesions have been known to initiate the process of epileptogenesis in acquired epilepsy. It has been reported that tumours, infections, status epilepticus, childhood febrile seizures, stroke, hypoxia and other neurodegenerative diseases increase the incidence of acquired epilepsy.[14-15] The latent phase or epileptogenesis is referred to as a process in which an initial central nervous system insult leads to the development of the epileptic condition that may take years after the initial insult, which suggest that development of the epileptic condition involves progression of changes in response to the initial insult.[7,16] It has been documented that the neuronal cell death acts as the propagating factor leading to the epileptic condition. It has been reported that seizures lead to neuronal cell death by various dynamic processes like genetic factors, excitotoxicity induced mitochondrial dysfunction, altered cytokine levels, oxidative stress, and activation of some late cell death pathways.[17] However, it was suggested that oxidative damage and consequent neuronal cell death contribute to epileptogenesis and to initiation and propagation of spontaneous recurrent epileptic seizures by common pathogenic processes.[18] The enhanced ROS production has been documented to induce a cascade of cellular and molecular changes leading to neuronal death. In recurrent phase, the excessive ROS production leads to increased intracellular concentration of calcium ions whose concentration reach high levels leading to the occurrence of neuroplasticity changes in the brain neurons, which results in necrosis and apoptosis.[11,19] Moreover, the higher calcium concentration maintains the spontaneous recurrent seizures in the epileptic neurons, which further alters the neuronal excitability leading to the phases of chronic epilepsy. In addition, the increased intracellular calcium concentration affects many cell physiological processes, like gene transcription, protein expression, neurogenesis and neuronal sprouting.[20-22]

EXPERIMENTAL MODELS OF SEIZURE-INDUCED OXIDATIVE DAMAGE

A number of experimental models have been designed and developed in order to study the development, propagation and progression of epileptic discharge like KA-induced seizures model, pilocarpine-induced seizure model, PTZ-induced seizure model and TMT-induced seizure models.[9-10] These experimental animal models have investigated the probable role of the antioxidant drugs in modulating the oxidative stress markers.

1. Kainic acid (KA)-induced seizures

This has been well accepted that KA-induced seizure model is particularly useful for the study of the evolution, propagation and pathological consequences of epileptic discharge in the limbic system. It has been demonstrated that the activation of the KA subtype of ionotropic gluatamate receptors results in sustained epileptic activity in hippocampus.[23] KA has been known to increase the ROS production, mitochondrial dysfunction and apoptosis in neurons in many brain regions, particularly in the dentate hilus and hippocampal regions of CA1 and CA3. It was reported that the KA resulted in the elevation of protein oxidation and lipid peroxidation in the hippocampus, leading to neuronal damage and death in vulnerable brain regions.[24] Moreover, the KA-induced seizures leads to excitotoxicity by a mechanism involving oxidative stress induced by mitochondrial production of superoxide radicals that oxidize mitochondrial proteins, DNA, and lipids; resulting in cell damage.[25] Also, the KA exposure has been noted to significantly increase the production of malondialdehyde (MDA) and 4-hydroxy-alkenals, suggesting an increase in lipid peroxidation.[26] Further, the systemic administration of KA showed a significant decrease in reduced form of glutathione (GSH) levels in the hippocampus; evidencing the potential of KA in inducing the epileptic seizures.[7,27]

2. Pilocarpine-induced seizures

Another model for the induction of epileptic seizure in experimental animals is the pilocarpine-induced seizure model.[28] The mechanism of pilocarpine-induced neurotoxic seizures is attributed to the pathological increases in neuronal lesions in response to enhanced production of reactive oxygen species (ROS). Also, the pilocarpine-induced seizures lead to the formation of lipid peroxidation and nitrite in the hippocampus, striatum and frontal cortex, causing the neuronal damage.[29] The pilocarpine-induced seizures have been known to produce several changes in variables related to the generation and elimination of oxygen free radicals in adult rats.[7,30] It has been suggested that the factors contributing to pilocarpine-induced seizure include increase in GSH concentration, lipid peroxidation and nitrite content.[31]

3. Pentylentetrazole (PTZ)-induced seizures

PTZ, a selective blocker of the GABAa receptor chloride ionophore complex, has been widely accepted to show convulsant effects after repeated or single administration involving many neurotransmitter systems.[32] A significant decrease in GSH, GSSG, cysteine and protein thiols as well as increases in the protein carbonyl and protein disulfides levels were observed in the mouse cerebral cortex, after PTZ induced seizures, evidencing the potential of PTZ in inducing experimental epileptic seizures.[33] It has been shown that protein thiol levels were decreased in mouse hippocampus without significant alterations of GSH and GSSG, whereas protein disulfides, MDA and carbonyl levels were increased after single treatment with PTZ.[34] Also, it has been demonstrated that a single convulsive dose of PTZ showed significant changes in many parameters such as GABAa receptor density and function, whole brain hydroxyl radicals and free fatty acid and glutathione

peroxidase (GPx) activity in specific brain areas.[35] Moreover, acute PTZ-induced seizures caused a significant elevation of NO in the cerebral cortex. In addition, the PTZ-induced epileptic seizures resulted in the reduction of total superoxide dysmutase (SOD) activity and lipid antioxidant content in rat brain homogenates.[7,36]

4. Trimethyltin (TMT)-induced seizures

TMT-induced epileptic seizure model is another potential model for the induction of experimental seizures. It has been demonstrated that the systemic TMT administration in rats caused hippocampal damage in the CA3 region of the hippocampus.[37] In addition, the TMT has been shown to produce selective neuronal damage as produced by KA. The TMT-induced epileptic seizures have been shown to result in behavioral symptoms including seizures, related to their interaction with activators of the endogenous excitatory transmitter systems.[38] The TMT has been shown to increase the concentration of free intracellular calcium by promoting the influx of extracellular and the release of intracellular calcium.[7] It has been demonstrated that the systemic administration of TMT resulted in significant increase of the formation of hydroxyl radicals, MDA and protein carbonyl in the rat hippocampus, providing an evidence of the TMT model in inducing the experimental seizures.[39] Moreover, TMT has been reported to induce a persistent disruption of glutathione homeostasis; and decrease the GPx and GR protein expression levels in the rat hippocampus.[7]

OXIDATIVE STRESS IN EPILEPSY: PROBABLE CAUSES

There are a number of causes which leads to oxidative stress in epilepsy like impairment of antioxidant systems, mitochondrial dysfunction, redox metals and arachidonic acid pathway. It has been widely accepted that the seizure generation may be attributed to the homeostatic imbalance of antioxidants and oxidants. A number of experimental models have been developed in order to investigate the role of various endogenous antioxidants in response to oxidative stress. It has been reported that the oxidative stress leads to the impairment of endogenous antioxidant factors, which are involved in seizure generation. The superoxide radicals are highly reactive and initiate the pathological oxidative metabolism, leading to the oxidation of the macromolecules like DNA, lipids and proteins.[40] Moreover, the brain has been known to contain a large quantity of iron and copper, which catalyze the formation of hydroxyl radicals that induce lipid peroxidation, leadinf to the enhanced oxidative stress in the brain neurons. Additionally, the neuronal cell membrane has been documented to contain high levels of polyunsaturated fatty acids, which makes the brain cells susceptible to peroxidative damage leading to epileptogenesis.[41] It has been shown that the brain is rich in mitochondria, the principal source of cellular superoxide formed during respiration. It has been reported that the prolonged seizures result in sufficient superoxide production in order to overcome the endogenous mitochondrial antioxidant defenses by a cascade of events initiated by increased neuronal firing, excessive glutamate release, NMDA receptor activation, mitochondrial calcium influx, and increased ATP consumption. It has been shown that the mitochondrial aconidase inactivation and hippocampal neuronal loss induced by KA-administration were attenuated in mice, suggesting a role of mitochondrial superoxide-induced hippocampal damage in experimentally induced epileptic seizures.[42] It has been noted that mitochondrial dysfunction due to mitochondrial DNA mutation causes certain types of epilepsy. Also, it has been shown that the mitochondrial free radical generation and resultant dysfunction contribute to the epileptic seizures associated with mitochondrial diseases. The seizure activity is enhanced by processes that increase the mitochondrial free radical load like local infusion of reductive iron salts, mitochondrial toxins and age-related neuronal disorders.[43] It has also been demonstrated that KA-induced increased seizure susceptibility is associated with mitochondrial oxidative stress in the hippocampus, which further potentiates neuronal degeneration.[26] The redox metals have been shown to play a vital role in the pathogensis of epileptic seizures. It has been shown that microgliosis and neuronal loss in the hippocampus got reduced in KA-treated rats fed an iron-deficient diet, suggesting the involvement of iron in KA injury pathogenesis.[44] Moreover, the increased amounts of both ferric and ferrous forms of iron were found to be involved in the degenerating hippocampus after KA lesion, evidencing that increased iron in the hippocampus is a prominent source of free radicals in brain. Another study showed KA-induced increase in ferrous iron promoted the free radical mediated damage in the rat hippocampus.[45] Also, it has been shown that KA-induced upregulation of iron regulatory proteins in rat hippocampus enhanced the iron influx into neurons, contributing to the neuronal damage.[46] In addition, Selenium (Se) has been known to possess positive biological function in various aspects of human health. Various experimental studies have revealed that Se provided protection from ROS-induced cell damage.[7] It has been shown that the plasma Se and blood glutathione peroxidase activity were significantly reduced in children presented with inflexible seizures. Moreover, it has been shown that seizures were controlled in the children receiving supplemental Se. Furthermore, Se application normalized the electroencephalographic pattern and reduced cerebral damage in a model of ferrous-induced epileptic discharge. In addition, it was noted that Se-deficient rats were found to be more susceptible to KA-induced excitotoxicity and showed enhanced seizure rate compared to controls receiving Se-adequate diet.[47] This has been a matter of interest that arachidonic acid released from membrane phospholipids during seizures is implicated in the pathogenesis and progression of epilepsy. The spontaneous epileptic seizures in gerbils were attributed to an association with increased

prostaglandin D2 concentrations in the cerebral cortex, hippocampus and striatum and the presence of a leukotriene (LT)C4-in the cortex; which participate in seizure generation and propagation.[48] The involvement of arachidonic acid pathway in epileptic seizures can be evidenced by the fact that the formation of immunoreactive PGF2α and LT-like activity was detected in the brains of spontaneously convulsing gerbils. Moreover, PGs and hydroxyl eicosa tetranoic acids were found to be present in the rat brains following bicuculine-induced seizures, which further indicated the stimulation of cyclooxygenase (COX) and lipoxygenase (LOX) activit. Also, the genetically epilepsy-susceptible E1 mouse showed upregulation of COX-2 expression in the hippocampus after epileptic seizures.[49] COX-2 inhibitor Celecoxib was found to be effective in reducing electroshock-induced convulsions in rats, further evidencing the involvement of arachidonic acid pathway in the pathogenesis of epilepsy.[7,50]

CONTRIBUTION OF OXIDATIVE STRESS IN EPILEPSY

This has been widely accepted that epilepsy is a highly prevalent serious brain disorder and oxidative stress is regarded as a possible mechanism involved in the development and progression of epilepsy. The oxidative stress has been found to be associated with neuronal hyperexcitation and severe brain damage.[51-53] Also, kainic acid-induced seizures induced the metallothionein-I and heme oxygenase-I gene expression, suggesting a possible role of oxidative stress in epilepsy. Numbers of experimental and clinical studies have shown the probable role of oxidative stress in the development and progression of epileptic seizures. Role of ketogenic diet in the treatment of refractory epilepsy was investigated. The study showed that an increase in antioxidant activity with an approximately four-fold increase of glutathione peroxidase levels, revealing the fact that oxidative stress resulted in the refractory epilepsy in wistar rats.[54] Also, the participation of Cystatin B, an inhibitor of lysosomal cathepsins, the primary genetic cause of progressive myoclonus epilepsy. The role of Cystatin B in regulating the redox homeostasis and oxidative stress responses was investigated in transfected mice using a plasmid-based RNA method. The damage induced by exposure to oxidants was found to be reduced in the neurons transfected with Cystatin B, that was evidenced by a decrease in the percentage of cell death. It was proposed that the deficiency of Cystatin B in cerebellum made the animals more susceptible to oxidative damage, further confirming the role of oxidative stress in epilepsy.[51,55] Oxidative stress is implicated in the pathogenesis epilepsy was further confirmed by the study in which oxidative stress was investigated in immature 12-day-old rats after status epilepticus. The study showed significantly higher levels of superoxide anion in the hippocampus, cerebral cortex and thalamus of immature rats during status, that confirmed the role of oxidative stress in epilepsy.[56]

Apart from the experimental studies, the clinical studies also determined the participation of oxidative stress in epilepsy, specially patients with progressive myoclonus epilepsies, refractory status epilepsy in the presence of encephalopathy and refractory epilepsy.[57-58] The level of different antioxidant enzymes in the blood of patients with progressive myoclonic epilepsies was determined. The comparison of the antioxidant enzymes of the patients was compared with the healthy controls. It was found that the activity of Cu-Zn-SOD in the patients was lower than in controls that showed the probable role of oxidative stress in the patients presented with epilepsy. Moreover, study was conducted in a patient presented with acute encephalopathy with refractory status epilepticus, showing bilateral mesial temporal and claustral lesions that may be attributed to oxidative DNA damage.[59] The studies like EEG, cranial CT and MRI were used to determine the alterations in the brain. The EEG studies showed multifocal spikes tending to burst alongwith bilateral mesial temporal and claustral lesions in cranial MRI. This has been documented that oxidative DNA damage could be evoked within a few days after epilepticus status begins and neuroimaging changes may continue beyond some time. The researchers speculated that the augmented oxidative stress was associated with refractory epilepticus status in the patient, confirming the probable role of oxidative stress in epilepsy.[53] Another study was conducted in order to investigate the impact of the epilepsy surgery on the markers of oxidative damage in the serum of drug-resistant epileptic patients. The samples were used to determine the activity of antioxidant enzymes SOD, CAT and GPx, as well as MDA and advanced oxidation protein products (AOPP). The study showed altered antioxidant enzyme activity and increased levels of the oxidative damage marker in the patients in comparison to control subjects, that further evidenced the probable role of oxidative stress in epilepsy.[51,58]

NEWER ANTIEPILEPTIC APPROACHES DRUGS AND OXIDATIVE STRESS

The generation of seizures in epilepsy has been found to be associated with changes in the intracellular levels of antioxidants and oxidants. Numbers of experimental animal models have been designed and investigated for the evaluation of the role of various antioxidant drugs and other strategies in modulating the oxidative stress markers.[7] The antiepileptic drugs have been reported to impair the antioxidant systems and hence produce antioxidant effect. The ability of antioxidants to attenuate seizure generation and the accompanying changes in the oxidative burden further support an important role of antioxidants as having accepted antiepileptic potential.[51] A number of antiepileptic drugs are available in the market but new drugs and chemicals have been investigated to substantiate their probable effect on epilepsy. Patients presented with epilepsy are well-controlled with the use of anti-epileptic drugs available in the market. Treatment with curcumin, Nigella sativa oil (NSO) or valproate showed amelioration of most of

the changes induced by pilocarpine and restored Na^+, K^+-ATPase activity in the hippocampus to control the levels. The study reflected the promising anticonvulsant and potent antioxidant effects of curcumin and NSO in reducing the oxidative stress, excitability and the induction of seizures in experimental model of epilepsy.[60] Administration of Neuropeptide S (NPS) attenuated the PTZ-induced oxidative damage to proteins and lipids in the hippocampus and cerebral cortex in mice, which showed the probable effect of NPS in epilepsy.[61] Temporal lobe epilepsy (TLE) has been considered as a common variant of epilepsy which is difficult to treat. This has been shown that thymoquinone pretreatment attenuated the seizure activity and lipid peroxidation, lowered hippocampal neuronal loss and alleviated the astrogliosis in kainate rat model of TLE.[62] Another study investigated the potential effect of curcumin, a polyphenol with pleiotropic properties, on mitochondrial dysfunctions, oxidative stress and cognitive deficits in a kindled model of epilepsy. The study showed that the curcumin supplemented PTZ rats had normal cell morphology and reduced cell loss, which suggested that curcumin supplementation has potential to prevent mitochondrial dysfunction and oxidative stress with improved cognitive functions in a chronic model of epilepsy.[63] Furthermore, a study showed that Ferula Assa Foetida gum extract reduced the seizure duration and its intensity in an experimental model of epilepsy. In addition, the extract reduced MDA and NO levels and increased the level of SOD in the brain tissue compared to the PTZ- kindled mice, showing its probable anti-epileptic effect because of its antioxidant properties.[64] Also, this has been reported that berberine pretreatment attenuated the spontaneous recurrent seizures, shown by the decrease in lipid peroxidation in kainate rats, confirming its effectiveness in lessening of oxidative stress in rats.[65] Montelukast, an anti-inflammatory drug with antioxidant properties, was investigated for a preventive effect against seizures and post-seizure oxidative stress in PTZ-induced seizures in rats. Montelukast administration significantly lowered the MDA levels and increased the SOD levels compared to the saline-treated group, which showed its potent anticonvulsant action that led to amelioration of oxidative stress markers in PTZ-induced seizures in rats.[66] Moreover, pretreatment with Panchagavya Ghrita (PG), an ayurvedic formulation, investigated for its effect in epileptic rats. PG significantly improved cognitive functions and the oxidative stress induced by seizures demonstrating its protective effect against PTZ induced seizures.[67] Another study investigated the effects of coadministration of melatonin and theanine (Mel/Thea) on PTZ-induced seizures in ovariectomized (OVX) and sham-operated rats. The PTZ exposure resulted in an increase of MDA levels and reduction in thiol concentrations in brain tissues of both the sham-PTZ and OVX-PTZ groups. Pretreatment with Mel/Thea resulted in MDA reduction and increase in thiol concentration in brain tissues, confirming their antiseizure potential in rats.[68] Lycopene, a carotenoid antioxidant and sodium valproate treatment showed significant attenuation of kindling score, reversal of oxidative damage and restoration of mitochondrial enzyme complex activities in comparison with control. The study demonstrated and confirmed the neuroprotective potential of lycopene in PTZ-induced kindling in mice.[69] Furthermore, Argan oil (AO) has been found to be rich in oleic and linoleic acids, polyphenols, sterols and tocopherols. Treatment with AO was investigated for its effects on latency to first seizure, seizure severity, weight loss, mortality rate, lipid peroxidation level, nitrite level and catalase activity in the hippocampus in pilocarpine induced status epilepticus SE. Pretreatment with AO increased the latency to first seizures, decreased the weight loss and reduced the mortality rate after SE. Also, AO pretreatment produced significant decrease of the lipid peroxidation and nitrite levels. The study suggested that AO pretreatment is capable of attenuating seizure severity and oxidative stress in the hippocampus of Wistar rats, indicating a neuroprotective effect of AO against temporal lobe epilepsy.[70] Adminsitarion of tianeptine, an antidepressant drug, attenuated the seizure-induced increased oxidative stress in PTZ-induced seizure model of rats. The results of the study confirmed the potential of tianeptine as an anticonvulsant drug along with amelioration of seizure-induced cognitive impairment and oxidative stress.[71] In addition, Ferulic acid, a phenolic phytochemical with antioxidant and neuroprotective properties, was investigated for its therapeutic potential against PTZ-kindled seizures in rats. Ferulic acid significantly reduced the seizure score, number of myoclonic jerks, cognitive decline and oxidative stress, which showed that ferulic acid exhibits antiepileptogenic effect and prevents oxidative stress and cognitive impairment induced by PTZ kindling.[72] A recent study explored the neuroprotective effects of Glycyrrhizin (GL), a triterpene present in the roots and rhizomes of Glycyrrhiza glabra against lithium/pilocarpine-induced status epilepticus in rats. GL administration suppressed the induction of the proinflammatory cytokines like interleukin-1 beta and tumor necrosis factor alpha in both cerebral regions, which suggested the neuroprotection exhibited by GL against pilocarpine damage via antioxidant and anti-inflammatory effects.[73] Furthermore, the anticonvulsant effect of rosmarinic acid against seizures induced by PTZ and pilocarpine has been investigated in the recent past. Rosmarinic acid showed dose-dependent increase in the latency to myoclonic jerks and generalized seizures in the PTZ model and increased the latency to myoclonic jerks induced by pilocarpine, that confirmed its acute anticonvulsant-like activity against seizures induced by PTZ or pilocarpine in mice.[74]

CONCLUSION

Epilepsy, a neurological disorder, is marked by sudden recurrent episodes of sensory disturbance and convulsions associated with abnormal electrical activity in the brain. Oxidative stress has been implicated in the development and progression of epileptic seizures. The

approval of many new antiepileptic drugs has not been able to substantially reduce the proportion of patients with epilepsy. Hence, newer and more expensive AEDs are now being prescribed with an increase in treatment costs. Further epidemiological studies are needed which would focus on the temporal changes in the incidence of epilepsy in defined populations.

REFERENCES

1. Ngugi AK, Bottemley C, Kleinschmidt I. Estimation of the burden of active and life-time epilepsy: a metaanalytic approach. Epilepsia, 2010; 51: 883-90.
2. Schmidt D, Sillanpaa M. Prevention of Epilepsy: Issues and Innovations. Curr Neurol Neurosci Rep, 2016; 16: 95.
3. Fisher RS, van Emde Boas W, Blume W. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia, 2005; 46: 470-2.
4. Jefferys JGR. Advances in understanding basic mechanisms of epilepsy and seizures. Seizure, 2010; 19: 638-46.
5. Jefferys JGR, Jiruska P. Basic mechanisms of seizure generation. In: Epilepsy: The Intersection of Neurosciences, Mathematics, and Engineering 2011; Taylor and Francis, London.
6. Patel M. Mitochondrial dysfunction and oxidative stress: cause and consequence of epileptic seizures. Free Radic Biol Med, 2004; 37: 1951-62.
7. Shin EJ1, Jeong JH, Chung YH, Kim WK, Ko KH, Bach JH, et al. Role of oxidative stress in epileptic seizures. Neurochem Int, 2011; 59: 122-37.
8. Devi PU, Manocha A, Vohora D. Seizures, antiepileptics, antioxidants and oxidative stress: an insight for researchers. Expert Opin Pharmacother, 2008; 9: 3169-77.
9. Raol YH, Brooks-Kayal AR. Experimental models of seizures and epilepsies. Prog Mol Biol Transl Sci, 2012; 105: 57-82.
10. Kandratavicius L, Balista PA, Lopes-Aguiar C, Ruggiero RN, Umeoka EH, Garcia-Cairasco N, et al. Animal models of epilepsy: use and limitations. Neuropsychiatr Dis Treat, 2014; 10: 1693-705.
11. Bostjan M, Iztok G, Tomaz V. The Role of Reactive Species in Epileptogenesis and Influence of Antiepileptic Drug Therapy on Oxidative Stress. Current Neuropharmacology, 2012; 10: 328-43.
12. Mares J, Stopka P, Nohejlova K, Rokyta R. Oxidative stress induced by epileptic seizure and its attenuation by melatonin. Physiol Res, 2013; 62: S67-74.
13. Kumar V, Sharma SK, Nagarajan K, Dixit PK. Effects of Lycopene and Sodium Valproate on Pentylenetetrazol-Induced Kindling in Mice. Iran J Med Sci, 2016; 41: 430-6.
14. Delorenzo RJ, Sun DA, Deshpande LS. Cellular mechanisms underlying acquired epilepsy: the calcium hypothesis of the induction and maintainance of epilepsy. Pharmacol Ther, 2005; 105: 229-66.
15. Pitkanen A, Sutula TP. Is epilepsy a progressive disorder? Prospects for new therapeutic approaches in temporal-lobe epilepsy. Lancet Neurol, 2002; 1: 173-81.
16. Pitkanen A, Lukasiuk K. Molecular and cellular basis of epileptogenesis in symptomatic epilepsy. Epilepsy Behav, 2009; 14: 16-25.
17. Henshall DC, Simon RP. Epilepsy and apoptosis pathways. J Cereb Blood Flow Metab, 2005; 25: 1557-72.
18. Chuang YC. Mitochondrial dysfunction and oxidative stress in seizure-induced neuronal cell death. Acta Neurol Taiwan, 2010; 19: 3-15.
19. Waldbaum S, Patel M. Mitochondrial dysfunction and oxidative stress: a contributing link to acquired epilepsy?. J Bioenerg Biomembr, 2010; 42: 449-55.
20. Morris TA, Jafari N, Rice AC, Vasconcelos O, DeLorenzo RJ. Persistent increased DNA-binding and expression of serum response factor occur with epilepsy-associated long-term plasticity changes. J Neurosci, 1999; 19: 8234-43.
21. Neligan A, Hauser WA, Sander JW. The epidemiology of the epilepsies. Handb Clin Neurol, 2012; 107: 113-33.
22. Abramovici S, Bagic A. Epidemiology of epilepsy. Handb Clin Neurol, 2016; 138: 159-71.
23. Ben-Ari Y, Cossart R. Kainate, a double agent that generates seizures: two decades of progress. Trends Neurosci, 2000; 23: 580-7.
24. Frantseva MV, Velazquez JL, Hwang PA, Carlen PL. Free radical production correlates with cell death in an in vitro model of epilepsy. Eur J Neurosci, 2000; 12: 1431-9.
25. Chuang YC, Chen SD, Liou CW, Lin TK, Chang WN, Chan SH, et al. Contribution of nitric oxide, superoxide anion and peroxynitrite to activation of mitochondrial apoptotic signaling in hippocampal CA3 subfield following experimental temporal lobe status epilepticus. Epilepsia, 2009; 50: 731-46.
26. Shin EJ, Jeong JH, Bing G, Park ES, Chae JS, Yen TP, et al. Kainate-induced mitochondrial oxidative stress contributes to hippocampal degeneration in senescence-accelerated mice. Cell Signal, 2008a; 20: 645-58.
27. Shin EJ, Ko KH, Kim WK, Chae JS, Yen TP, Kim HJ, et al. Role of glutathione peroxidase in the ontogeny of hippocampal oxidative stress and kainate seizure sensitivity in the genetically epilepsy-prone rats. Neurochem Int, 2008b; 52: 1134-47.
28. de Freitas RM, de Sousa FC, Vasconcelos SM, Viana GS, Fonteles MM. Acute alterations of neurotransmitters levels in striatum of young rat after pilocarpine-induced status epilepticus. Arq Neuropsiquiatr, 2003; 61: 430-3.
29. Freitas RM, Sousa FC, Vasconcelos SM, Viana GS, Fonteles MM. Pilocarpine-induced status epilepticus in rats: lipid peroxidation level, nitrite formation,

GABAergic and glutamatergic receptor alterations in the hippocampus, striatum and frontal cortex. Pharmacol Biochem Behav, 2004; 78: 327-32.
30. Pazdernik TL, Emerson MR, Cross R, Nelson SR, Samson FE. Soman-induced seizures: limbic activity, oxidative stress and neuroprotective proteins. J Appl Toxicol, 2001; 21: S87-94.
31. Freitas RM, Vasconcelos SM, Souza FC, Viana GS, Fonteles MM. Oxidative stress in the hippocampus after pilocarpine-induced status epilepticus in Wistar rats. FEBS J, 2005; 272: 1307-12.
32. Huang RQ, Bell-Horner CL, Dibas MI, Covey DF, Drewe JA, Dillon GH. Pentylenetetrazole-induced inhibition of recombinant gamma-aminobutyric acid type A GABA(A) receptors: mechanism and site of action. J Pharmacol Exp Ther, 2001; 298: 986-95.
33. Patsoukis N, Zervoudakis G, Georgiou CD, Angelatou F, Matsokis NA, Panagopoulos NT. Effect of pentylenetetrazol-induced epileptic seizure on thiol redox state in the mouse cerebral cortex. Epilepsy Res, 2004a; 62: 65-74.
34. Patsoukis N, Zervoudakis G, Panagopoulos NT, Georgiou CD, Angelatou F, Matsokis NA. Thiol redox state (TRS) and oxidative stress in the mouse hippocampus after pentylenetetrazol-induced epileptic seizure. Neurosci Lett, 2004b; 357: 83-6.
35. Erakovic V, Zupan G, Varljen J, Simonic A. Pentylenetetrazol-induced seizures and kindling: changes in free fatty acids, superoxide dismutase and glutathione peroxidase activity. Neurochem Int, 2003; 42: 173-8.
36. Rauca C, Wiswedel I, Zerbe R, Keilhoff G, Krug M. The role of superoxide dismutase and alphatocopherol in the development of seizures and kindling induced by pentylenetetrazol - influence of the radical scavenger alpha-phenyl-N-tert-butyl nitrone. Brain Res., 2004; 1009: 203-12.
37. Ishida N, Akaike M, Tsutsumi S, Kanai H, Masui A, Sadamatsu M, et al. Trimethyltin syndrome as a hippocampal degeneration model: temporal changes and neurochemical features of seizure susceptibility and learning impairment. Neuroscience, 1997; 81: 1183-91.
38. Kim HC, Suh JH, Won JS, Jhoo WK, Song DK, Kim YH, et al. Phenidone blocks the increases of proenkephalin and prodynorphin gene expression induced by kainic acid in rat hippocampus: involvement of Fos-related antigene protein. Brain Res, 1998; 782: 337-42.
39. Shin EJ, Suh SK, Lim YK, Jhoo WK, Hjelle OP, Ottersen OP, et al. Ascorbate attenuates trimethyltin-induced oxidative burden and neuronal degeneration in the rat hippocampus by maintaining glutathione homeostasis. Neuroscience, 2005; 133: 715-27.
40. Shivakumar BR, Anandatheerthavarada HK, Ravindranath V. Free radical scavenging systems in developing rat brain. Int J Dev Neurosci, 1991; 9: 181-5.
41. Benatti P, Peluso G, Nicolai R, Calvani M. Polyunsaturated fatty acids: biochemical, nutritional and epigenetic properties. J Am Coll Nutr, 2004; 23: 281-302.
42. Waldbaum S, Patel M. Mitochondria, oxidative stress and temporal lobe epilepsy. Epilepsy Res, 2010; 88: 23-45.
43. Liang LP, Patel M. Mitochondrial oxidative stress and increased seizure susceptibility in Sod2-/+ mice. Free Radic Biol Med, 2004; 36: 542-54.
44. Shoham S, Youdim MB. Nutritional iron deprivation attenuates kainate-induced neurotoxicity in rats: implications for involvement of iron in neurodegeneration. Ann N Y Acad Sci, 2004; 1012: 94-114.
45. Wang XS, Ong WY, Connor JR. Increase in ferric and ferrous iron in the rat hippocampus with time after kainate-induced excitotoxic injury. Exp Brain Res, 2002; 143: 137-48.
46. Huang E, Ong WY, Go ML, Connor JR. Upregulation of iron regulatory proteins and divalent metal transporter-1 isoforms in the rat hippocampus after kainate induced neuronal injury. Exp Brain Res, 2006; 170: 376-86.
47. Savaskan NE, Brauer AU, Kuhbacher M, Eyupoglu IY, Kyriakopoulos A, Ninnemann O, et al. Selenium deficiency increases susceptibility to glutamate-induced excitotoxicity. FASEB J, 2003; 17: 112-4.
48. Leifke E, Seregi A, Heldt R, Hertting G. In vivo cpmparative study of the seizure- and ischemiainduced synthesis of eicosanoids in the brain of gerbils. Arch Int Pharmacoodyn Ther, 1994; 328: 145-54.
49. Okada K, Yuhi T, Tsuji S, Yamashita U. Cyclooxygenase-2 expression in the hippocampus of genetically epilepsy susceptible mice was increased after seizure. Brain Res, 2001; 894: 332-5.
50. Shafiq N, Malhotra S, Pandhi P. Anticonvulsant action of cerecoxib (alone and incombination with sub-threshold dose of phenytoin) in electroshock induced convulsion. Methods Find Exp Clin Pharmacol, 2003; 25: 87-90.
51. Cardenas-Rodriguez N, Huerta-Gertrudis B, Rivera-Espinosa L, Montesinos-Correa H, Bandala C, Carmona-Aparicio L, et al. Role of oxidative stress in refractory epilepsy: evidence in patients and experimental models. Int J Mol Sci, 2013; 14: 1455-76.
52. Aguiar CC, Almeida AB, Araujo PV, de Abreu RN, Chaves EM, do Vale OC, et al. Oxidative stress and epilepsy: literature review. Oxid Med Cell Longev, 2012; 2012: 795259.
53. Azam F, Prasad MV, Thangavel N. Targeting oxidative stress component in the therapeutics of epilepsy. Curr Top Med Chem, 2012; 12: 994-1007.
54. Ziegler DR, Ribeiro LC, Hagenn M, Siqueira IR, Araujo E, Torres IL, et al. Ketogenic diet increases glutathione peroxidase activity in rat hippocampus. Neurochem Res, 2003; 28: 1793-7.
55. Lehtinen MK, Tegelberg S, Schipper H, Su H, Zukor H, Manninen O, et al. Cystatin B deficiency

sensitizes neurons to oxidative stress in progressive myoclonus epilepsy. EPM J Neurosci, 2009; 29: 5910-5.
56. Folbergrova J, Jesina P, Kubova H, Druga R, Otahal J. Status Epilepticus in Immature Rats Is Associated with Oxidative Stress and Mitochondrial Dysfunction. Front Cell Neurosci, 2016; 10: 136.
57. Hayashi M, Tanuma N, Miyata R. The involvement of oxidative stress in epilepsy. In Handbook of Free Radicals: Formation, Types and Effects, Kozyrev, D., Slutsky, V., Eds.; Nova Science Publishers: New York, NY, USA, 2010; 305-18.
58. Lopez J, Gonzalez ME, Lorigados L, Morales L, Riveron G, Bauza JY. Oxidative stress markers in surgically treated patients with refractory epilepsy. Clin Biochem, 2007; 40: 292-8.
59. Shiihara T, Kato M, Ichiyama T, Takahashi Y, Tanuma N, Miyata R, et al. Acute encephalopathy with refractory status epilepticus: Bilateral mesial temporal and claustral lesions, associated with a peripheral marker of oxidative DNA damage. J Neurol Sci, 2006; 250: 159-61.
60. Ezz HS, Khadrawy YA, Noor NA. The neuroprotective effect of curcumin and Nigella sativa oil against oxidative stress in the pilocarpine model of epilepsy: a comparison with valproate. Neurochem Res, 2011; 36: 2195-204.
61. Ramos SF, Mendonça BP, Leffa DD, Pacheco R, Damiani AP, Hainzenreder G, et al. Effects of neuropeptide S on seizures and oxidative damage induced by pentylenetetrazole in mice. Pharmacol Biochem Behav, 2012; 103: 197-203.
62. Dariani S, Baluchnejadmojarad T, Roghani M. Thymoquinone attenuates astrogliosis, neurodegeneration, mossy fiber sprouting, and oxidative stress in a model of temporal lobe epilepsy. J Mol Neurosci, 2013; 51: 679-86.
63. Kaur H, Bal A, Sandhir R. Curcumin supplementation improves mitochondrial and behavioral deficits in experimental model of chronic epilepsy. Pharmacol Biochem Behav, 2014; 125: 55-64.
64. Kiasalari Z, Khalili M, Roghani M, Heidari H, Azizi Y. Antiepileptic and Antioxidant Effect of Hydroalcoholic Extract of Ferula Assa Foetida Gum on Pentylentetrazole- induced Kindling in Male Mice. Basic Clin Neurosci, 2013; 4: 299-306.
65. Mojarad TB, Roghani M2. The Anticonvulsant and Antioxidant Effects of Berberine in Kainate-induced Temporal Lobe Epilepsy in Rats. Basic Clin Neurosci, 2014; 5: 124-30.
66. Cevik B, Solmaz V, Aksoy D, Erbas O. Montelukast inhibits pentylenetetrazol-induced seizures in rats. Med Sci Monit, 2015; 21: 869-74.
67. Joshi R, Reeta KH, Sharma SK, Tripathi M, Gupta YK. Panchagavya Ghrita, an Ayurvedic formulation attenuates seizures, cognitive impairment and oxidative stress in pentylenetetrazole induced seizures in rats. Ind J Exp Biol, 2015; 53: 446-51.
68. Choopankareh S, Vafaee F, Shafei MN, Sadeghnia HR, Salarinia R, Zarepoor L, et al. Effects of melatonin and theanine administration on pentylenetetrazole-induced seizures and brain tissue oxidative damage in ovariectomized rats. Turk J Med Sci, 2015; 45: 842-9.
69. Bhardwaj M, Kumar A. Neuroprotective Effect of Lycopene Against PTZ-induced Kindling Seizures in Mice: Possible Behavioural, Biochemical and Mitochondrial Dysfunction. Phytother Res, 2016; 30: 306-13.
70. Bahbiti Y, Ammouri H, Berkiks I, Hessni AE, Ouichou A, Nakache R, et al. Anticonvulsant effect of argan oil on pilocarpine model induced status epilepticus in wistar rats. Nutr Neurosci, 2016; 12: 1-7.
71. Reeta KH, Prabhakar P, Gupta YK. Anticonvulsant activity of the antidepressant drug, tianeptine, against pentylenetetrazole-induced seizures mitigates cognitive impairment in rats. Behav Pharmacol, 2016; 27: 623-32.
72. Hassanzadeh P, Arbabi E, Atyabi F, Dinarvand R. Ferulic acid exhibits antiepileptogenic effect and prevents oxidative stress and cognitive impairment in the kindling model of epilepsy. Life Sci, 2016: in press.
73. Gonzalez-Reyes S, Santillan-Cigales JJ, Jimenez-Osorio AS, Pedraza-Chaverri J, Guevara-Guzman R. Glycyrrhizin ameliorates oxidative stress and inflammation in hippocampus and olfactory bulb in lithium/pilocarpine-induced status epilepticus in rats. Epilepsy Res, 2016; 126: 126-33.
74. Grigoletto J, Oliveira CV, Grauncke AC, Souza TL, Souto NS, Freitas ML, et al. Rosmarinic acid is anticonvulsant against seizures induced by pentylenetetrazol and pilocarpine in mice. Epilepsy Behav, 2016; 62: 27-34.