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Epilepsy and vitamin D: a comprehensive review of current knowledge

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Abstract: Vitamin D has been considered as neurosteroid, and its pivotal role in neuroprotection, brain development, and immunomodulation has been noticed in studies; however, our knowledge regarding its role in neurological disorders is still developing. The potential role of vitamin D in the pathophysiology and treatment of epilepsy, as one the most prevalent neurological disorders, has received less attention in recent years. In this article, we review the possible relationship between vitamin D and epilepsy from different aspects, including the action mechanism of vitamin D in the central nervous system and ecological and epidemiological findings. We also present the outcome of studies that evaluated the level of vitamin D and the impact of administrating vitamin D in epileptic patients or animal subjects. We also review the current evidence on interactions between vitamin D and antiepileptic drugs.

Keywords: antiepileptic drugs; epilepsy; vitamin D.

Introduction

A seizure is one of the most prevalent neurological disorders. It has been estimated that at least 50 million people worldwide suffer from one kind of epilepsy, and it contributed more than 7 million disability-adjusted life years (DALY) to the global burden of the disease in 2000. In a study that was conducted in India, it has been estimated that the total cost that this disease imposes on the financial system of this country is equivalent to 0.5% of its gross national products (De Boer et al., 2008). Regarding this dimension, any attempts in discovering the underlying pathophysiology and finding new therapeutic strategies are highly appreciated.

The effect of seasonal factors on epilepsy has been well documented. A peak in winter births for people with epilepsy has been shown in both the northern and southern hemispheres. A meta-review of seasonal birth patterns associated with neurological conditions concluded that epilepsy has the most consistent pattern of winter births (Procopio et al., 1997, 2006; Torrey et al., 2000). The onset frequency of infantile spasms is more than two times in the winter compared with the rates in April and May (Cortez et al., 1997). The incidence of first febrile convulsions in pediatrics increases in January as well (Manfredini et al., 2004). It has been reported that in epileptic patients, both seizure frequency and severity increase with higher incidences of sudden unexpected death in epilepsy in the winter (Scorza et al., 2007). Circannual rhythms in the efficacy and potency of antiepileptic drugs in animal studies, with a loss of efficacy in late winter and early spring, have also been reported in the literature (Löscher and Fiedler, 2000). Additionally, complex partial seizures were significantly less likely to occur on sunny days compared to other days with fewer hours of sunshine, regardless of the time of year (Baxendale, 2009). Since sunlight has a pivotal role providing the body with the substantial amount of vitamin D that it needs, all of these data associate a possible role of vitamin D with the pathophysiologic basis of seizure. In recent years, quite a few studies have been done to elucidate the association between epilepsy and vitamin D. This review was aimed to have a brief look at these studies and summarize the currently available studies regarding the direct or indirect role of vitamin D in epilepsy pathophysiology and treatment.

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Materials and methods

We performed a comprehensive literature search for the relationship of epilepsy and vitamin D and for the potential role of antiepileptic drugs to change vitamin D level during the treatment of epilepsy. Strategies for the search were developed by investigators with the support

of a research librarian. We searched electronic databases of peer-reviewed literature for any available article available until July 1, 2016. The keywords/phrases we used for the search were epilepsy, vitamin D, Antiepileptic drugs, sun exposure, brain development, neuroprotection, immunomodulation, and brain cell differentiation. Also, we hand-searched the reference lists of identified articles during the initial search to pinpoint other potentially relevant studies. The initial goal was to grasp a broad knowledge of what work has been conducted to assess the possible role of vitamin D in epilepsy pathophysiology and treatment. We also searched the literature to evaluate the relationship between vitamin D and antiepileptic drugs. We also did a series of searches for individual antiepileptic drugs or category of drugs based on their mechanisms with which they affect vitamin D level. Also, we searched for the mechanisms by which antiepileptic drugs affect vitamin D level and proposed vitamin D supplementation dosage for epileptic patients treated with antiepileptic drugs. Articles were critically appraised and evaluated independently by reviewers, and data were extracted by one reviewer and were studied by other authors. Disagreements were resolved by consensus meeting.

Vitamin D, biosynthesis, biochemistry, and metabolism

Although fortified foods and diets with vitamin D have turned to be an important source of this vitamin in certain countries, vitamin D and its metabolites are not essentially vitamins and can be synthesized in the body. 7-Dehydrocholestriol under the radiation of the UV component of sunlight (290-315) on the exposed skin turns into cholecalciferol, the so-called vitamin D (Holick et al., 1987). Cholecalciferol then binds to the vitamin D binding protein, which is an α-globulin synthesized in the liver (Brown, 1999; Christakos et al., 2012). To become active, vitamin D must be hydroxylated in a two-step reaction at C25 and C1 sites in the liver and kidney, respectively (Grant and Soles, 2009). Hydroxylation occurs in both organs in mitochondria and microsomes and is catalyzed by enzymes of the cytochrome P-450 family. 25-Hydroxyvitamin D (25(OH)D) is the major circulating and storage form of vitamin D and has a half-life of 2–3 weeks. In certain situations, in which the level of circulating vitamin D-binding protein is declined, this period can decrease significantly (Vaziri, 1993) (Figure 1).

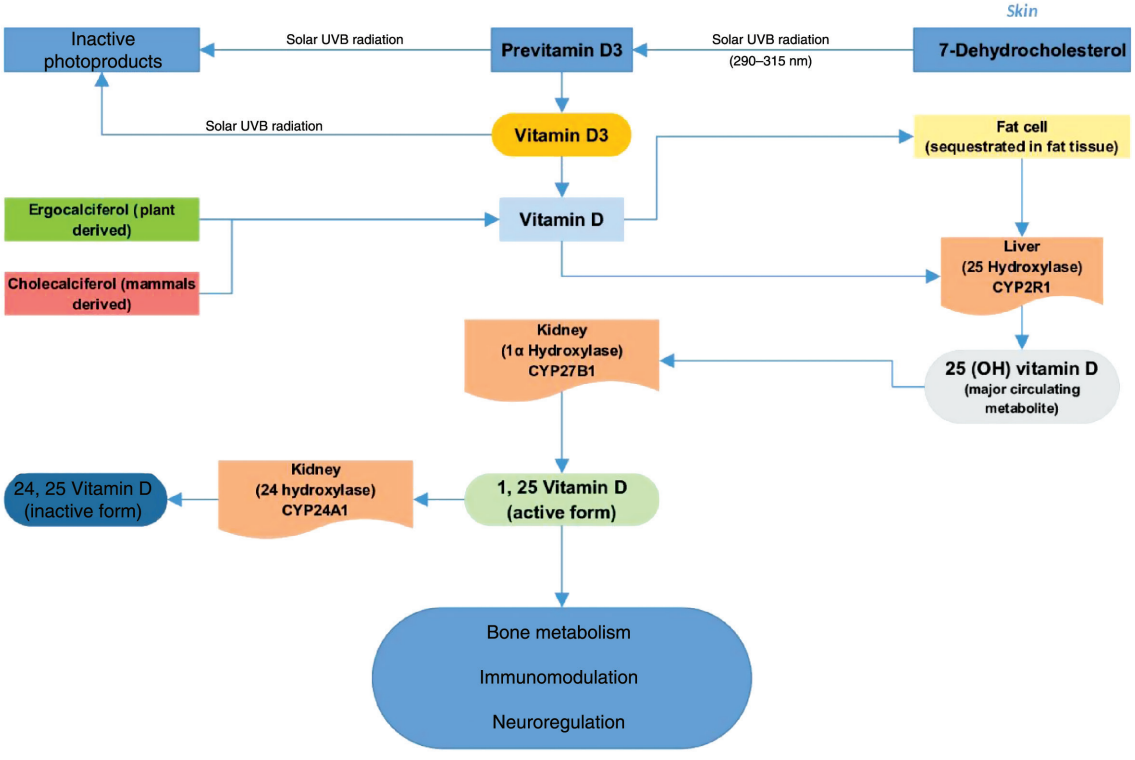

Figure 1: Vitamin D metabolism.
See text for detailed description.

$1,25(OH)_2D$ further diffuses to interstitial fluid, passes through the cellular membrane and attaches its receptor, the vitamin D receptor (VDR), which is a member of the nuclear receptor superfamily. Binding the hormone to its receptor changes confirmation of the complex and forms a hetrodimer with the retinoid X receptor (Eyles et al., 2005). The ultimate complex binds to specific DNA regulatory regions called hormone response elements (HREs). These elements, although very similar in length and arrangement, have a specific sequence of nucleotide for each member of steroid hormones. This sequence for vitamin D is AGGTCAN3AGGTCA (N stands for any nucleotide) and provides the possibility of a tight adhesion between two zinc fingers of hormone-receptor complex and the HRE (zinc finger domain of each monomer recognizes one of the six nucleotide sequences) (Umesono et al., 1991; DeLuca, 2004).

After attachment to HRE, different coactivators or cosupressors bind to a regulatory region of DNA and up-regulate or down-regulate the expression of the adjacent gene.

Receptors of vitamin D are spread in different cells and tissues and, with regulating the genes of different executive proteins, modulate the function of different organs (Lowe et al., 1991). No genomic effects have also been described for vitamin D. These nongenomic effects, which are much faster than the conventional nuclear pathway, are thought to be modulated via certain membranous receptors by activating protein kinase C and mitogen-activated protein (Norman et al., 1992). The gene of calbindin 9k is one of the most characteristic and well-known genes, whose expression is induced by vitamin D. Calbindin 9 is a calcium-binding protein that is expressed in the intestine and plays an important role in the active transport of calcium across enterocytes (Van Cromphaut et al., 2001). Moreover, subgroups of transient receptor potential vanilloid (TRPV5 and TRPV6) that are expressed in intestinal epithelial and are crucial calcium transporters are sensitive to vitamin D (Meyer et al., 2006). Although the role of vitamin D has been investigated extensively in tissues and organs that are involved in mineral ion homeostasis, there are cumulative data, representing the role of this hormone in the function of other organs.

Additional hydroxylation at the C24 site inactivates vitamin D. Vitamin D 24-hydroxylase is expressed in almost all tissues. Metabolites of $1,25(OH)_2D$ are further secreted in to bile and reabsorbed through the enterohepatic circulation (Kawashima et al., 1981; Zierold et al., 1994).

Vitamin D and the central nervous system

Bioavailability of vitamin D in the central nervous system and neuroanatomy of its receptors and metabolizing enzymes

Vitamin D and its metabolites can traverse the blood-brain barrier, and these neurosteroids have been found in the CSF of humans (Balabanova et al., 1984; Pardridge et al., 1985). Both these facts point to the access of systemic vitamin D and its metabolite to the central nervous system (CNS). In order to investigate whether these steroid hormones have targets in the CNS, researchers have localized VDR in neural as well as glial cells. Primary studies of this kind were done on rodent brains. The first study that was done on a human was limited to patients suffering from Alzheimer and Huntington (Moore et al., 1996). In this study, with the application of radiolabeled cDNA probes for *in situ* hybridization, researchers showed that VDR messenger RNA (mRNA) is expressed in the brain of these patients. Further research that was conducted using immunohistochemistry showed that both neurons and glias were positive for VDR. The intensity of immunoreactivity was, however, largely variable, and white matter, in general, got stained less intensely than gray matter zones were, and the strongest immunoreactivity was observed in the hypothalamus and in the large neurons of the substantia nigra (Eyles et al., 2005). Besides the mentioned evidence that makes an endocrine mode of action of vitamin D on CNS cells convincing, there are investigations providing clues of the autocrine and paracrine system of intercellular communication modulated by this hormone. Certain areas in the cerebellum are a good instance for this phenomenon: Whereas Purkinje cells and the molecular layer of the cerebellum were immunoreactive for 1α-hydroxylase, they showed definitely no reaction for VDR. These cerebellar cells thus activate vitamin D to execute its effect on other cells and not on themselves and use a paracrine mode of cellular communication (Eyles et al., 2005).

Members of P450 family enzymes that are involved in hydroxylation and subsequent activation or inactivation of vitamin D are expressed in brain cells. CYP27B1, which is responsible for cholecalciferol hydroxylation at site C1, has been identified in both fetal and adult human brains. There is also evidence regarding the presence of CYP27B1 in cultured glial cells. In the adult human brain, CYP27B1 was expressed most intensively in the substantia nigra and the supraoptic and paraventricular nuclei of

the hypothalamus. Evidence of the presence of CYP24A, a member of the P 450 enzyme superfamily that converts $1,25(OH)_2D$ to inactive $24,25(OH)_2D$, in brain cells has been shown in rodent studies (Neveu et al., 1994a,b; Fu et al., 1997; Zehnder et al., 2001; Eyles et al., 2005). There is also information regarding the increased expression of this enzyme in reaction to increased level of $1,25(OH)_2D$, which indicates a fine local control of level of this neurosteroid and its metabolites in the CNS (Naveilhan et al., 1993).

Vitamin D and neurogenesis

In 1991, researchers reported that $1,25(OH)_2D$ is a potent inducer of nerve growth factor (NGF) (Wion et al., 1991). Since then, cumulative data appeared in the literature showing the effect of vitamin D on neurotrophic factors, which modulate the development and differentiation of neural as well as glial cells. Neurotrophine 3 and 4 (NT3 and NT4), as well as glial cell line-derived neurotrophic factor (GDNF), have been shown to be regulated by $1,25(OH)_2D$ (Neveu et al., 1994a,b; Saporito et al., 1994; Cornet et al., 1998). Neurotrophic factors stimulate the growth of neural cells and promote the survival and differentiation of selected populations of central and peripheral neurons (Furth et al., 1990). NT3 is specifically the most abundant neurotrophine during early development and has been postulated to play a fundamental role in embryonic neurogenesis (Farinas et al., 1994). Interestingly, animal studies have proposed that neurotrophines may be of value in the treatment of degenerative neurologic disease (Furth et al., 1990), and they can partially explain the suggested protective effect of vitamin D in neurodegenerative diseases. Animal models have also proved the fundamental role of vitamin D in brain development. Increased proliferation and mitosis rate, as well as decreased levels of NGF and GDNF, were found in embryonic and infantile vitamin D-deficient rats. Researchers also reported morphologically misshaped brain with enlarged ventricles and longer but not wider hemispheres in deficient rats compared with controls (Eyles et al., 2003; Ko et al., 2004; Féron et al., 2005).

Neuroprotective effect of vitamin D

The neuroprotective characteristic of vitamin D involves the synthesis of calcium-binding proteins, including parvalbumin and calbindin, therefore regulating cellular calcium homeostasis, which is essential for brain cell function (de Viragh et al., 1989; Garcion et al., 2002; Kalueff et al., 2004; de Abreu et al., 2009; Tuohimaa et al., 2009). Additionally, $1,25(OH)_2D$ administration resulted in down-regulating L-type voltage-sensitive Ca channel expression in rat hippocampal cultures which also points to the protective effect of vitamin D in the brain by reducing the influx of calcium ions into neurons (Brewer et al., 2001; Zanatta et al., 2012). It is worth mentioning that excess calcium in nerve cells can result in excitability of neurons because it leads to an increased release of stimulating amino acids and other neurotransmitters. Moreover, excess calcium can cause the activation of nitric oxide synthase (NOS), the formation of reactive oxygen species (ROS), and the activation of proteases and lipases, leading to plasmic and mitochondrial membrane damage (Dong et al., 2009). Furthermore, vitamin D inhibits the synthesis of inducible NOS (iNOS), an enzyme induced under stress situations and diseases like Alzheimer's disease, Parkinson's disease, multiple sclerosis, autoimmune encephalomyelitis, and even in certain infections and AIDS. The active form of iNOS produces nitric oxide (NO). A high level of NO can start a cascade of neurotoxicity, which can subsequently damage both neurons and oligodendrocytes and lead to neural death (Mitrovic et al., 1994; Dawson and Dawson, 1996; Pannu and Singh, 2006; Emmanuel et al., 2011). Vitamin D also increases glutathione (GSH) levels in cultured neurons of rats. A reduced form of GSH, provided by astrocytes, is a primary antioxidant against ROS and apoptosis. Increased GSH levels suggests a significant neuroprotective effect for the active form of vitamin D, by neutralizing oxidative damage to the CNS (Shinpo et al., 2000; Harms et al., 2011).

The neuroprotective effect of vitamin D can also be sought in the immunomodulating properties of this neurosteroid. Studies have demonstrated that the active form of vitamin D suppresses inflammation and changes the balance between inhibitory and excitatory cytokines in favor of inhibitory ones. Suppressive effects of vitamin D on interferon gamma (IFγ) and interleukin-2 (IL-2) production by stimulating the synthesis of IL-10 have been shown (Bartels et al., 2007; Norman, 2008). Additionally, administration of the active form of vitamin D was shown to inhibit the production of TNF-α, IL-6, and NO in the EOC13 microglial cell line, depicting the direct anti-inflammatory properties of vitamin D on microglia (Lefebvre d'Hellencourt et al., 2003). It has also been shown that lipopolysaccharide causes less inflammation by inducting comparatively less inflammatory agents like macrophage colony-stimulating factor and TNF in astrocytes treated with vitamin D (Pardridge et al., 1985).

Clinical clues of neuroprotective property of vitamin D

Besides molecular and cellular data regarding the neuroprotective effect of vitamin D, there are a tremendous number of clinical studies presenting the neuroprotective effects of vitamin D in different neurological disorders. These neurological disorders comprise a very large range of disorders, including neuropsychiatric and behavioral (McGrath et al., 2010), neurodegenerative and dementia (Knekt et al., 2010; Pogge, 2010; Balion et al., 2012; Annweiler et al., 2013), demyelinating (Smolders et al., 2008) as well as ischemic (Wang et al., 2000) disorders. Reviewing the literature for each of these disorders could be the topic of separated articles and is beyond the scope of this review. Some of the most important findings of autism spectrum disorder (ASD) as a neurodevelopmental disorder that is frequently associated with seizure are summarized in Table 1.

Vitamin D and epilepsy

Epidemiologic studies provided most likely the first clues of probable association between vitamin D and epilepsy and so aroused the interest of scientists for further studies in this field. Researchers from the United Kingdom and Denmark reported a seasonal pattern of epilepsy in newborns and found that the rate of epileptic births is highest in January and least in September (Procopio et al., 1997; Procopio and Marriott, 1998). Another study that was conducted in the Southern Hemisphere reported a seasonal pattern of epileptic births too. The proposed pattern was, however, different from the one described in the two previous studies (Procopio et al., 2006).

Afterward, animal models appeared in the literature that proposed anticonvulsant effects of vitamin D. Researchers showed that administration of vitamin D can significantly increase seizure threshold, decrease the severity of chemically induced seizures, and augment the anticonvulsant effect of phenytoin and valproate (Siegel et al., 1984; Kalueff et al., 2005; Borowicz et al., 2007). Moreover, there was evidence of increased seizure susceptibility in rats with VDR knockout genes (Kalueff et al., 2006a,b). A very few clinical studies of vitamin D administration in epileptic patients also reported promising results. In one of these studies that has been done more than 40 years ago, vitamin D administration decreased seizure episodes by 30% in the cases (Christiansen et al.,

Table 1: Clues of association between vitamin D and ASD in the literature at a glance.

Animal models	Epidemiologic studies	Case reports or case series	Noninterventional clinical studies	Clinical trials
Not found	Increased rate of ASD in dark-skinned children living at Northern latitudes (Gillberg, 1990; Goodman and Richards, 1995; Barnevik-Olsson et al., 2008; Cannell, 2008; Eyles, 2010; Keen et al., 2010)	Comorbidity of ASD and autism in a 6-year-old boy (Kočovská et al., 2012)	Plasma level of Egyptian children with autism was significantly lower than that in controls (Meguid et al., 2010)	Not found
Not found	Vitamin D deficiency during pregnancy or early childhood as a possible environmental risk factor for ASD (Cannell, 2008; Grant and Soles, 2009)	Comorbidity of nutritional rickets and ASD in a teenager (Stewart and Latif, 2008)	No significant difference in level of vitamin D was found between cases and controls (Molloy et al., 2010)	Not found
Not found		Comorbidity of scurvy, rickets, and ASD (Noble et al., 2007)	Level of vitamin D was measured in different neuropsychiatric patients; the least value was found in cases with ASD (Humble et al., 2010)	Not found
Not found		Comorbidity of vitamin A, vitamin D deficiency, and ASD in an 8-year-old (Clark et al., 1993)	There was a trend of lower level of vitamin D in mothers with autistic children (Fernell et al., 2010)	Not found
Not found		Supplementation of vitamin D improved core symptoms in a 32-month old boy (Jia et al., 2015)		Not found

ASD, Autism spectrum disorder.

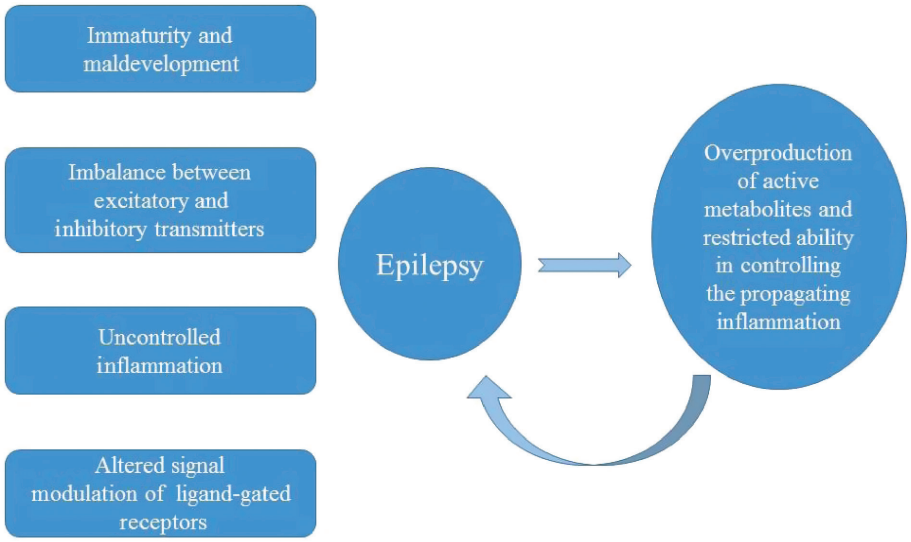

Figure 2: Schematic view of the probable mechanisms through which vitamin D deficiency makes CNS vulnerable to seizure. See text for detailed description.

1974), and another study that was conducted in 2011 reported a significant reduction of seizure numbers (Holló et al., 2012).

At a basic level, an epileptic seizure is the result of an imbalance between excitatory and inhibitory currents (McCormick and Contreras, 2001). Ion channels are the mainstay of current conduction both in axonal propagation and synaptic transmission. Two major types of ion channels are responsible for inhibitory and excitatory activity:

1. Voltage-gated channels: These channels get activated by the changes in the membrane potential and permit passage of charged ion. Calcium and sodium voltage-gated channels are excitatory, for they permit inward passage of positive ions and depolarize the cell membrane toward action potential threshold. Potassium voltage-gated channels are in contrast inhibitory and hyperpolarize the cell membrane.
2. Ligand-gated channels: These channels are in fact receptors of neurotransmitters. After the release of neurotransmitters from presynaptic neurons, neurotransmitters like glutamate and γ-amino butyric acid (GABA) attach to their postsynaptic membranous receptors and activate a cascade of intracellular events and changes simultaneously the confirmation of the receptor and creates a membranous pore, which allows the passage of charged ions (Davis and Crozier, 2015).

As mentioned above ('Vitamin D and neurogenesis' section), it has been shown in the literature that vitamin D plays a fundamental role in the development, differentiation, and maintenance of CNS (both neurons and glias). Immature neurons or neurons with retarded development for different reasons represent more susceptibility to seizure because of at least one of the following reasons (Figure 2):

1. Ion channels that are responsible for depolarization appear first and excitatory neurotransmitters develop before inhibitory ones (Simeone et al., 2004; Raol et al., 2006).
2. GABA neurotransmitter that is expectably an inhibitory neurotransmitter functions as an excitatory neurotransmitter (Ben-Ari et al., 2012).
3. In the developing brain, synapses are more prevalent than in mature brain; fast electrical transmission makes rapid synchrony of the neural network possible and provokes seizures (Margineanu, 2010; Mylvaganam et al., 2014).
4. The expression of Na^+/K^+-ATPase as the major dynamic for keeping the stability of cell membrane potential experiences a developmental time course (Swann et al., 2007).
5. Moreover, glial cells act as reservoirs for charged ions, specifically extracellular potassium. This 'buffer' ability of glial cells improves in course of development (Benarroch, 2011).

These factors could be especially important in infantile and pediatric seizures, and they certainly have the potentials to become subjects of basic studies to seek these pathologies directly in neural and glial cells that have

been cultured under vitamin D deficient conditions. These results could be further compared with control models in the same phase of development.

Susceptibility of neural networks to seizure could be simplified with the help of the proconvulsant and anticonvulsant model, that is, categorizing the internal and external stimuli as two major entities: (1) Those factors that directly or indirectly depolarize the cell membrane toward action potential threshold and/or those that decrease the threshold and/or those which facilitate the synapses and (2) those factors that directly or indirectly hyperpolarize the cell membrane and/or those that increase the threshold. In this part of our review, we will try to have a glance at studies that provide data regarding the role of vitamin D as an anticonvulsant agent.

There is the capacious amount of data representing the possible role of inflammation in provoking and maintaining the seizure.

A very complex interaction between an enormous number of cytokines, chemokines, and prostaglandins and their effects on different receptors during epilepsy makes a simple interpretation of the role of each of these cytokines almost impossible. In neural tissues at rest, IL-1β, TNF-α, and IL-6 are expressed very infrequently, after induction of the seizure; however, the mRNA and the subsequent protein levels increase rapidly and return to a normal level only after 48–72 h.

IL-1β remains overexpressed even 60 days after status epilepticus (De Simoni et al., 2000). Concomitant with overexpression of inflammatory factors, receptors of these agents get unregulated (Balosso et al., 2005; Ravizza and Vezzani, 2006). Members of the Toll-like receptor (TLR) family are also unregulated (Turrin and Rivest, 2004). TLRs are specific receptors and belong to the family of type I transmembrane proteins that are expressed by cells of the immune system (Akira et al., 2001). The stimulation of these receptors and costimulatory factors like CD14 induces the expression of transcriptional factors like nuclear factor κB, which can induce the expression of different inflammatory genes like macrophage inflammatory protein-1α (MIP-1α), monocyte chemo attractant protein-1 (MCP-1), and cyclooxigenase 2 (COX-2) (Nguyen et al., 2002; Laflamme et al., 2003; Rivest, 2003). Something very interesting about the effects of these cytokines is their potentially antithetical effects on glial cells. One particular cytokine depending on its extracellular concentration and length of the injury time could induce the production of either cytotoxic or neurotrophic agents (Bernardino et al., 2005).

It must be mentioned that the relationship between inflammation and seizure is not one sided. Whereas there are cumulative data regarding the prominent inflammatory response of CNS to an induced seizure, there is also solid evidence of the role of inflammation in provoking seizures. Scientists have depicted that injection of antibodies against IL-1β and TNF-α could effectively prevent infected related seizures (Yuhas et al., 1999). Moreover, IL-1β has shown to increase the duration of electrographic and behavioral seizures (Vezzani et al., 1999), and intracerebral injection of IL-1-antagonist receptor IL-1Ra represented powerful anticonvulsant properties (Vezzani et al., 2002). Pharmacological inhibition or gene knockout of caspase-1 enzyme, which makes biologically active form of IL-1β, could inhibit episodes of seizures as well (Vezzani et al., 2002).

As discussed in the 'Neuroprotective effect of vitamin D' section, the active form of vitamin D exhibits its immunomodulatory effects and can effectively suppress the inflammation and so execute its anticonvulsant effects. Nevertheless, there are very few studies that have focused on the immunomodulatory effects of vitamin D and its direct effect on controlling seizure. In a study that has been published recently, researchers treated their patients with retractable seizures with 50 000 units of vitamin D_2 weekly and 200 mg/kg twice daily of vitamin B12. They further measured the value of some oxidative status indices as well as cytokines. The mean value of salivary super oxidase dismutase activity and salivary metalloproteinase (MMP2, MMP3, and MMP9) decreased. The decrease in the level of IL-β, IL-6, IL-8, MIP-1β, MCP-1 was significant. Interestingly, researchers in this study found fewer activation sites of the left and right temporal epilepsy after treatment and concluded that this treatment could decrease the intensity of seizure retractable (Li et al., 2015). Although there are some methodological limitations (lack of randomization, the unclear length of treatment, and ignorance of probable confounding variables), this study is one of the very few clinical trials that have tried to directly assess the relationship between vitamin D supplement and control of seizure regarding its immunomodulatory effects. Another aspect of the role of inflammation that should be emphasized is that the produced cytokines after the onset of the seizure could exacerbate the cell injury and promote further seizures. In an animal study, researchers could show that antagonizing the peripheral inflammation could decrease the severity of the status epilepticus. This concept gets even more importance considering the fact that CNS is less effective in antagonizing the inflammation from the periphery and might be more vulnerable to injury caused by uncontrolled inflammation (Dinarello, 1996).

The exact cellular mechanism underlying the modulating effect of inflammation on the induction and the severity and duration of seizure is not clear. Yet there are some clues connecting the inflammation to inhibitory and excitatory neurotransmitters and thus justifying its proconvulsant effects at least partially. The function of GABA and glutamate as crucial neurotransmitters in the initiation and propagation of seizure is widely well known. Glutamate exerts its function by attaching two types of receptors: *N*-methyl-D-aspartate (NMDA) receptors and non-NMDA receptors. Besides a site for adhesion of glutamate, there is also a recognition site in NMDA receptors for other modulators like zinc, polyamines, and MK-801. Activation of NMDA receptors facilitates the influx of sodium and calcium and under pathologic conditions could lead to epileptiform charge (Kalia et al., 2008; Vyklicky et al., 2014).

Researchers have shown that the induction of COX-2 can activate NMDA receptors (Adams et al., 1996). A similar function has been introduced for IL-1β as part of its proconvulsant effect on kainite seizure in rats (Vezzani et al., 1999). Moreover, IL-1β and TNF-α increase release of glutamate from astrocytes (Kamikawa et al., 1998; Bezzi et al., 2001) and inhibit its reuptake by glial cells (Ye and Sontheimer, 1996). There is also evidence that TNF-α can react with NMDA receptor and augment its functions (Viviani et al., 2003). IL-1β has also shown to block GABAergic inhibitory conduction (Zeise et al., 1997). Another interesting finding that links inflammation to the function of neurotransmitters is the interaction of TNF-α and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors. After adhering to p55 receptors, TNF-α increases the membranous expression of AMPA receptors in a particular molecular confirmation that reinforces glutamate responses. Additionally, TNF-α facilitates endocytosis of GABA receptors and in this way diminishes the inhibitory effect of GABA (Beattie et al., 2002; Stellwagen et al., 2005).

Complementary to these findings that could explain the anticonvulsant effects of vitamin D via its immunomodulatory effects, there are extremely few studies conducted that studied the direct effect of vitamin D on ligand-gated channels as well as neurotransmitters.

There is evidence that vitamin D can change the expression of α4 and α1 subunits of GABA receptors (Kalueff et al., 2006a,b). As there is evidence of nongenomic effects for other neurosteroids, such a mode of action has also been postulated for vitamin D in the literature (Kalueff et al., 2006a,b).

A transient vitamin D deficiency in infancy in rodents has also shown to affect NMDA-mediated signaling. Although these animal models have been described as plausible models for schizophrenia, they could be helpful in completing the puzzle of the effect of vitamin D on the pathophysiology of epilepsy (Kesby et al., 2006, 2012).

Vitamin D and therapeutic strategies of epilepsy

According to the available data in the literature, the role of vitamin D in therapeutic strategies of seizure was assessed based mainly on its interaction with antiepileptic drugs (AEDs). Since a growing body of evidence has shown the negative impact of AEDs on bone health and metabolism. Also few clinical studies reported the effect of vitamin D administration on seizure control. Hence, the role of vitamin D in therapeutic strategies can be evaluated in four separate entities: (1) direct or indirect effect of vitamin D in body response to AEDs, (2) vitamin D as an independent antiepileptic drug, (3) vitamin D and antiepileptics, and (4) vitamin D screening and supplementation in epilepsy.

Direct or indirect effect of vitamin D in body response to AEDs

Microglia and astrocytes activated by epileptogenic injury increase their synthesis and release of proinflammatory molecules, therefore contributing to the generation of inflammation of neural tissue. This is now regarded as an established hallmark of epileptogenic foci in various forms of drug-resistant epilepsies (DREs). Therefore, an anti-inflammatory approach to DRE is being proposed as disease-modifying therapies with which we can convert DRE to drug-sensitive epilepsy (Löscher and Brandt, 2010; Vezzani, 2015). Moreover, a rich inflammatory response has been noticed in the hyperexcitable brain, which showed increased levels of microglia-derived inflammatory cytokines in brain materials of both mice after status epilepticus and recurrent seizures and epileptic patients (Vezzani and Granata, 2005). As previously discussed, due to a potential anti-inflammatory property of vitamin D, we can postulate that the response to antiepileptic drugs can be potentially augmented by administration of vitamin D (Bartels et al., 2007; Lefebvre d'Hellencourt et al., 2003; Norman, 2008); however, this hypothesis could be questioned since some studies reported that DRE patients were not different from their responsive

epileptic patients with respect to serum vitamin D level (Lee et al., 2015; Nagarjunakonda et al., 2016).

Vitamin D as an independent antiepileptic drug

Studies that evaluated the direct role of vitamin D in controlling epilepsy are limited. As previously discussed, in our literature review, we found only three human studies suggesting a role of vitamin D as a potential antiepileptic agent in controlling seizures. In the earliest study in 1974, the supplementation of vitamin D (4000 IU/day) resulted in a mean seizure reduction of 30% in the treatment, while no significant seizure reduction was observed in the control group. Also, results showed that seizure reduction was not associated with a change in the serum level of calcium and magnesium (Christiansen et al., 1974). In another study in 2011, the level of vitamin D was investigated in 13 patients with refractory epilepsy. After correcting the low level of vitamin D in patients by supplementing vitamin D, the effect of treatment by means of seizure reduction was assessed and the significant decrease in seizure numbers with a median of 40% was reported. Also, a higher percentage of seizure reduction in patients with a larger increase in vitamin D level was noticed (Holló et al., 2012). In a case report of loss of seizure control due to hypocalcemia in a long-term user of an antiepileptic drug, a patient's seizure was controlled after calcium had been normalized with the administration of vitamin D and calcium, showing the possibility of an antiepileptic feature of vitamin D (Ali et al., 2004).

Animal studies also support an antiepileptic effect of vitamin D. In a study in 2007, vitamin D3 used at doses of 37.5 and 75 μg/kg considerably increased the electroconvulsive threshold. Also, cholecalciferol (at its highest subthreshold dose of 18.75 μg) raised the antiepileptic activity of phenytoin and valproate. When administrated at the upper dose of 37.5 μg/kg, vitamin D3 also potentiated the action of carbamazepine and phenobarbital (Borowicz et al., 2007). In another study, the possible role of VDRs in experimental epilepsy in mice was investigated and the seizure profiles in VDR knockout mice following a systemic injection of pentylenetetrazole (70 mg/kg) was assessed. The VDR knockout group meaningfully showed shorter latencies to the onset, higher Racine scores, and increased mortality rates in comparison to control group. The authors concluded that VDRs exert a modifying influence on seizure susceptibility in mice and vitamin D/receptor might be involved in the pathogenesis of epilepsy (Kalueff et al., 2006a,b).

Antiepileptic drugs and vitamin D

Antiepileptic drugs exert their effect on lowering vitamin D level primarily through induction of cytochrome P-450. This mechanism is mediated through orphan nuclear and pregnane X receptor (PXR). The activation of PXR by AEDs can result in the induction of CYP 2 and CYP 3, the cytochrome P450 enzymes involved in drug metabolism. Furthermore, since PXR and VDR share homology in their respective DNA-binding domains, PXR activators such as AEDs can lead to increased expression of CYP24, a target gene of VDR. CYP24 is a major enzyme involved in the metabolism of $1,25(OH)_2D$ and thereby decreases the level of active form of vitamin D. This mechanism accounts mostly for older AEDs such as phenytoin, which are known for being enzyme inducers (Pascussi et al., 2005; Zhou et al., 2006).

The effect of antiepileptic drugs on bone mineral density, vitamin D, calcium, and phosphorus has been investigated vastly and specifically thoroughly in the older generation of antiepileptic drugs. Herein, we present the current findings regarding vitamin D level changes during AED therapy in two major groups: enzyme-inducing and non-enzyme-inducing AEDs. Table 2 summarizes the net effect of AEDs on vitamin D and calcium levels.

Enzyme-inducing antiepileptic drugs

These drugs are known to have an effect of inducing the cytochrome P-450 system, which will eventually increase catabolism of vitamin D by up-regulating enzymes, converting vitamin D into inactive metabolites. These drugs included phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and primidone (Brodie et al., 2013).

Phenytoin: A reduction in the level of serum 25(OH) D in both adults and children has been noticed in many studies (Tjellesen and Christiansen, 1982; Lau et al., 1995; Feldkamp et al., 2000; Kulak et al., 2004; Pack et al., 2008). Evidence also exists for declined serum level of calcium and hypophosphatemia (Schmitt et al., 1984; Gough et al., 1986; Telci et al., 2000; Pack et al., 2005).

Phenobarbital: Early 1970s studies and also recent studies demonstrated a decrease in 25(OH) D (Hahn et al., 1972; Lifshitz and Maclaren, 1973; Foss et al., 1978; Weisman et al., 1979; Hosseinpour et al., 2007), and no alteration in calcium and phosphorus has been reported (Voudris et al., 2002; Tekgul et al., 2006), except for one study that reported decreased serum calcium level that was independent from vitamin D level (Weinstein et al., 1984).

Carbamazepine: Although many studies reported decreased level of 25(OH) D (Kumandas et al., 2006;

Table 2: AEDs and vitamin D and calcium/phosphorus levels.

Antiepileptic drug	Vitamin D	Calcium
Phenytoin[a]	Decreased (Tjellesen and Christiansen, 1982; Lau et al., 1995; Feldkamp et al., 2000; Kulak et al., 2004; Pack et al., 2008)	Decreased (Schmitt et al., 1984; Gough et al., 1986; Telci et al., 2000; Pack et al., 2005)
Phenobarbital[a]	Decreased (Hahn et al., 1972; Lifshitz and Maclaren, 1973; Foss et al., 1978; Weisman et al., 1979; Hosseinpour et al., 2007)	Not changed (Voudris et al., 2002; Tekgul et al., 2006)
Carbamazepine[a]	Decreased (Kumandas et al., 2006; Mintzer et al., 2006; Nicolaidou et al., 2006; Kim et al., 2007; Fuleihan et al., 2008) Not changed (Erbayat Altay et al., 2000; Ecevit et al., 2004; Tekgul et al., 2006; Pack, 2008)	Not changed (Erbayat Altay et al., 2000; Ecevit et al., 2004; Tekgul et al., 2006; Pack, 2008)
Oxcarbazepine[a]	Decreased (Mintzer et al., 2006; Cansu et al., 2008)	Decreased (Mintzer et al., 2006; Cansu et al., 2008)
Primidone[a]	Decreased/not changed (Christiansen et al., 1973; Bouillon et al., 1975; Hahn et al., 1975; Ensrud et al., 2004)	Not changed (Christiansen et al., 1973; Bouillon et al., 1975; Hahn et al., 1975; Ensrud et al., 2004)
Valproic acid	Decreased (Nicolaidou et al., 2006; Krishnamoorthy et al., 2010; Menon and Harinarayan, 2010) Not changed (Kim et al., 2007; Verrotti et al., 2010)	Not changed (Kim et al., 2007; Verrotti et al., 2010)
Lamotrigine	Not changed (Stephen et al., 1999; Pack et al., 2005, 2011; Kim et al., 2007)	Not changed (Stephen et al., 1999; Pack et al., 2005, 2011; Kim et al., 2007)
Gabapentine	Not mentioned	Not mentioned
Zonisamide	Not mentioned	Not mentioned
Levetiracetam	Not changed (Ali et al., 2006; Heo et al., 2011; Koo et al., 2013)	Not changed (Ali et al., 2006; Heo et al., 2011; Koo et al., 2013)
Topiramate	Not changed (Ali et al., 2011; Heo et al., 2011)	Decreased (Ali et al., 2011; Heo et al., 2011)

[a]Enzyme-inducing antiepileptic drugs.

Mintzer et al., 2006; Nicolaidou et al., 2006; Kim et al., 2007; Fuleihan et al., 2008), some authors reported unchanged levels of vitamin D during treatment with this drug (Erbayat Altay et al., 2000; Ecevit et al., 2004; Tekgul et al., 2006; Pack, 2008).

Oxcarbazepine: Oxcarbazepine is a new antiepileptic drug with a similar chemical structure to carbamazepine. Its mechanism of action is similar to carbamazepine, but it minimally affects cytochrome p450 (Freidel et al., 2007). In our literature review, we found a few articles evaluating the effect of this drug on vitamin D level. In general, oxcarbazepine was associated with decreased 25(OH) D level (Mintzer et al., 2006); however, a significant reduction in vitamin D level was also reported (Cansu et al., 2008).

Primidone: Primidone also induces cytochrome P450. Studies have revealed its negative impact on 25(OH) D level (Christiansen et al., 1973; Bouillon et al., 1975; Hahn et al., 1975; Ensrud et al., 2004).

Non-enzyme-inducing antiepileptic drugs

This category of drugs may also have effects on the level of vitamin D. These antiepileptic drugs are valproic acid, lamotrigine, gabapentin, zonisamide, levetiracetam, and topiramate.

Valproic acid: Data regarding the change in 25(OH) D level are controversial: while several studies reported a reduction in 25(OH) D (Nicolaidou et al., 2006; Krishnamoorthy et al., 2010; Menon and Harinarayan, 2010), some studies revealed an unchanged level of 25(OH) D during therapy with valproic acid (Kim et al., 2007; Verrotti et al., 2010).

Lamotrigine: Available studies regarding the effect of lamotrigine on vitamin D indicate that there is no decrease in the level of vitamin D; however, more study needs to be done to confirm these findings (Stephen et al., 1999; Pack et al., 2005, 2011; Kim et al., 2007).

Gabapentine: To date, there is no study regarding the effect of gabapentin on vitamin D as a monotherapy or polytherapy.

Zonisamide: In our literature review, we did not find any article that assessed the level of 25(OH) D during therapy with this drug.

Levetiracetam: Data regarding changes in vitamin D level during monotherapy with levetiracetam are very limited, and we found only four articles in this matter which are generally in line. Three studies reported an unchanged

level of 25(OH) D during monotherapy (Ali et al., 2006; Heo et al., 2011; Koo et al., 2013) and the fourth one reported improved vitamin D level when patient switched from phenytoin to levetiracetam (Phabphal et al., 2013).

Topiramate: Few studies are available assessing the effect of topiramate on vitamin D; these cross-sectional studies did not show a decreased level of 25(OH) D (Ali et al., 2011; Heo et al., 2011).

Polytherapy with AED: Also worth mentioning is that patients receiving many antiepileptic drugs are more likely to have lower 25(OH) D compared to those undergoing monotherapy (Sumi et al., 1978; Gough et al., 1986; Bergqvist et al., 2007; Fuleihan et al., 2008; Nettekoven et al., 2008).

Vitamin D screening and supplementation in epilepsy

Presently, according to the American Endocrine Society guidelines, patients on AED therapy should be screened for decreased levels of vitamin D. Also, prophylaxis with vitamin D has been recommended (Holick et al., 2011). In general, it could be said that the amount of prescribed vitamin D should be sufficient enough to keep the level of 25(OH) D within the normal range (above 30 ng/ml), which is usually achieved by administration of higher than 400 IU per day of vitamin D in adults (Holick and Garabedian, 2006). Calcium supplementation should also be given to patients on AED, especially to those who have multiple risks or low bone mineral density. The amount of Ca supplementation should be between 1000 and 1500 mg/day, considering higher doses for elderly and lower doses for young patients (Pack and Morrell, 2004; Sheth, 2004). Also, epileptic children should receive vitamin D besides the current recommendation on vitamin D supplementation for healthy children because they are at higher risk (Sheth, 2004). As for pregnant women, even if they receive vitamin D supplementation, they are still considered as a high-risk group; therefore, they should be screened for vitamin D deficiency. Screening becomes more important when pregnant women take an AED for epilepsy (Holick et al., 2011).

Discussion

The main function of a review article is summarizing the current available data and elucidating the existing gap in our knowledge to become the basis for further investigations. Like other neuropsychiatric diseases, our data regarding the effect of vitamin D on pathophysiologic course of the epilepsy comes mostly from epidemiologic and noninterventional clinical studies, which provide indirect evidence supporting the role of vitamin D in this neurological disorder. With the current situation, randomized clinical trials on different categories of patients, considering their antiepileptic regimen, are highly recommended. Such studies could provide unbiased and direct information regarding the probable protective effect of vitamin D in preventing, decreasing the severity of, and managing epilepsy. Moreover, the protective goal level of vitamin D in different age groups, especially in high-risk groups like children and pregnant women, must be sought. In a study that was conducted in the United States, 12% of all child-bearing women in the United States were vitamin D deficient (Thomas et al., 1998). Although the optimal level of vitamin D during pregnancy is not clear, the requirement of vitamin D increases in this period and especially in the third trimester (Holick, 2007). In a study that was conducted in Denmark, the prevalence of vitamin D deficiency was 36.7%, and even after 15 months of vitamin D supplementation ranging between 400 and 1200 IU/day, 64% of vitamin-deficient patients failed to attain a sufficient level (Snoeijen-Schouwenaars et al., 2015). This fact points to the need for a revision of current standard protocols. Regarding the fundamental role of vitamin D in neurogenesis, investigating and defining the sufficient protecting yet concurrently safe level of vitamin D in pregnant women and children must be emphasized.

At the basic level, the condition is not much better. Although there are large number of studies representing and highlighting the role of vitamin D in neurogenesis and neural development, there is extremely rare information concerning the effect of vitamin D deficiency on neural and glial tissues at the cellular level. Special focus seems to be needed on aspects of immaturity that render the neural tissue to epileptiform currents like ion channels, inhibitory and excitatory neurotransmitters, ligand-gated receptors, and buffer capacity of glial cells. Whether vitamin D deficiency solely postpones neural development or leads to maldevelopment and whether these abnormalities could be corrected after subsequent exposure to vitamin D have the potentials to become fascinating issues for basic studies.

Inflammation is another link between seizure and vitamin D. Immunomodulatory properties of vitamin D and its immunosuppressive effects have been investigated properly; moreover, results regarding the role of inflammation in provoking and propagating the seizure seem to be convincing. Nevertheless, direct anticonvulsive effect of vitamin D through its immunomodulatory effects have

been assessed in absolutely limited number of studies. In the orchestra of hundreds of cytokines and chemokines with a complex interplay between them, the role of each of these active agents must be interoperated in connection with others, and a dogmatic view of the role of each separately could not be helpful in solving the final puzzle. Even so, the role of some of these agents in the pathogenesis of seizure appears to be more prominent, and cytokines like TNF-α, IL-6, and particularly IL-1β are tempting subjects for further studies in this regard.

A very important argument regarding the proconvulsive role of inflammation is considering its dichotomous effect in this field. As mentioned in the text, inflammation depending on the concentration of certain cytokines and chemokines and the duration of their contacts with the tissue could induce even neuroprotective agents. It must be considered that inflammation is potentially a defense mechanism against a variety of insults and pathogens and plays a fundamental role in repairing the tissues after different injuries and damages. Therefore, every anti-inflammatory process should not be regarded as an advantageous and positive process, and the final beneficiary effect must be assed with a holistic vision and interpreted with caution.

As regard to the relationship between antiepileptic drugs and vitamin D, it can be concluded that old enzyme-inducing drugs are more likely to cause vitamin D deficiency, and there is an overwhelming body of evidence to support this conclusion. Although the number of studies about the effect of non-enzyme-inducing antiepileptic drugs is limited, it appears that there is no unchanged level of vitamin D during the therapy with these drugs except for controversial results from valproic acid studies. Further, it seems that patients on polytherapy with antiepileptic drugs are more susceptible to vitamin D deficiency.

It has been proposed that epileptic patients should be screened for vitamin D deficiency, and the supplementation of vitamin D has also been proposed, and this becomes more important for those who are already at risk of vitamin d deficiency.

We realize the limitation to our study. We did not include non-English studies; however, we identified few articles during the study search process, which would not have significantly changed our findings. Further, we did not provide any additional statistical analysis to assess existing data and to draw a better conclusion.

Vitamin D deficiency has been noticed in many antiepileptic drugs; however, there is no recommendation regarding the optimal dose of administration and preferred level of vitamin D in epileptic patients, especially in those who are already at high risk for vitamin D deficiency, including elderly, children, and pregnant women. Furthermore, currently, no clear guideline regarding which one of antiepileptic drugs needs vitamin D supplementation exists.

We suggest that future studies should focus on evaluating the direct impact of vitamin D deficiency in an epileptic patient, and more attention needs to be paid to determine what the optimal dose of vitamin D in epilepsy is. We also suggest more studies should be done to investigate the possible role of vitamin D in the pathogenesis of epilepsy. Furthermore, the relationship between VDR gene polymorphism and epilepsy should also be investigated.

Conflict of interest statement: All authors declare that they have no conflict of interest.

References

Adams, J., Collaço-Moraes, Y., and De Belleroche, J. (1996). Cyclooxygenase-2 induction in cerebral cortex: an intracellular response to synaptic excitation. J. Neurochem. *66*, 6–13.

Akira, S., Takeda, K., and Kaisho, T. (2001). Toll-like receptors: critical proteins linking innate and acquired immunity. Nat. Immunol. *2*, 675–680.

Ali, F.E., Al-Bustan, M.A., Al-Busairi, W.A., and Al-Mulla, F.A. (2004). Loss of seizure control due to anticonvulsant-induced hypocalcemia. Ann. Pharmacother. *38*, 1002–1005.

Ali, I.I., Herial, N.A., Horrigan, T., Kellough, L., and Tietjen, G.E. (2006). Measurement of bone mineral density in patients on levetiracetam monotherapy. Epilepsia *47*, 276–276.

Ali, I.I., Herial, N.A., Orris, M., Horrigan, T., and Tietjen, G.E. (2011). Migraine prophylaxis with topiramate and bone health in women. Headache *51*, 613–616.

Annweiler, C., Llewellyn, D.J., and Beauchet, O. (2013). Low serum vitamin D concentrations in Alzheimer's disease: a systematic review and meta-analysis. J. Alzheimers Dis. *33*, 659–674.

Balabanova, S., Richter, H.-P., Antoniadis, G., Homoki, J., Kremmer, N., Hanle, J., and Teller, W. (1984). 25-Hydroxyvitamin D, 24, 25-dihydroxyvitamin D and 1, 25-dihydroxyvitamin D in human cerebrospinal fluid. Klin. Wochenschr. *62*, 1086–1090.

Balion, C., Griffith, L.E., Strifler, L., Henderson, M., Patterson, C., Heckman, G., Llewellyn, D.J., and Raina, P. (2012). Vitamin D, cognition, and dementia A systematic review and meta-analysis. Neurology *79*, 1397–1405.

Balosso, S., Ravizza, T., Perego, C., Peschon, J., Campbell, I.L., De Simoni, M.G., and Vezzani, A. (2005). Tumor necrosis factor-α inhibits seizures in mice via p75 receptors. Ann. Neurol. *57*, 804–812.

Barnevik-Olsson, M., Gillberg, C., and Fernell, E. (2008). Prevalence of autism in children born to Somali parents living in Sweden: a brief report. Dev. Med. Child Neurol. *50*, 598–601.

Bartels, L.E., Jørgensen, S.P., Agnholt, J., Kelsen, J., Hvas, C.L., and Dahlerup, J.F. (2007). 1, 25-Dihydroxyvitamin D3 and dexamethasone increase interleukin-10 production in CD4+ T cells

from patients with Crohn's disease. Int. Immunopharmacol. *7*, 1755–1764.

Baxendale, S. (2009). Seeing the light? Seizures and sunlight. Epilepsy Res. *84*, 72–76.

Beattie, E.C., Stellwagen, D., Morishita, W., Bresnahan, J.C., Ha, B.K., Von Zastrow, M., Beattie, M.S., and Malenka, R.C. (2002). Control of synaptic strength by glial TNFα. Science *295*, 2282–2285.

Ben-Ari, Y., Khalilov, I., Kahle, K.T., and Cherubini, E. (2012). The GABA excitatory/inhibitory shift in brain maturation and neurological disorders. Neuroscientist *18*, 467–486.

Benarroch, E.E. (2011). Na^+, K^+-ATPase functions in the nervous system and involvement in neurologic disease. Neurology *76*, 287–293.

Bergqvist, A., Schall, J.I., and Stallings, V.A. (2007). Vitamin D status in children with intractable epilepsy, and impact of the ketogenic diet. Epilepsia *48*, 66–71.

Bernardino, L., Xapelli, S., Silva, A.P., Jakobsen, B., Poulsen, F.R., Oliveira, C.R., Vezzani, A., Malva, J.O., and Zimmer, J. (2005). Modulator effects of interleukin-1β and tumor necrosis factor-α on AMPA-induced excitotoxicity in mouse organotypic hippocampal slice cultures. J. Neurosci. *25*, 6734–6744.

Bezzi, P., Domercq, M., Brambilla, L., Galli, R., Schols, D., De Clercq, E., Vescovi, A., Bagetta, G., Kollias, G., and Meldolesi, J. (2001). CXCR4-activated astrocyte glutamate release via TNFα: amplification by microglia triggers neurotoxicity. Nat. Neurosci. *4*, 702–710.

Borowicz, K.K., Morawska, M., Furmanek-Karwowska, K., Luszczki, J.J., and Czuczwar, S.J. (2007). Cholecalciferol enhances the anticonvulsant effect of conventional antiepileptic drugs in the mouse model of maximal electroshock. Eur. J. Pharmacol. *573*, 111–115.

Bouillon, R., Reynaert, J., Claes, J.H., Lissens, W., and De Moor, P. (1975). The effect of anticonvulsant therapy on serum levels of 25-hydroxy-vitamin D, calcium, and parathyroid hormone. J. Clin. Endocrinol. Metab. *41*, 1130–1135.

Brewer, L.D., Thibault, V., Chen, K.-C., Langub, M.C., Landfield, P.W., and Porter, N.M. (2001). Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type calcium channel expression in hippocampal neurons. J. Neurosci. *21*, 98–108.

Brodie, M.J., Mintzer, S., Pack, A.M., Gidal, B.E., Vecht, C.J., and Schmidt, D. (2013). Enzyme induction with antiepileptic drugs: cause for concern? Epilepsia. *54*, 11–27.

Brown, A. (1999). Regulation of vitamin D action. Nephrol. Dial. Transplant. *14*, 11–16.

Cannell, J.J. (2008). Autism and vitamin D. Med. Hypotheses *70*, 750–759.

Cansu, A., Yesilkaya, E., Serdaroğlu, A., Hırfanoğlu, T.L., Çamurdan, O., Gülbahar, Ö., Gücüyener, K., and Cinaz, P. (2008). Evaluation of bone turnover in epileptic children using oxcarbazepine. Pediatr. Neurol. *39*, 266–271.

Christakos, S., Ajibade, D.V., Dhawan, P., Fechner, A.J., and Mady, L.J. (2012). Vitamin D: metabolism. Rheum. Dis. Clin. North Am. *38*, 1–11.

Christiansen, C., Rødbro, P., and Lund, M. (1973). Incidence of anticonvulsant osteomalacia and effect of vitamin D: controlled therapeutic trial. Br. Med. J. *4*, 695–701.

Christiansen, C., Rødbro, P., and Sjö, O. (1974). "Anticonvulsant action" of vitamin D in epileptic patients? A controlled pilot study. Br. Med. J. *2*, 258–259.

Clark, J.H., Rhoden, D.K., and Turner, D.S. (1993). Symptomatic vitamin A and D deficiencies in an eight-year-old with autism. J. Parenter. Enteral Nutr. *17*, 284–286.

Cornet, A., Baudet, C., Neveu, I., Evercooren, B.V., Brachet, P., and Naveilhan, P. (1998). 1, 25-Dihydroxyvitamin D3 regulates the expression of VDR and NGF gene in Schwann cells *in vitro*. J. Neurosci. Res. *53*, 742–746.

Cortez, M.A., Burnham, W.M., and Hwang, P.A. (1997). Infantile spasms: seasonal onset differences and zeitgebers. Pediatr. Neurol. *16*, 220–224.

Davis, R.L. and Crozier, R.A. (2015). Dynamic firing properties of type I spiral ganglion neurons. Cell Tissue Res. *361*, 115–127.

Dawson, V.L. and Dawson, T.M. (1996). Nitric oxide actions in neurochemistry. Neurochem. Int. *29*, 97–110.

de Abreu, D.F., Eyles, D., and Feron, F. (2009). Vitamin D, a neuroimmunomodulator: implications for neurodegenerative and autoimmune diseases. Psychoneuroendocrinology *34*, S265–S277.

De Boer, H.M., Mula, M., and Sander, J.W. (2008). The global burden and stigma of epilepsy. Epilepsy Behav. *12*, 540–546.

De Simoni, M.G., Perego, C., Ravizza, T., Moneta, D., Conti, M., Marchesi, F., De Luigi, A., Garattini, S., and Vezzani, A. (2000). Inflammatory cytokines and related genes are induced in the rat hippocampus by limbic status epilepticus. Eur. J. Neurosci. *12*, 2623–2633.

de Viragh, P.A., Haglid, K., and Celio, M. (1989). Parvalbumin increases in the caudate putamen of rats with vitamin D hypervitaminosis. Proc. Natl. Acad. Sci. USA *86*, 3887–3890.

DeLuca, H.F. (2004). Overview of general physiologic features and functions of vitamin D. Am. J. Clin. Nutr. *80*, 1689S–1696S.

Dinarello, C.A. (1996). Biologic basis for interleukin-1 in disease. Blood. *87*, 2095–2147.

Dong, X.-x., Wang, Y., and Qin, Z.-h. (2009). Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. Acta Pharmacol. Sin. *30*, 379–387.

Ecevit, Ç., Aydoğan, A., ülay Kavakli, T., and Altinöz, S. (2004). Effect of carbamazepine and valproate on bone mineral density. Pediatr. Neurol. *31*, 279–282.

Emmanuel, R., Alexandre, D., Benoit, V., Mohamed, H.S., and Remi, N. (2011). Nitric oxide scavenging modulates mitochondrial dysfunction induced by hypoxia/reoxygenation. Pharmacol. Rep. *63*, 1189–1194.

Ensrud, K., Walczak, T., Blackwell, T., Ensrud, E., Bowman, P., and Stone, K. (2004). Antiepileptic drug use increases rates of bone loss in older women: a prospective study. Neurology *62*, 2051–2057.

Erbayat Altay, E., Serdaroğlu, A., Tümer, L., Gücüyener, K., and Hasanoğlu, A. (2000). Evaluation of bone mineral metabolism in children receiving carbamazepine and valproic acid. J. Pediatr. Endocrinol. Metab. *13*, 933–940.

Eyles, D.W. (2010). Vitamin D and autism: does skin colour modify risk? Acta Paediatr. *99*, 645–647.

Eyles, D., Brown, J., Mackay-Sim, A., McGrath, J., and Feron, F. (2003). Vitamin D3 and brain development. Neuroscience *118*, 641–653.

Eyles, D.W., Smith, S., Kinobe, R., Hewison, M., and McGrath, J.J. (2005). Distribution of the vitamin D receptor and 1α-hydroxylase in human brain. J. Chem. Neuroanat. *29*, 21–30.

Farinas, I., Jones, K.R., Backus, C., Wang, X.-Y., and Reichardt, L.F. (1994). Severe sensory and sympathetic deficits in mice lacking neurotrophin-3. Nature *369*, 658–661.

Feldkamp, J., Becker, A., Witte, O., Scharff, D., and Scherbaum, W. (2000). Long-term anticonvulsant therapy leads to low bone mineral density – evidence for direct drug effects of phenytoin and carbamazepine on human osteoblast-like cells. Exp. Clin. Endocrinol. Diabetes. *108*, 37–43.

Fernell, E., Barnevik-Olsson, M., Bågenholm, G., Gillberg, C., Gustafsson, S., and Sääf, M. (2010). Serum levels of 25-hydroxyvitamin D in mothers of Swedish and of Somali origin who have children with and without autism. Acta Paediatr. *99*, 743–747.

Féron, F., Burne, T.H.J., Brown, J., Smith, E., McGrath, J.J., Mackay-Sim, A., and Eyles, D. (2005). Developmental Vitamin D3 deficiency alters the adult rat brain. Brain Res. Bull. *65*, 141–148.

Foss, M., Meneghelli, U., and Tabosa, V.J. (1978). The effect of the anticonvulsants phenobarbital and diphenylhydantoin on intestinal absorption of calcium. Acta Physiol. Lat. Am. *29*, 223–228.

Freidel, M., Krause, E., Kuhn, K., Peper, R., and Vogel, H. (2007). [Oxcarbazepine in the treatment of epilepsy]. Fortschr. Neurol. Psychiatr. *75*, 100–106.

Fu, G.K., Lin, D., Zhang, M.Y., Bikle, D.D., Shackleton, C.H., Miller, W.L., and Portale, A.A. (1997). Cloning of human 25-hydroxyvitamin D-1α-hydroxylase and mutations causing vitamin D-dependent rickets type 1. Mol. Endocrinol. *11*, 1961–1970.

Fuleihan, G.E.-H., Dib, L., Yamout, B., Sawaya, R., and Mikati, M.A. (2008). Predictors of bone density in ambulatory patients on antiepileptic drugs. Bone. *43*, 149–155.

Furth, M.E., Ronald, M.L., and George, D.Y. (1990). Neurotrophin-3: a neurotrophic factor related to NGF and BDNF. Science. *247*, 1446–1451.

Garcion, E., Wion-Barbot, N., Montero-Menei, C.N., Berger, F., and Wion, D. (2002). New clues about vitamin D functions in the nervous system. Trends Endocrinol. Metab. *13*, 100–105.

Gillberg, C. (1990). Do children with autism have March birthdays? Acta Psychiatr. Scand. *82*, 152–156.

Goodman, R. and Richards, H. (1995). Child and adolescent psychiatric presentations of second-generation Afro-Caribbeans in Britain. Br J Psychiatry *167*, 362–369.

Gough, H., Goggin, T., Bissessar, A., Baker, M., Crowley, M., and Callaghan, N. (1986). A comparative study of the relative influence of different anticonvulsant drugs, UV exposure and diet on vitamin D and calcium metabolism in out-patients with epilepsy. Q. J. Med. *59*, 569–577.

Grant, W.B. and Soles, C.M. (2009). Epidemiologic evidence for supporting the role of maternal vitamin D deficiency as a risk factor for the development of infantile autism. Dermatoendocrinology *1*, 223–228.

Hahn, T., Birge, S., Scharp, C., and Avioli, L. (1972). Phenobarbital-induced alterations in vitamin D metabolism. J. Clin. Invest. *51*, 741.

Hahn, T.J., Hendin, B.A., Scharp, C.R., Boisseau, V.C., and Haddad Jr, J.G. (1975). Serum 25-hydroxycalciferol levels and bone mass in children on chronic anticonvulsant therapy. N. Engl. J. Med. *292*, 550–554.

Harms, L.R., Burne, T.H., Eyles, D.W., and McGrath, J.J. (2011). Vitamin D and the brain. Best Pract. Res. Clin. Endocrinol. Metab. *25*, 657–669.

Heo, K., Rhee, Y., Lee, H.W., Lee, S.A., Shin, D.J., Kim, W.J., Song, H.K., Song, K., and Lee, B.I. (2011). The effect of topiramate monotherapy on bone mineral density and markers of bone and mineral metabolism in premenopausal women with epilepsy. Epilepsia *52*, 1884–1889.

Holick, M.F. (2007). Vitamin D deficiency. N. Engl. J. Med. *357*, 266–281.

Holick, M.F. and Garabedian, M. (2006). Vitamin D: Photobiology, Metabolism, Mechanism of Action, and Clinical Applications. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 6th ed. (Washington, DC: American Society for Bone and Mineral Research), pp. 106–114.

Holick, M.F., Smith, E., and Pincus, S. (1987). Skin as the site of vitamin D synthesis and target tissue for 1, 25-dihydroxyvitamin D3: use of calcitriol (1, 25-dihydroxyvitamin D3) for treatment of psoriasis. Arch. Dermatol. *123*, 1677–1683.

Holick, M.F., Binkley, N.C., Bischoff-Ferrari, H.A., Gordon, C.M., Hanley, D.A., Heaney, R.P., Murad, M.H., and Weaver, C.M. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab. *96*, 1911–1930.

Holló, A., Clemens, Z., Kamondi, A., Lakatos, P., and Szücs, A. (2012). Correction of vitamin D deficiency improves seizure control in epilepsy: a pilot study. Epilepsy Behav. *24*, 131–133.

Hosseinpour, F., Ellfolk, M., Norlin, M., and Wikvall, K. (2007). Phenobarbital suppresses vitamin D 3 25-hydroxylase expression: a potential new mechanism for drug-induced osteomalacia. Biochem. Biophys. Res. Commun. *357*, 603–607.

Humble, M.B., Gustafsson, S., and Bejerot, S. (2010). Low serum levels of 25-hydroxyvitamin D (25-OHD) among psychiatric outpatients in Sweden: relations with season, age, ethnic origin and psychiatric diagnosis. J. Steroid Biochem. Mol. Biol. *121*, 467–470.

Jia, F., Wang, B., Shan, L., Xu, Z., Staal, W.G., and Du, L. (2015). Core symptoms of autism improved after vitamin D supplementation. Pediatrics. *135*, e196–e198.

Kalia, L.V., Kalia, S.K., and Salter, M.W. (2008). NMDA receptors in clinical neurology: excitatory times ahead. Lancet Neurol. *7*, 742–755.

Kalueff, A., Eremin, K., and Tuohimaa, P. (2004). Mechanisms of neuroprotective action of vitamin D3. Biochemistry (Mosc.) *69*, 738–741.

Kalueff, A.V., Minasyan, A., and Tuohimaa, P. (2005). Anticonvulsant effects of 1, 25-dihydroxyvitamin D in chemically induced seizures in mice. Brain Res. Bull. *67*, 156–160.

Kalueff, A., Minasyan, A., Keisala, T., Kuuslahti, M., Miettinen, S., and Tuohimaa, P. (2006a). The vitamin D neuroendocrine system as a target for novel neurotropic drugs. CNS Neurol. Disord. Drug Targets *5*, 363–371.

Kalueff, A.V., Minasyan, A., Keisala, T., Kuuslahti, M., Miettinen, S., and Tuohimaa, P. (2006b). Increased severity of chemically induced seizures in mice with partially deleted vitamin D receptor gene. Neurosci. Lett. *394*, 69–73.

Kamikawa, H., Hori, T., Nakane, H., Aou, S., and Tashiro, N. (1998). IL-1β increases norepinephrine level in rat frontal cortex: involvement of prostanoids, NO, and glutamate. Am. J. Physiol. Regul. Integr. Comp. Physiol. *275*, R803–R810.

Kawashima, H., Torikai, S., and Kurokawa, K. (1981). Localization of 25-hydroxyvitamin D3 1 alpha-hydroxylase and 24-hydroxylase along the rat nephron. Proc. Natl. Acad. Sci. USA *78*, 1199–1203.

Keen, D., Reid, F., and Arnone, D. (2010). Autism, ethnicity and maternal immigration. Br. J. Psychiatry *196*, 274–281.

Kesby, J.P., Burne, T.H., McGrath, J.J., and Eyles, D.W. (2006). Developmental vitamin D deficiency alters MK 801-induced hyperlocomotion in the adult rat: an animal model of schizophrenia. Biol. Psychiatry *60*, 591–596.

Kesby, J.P., O'Loan, J.C., Alexander, S., Deng, C., Huang, X.-F., McGrath, J.J., Eyles, D.W., and Burne, T.H. (2012). Developmental vitamin D deficiency alters MK-801-induced behaviours in adult offspring. Psychopharmacology (Berl.). *220*, 455–463.

Kim, S.H., Lee, J.W., Choi, K.-G., Chung, H.W., and Lee, H.W. (2007). A 6-month longitudinal study of bone mineral density with antiepileptic drug monotherapy. Epilepsy Behav. *10*, 291–295.

Knekt, P., Kilkkinen, A., Rissanen, H., Marniemi, J., Sääksjärvi, K., and Heliövaara, M. (2010). Serum vitamin D and the risk of Parkinson disease. Arch. Neurol. *67*, 808–811.

Ko, P., Burkert, R., McGrath, J., and Eyles, D. (2004). Maternal vitamin D 3 deprivation and the regulation of apoptosis and cell cycle during rat brain development. Brain Res. Dev. Brain Res. *153*, 61–68.

Kočovská, E., Fernell, E., Billstedt, E., Minnis, H., and Gillberg, C. (2012). Vitamin D and autism: clinical review. Res. Dev. Disabil. *33*, 1541–1550.

Koo, D.L., Joo, E.Y., Kim, D., and Hong, S.B. (2013). Effects of levetiracetam as a monotherapy on bone mineral density and biochemical markers of bone metabolism in patients with epilepsy. Epilepsy Res. *104*, 134–139.

Krishnamoorthy, G., Nair, R., Sundar, U., Kini, P., and Shrivastava, M. (2010). Early predisposition to osteomalacia in Indian adults on phenytoin or valproate monotherapy and effective prophylaxis by simultaneous supplementation with calcium and 25-hydroxy vitamin D at recommended daily allowance dosage: a prospective study. Neurol. India *58*, 213.

Kulak, C.A., Borba, V.Z., Bilezikian, J.P., Silvado, C.E., Paola, L.D., and Boguszewski, C.L. (2004). Bone mineral density and serum levels of 25 OH vitamin D in chronic users of antiepileptic drugs. Arq. Neuropsiquiatr. *62*, 940–948.

Kumandas, S., Koklu, E., Gümüs, H., Koklu, S., Kurtoglu, S., Karakukcu, M., and Keskin, M. (2006). Effect of carbamezapine and valproic acid on bone mineral density, IGF-I and IGFBP-3. J. Pediatr. Endocrinol. Metab. *19*, 529–534.

Laflamme, N., Echchannaoui, H., Landmann, R., and Rivest, S. (2003). Cooperation between toll-like receptor 2 and 4 in the brain of mice challenged with cell wall components derived from gram-negative and gram-positive bacteria. Eur. J. Immunol. *33*, 1127–1138.

Lau, K., Nakade, O., Barr, B., Taylor, A.K., Houchin, K., and Baylink, D.J. (1995). Phenytoin increases markers of osteogenesis for the human species *in vitro* and *in vivo*. J. Clin. Endocrinol. Metab. *80*, 2347–2353.

Lee, Y.-J., Park, K.M., Kim, Y.M., Yeon, G.M., and Nam, S.O. (2015). Longitudinal change of vitamin D status in children with epilepsy on antiepileptic drugs: prevalence and risk factors. Pediatr. Neurol. *52*, 153–159.

Lefebvre d'Hellencourt, C., Montero-Menei, C.N., Bernard, R., and Couez, D. (2003). Vitamin D3 inhibits proinflammatory cytokines and nitric oxide production by the EOC13 microglial cell line. J. Neurosci. Res. *71*, 575–582.

Li, X.-H., Hou, X.-Y., and Chen, R. (2015). The roles of vitamin B12 and vitamin D in children with intractable epilepsy. Int. J. Clin. Exp. Med. *8*, 764.

Lifshitz, F. and Maclaren, N.K. (1973). Vitamin D-dependent rickets in institutionalized, mentally retarded children receiving long-term anticonvulsant therapy. I. A survey of 288 patients. J. Pediatr. *83*, 612–620.

Löscher, W. and Brandt, C. (2010). Prevention or modification of epileptogenesis after brain insults: experimental approaches and translational research. Pharmacol. Rev. *62*, 668–700.

Löscher, W. and Fiedler, M. (2000). The role of technical, biological, and pharmacological factors in the laboratory evaluation of anticonvulsant drugs. VII. Seasonal influences on anticonvulsant drug actions in mouse models of generalized seizures. Epilepsy Res. *38*, 231–248.

Lowe, K., Maiyar, A., and Norman, A. (1991). Vitamin D-mediated gene expression. Crit. Rev. Eukaryot. Gene Expr. *2*, 65–109.

Manfredini, R., Vergine, G., Boari, B., Faggioli, R., and Borgna-Pignatti, C. (2004). Circadian and seasonal variation of first febrile seizures. J. Pediatr. *145*, 838–839.

Margineanu, D.G. (2010). Epileptic hypersynchrony revisited. Neuroreport. *21*, 963–967.

McCormick, D.A. and Contreras, D. (2001). On the cellular and network bases of epileptic seizures. Annu. Rev. Physiol. *63*, 815–846.

McGrath, J.J., Burne, T.H., Féron, F., Mackay-Sim, A., and Eyles, D.W. (2010). Developmental vitamin D deficiency and risk of schizophrenia: a 10-year update. Schizophr. Bull., sbq101.

Meguid, N.A., Hashish, A.F., Anwar, M., and Sidhom, G. (2010). Reduced serum levels of 25-hydroxy and 1, 25-dihydroxy vitamin D in Egyptian children with autism. J. Altern. Complement. Med. *16*, 641–645.

Menon, B. and Harinarayan, C. (2010). The effect of anti epileptic drug therapy on serum 25-hydroxyvitamin D and parameters of calcium and bone metabolism – a longitudinal study. Seizure. *19*, 153–158.

Meyer, M.B., Watanuki, M., Kim, S., Shevde, N.K., and Pike, J.W. (2006). The human transient receptor potential vanilloid type 6 distal promoter contains multiple vitamin D receptor binding sites that mediate activation by 1, 25-dihydroxyvitamin D3 in intestinal cells. Mol. Endocrinol. *20*, 1447–1461.

Mintzer, S., Boppana, P., Toguri, J., and DeSantis, A. (2006). Vitamin D levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine. Epilepsia *47*, 510–515.

Mitrovic, B., Pierre, B.A., Mackenzie-Graham, A.J., and Merrill, J E. (1994). The role of nitric oxide in glial pathologya. Ann. N. Y. Acad. Sci. *738*, 436–446.

Molloy, C.A., Kalkwarf, H.J., Manning-Courtney, P., Mills, J.L., and Hediger, M.L. (2010). Plasma 25 (OH) D concentration in children with autism spectrum disorder. Dev. Med. Child Neurol. *52*, 969–971.

Moore, T.B., Koeffler, H.P., Yamashiro, J.M., and Wada, R.K. (1996). Vitamin D3 analogs inhibit growth and induce differentiation in LA-N-5 human neuroblastoma cells. Clin. Exp. Metastasis *14*, 239–245.

Mylvaganam, S., Ramani, M., Krawczyk, M., and Carlen, P.L. (2014). Roles of gap junctions, connexins, and pannexins in epilepsy. Front. Physiol. *5*, 172.

Nagarjunakonda, S., Amalakanti, S., Uppala, V., Rajanala, L., and Athina, S. (2016). Vitamin D in epilepsy: vitamin D levels in epilepsy patients, patients on antiepileptic drug polytherapy and drug-resistant epilepsy sufferers. Eur. J. Clin. Nutr. *70*, 140–142.

Naveilhan, P., Neveu, I., Baudet, C., Ohyama, K., Brachet, P., and Wion, D. (1993). Expression of 25 (OH) vitamin D3 24-hydroxylase gene in glial cells. Neuroreport *5*, 255–257.

Nettekoven, S., Ströhle, A., Trunz, B., Wolters, M., Hoffmann, S., Horn, R., Steinert, M., Brabant, G., Lichtinghagen, R., and Welkoborsky, H.-J. (2008). Effects of antiepileptic drug therapy on vitamin D status and biochemical markers of bone turnover in children with epilepsy. Eur. J. Pediatr. *167*, 1369–1377.

Neveu, I., Naveilhan, P., Baudet, C., Brachet, P., and Metsis, M. (1994a). 1, 25-dihydroxyvitamin D3 regulates NT-3, NT-4 but not BDNF mRNA in astrocytes. Neuroreport. *6*, 124–126.

Neveu, I., Naveilhan, P., Baudet, C., Wion, D., De Luca, H.F., and Brachet, P. (1994b). 1, 25-dihydroxyvitamin D3 regulates the synthesis of nerve growth factor in primary cultures of glial cells. Brain Res. Mol. Brain Res. *24*, 70–76.

Nguyen, M.D., Julien, J.-P., and Rivest, S. (2002). Innate immunity: the missing link in neuroprotection and neurodegeneration? Nat. Rev. Neurosci. *3*, 216–227.

Nicolaidou, P., Georgouli, H., Kotsalis, H., Matsinos, Y., Papadopoulou, A., Fretzayas, A., Syriopoulou, V., Krikos, X., Karantana, A., and Karpathios, T. (2006). Effects of anticonvulsant therapy on vitamin D status in children: prospective monitoring study. J. Child Neurol. *21*, 205–210.

Noble, J.M., Mandel, A., and Patterson, M.C. (2007). Scurvy and rickets masked by chronic neurologic illness: revisiting "psychologic malnutrition". Pediatrics *119*, e783–e790.

Norman, A.W. (2008). From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am. J. Clin. Nutr. *88*, 491S–499S.

Norman, A.W., Nemere, I., Zhou, L.-X., Bishop, J.E., Lowe, K.E., Maiyar, A.C., Collins, E.D., Taoka, T., Sergeev, I., and Farach-Carson, M.C. (1992). 1, 25 (OH) 2-vitamin D 3, a steroid hormone that produces biologic effects via both genomic and nongenomic pathways. J. Steroid Biochem. Mol. Biol. *41*, 231–240.

Pack, A. (2008). Bone health in people with epilepsy: is it impaired and what are the risk factors? Seizure *17*, 181–186.

Pack, A.M. and Morrell, M.J. (2004). Epilepsy and bone health in adults. Epilepsy Behav. *5*, 24–29.

Pack, A.M., Morrell, M.J., Marcus, R., Holloway, L., Flaster, E., Doñe, S., Randall, A., Seale, C., and Shane, E. (2005). Bone mass and turnover in women with epilepsy on antiepileptic drug monotherapy. Ann. Neurol. *57*, 252–257.

Pack, A., Morrell, M., Randall, A., McMahon, D., and Shane, E. (2008). Bone health in young women with epilepsy after one year of antiepileptic drug monotherapy. Neurology *70*, 1586–1593.

Pack, A.M., Morrell, M.J., McMahon, D.J., and Shane, E. (2011). Normal vitamin D and low free estradiol levels in women on enzyme-inducing antiepileptic drugs. Epilepsy Behav. *21*, 453–458.

Pannu, R. and Singh, I. (2006). Pharmacological strategies for the regulation of inducible nitric oxide synthase: neurodegenerative versus neuroprotective mechanisms. Neurochem. Int. *49*, 170–182.

Pardridge, W.M., Sakiyama, R., and Coty, W.A. (1985). Restricted transport of vitamin D and A derivatives through the rat blood-brain barrier. J. Neurochem. *44*, 1138–1141.

Pascussi, J.M., Robert, A., Nguyen, M., Walrant-Debray, O., Garabedian, M., Martin, P., Pineau, T., Saric, J., Navarro, F., and Maurel, P. (2005). Possible involvement of pregnane X receptor-enhanced CYP24 expression in drug-induced osteomalacia. J. Clin. Invest. *115*, 177–186.

Phabphal, K., Geater, A., Limapichat, K., Sathirapanya, P., Setthawatcharawanich, S., and Leelawattana, R. (2013). Effect of switching hepatic enzyme-inducer antiepileptic drug to levetiracetam on bone mineral density, 25 hydroxyvitamin D, and parathyroid hormone in young adult patients with epilepsy. Epilepsia *54*, e94–e98.

Pogge, E. (2010). Vitamin D and Alzheimer's disease: is there a link? Consult. Pharm. *25*, 440–450.

Procopio, M. and Marriott, P.K. (1998). Seasonality of birth in epilepsy: a Danish study. Acta Neurol. Scand. *98*, 297–301.

Procopio, M., Marriott, P.K., and Williams, P. (1997). Season of birth: aetiological implications for epilepsy. Seizure *6*, 99–105.

Procopio, M., Marriott, P.K., and Davies, R.J. (2006). Seasonality of birth in epilepsy: a Southern Hemisphere study. Seizure *15*, 17–21.

Raol, Y.H., Lund, I.V., Bandyopadhyay, S., Zhang, G., Roberts, D.S., Wolfe, J.H., Russek, S.J., and Brooks-Kayal, A.R. (2006). Enhancing GABAA receptor α1 subunit levels in hippocampal dentate gyrus inhibits epilepsy development in an animal model of temporal lobe epilepsy. J. Neurosci. *26*, 11342–11346.

Ravizza, T. and Vezzani, A. (2006). Status epilepticus induces time-dependent neuronal and astrocytic expression of interleukin-1 receptor type I in the rat limbic system. Neuroscience *137*, 301–308.

Rivest, S. (2003). Molecular insights on the cerebral innate immune system. Brain. Behav. Immun. *17*, 13–19.

Saporito, M.S., Brown, E.R., Hartpence, K.C., Wilcox, H.M., Vaught, J.L., and Carswell, S. (1994). Chronic 1, 25-dihydroxyvitamin D3-mediated induction of nerve growth factor mRNA and protein in L929 fibroblasts and in adult rat brain. Brain Res. *633*, 189–196.

Schmitt, B., Nordlund, D., and Rodgers, L. (1984). Prevalence of hypocalcemia and elevated serum alkaline phosphatase in patients receiving chronic anticonvulsant therapy. J. Fam. Pract. *18*, 873–877.

Scorza, F.A., de Albuquerque, M., Arida, R.M., and Cavalheiro, E.A. (2007). Sudden unexpected death in epilepsy: are winter temperatures a new potential risk factor? Epilepsy Behav. *10*, 509–510.

Sheth, R.D. (2004). Bone health in pediatric epilepsy. Epilepsy Behav. *5*, 30–35.

Shinpo, K., Kikuchi, S., Sasaki, H., Moriwaka, F., and Tashiro, K. (2000). Effect of 1, 25-dihydroxyvitamin D3 on cultured mesencephalic dopaminergic neurons to the combined toxicity caused by L-buthionine sulfoximine and 1-methyl-4-phenylpyridine. J. Neurosci. Res. *62*, 374–382.

Siegel, A., Malkowitz, L., Moskovits, M.J., and Christakos, S. (1984). Administration of 1, 25-dihydroxyvitamin D 3 results in the elevation of hippocampal seizure threshold levels in rats. Brain Res. *298*, 125–129.

Simeone, T.A., Sanchez, R.M., and Rho, J.M. (2004). Molecular biology and ontogeny of glutamate receptors in the mammalian central nervous system. J. Child Neurol. *19*, 343–360.

Smolders, J., Damoiseaux, J., Menheere, P., and Hupperts, R. (2008). Vitamin D as an immune modulator in multiple sclerosis, a review. J. Neuroimmunol. *194*, 7–17.

Snoeijen-Schouwenaars, F.M., van Deursen, K.C., Tan, I.Y., Verschuure, P., and Majoie, M.H. (2015). Vitamin D supplementation in children with epilepsy and intellectual disability. Pediatr. Neurol. *52*, 160–164.

Stellwagen, D., Beattie, E.C., Seo, J.Y., and Malenka, R.C. (2005). Differential regulation of AMPA receptor and GABA receptor trafficking by tumor necrosis factor-α. J. Neurosci. *25*, 3219–3228.

Stephen, L., McLellan, A., Harrison, J., Shapiro, D., Dominiczak, M., Sills, G., and Brodie, M. (1999). Bone density and antiepileptic drugs: a case-controlled study. Seizure. *8*, 339–342.

Stewart, C. and Latif, A. (2008). Symptomatic nutritional rickets in a teenager with autistic spectrum disorder. Child Care Health Dev. *34*, 276–278.

Sumi, K., Sugita, T., Shimotsuji, T., Seino, Y., Mimaki, T., and Yabuuchi, H. (1978). Effect of anticonvulsant therapy on serum 25-hydroxyvitamin D level. Tohoku J. Exp. Med. *125*, 265–269.

Swann, J.W., Le, J.T., Lam, T.T., Owens, J., and Mayer, A.T. (2007). The impact of chronic network hyperexcitability on developing glutamatergic synapses. Eur. J. Neurosci. *26*, 975–991.

Tekgul, H., Serdaroglu, G., Huseyinov, A., and Gökben, S. (2006). Bone mineral status in pediatric outpatients on antiepileptic drug monotherapy. J. Child Neurol. *21*, 411–414.

Telci, A., Çakatay, U., Kurt, B.B., Kayali, R., Sivas, A., Akçay, T., and Gökyiğit, A. (2000). Changes in bone turnover and deoxypyridinoline levels in epileptic patients. Clin. Chem. Lab. Med. *38*, 47–50.

Thomas, M.K., Lloyd-Jones, D.M., Thadhani, R.I., Shaw, A.C., Deraska, D.J., Kitch, B.T., Vamvakas, E.C., Dick, I.M., Prince, R.L., and Finkelstein, J.S. (1998). Hypovitaminosis D in medical inpatients. N. Engl. J. Med. *338*, 777–783.

Tjellesen, L. and Christiansen, C. (1982). Serum vitamin D metabolites in epileptic patients treated with 2 different anti-convulsants. Acta Neurol. Scand. *66*, 335–341.

Torrey, E.F., Miller, J., Rawlings, R., and Yolken, R.H. (2000). Seasonal birth patterns of neurological disorders. Neuroepidemiology *19*, 177–185.

Tuohimaa, P., Keisala, T., Minasyan, A., Cachat, J., and Kalueff, A. (2009). Vitamin D, nervous system and aging. Psychoneuroendocrinology *34*, S278–S286.

Turrin, N.P. and Rivest, S. (2004). Innate immune reaction in response to seizures: implications for the neuropathology associated with epilepsy. Neurobiol. Dis. *16*, 321–334.

Umesono, K., Murakami, K.K., Thompson, C.C., and Evans, R.M. (1991). Direct repeats as selective response elements for the thyroid hormone, retinoic acid, and vitamin D3 receptors. Cell *65*, 1255–1266.

Van Cromphaut, S.J., Dewerchin, M., Hoenderop, J.G., Stockmans, I., Van Herck, E., Kato, S., Bindels, R.J., Collen, D., Carmeliet, P., and Bouillon, R. (2001). Duodenal calcium absorption in vitamin D receptor-knockout mice: functional and molecular aspects. Proc. Natl. Acad. Sci. USA *98*, 13324–13329.

Vaziri, N. (1993). Endocrinological consequences of the nephrotic syndrome. Am. J. Nephrol. *13*, 360–364.

Verrotti, A., Agostinelli, S., Coppola, G., Parisi, P., and Chiarelli, F. (2010). A 12-month longitudinal study of calcium metabolism and bone turnover during valproate monotherapy. Eur. J. Neurol. *17*, 232–237.

Vezzani, A. (2015). Anti-inflammatory drugs in epilepsy: does it impact epileptogenesis? Expert Opin. Drug Saf. *14*, 583–592.

Vezzani, A. and Granata, T. (2005). Brain inflammation in epilepsy: experimental and clinical evidence. Epilepsia *46*, 1724–1743.

Vezzani, A., Conti, M., De Luigi, A., Ravizza, T., Moneta, D., Marchesi, F., and De Simoni, M.G. (1999). Interleukin-1β immunoreactivity and microglia are enhanced in the rat hippocampus by focal kainate application: functional evidence for enhancement of electrographic seizures. J. Neurosci. *19*, 5054–5065.

Vezzani, A., Moneta, D., Richichi, C., Aliprandi, M., Burrows, S.J., Ravizza, T., Perego, C., and De Simoni, M.G. (2002). Functional role of inflammatory cytokines and antiinflammatory molecules in seizures and epileptogenesis. Epilepsia *43*, 30–35.

Viviani, B., Bartesaghi, S., Gardoni, F., Vezzani, A., Behrens, M., Bartfai, T., Binaglia, M., Corsini, E., Di Luca, M., and Galli, C. (2003). Interleukin-1β enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases. J. Neurosci. *23*, 8692–8700.

Voudris, K., Moustaki, M., Zeis, P.M., Dimou, S., Vagiakou, E., Tsagris, B., and Skardoutsou, A. (2002). Alkaline phosphatase and its isoenzyme activity for the evaluation of bone metabolism in children receiving anticonvulsant monotherapy. Seizure *11*, 377–380.

Vyklicky, V., Korinek, M., Smejkalova, T., Balik, A., Krausova, B., Kaniakova, M., Lichnerova, K., Cerny, J., Krusek, J., and Dittert, I. (2014). Structure, function, and pharmacology of NMDA receptor channels. Physiol. Res. *63*, S191.

Wang, Y., Chiang, Y.-H., Su, T.-P., Hayashi, T., Morales, M., Hoffer, B., and Lin, S.-Z. (2000). Vitamin D3 attenuates cortical infarction induced by middle cerebral arterial ligation in rats. Neuropharmacology *39*, 873–880.

Weinstein, R.S., Bryce, G.F., Sappington, L.J., King, D.W., and Gallagher, B.B. (1984). Decreased serum ionized calcium and normal vitamin D metabolite levels with anticonvulsant drug treatment. J. Clin. Endocrinol. Metab. *58*, 1003–1009.

Weisman, Y., Fattal, A., Eisenberg, Z., Harel, S., Spirer, Z., and Harell, A. (1979). Decreased serum 24, 25-dihydroxy vitamin D concentrations in children receiving chronic anticonvulsant therapy. Br. Med. J. *2*, 521.

Wion, D., MacGrogan, D., Neveu, I., Jehan, F., Houlgatte, R., and Brachet, P. (1991). 1, 25-Dihydroxyvitamin D3 is a potent inducer of nerve growth factor synthesis. J. Neurosci. Res. *28*, 110–114.

Ye, Z.-C. and Sontheimer, H. (1996). Cytokine modulation of glial glutamate uptake: a possible involvement of nitric oxide. Neuroreport. *7*, 2181–2185.

Yuhas, Y., Shulman, L., Weizman, A., Kaminsky, E., Vanichkin, A., and Ashkenazi, S. (1999). Involvement of tumor necrosis factor alpha and interleukin-1β in enhancement of pentylenetetrazole-induced seizures caused by *Shigella dysenteriae*. Infect. Immun. *67*, 1455–1460.

Zanatta, L., Goulart, P.B., Gonçalves, R., Pierozan, P., Winkelmann-Duarte, E.C., Woehl, V.M., Pessoa-Pureur, R., Silva, F.R.M.B., and Zamoner, A. (2012). 1α, 25-Dihydroxyvitamin D3 mechanism of action: modulation of L-type calcium channels leading to calcium uptake and intermediate filament phosphorylation in cerebral cortex of young rats. Biochim. Biophys. Acta *1823*, 1708–1719.

Zehnder, D., Bland, R., Williams, M.C., McNinch, R.W., Howie, A.J., Stewart, P.M., and Hewison, M. (2001). Extrarenal expression of 25-hydroxyvitamin D3-1α-hydroxylase 1. J. Clin. Endocrinol. Metab. *86*, 888–894.

Zeise, M., Espinoza, J., Morales, P., and Nalli, A. (1997). Interleukin-1β does not increase synaptic inhibition in hippocampal CA3 pyramidal and dentate gyrus granule cells of the rat *in vitro*. Brain Res. *768*, 341–344.

Zhou, C., Assem, M., Tay, J.C., Watkins, P.B., Blumberg, B., Schuetz, E.G., and Thummel, K.E. (2006). Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced osteomalacia. J. Clin. Invest. *116*, 1703–1712.

Zierold, C., Darwish, H.M., and DeLuca, H.F. (1994). Identification of a vitamin D-response element in the rat calcidiol (25-hydroxyvitamin D3) 24-hydroxylase gene. Proc. Natl. Acad. Sci. USA *91*, 900–902.