Neuroinflammation impact in epileptogenesis and new treatment strategy

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Epilepsy is considered a major serious chronic neurological disorder, characterized by recurrent seizures. It is usually associated with a history of a lesion in the nervous system. Irregular activation of inflammatory molecules in the injured tissue is an important factor in the development of epilepsy. It is unclear how the imbalanced regulation of inflammatory mediators contributes to epilepsy. A recent research goal is to identify interconnected inflammation pathways which may be involved in the development of epilepsy. The clinical use of available antiepileptic drugs is often restricted by their limitations, incidence of several side effects, and drug interactions. So development of new drugs, which modulate epilepsy through novel mechanisms, is necessary. Alternative therapies and diet have recently reported positive treatment outcomes in epilepsy. Vitamin D (Vit D) has shown prophylactic and therapeutic potential in different neurological disorders. So, the aim of current study was to review the associations between different brain inflammatory mediators and epileptogenesis, to strengthen the idea that targeting inflammatory pathway may be an effective therapeutic strategy to prevent or treat epilepsy. In addition, neuroprotective effects and mechanisms of Vit D in clinical and preclinical studies of epilepsy were reviewed. *Behavioural Pharmacology* 30: 660–674 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Epilepsy is a common complex neurological disorder that affects peoples of all ages in about 0.5–1% of the population (Haut *et al.*, 2006). It is identified by impaired neuronal activity, seizures, and behavioral changes (Fisher, 2015). High incidence of epilepsy was observed in children and geriatrics (Téllez-Zenteno and Hernández-Ronquillo, 2012). Status epilepticus, which may result from the failure of seizure termination mechanisms (Trinka *et al.*, 2012), is considered the most dangerous form of epilepsy due to a high mortality rate. Status epilepticus is characterized by an increase in reactive oxygen species (ROS) and excitatory neurotransmitters in the brain along with cognitive impairment (Coyle and Puttfarcken, 1993).

Pathophysiology of epilepsy

The pathophysiology of epilepsy and seizures is diverse. However, one common attribute across epilepsies is a disrupted balance between excitatory (glutamatergic signaling) and inhibitory (GABAergic signaling) drive at the synaptic level that can result in seizure activity. Early pharmacologic studies demonstrated that $GABA_A$-receptor antagonists and glutamate-receptor [N-methyl-D-aspartate (NMDA)] agonists could elicit seizure activity in normal animals. Further studies would demonstrate that interictal spikes commonly observed on electroencephalogram (EEG) recordings from epilepsy patients are associated with a large depolarization and subsequent flurry of action potentials in individual neurons. The highly organized structure of cortical tissue with its laminar cell layers facilitates the flow of normal neuronal processing, while also providing a structure highly susceptible to abnormal synchronous activity that can lead to seizure generation. Under normal circumstances, excitatory synaptic activity is tightly regulated by inhibitory interneurons; however, genetic mutation, trauma, abnormal development, or a number of other insults can disrupt this regulation, allowing cortical networks to become hyperexcitable (Flynn and Babi, 2017).

Experimental animal models are used to find new treatment strategies for improving the therapy of status epilepticus (Martín and Pozo, 2006), such as pilocarpine (Pc) which induces seizures that start in limbic regions, causing structural damage and spontaneous recurrent seizures which resemble complex partial seizures in human (Schmidt-Kastner *et al.*, 1996).

Previous studies in animal models (Folbergrová, 2013; Cárdenas-Rodríguez *et al.*, 2014) and patients with epilepsy (Carmona-Aparicio *et al.*, 2015) have reported an imbalance between the oxidant and antioxidant systems and high inflammation. Neuroinflammation is a critical part of brain innate immunity. However, chronic inflammatory processes cause neurotoxicity and hyperexcitability, showing a possible relationship between inflammation and epilepsy.

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Neuroinflammation and epilepsy

Neuroinflammation has been reported to be caused by an abnormal increase in proinflammatory mediators in the epileptogenic foci (Fig. 1). Brain tissues are extremely liable to oxidative stress, which has been reported to play a vital role in the pathogenesis of seizures (Sudha *et al.*, 2001). Oxidative stress has been shown cause in neurodegeneration, which is considered the most vital factor in epileptogenesis and the decline in cognitive behavior (Gorter *et al.*, 2006; Martinc *et al.*, 2014; Vezzani, 2014). Epilepsy generation is related to the endogenous chemical imbalance of oxidants and antioxidants.

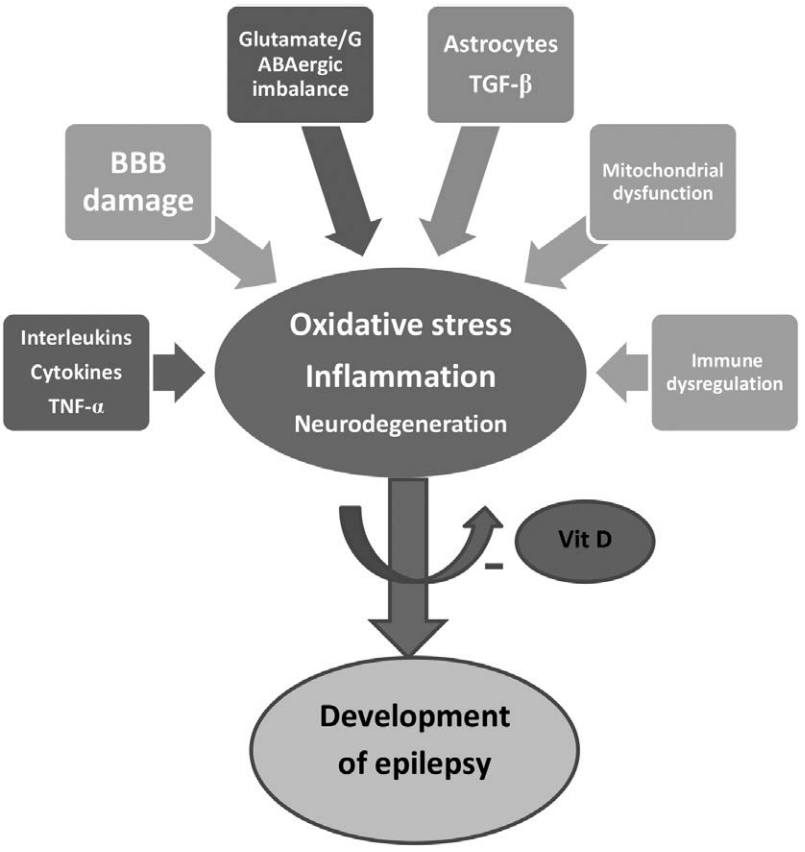
Experimental animal models of epilepsy have demonstrated a rapid onset of the release of inflammatory mediators contributing to the pathogenesis of epilepsy (Vezzani and Granata, 2005; Riazi *et al.*, 2010; Vezzani *et al.*, 2011). Several chemical mediators have been reported in epilepsy, including interleukin-1β (IL-1β), toll-like receptor 4, transforming growth factor-β (TGF-β), and tumor necrosis factor-α (TNF-α), cyclooxygenase-2 (COX 2), and prostaglandin E2 (PGE2) (Borham *et al.*, 2016; Yifeng *et al.*, 2016).

Proinflammatory cytokines

Proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, are normally present at low levels in the brain and are highly upregulated as a result of acute brain insults as seizures. High levels of IL-1β, its receptor, and biosynthetic enzyme, caspase-1/interleukin converting enzyme, have been demonstrated in neurons in the epileptic patient and in experimental models of epilepsy (Henshall *et al.*, 2000; Ravizza and Vezzani 2006). Cytokines have reported to contribute to pathogenesis of epilepsy in three different ways: increasing neuronal excitability by blocking reuptake of glutamate (Hu *et al.*, 2000); enhancing NMDA receptor function (Viviani *et al.*, 2003); altering GABA neurotransmission (Roseti *et al.*, 2015); and activation of caspase-1 (Lamkanfi *et al.*, 2010).

TNF-α is the important proinflammatory cytokine, which is associated with the activation and infiltration of

Fig. 1



A schematic diagram represents the cascade of events through which oxidative stress and inflammation result in neurodegeneration and development of epilepsy. Imbalance of glutamate/GABAergic system; increase inflammatory mediators as: interleukins, cytokines, TNF-α, TGF-β; immune dysregulation, mitochondrial dysfunction and damage of BBB are the main factors lead to epileptogenesis. These neuroinflammation and neurodegeneration can be prevented by Vit D. BBB, blood brain barrier; TGF-β, transforming growth factor – beta; TNF-α, tumor necrosis factor – alpha.

immune cells during inflammation (Sonar and Lal, 2015). TNF-α administration 24 hours after kindling in rats enhances the seizures (Shandra *et al.*, 2002).

Uludag *et al.* (2015) reported that IL-6, IL-1β, and TNF-α are activated after seizures, and were found to be increased chronically in cerebrospinal fluid than in plasma (Billiau *et al.*, 2007; Riazi *et al.*, 2010). IL-6 and IFN-γ are reported to be increased in patients having epilepsy (Mao *et al.*, 2013). IFN-γ has a vital role in developing brain excitatory seizure pathways (Getts *et al.*, 2007).

Heat shock protein 70

Heat shock proteins (HSPs), such as HSP70 (Borham *et al.*, 2016), can induce the innate immune system through their interactions with cell surface receptors, leading to the expression of proinflammatory cytokines, chemokines (Asea *et al.*, 2000), and the activation of dendritic cells (Floto *et al.*, 2006). HSPs are stress markers in temporal lobe epilepsy and are induced in response to some neurological diseases. Levels of HSP70 in serum and duration of epilepsy are positively correlated. Also, neuronal degeneration and disturbed memory function indicate that it may be used as a biomarker for stress-induced neuronal damage (Chang *et al.*, 2012).

Transforming growth factor-β1

TGF-β1 is an important cytokine involved in immune regulation. It is possess both proinflammatory and anti-inflammatory reactions. Previous studies showed that TGF-β1 makes a microglia phenotype and plays a pathogenic role in epilepsy and neuronal excitability. Serum albumin extra vacation into the cerebral cortex microenvironment due to gaps in the blood-brain-barrier (BBB) stimulates the TGF-β receptor-mediated signaling cascade in astrocytes (Cacheaux *et al.*, 2009). TGF-β receptors were reported to facilitate albumin uptake into astrocytes and to stimulate NMDA-receptor-dependent pathological plasticity. This leads to BBB disruption and neurological disorders (Ivens *et al.*, 2007). TGF-β signaling was reported to induce upregulation of IL-6 in astrocytes. IL-6 leads to increasing cortical excitability in EEG and increase spontaneous seizures in mice (Levy *et al.*, 2015). The pleiotropic effects of the TGF-β signaling pathway produce a reasonable mechanism for epileptogenesis following brain injury and promote a specific therapeutic target (Weissberg *et al.*, 2015).

Reactive oxygen species

Other studies have reported that epileptogenesis is associated with elevated levels of ROS, free radical generation, lipid peroxidation, NO, and oxidative stress which leads to neuronal dysfunction (Rauca *et al.*, 1999; Sudha *et al.*, 2001; Bashkatova *et al.*, 2003; Arora *et al.*, 2010; Militão *et al.*, 2010; Tomé *et al.*, 2010; Xie *et al.*, 2012; Rathor *et al.*, 2014).

Brain oxidative stress is induced by the imbalance between the generation and detoxification of ROS and reactive nitrogen species (RNS), which attack brain cells and lead to brain inflammation, aging and degeneration (Uttara *et al.*, 2009). Activated NADPH oxidases (NOXs) are a family including NOX1, NOX2, NOX3, NOX4, NOX5, dual oxidase 1 (DUOX1), and DUOX2. They are a main source of ROS by transporting electrons from intracellular NADPH, and then to extracellular oxygen, this generating superoxide (Panday *et al.*, 2015). NOX2 is the prototype form. It plays a central role in neurodegeneration, neuroinflammation, and associated deficits in neurological disorders such as epilepsy (Puttachary *et al.*, 2015).

Superoxide radicals are highly active and possess the ability to initiate a pathological oxidative state, leading to oxidation of macromolecules such as DNA, proteins, and lipids. The central nervous system has antioxidant enzymes including superoxide dismutase (SOD) (Shivakumar *et al.*, 1991). This enzymatic defense metabolizes superoxide, but cannot eliminate hydrogen peroxide (H_2O_2) (i.e., superoxide dismutation). H_2O_2 accumulation is a major concern, as brain tissues contain large amounts of iron and copper, which catalyze the formation of hydroxyl radicals that can induce lipid peroxidation (Oubidar *et al.*, 1996). In addition, neuronal cell membrane contains a high level of polyunsaturated fatty acids (Benatti *et al.*, 2004). So, brain cells are highly susceptible to oxidative damage, thus reflecting the important role of the antioxidant defense mechanisms against oxidative stress in epileptogenesis.

Prolonged seizures result in high superoxide production, overwhelming the endogenous brain mitochondrial antioxidant defense mechanism. This occurs by a cascade of events started by increased glutamate release, neuronal firing, and activation of NMDA receptor, calcium influx, and high ATP consumption (Liang *et al.*, 2000).

Cyclooxygenase enzyme

Cyclooxygenase (COX) is the rate-limiting enzyme in the biosynthesis of prostanoids which include prostaglandin D2 (PGD2), PGE2, PGF2α and PGI2, and thromboxane A2 (TXA2). There are two COX isoforms, COX-1, which is constitutive to maintain normal physiological functions and COX-2, which is inducible in fever, infection, and inflammation. COX-2 is induced in the brain after seizures in both patients and experimental animals (Desjardins *et al.*, 2003; Serrano *et al.*, 2011). Chronic increase in COX-2 aggravates neuroinflammation and contributes to the pathophysiology of seizures. Neuronal overexpression of COX-2 has been reported to facilitate kainite-induced convulsions in mice (Kelley *et al.*, 1999).

Seizures result in the activation of arachidonic acid and cytosolic phospholipase A2 (Visioli *et al.*, 1994; Kajiwara

et al., 1996). In addition, high concentrations of prostaglandins are observed in the cerebral cortex, striatum, and hippocampus (Leifke *et al.*, 1994). These are areas that participate in the generation and propagation of seizures. Immunoreactive PGF2α and LT-like activity has been detected in the brains of spontaneously convulsing gerbils (Simmet *et al.*, 1988). Increased PG levels after epilepsy induction were confirmed by Takemiya *et al.* (2010), who noted that epileptic seizures rapidly induce COX-2 in excitatory neurons and increase brain PGE2 levels. COX-2 and PGE2 can enhance seizures by mechanisms that drive epilepsy, such as stimulation of inflammatory processes, and neurons death (Salvadori *et al.*, 2012).

PGE2 is a major COX-2 product in the central nervous system (CNS). It is now widely recognized for its roles in neuroinflammation and neuronal hyperexcitability by stimulating local vasodilation, permeation of immune cells, and stimulation of proinflammatory mediators (Takemiya *et al.*, 2007). PGE2 works on G protein-coupled receptors, namely EP1, EP2, EP3, and EP4. Studies have reported that genetic ablation or inhibition of Gαq-coupled EP1 is neuroprotective (Zhen *et al.*, 2012). These suggest that the EP1 receptor might contribute to PGE2-mediated neurotoxicity. Furthermore, EP1 activation plays a main role in the BBB impairment following ischemic strokes (Frankowski *et al.*, 2015).

Toll-like receptors

Toll-like receptors (TLRs) possess significant homology in the cytosolic region to the IL-1R family (Bowie and O'Neil, 2000). Among TLR members, TLR4 is the lipopolysaccharide sensing receptor, and a crucial component of innate immunity. TLR4 is activated by HMGB1, an endogenous danger protein released by immune cells or neurons in the CNS in response to cell damage or neuronal excitability. Both HMGB1 and TLR4 are increased in brain samples from epileptic patients and in brain tissues isolated from animals with chronic seizures (Vezzani *et al.*, 2011; Walker *et al.*, 2016). HMGB1 enhances NMDA receptor activity and increases kainate-induced seizures by activating TLR4 in hippocampal neurons (Balosso *et al.*, 2014).

During seizures degeneration of neurons and destruction of the BBB have been reported (Ravizza *et al.*, 2008). Destruction of the BBB and increases in its permeability can increase neuronal excitability by increasing inflammatory mediators in brain tissue (Ransohoff *et al.*, 2003; Heinemann *et al.*, 2012). At the cellular level, significant calcium influx leads to cascades, which induce ROSs and stimulate acute neurons death during seizure activity (Fujikawa *et al.*, 2000).

Significance

It could be concluded from both clinical and experimental studies that the presence of activated inflammatory cells (astrocytes, microglia, and leukocytes) and the increase in many proinflammatory molecules along with the stimulation of the related signaling pathways are involved in generation of drug-resistant forms of epilepsy. This evidence highlights the possible pathogenic role of either: innate or adaptive immune response or both in epilepsy. So, in some cases of drug-resistant epilepsy, neuroprotective anti-inflammatory or immunosuppressive treatments may have supportive therapeutic effects.

There is also evidence of serum autoantibodies in some forms of epilepsy. The relative contribution of both innate and adaptive immune systems to brain inflammation appears to vary depending on the underlying epilepsy etiology. Although activation of innate immunity, chiefly involving glial cells, is commonly observed in brain tissue surgically resected for therapeutic reasons from drug-resistant epilepsies, activated T cells, or circulating autoantibodies are restricted to more specific cases (Vezzani *et al.*, 2016).

Behavioral and neurochemical alterations in epilepsy

Epilepsy is accompanying by a high frequency of comorbid neurologic and psychiatric illnesses. There is great concordance of these behavioral pathologies with epilepsy. Behavioral manifestations in epilepsy may create several problems in differential diagnosis. In fact, psychiatric manifestations are usually reported among epilepsy patients (Lin *et al.*, 2012). These symptoms frequently occur around the ictus as an epiphenomenon of seizures themselves (Mula and Monaco, 2011).

Epilepsy-related behavioral symptoms were described by Gowers (1881), Jackson (1889), and Bleuler (1916), and classified according to the temporal relation to the seizure as ictal, preictal, and postictal. These psychiatric symptoms were induced by electrical stimulation of temporal lobe structures, suggesting the presence of integrated cortical networks with high cognitive functions (Gloor, 1990). From clinical practice, ictal psychiatric symptoms represent simple partial seizures where the psychic part is predominant. In most cases, they are brief, stereotyped, and associated with postictal confusion. These symptoms may in some cases be followed by alteration of consciousness as the ictus evolves to a complex partial seizure or, less frequently, to a generalized tonic–clonic seizure.

Anxiety, panic, depression, ictal fear or ictal panic, and, aggression are the most reported psychiatric symptoms that occur during epilepsy (Gaitatzis *et al.*, 2004; Mula *et al.*, 2010; Mula and Monaco 2011). Euphoria or ictal mania has been rarely reported: it can appear in the context of a partial status usually with psychotic symptoms such as hallucinations and delusions (Guillem *et al.*, 2000).

Depression is one of the commonest comorbidities of epilepsy. The occurrence of depression among epileptic patients is 30–50% against 5–17% among other people

without epilepsy (Frye *et al.*, 2016). Brain inflammation disturbs 5-HT metabolism and transmission. Several cytokines have been associated (IL-6, IL-1b, and TNF-a). In the raphe nuclei, IL-b inhibits tryptophan hydroxylase (TPH) and stimulates indoleamine 2,3-dioxygenase (IDO) (Kanner *et al.*, 2012). Thus, tryptophan metabolism is affected. As TPH is important as the rate-limiting step of 5-HT synthesis, disturbance of TPH by inflammation would decrease 5-HT synthesis. IDO catalyzes the rate-limiting step in the kynurenine pathway of tryptophan breakdown. Thus, the stimulation of IDO would result in 5-HT insufficiency due to the partial availability of substrate for TPH. In addition, quinolinic acid, a metabolite in the kynurenine pathway, is a neurotoxin (Guillemin, 2012); its accumulation in the aphe nuclei as a result of IDO stimulation would be expected to contribute to damage of serotonergic neurons (Brambilla *et al.*, 2007).

In experimental studies, a depression-like state is evaluated by two classical standard tests: the forced swimming test and the sucrose taste preference test. The forced swimming test depends on the adaptive behavior of rodents under a stressful situation, in which rodents display a gradual shift from active escape behavior to immobility (Kandratavicius *et al.*, 2012). The taste preference test measures rodents' natural preference for sweets. Experimental stressed animals show a low consumption of the sweet solution, indicating an alteration of underlying reward mechanisms (Pucilowski *et al.*, 1993). Previous studies have reported that rats exposed to status epilepticus, induced by Li Pc, kainate or electrical kindling, spent a significantly higher immobility time in the forced swimming test and showed loss of preference for sucrose solution, as compared with nonepileptic animals (Koh *et al.*, 2007; Mazarati et al., 2007, 2008, 2009; Krishnakumar *et al.*, 2009). This is indicates that epileptic rats demonstrate an increase in depressive-like behavior. There is a positive correlation between the severity of depression-like behavior and hippocampal hyperexcitability, suggesting that depressive symptoms may be a net result of limbic dysfunction which occurs with epilepsy (Mazarati *et al.*, 2010).

A relationship between autism and epilepsy has long been noted, and 5–40% of people with autism may have epilepsy (Thomas *et al.*, 2017). Both autism and epilepsy are accompanied by a number of irregularities, such as changes in minicolumn architecture and GABA neurotransmission, which may alter excitation inhibition balance (Frye *et al.*, 2016).

Impairment of cognition is also a common condition in epilepsy. Features include mental, memory, and attention deficiencies in adults, while learning impairments, poor academic performance, behavioral difficulties, and language deterioration are features observed in children. The underlying cause of cognitive impairment may be the injury in particular brain area correlated to seizures or epileptic dysfunction (Van Rijckevorsel, 2006). The Morris water maze (Morris *et al.*, 2003) is a commonly used behavioral test to evaluate cognitive functions of rodents. Twenty-four hours after Pc, behavior of animals was evaluated in Morris water maze daily for 6 days according to the method described in Spiers *et al.* (2001). The epileptic group showed deterioration of spatial memory, and a higher time to reach the escape platform (Tariq *et al.*, 2008; Reddy and Kuruba 2013; Mahfoz *et al.*, 2017). In addition, epileptic rats spent less time in the target quadrant. Neurotransmitter alteration may be responsible for the observed neurobehavioral changes (Kubová *et al.*, 2004; Nascimento *et al.*, 2005).

Paralleling this development of cognitive impairment, a number of morphological and physiological alterations occur in brain networks as a result of status epilepticus. Neuronal loss becomes clear in the hippocampus, dentate hilus, and entorhinal cortex (Kleen *et al.* 2012). Different anxiety levels and the extension of brain lesions affecting the hippocampus and the amydgala concur with spatial memory deficits were observed in epileptic rats in the Li-Pc or kainic acid model of epilepsy (Inostroza *et al.*, 2011).

The hippocampus plays a vital role in cognition, and is involved in minute-to-minute cognitive processing (Sweatt, 2004). The hippocampus has been shown to be critically affected in epilepsy, especially in temporal lobe epilepsy (Noebels *et al.*, 2012).

The basal ganglia are part of the modulatory control system over seizures rather than a propagation pathway (Dematteis *et al.*, 2003). While no specific epileptic EEG alterations were observed in the basal ganglia, involvement of the basal ganglia in spreading of epileptic activity has been reported (Rektor *et al.*, 2002). Dopamine is involved in the control of seizures related to the type of epilepsy (Bouilleret *et al.*, 2005). Continued seizures can cause damage to the substantia nigra pars reticulate (SNR) and globus pallidus (Inamura *et al.*, 1989). Epilepsy has an inverse relationship with Parkinson's disease as incidence of seizures is less in patients with Parkinson's disease (Vercueil and Hirsch, 2002).

Cortical, subcortical neuronal networks play an important role in production, preservation, and spread of epileptic activity. The piriform cortex and amygdala produce seizures in response to chemical and electrical stimulation and as an amplifier of epileptic activity when seizures are generated elsewhere. Structural abnormalities were observed in piriform cortex in frontal lobe epilepsy (Centeno *et al.*, 2014).

It was demonstrated that gray matter volume was related to cognitive functions (Bernasconi *et al.*, 2004). Decreased gray matter was reported in epilepsy patients (Bonilha *et al.*, 2004). This is most evident in hippocampus; other areas include parietal lobe, thalamus, and

cingulate gyrus (Keller *et al.*, 2007). Deficiencies in glial cells, especially astrocytes, may cause epilepsy (Binder and Steinhausen, 2006).

Cerebellar atrophy has also been demonstrated in epileptic patients (Liu *et al.*, 2005). While peri-ictal changes in cerebellar perfusion were reported in epilepsy, their contribution to cerebellar atrophy was minimum (Bohnen, 1998). Cerebellar stimulation especially in anterior lobe and thalamic region has been shown to be effective in epileptic patients (Krauss and Koubeissi *et al.*, 2007).

Primary olfactory cortex, which is central to olfactory identification, is another epileptogenic structure (Menassa *et al.*, 2017). Epilepsy seems to cause a generalized reduction in olfactory functioning, which may occur in some epileptic patients at some time in the preictal period. After stimulation of amygdale, a full spectrum of symptoms is observed in temporal lobe epilepsy patients. Selective amygdalotomy has been shown to be an effective therapy for temporal lobe epilepsy. The lateral amygdala is a nucleus of the amygdala that projects to the temporal neocortex and hippocampus. Rodent studies have shown that spontaneous discharges occur in the lateral amygdala of epileptics (Kullmann, 2011).

Oxidative stress biomarkers TBARS and NO were significantly increased in brain tissues isolated from the status epilepticus group, and the glutathione level was significantly decreased. Oxidative stress and inflammation may be considered as possible underlying mechanisms of epilepsy and also many neurodegenerative diseases characterized by progressive cognitive deficits (Coyle and Puttfarcken 1993; Mahfoz *et al.*, 2017; Tariq *et al.*, 2008). Also, increased excitatory neurotransmitter, glutamate, and, decreased inhibitory neurotransmitter, GABA have been demonstrated in brains isolated from the status epilepticus group (Mahfoz *et al.*, 2017). Glutamate was observed to be increased in human and animal models of epilepsy, and it is recognized that increased glutamate excitation leads to neuronal death in epilepsy (Coulter and Eid, 2012). The glutamate-glutamine cycle is a main recycling mechanism of glutamate and GABA in the brain. The enzyme glutamine synthetase, which is responsible for glutamate degradation, was demonstrated to be decreased in epileptic patients (Eid *et al.*, 2004). In accordance with these observations, the pathophysiology of different brain regions showed degeneration in neuronal cells of the cerebral cortex and hippocampus in the status epilepticus group. Nuclear pyknosis associated with gliosis and plaque formation is also seen in the striatum in the Li-Pc model of status epilepticus (Mahfoz *et al.*, 2017).

In addition, kainic acid, an experimental model of epilepsy, resulted in high ROS production, apoptosis, and mitochondrial dysfunction in neurons. Oxidative stress and high glutamate receptor activation are factors that activate pathways of neuronal vulnerability, which may precede neuronal damage and death in vulnerable brain regions (Coyle and Puttfarcken, 1993; Dugan *et al.*, 1995; Frantseva *et al.*, 2000).

Pentylenetetrazol (PTZ), a selective GABAA receptor blocker (Huang *et al.*, 2001), is used as a convulsant in rodents due to its effects on GABAergic, adenosinergic, and glutamatergic systems (Pagonopoulou and Angelatou, 1998; Ekonomou and Angelatou, 1999). PTZ resulted in significant reduction in GSH, GSSG, SOD, cysteine, and protein thiols (Patsoukis *et al.*, 2004a), while MDA, protein disulfides, and carbonyl levels are elevated (Patsoukis *et al.*, 2004b).

Trimethyltin (TMT) administration in rats resulted in hippocampal damage, to hyperactivity and aggression and shown to result in behavioral symptoms that include seizures, which may be related to their interaction with activators of the endogenous excitatory transmitter systems (Dyer *et al.*, 1982; Patel *et al.*, 1990; Sperk, 1994, Ishida *et al.*, 1997; Kim *et al.*, 1998). TMT increases intracellular Ca2+, which activates degradative enzymes and initiating the production of superoxide radicals, MDA, and protein carbonyl (Oury *et al.*, 1993; Shin *et al.*, 2005).

Drawbacks of traditional antiepileptic medications

Epilepsy affects about 65 million people all over the world. About 22–30% of epileptic patients have drug-resistant epilepsy. Drug-resistant epilepsy causes cognitive and mood impairment, injuries, and increased risk of death including sudden death (Kwan and Brodie 2000; Kwan *et al.*, 2011; Chen *et al.*, 2016). Antiepileptic drugs are the primary medical treatment for epilepsy. They have been available for many decades; however, their clinical use is often restricted by the incidence of several side effects and drug interactions. Even for patients with well-controlled seizures by antiepileptic drugs (AEDs), allergies, neurological and systemic toxicity, depression, memory loss, and osteoporosis are common problems (Meier and Kraenzlin, 2011; Reynolds, 1975). Because of the limitations and potential toxicity of existing AEDs, there is significant clinical interest in finding alternative therapies for epilepsy. It is considered a challenge to prevent or treat epilepsy with a highly efficient agent with the least adverse effects. So research for more effective and safe antiepileptic medication is critical.

It has also been reported that 20–30% of epileptic patients have low seizure control despite optimum medication therapy (Weintraub *et al.*, 2007). Previous studies have shown that 50% of patients with epilepsy developed psychological cognitive impairment (Motamedi and Meador, 2003; Xie *et al.*, 2012).

There are two main groups of AEDs: cytochrome p450 inducers of liver enzymes (carpamazepine, phenobarbitale, phenytoin, primidone) and noninducer AEDs (lamotrigine, valproate acid, gabapentin, clonazepam,

topiramate). Daily treatment with AEDs affects bone turnover and reduces levels of vit-D, which has a negative impact on bone health (Fong and Riney 2014). The effects of noncytochrome p450 inducer AEDs on bone turnover involves different pathways: resistance to parathyroid hormone, decreased calcium absorption, inhibition of calcitonin production, and direct effects on osteoblasts (Wallace, 1996), in addition to, decreasing Bone Mineral Density (BMD) in children with epilepsy (Kafali *et al*., 1999; Tsukahara *et al*., 2002). Twenty percent of Malaysian children with epilepsy on chronic AED therapy have low BMD (Vestergaard, 2015; Fong *et al*., 2018). Nevertheless, both types of AEDs have been shown to decrease BMD in epileptic children (Yaghini *et al*., 2015). In children bone, physiology is different from adults due to the presence of growth plates. AEDs such as valproate have a direct negative effect on bone growth plates (Lee *et al*., 2013), in addition to altering bone biochemical, radiologic markers, and mineral status (Hasaneen *et al*., 2017).

Inflammation targeting approaches for epilepsy management

As clinical and experimental evidence has demonstrated that oxidative stress is involved in the pathogenesis of epilepsy, many researchers have studied the effect of various antioxidants in epilepsy. Molecules which target the proinflammatory mediators have been evaluated for their antiepileptic effect in different animal models (Jiang *et al*., 2015; Dey *et al*., 2016). Many substances with antioxidative effects, such as alpha-tocopherol (Tomé *et al*., 2010), Aloe vera (Rathor *et al*., 2014), curcumin (Ataie *et al*., 2010), lipoic acid (Militão *et al*., 2010), pentoxifylline (Tariq *et al*., 2008), melatonin (Costa-Lotufo *et al*., 2002; Yamamoto and Mohanan, 2003; Solmaz *et al*., 2009), and *Centella asiatica* (Gupta *et al*., 2003), have been reported to have significant anticonvulsant effects.

Dietary and herbal antioxidants have also been evaluated in epilepsy, Flavonoid and nonflavonoid polyphenolics. Curcumin attenuated Kainic acid-induced seizure, oxidative stress, and consequent neuronal death (Shin *et al*., 2007). Anticonvulsant effects of ginsenosides, the terpenoid saponins from *Panax ginseng*, have been extensively studied in epileptic models *in vitro* (Kim and Rhim, 2004) and *in vivo* (Lian *et al*., 2006; Shin et al., 2009a,b). Ginsenosides have been shown to attenuate seizure activity induced by kainic acid (Lian *et al*., 2006; Shin et al., 2009a,b), pilocarpine, or PTZ (Lian *et al*., 2006).

These agents produce antioxidative effects associated with neuroprotective effects in the brain of many animal models for epilepsy, although it has been reported that some antiepileptic medications, such as valproic acid (Martinez *et al*., 2004) or carbamazepine (Gilham *et al*., 2000), are associated with increased oxidative stress on chronic use. So, the addition of neuroprotective antioxidants therapy to patients with epilepsy is reasonable, and leads to a reduction of neurodegeneration, cognitive impairment and epileptogenesis.

Accordingly, the use of antioxidants as supportive therapy offers beneficial neuroprotective effects in animal models of seizures and in epileptic patients. Both selective and nonselective COX-2-inhibitors, such as aspirin, indomethacin, celecoxib, rofecoxib, etoricoxib, nimesulide, and parecoxib, have been studied for their antiepileptic and neuroprotective effects in different models of epilepsy (Takemiya *et al*., 2006; *et al*., 2010; Rojas *et al*., 2014). Interestingly, the antiepileptic action of celecoxib in PTZ-induced seizures was reported to be reversed by intracerebroventricular administration of PGE2 (Oliveira *et al*., 2008), suggesting that COX-2 may facilitates seizures through PGE2.

Intrahippocampal IL-1 receptor antagonist administration or overexpression in astrocytes leads to inhibition of behavioral and EEG changes induced by injection of bicuculline or kainite, or by electrical stimulation, in mice (Vezzani *et al*., 2002). Furthermore, IV administration of IL-1 receptor antagonist reduces status epilepticus and BBB disruption in the Li-Pc rat model (Marchi *et al*., 2009). This suggests that IL-1β signaling blocking might prevent epilepsy.

Albumin-induced seizures can be prevented by SJN2511 (RepSox), a TGF-β/ALK5 inhibitor (Weissberg *et al*., 2015). In addition, losartan, an antagonist at the angiotensin II receptor, has been shown to block peripheral TGF-β, and can suppress albumin induced TGF-β activation in the brain and prevent seizures (Bar-Klein *et al*., 2014). These findings reinforce the hypothesis that targeting TGF-β signaling may be a strategy for prevention of epilepsy.

In addition, ROS generated by NOX contributes to neurodegeneration in Pc treated rats, which is suppressed by novel selective NOX2 inhibitors (Pestana *et al*., 2010; Altenhöfer *et al*., 2015). Activated NADPH oxidases (NOXs, a family including NOX1, NOX2, NOX3, NOX4, and NOX5) are a primary source of ROS by transporting electrons from intracellular NADPH to extracellular oxygen-generating superoxide (Panday *et al*., 2015).

TNF-α also plays a role in epileptogenesis through TNF receptor type 1 (TNFR1) and to an antiepileptic effect through type 2 (TNFR2) (Balosso *et al*., 2013). So, inhibition of TNFR1 or activation of TNFR2 represents a novel strategy in epilepsy treatment (Kitagaki *et al*., 2012; Varvel *et al*., 2015; Iori *et al*., 2016).

Lipoic acid reduced ROS in seizures induced by Pc in rats (Bellissimo *et al*., 2001; Maczurek *et al*., 2008; Militão *et al*., 2010). Melatonin and curcumin also have neuroprotective and antiepileptic impacts through their antioxidant effect by stimulating glutathione activity and by

inhibiting NO synthase and decreasing MDA activity (de Lima *et al*., 2005; Nabiuni *et al*., 2011).

Conversely, numerous older AEDs have been reported to produce reactive metabolites that bind to different endogenous macromolecules; or increase the formation of ROS and free radicals (Higuch *et al*., 2012). Taking into consideration that epilepsy itself causes oxidative stress, increased oxidative stress caused by AEDs also contributes to the induction of seizures and cognitive impairment in epilepsy patients (Sudha *et al*., 2001; Hamed *et al*., 2004; Reeta *et al*., 2010). For example, carbamazepine and lamotrigine have been shown to decrease performance in learning and memory tests (Arora *et al*., 2010), and significant cognitive decline has been reported after carbamazepine treatment in epileptic patients (Wesnes *et al*., 2009). Furthermore, Reeta *et al*. (2010) reported that phenobarbital and carbamazepine caused significant oxidative stress and deterioration of learning and memory in rats. Comparable results have been already reported in humans (Tonekaboni *et al*., 2006; Park and Kwon 2008).

Vitamin D

Vitamin D (Vit-D) is a fat-soluble steroid hormone that plays a vital role in brain development in early life (Berridge, 2015; Cui *et al*., 2015). It is essential for calcium metabolism, bone health, cardiac function, and blood pressure maintenance (Stewart *et al*., 2010). Vit-D deficiency is a marker of poor health. The primary source of Vit-D is exposure of the skin to ultraviolet sunlight. The metabolic pathway of Vit-D3 involves the conversion of dehydrocholesterol to Vit-D3 in the skin after exposure to sunlight. Vit-D3 is converted to 25-hydroxy-cholecalciferol (25-OH Vit-D3) in the liver (Holick, 2015). 25-OH Vit-D3 is the major circulating form of Vit-D, but itself is biologically inactive and must be converted to the active form 1,25-dihydroxy- Vit D3 (1,25 Vit-D3) in the kidneys (Garcion *et al*., 2002; Stewart *et al*., 2010). Cholecalciferol (Vit-D3) should be supplied from food or synthesized in the exposure of skin to sunlight (Garland *et al*., 2006), and can also be obtained from foods such as fortified margarine and fish oil. Historically, vit-D3 is considered as a hormonal regulator of serum calcium and phosphate (Melamed *et al*., 2008). Vit-D3 nuclear receptors are found in both the central and peripheral nervous system (Cebeci and Ekici, 2014).

A previous study has shown that vit-D regulates the release of nerve growth factor, which is an essential molecule for the survival of hippocampal and cortical neurons (Gezen-Ak *et al*., 2014). Vit-D deficiency in mothers and offspring causes disabilities in early life, including memory and learning problems. Altered neural expression of genes involved in dopamine and glucocorticoid-related pathways has been also reported, suggesting autism and schizophrenic-like disorders (Yates *et al*., 2018).

Vit-D receptor (VDR) is a nuclear steroid receptor through which Vit-D performs its functions in the brain. It has been found that synthesis and destruction of Vit-D occurs in the brain, and VDR, which is required for vitamin D to show its effects, is seen in different regions of the brain. Vit-D has many physiological effects in the nervous system. VDR are widespread in brain tissue, and the biologically active form of Vit-D (1,25(OH)(2) D3) has shown neuroprotective effects including the clearance of amyloid plaques, a hallmark of Alzheimer's disease (Boucher, 2012). Recent studies have confirmed an association between cognitive impairment, dementia, and Vit-D deficiency. A growing body of the literature also suggests that higher serum 25-hydroxyvitamin D (25(OH)D) concentrations, either in uterine or early life, may reduce the risk of autism (Cannell and Grant, 2013). Indeed, vit-D was reported to modulate the biosynthesis of neurotransmitters and neurotrophic factors (Macova *et al*., 2017).

Vit-D deficiency occurs as a result of a diet low in vit-D, a decrease in cutaneous vit-D synthesis, poor sunlight exposure, intake of certain medications, excessive alcohol intake, poor mobility, and tobacco smoking. Vit-D deficiency has been correlated with a host of adverse conditions, including rickets, osteoporosis, osteomalacia, muscle diseases, depression, cognitive dysfunction, and even certain cancers (Cuomo *et al*., 2019).

Antiepileptic treatment and epilepsy comorbidities are associated with negative impacts on Vit-D levels. Vit-D is reported to be deficient in 50% of epileptic people (Teagarden *et al*., 2014). This deficiency may affect several aspects of neuronal function and the response to antiepileptic medications (Cebeci and Ekici, 2014). Seizures in epileptic patients show seasonal variations, with a high peak observed in January, which may reflect the fluctuations in Vit-D levels (Clemens *et al*., 2013).

In addition, a low Vit-D level has been reported in the pathology of many other neurological disorders, such as dementias (Breitling *et al*., 2012), Parkinson's disease, Alzheimer disease (Evatt *et al*., 2008), and multiple sclerosis (Mowry, 2011). Previous studies have shown that Vit-D is deficient and associated with bone loss in patients with epilepsy (Lee *et al*., 2010). However, antiepileptic medications have been reported to be involved in bone growth retardation in children (Khanna *et al*., 2009; Lee *et al*., 2013). Epidemiological and experimental data have suggested a beneficial role of Vit-D in the treatment of mania (Sikoglu *et al*., 2015) and epilepsy (Holló *et al*., 2012). An acute anticonvulsant activity of Vit-D has been demonstrated in experimental rodent models with electrical hippocampal seizures (Siegel *et al*., 1984) or PTZ-induced convulsions (Kalueff *et al*., 2005). Other preclinical (Kalueff *et al*., 2006) and clinical studies (Agarwal *et al*., 2000; Camadoo *et al*., 2007) have reported

associations between deficiency of Vit-D and seizures, which was prevented by Vit-D treatment. In addition, Vit-D3 has been found to play a vital role in seizure frequency in epileptic patients (Borowicz *et al*., 2007; Holló *et al*., 2012).

Effects of vitamin D in epilepsy

Pretreatment with Vit-D before induction of status epilepticus showed clear anticonvulsive activity against Li-Pc-induced seizures, as compared to status epilepticus or to lamotrigine-pretreated groups (Mahfoz *et al*., 2017). This was evidenced by the reduction in the incidence of epilepsy with increasing seizure latency. Morris water maze test results revealed that Vit-D improved cognitive behavior as compared to status epilepticus or lamotrigine-pretreated groups. Moreover, Vit-D significantly reduced Li-Pc-induced oxidative stress and increased antioxidants in the brain, as compared to the status epilepticus group. The antioxidant efficacy and neuroprotection was demonstrated by a reduction in TBARS and NO and GSH elevation in brain tissues (Garcion *et al*., 2002; Chen *et al*., 2003; Lin *et al*., 2005; Mahfoz *et al*., 2017). In addition, Tetich *et al*. (2005) have demonstrated that administration of a low dose of Vit-D3 significantly modulated seizure-associated changes in the rat brain. Moreover, Janjoppi *et al*. (2008) reported that VDRs are also involved in the process of epileptogenesis in the Li-Pc model of epilepsy. They analyzed the relative expression of VDR mRNA in the hippocampal formation of rats during different periods of Pc-induced epilepsy using real-time PCR. The results showed an increase in the relative expression of VDR mRNA in Pc-treated groups. These data suggest that VDR is a possible candidate participating in epileptogenesis in the Pc model of epilepsy.

Increased GABA and decreased glutamate content of brain tissue were demonstrated in the Vit-D-pretreated group in Li-Pc model (Mahfoz *et al*., 2017). This result supported that of a previous study of Sikoglu *et al*. (2015), who found that Vit-D supplementation increased GABA levels in bipolar disorder patients. High GABA and low glutamate levels were reported as a strategy for epilepsy management (Toffano *et al*., 1984). Vit-D is the main steroid hormone responsible for calcium regulation and modulation of calcium channels in brain (Brewer *et al*., 2001). These beneficial effects of Vit-D protect brain neurons from glutamate excitotoxicity.

Cytosolic calcium [Ca 21]i has a vital role in brain signal transduction and several biochemical reactions, and is reported to be increased in neuronal injury. Excess glutamate and glutamate receptor activation is associated with excess [Ca 21]I, which leads to neuronal excitation in epilepsy (Hyrc *et al*., 1997). Vit-D reduces levels of Ca2+ in neurons this may explain its neuroprotective effects and its ability to reduce the onset of neuronal excitation (Berridge, 2017).

Significant anticonvulsant; and cognitive enhancing effects of Vit-D3 were reported in the kindled rat model of epilepsy. Moreover, Vit-D improves the antiepileptic and cognitive effects of lamotrigine in pentetrazol-kindled rats (Gupta *et al*., 2003; Arora *et al*., 2010; Abdel-Wahab *et al*., 2017). Pentetrazol neuroexcitation is reported to be mediated by GABAergic inhibition which leads to the emergence of spontaneous seizures and cognitive impairments (Sayin *et al*., 2003; Morimoto *et al*., 2004). Abdel-Wahab *et al*. (2017) reported that administration of Vit-D, 1.5 mg/kg/day, resulted in an anticonvulsant effect in kindled rats. In addition, Vit-D treatment led to cognitive improvement in the Morris water maze test, while Taghizadeh *et al*. (2013) demonstrated that Vit-D deprived rats had significantly lower cognitive performance in the Morris water maze test. An important role of Vit-D in learning and cognitive functions has been proposed, which possibly involve its neuroprotective and antioxidative mechanisms (Breitling *et al*., 2012; Byrne *et al*., 2013; Taylor and Mulligan, 2014). Cognitive impairments occur usually in epileptic patients with long-term use of antiepileptic medications, which probably reflect the status of oxidative stress, and impaired cognition has been reported in Vit-D deficiency (Becker *et al*., 2005; Annweiler *et al*., 2010).

Another in-vitro study has shown that Vit-D has a strong antioxidative effect against zinc-induced lipid peroxidation (Lin *et al*., 2005). Vit-D action may be related to activation of brain gamma glutamyl transpeptidase, which is a key enzyme in the glutathione cycle, which leads to elevation of brain glutathione (Neveu *et al*., 1994). Moreover, Vit-D has been shown to inhibit expression of inducible NOS in rat brain (Garcion *et al*., 1997) and to interact with ROS in the brain (Byrne *et al*., 2013)

Understanding the important role of Vit-D in epilepsy and response to antiepileptic medications is a complicated issue of interest. Several previous studies demonstrated a link between deficiency of Vit-D and epilepsy. This indicates a promising antiepileptic effect of Vit-D (Christiansen *et al*., 1974; Siegel *et al*., 1984; Oki *et al*., 1991; Kalueff *et al*., 2005; Camadoo *et al*., 2007; Holló *et al*., 2012). Many mechanisms are suggested to clarify the anticonvulsant effects of Vit-D. Nuclear VDRs in the brain neurons are linked to genomic and nongenomic pathways. Activation of VDR has been involved in Vit-D induced neuroprotection (Garcion *et al*., 2002). The genomic effects of Vit-D may involve low expression of pro-convulsant cytokines, as IL-1b and TNF-α (Berridge, 2017).

In addition to its own anticonvulsant effects, Vit-D can improve the antiepileptic activity of other antiepileptic medications such as phenytoin, valproate and carbamazepine (Borowicz *et al*., 2007), and lamotrigine (Abdel-Wahab *et al*., 2017; Mahfoz *et al*., 2017), in animal models of epilepsy.

Unfortunately, there are few clinical data concerning the effect of Vit-D supplements in epilepsy. A pilot clinical study done by Christiansen *et al*. (1974) concluded that Vit-D supplements significantly reduced seizures frequency in patients with drug resistant epilepsy, and it did so independently of magnesium or calcium levels. Holló *et al*. (2012) conducted another clinical study of Vit-D supplementation in drug-resistant epilepsy. Vit-D treatment aimed to normalize the serum level of Vit-D. For subjects with deficient Vit-D, an oral loading dose of 40 000–200 000 IU of Vit-D was given, and continued on a daily maintenance dose of 2000–2600 IU/day. Subjects with normal Vit-D level received only maintenance doses. Vit-D was well tolerated, as no subjects showed toxic levels of Vit-D at 3-months follow-up. Seizures frequency was compared before therapy and 90 days after treatment onset, and most subjects experienced lower seizures after Vit-D treatment. Overall, the existing evidence supports the suggestion that Vit-D supplementation in patients with epilepsy may result in better control of seizures than the existing antiepileptic medications.

Conclusion

There is an accumulation of evidence that oxidative stress is one of the most important processes causing neuronal cell death and epileptogenesis. Identification of key proinflammatory mediators involved in epilepsy, and the development of brain permeable molecules with anti-inflammatory activity, may lead to novel antiepileptic therapies. Most of the conventional AEDs do not prevent neuronal damage or improve cognition and behavior of epileptic patient. So, there is a need to develop new antiepileptic therapies, including novel AEDs with anti-inflammatory activity or combining AEDs with potent antioxidants that will have neuroprotective and antiepileptogenic effects. In addition, a high prevalence of Vit-D deficiency has been observed in the epileptic population. Treatment with antiepileptic drugs influences bone metabolism, bone mass and Vit-D deficiency, which may cause rickets and osteomalacia, resulting in a higher risk of fracture and increased incidence of osteoporosis in adult life. Vit-D was reported to have a promising effect in epilepsy reduction or prevention in different preclinical studies, associated with improvement of memory and cognition through its neuroprotective and antioxidant effects, and neuronal calcium regulation. Vit-D is a nutrient that can be provided to epileptic patients without any life-threatening adverse effects. However, there have been few clinical studies of the effects of Vit-D supplements in epileptic patients. There is still a debate regarding the optimal level of Vit-D supplementation and its exact impact. There is a need for more large-scale Phase I and II clinical trials on epileptic patients with normal or low Vit-D level, testing trying different dose levels of Vit-D to prove the safety and efficacy of Vit-D supplement, or any other novel anti-inflammatory drug, in the treatment or prevention of epilepsy.

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Conflicts of interest

There are no conflicts of interest.

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