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Basic and clinical role of vitamins in epilepsy

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Abstract

***Background & Aims*:** Epilepsy is a brain disorder which affects about 50 million people worldwide. Good diet is an essential measure to controlling seizure attacks. Since some combination therapy can reduce epileptogenesis, therefore this review summarizes the available evidences about the application of vitamins in animal models and humans for understanding what specific combinations of antiepileptic drugs and vitamins are likely to be effective for epilepsy therapy.

Material and methods: In this review, electronic databases including PubMed and Google Scholar were searched for monotherapy and polytherapy by vitamins.

Results: Administration of vit A inhibits development of seizures and lethality in animal models. Also vitamins B1, B6 and B12 pre-treatment might lead to a protective effect against degenerative cellular in mice. In addition use of low dose of sodium valproate with vitamins C or E increase the anticonvulsant activity of the drug in mice. Moreover, Vitamin D enhances antiepileptic effects of lamotrigine, phenytoin and valproate in animal's models. Vitamin E has an anticonvulsant effect in ferrous chloride seizures, hyperbaric oxygen seizures as well as penicillin-induced seizures in contrast kindling, maximal electroshock and kainite models. Some researches demonstrated that vitamins D and B as adjunctive therapy in epileptic patient can relieve seizures. A clinical data have shown beneficial effects of vitamin E in raising total antioxidant capacity, catalase, and glutathione in patients with uncontrolled epilepsy. Only few clinical studies exist to support the efficacy of the vitamin A and K in epilepsy.

Conclusion: However vitamin therapy is not a substitute for antiepileptic drugs but add on therapy by them may relieve drugs- induced deficiencies as well as more researches are needed to evaluate the effectiveness of vitamins in epileptic humans.

***Keywords*:** Vitamins, Antiepileptic drugs, Epilepsy

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Introduction

Epilepsy, the second major neurological disorder is characterized by a state of recurrent and unprovoked seizures which can occur at all ages and estimated to exceed 40% patients have drug-resistant epilepsy (1, 2). Drug resistant epilepsy is defined as failure of two antiepileptic drugs at appropriate doses to achieve seizure remission (3). The sequence of events is reported to convert the normal brain to epileptic brain. Generation of reactive oxygen species (oxidative stress)

in the brain is one of the key causes in induction of recurrent seizures (4). Reactive oxygen species are natural byproducts of normal metabolism of oxygen which excess amounts of them is associated with detrimental effects on cells through damaging molecules. The central nervous system due to its high oxygen consumption and lipid-rich content is vulnerable to oxidative stress (5).

Ineffectiveness and the serious side effects of antiepileptic drugs pose variable risks to patients. Some antiepileptic drugs including phenobarbital, phenytoin, carbamazepine and valproic acid are known to increase the formation of reactive oxygen species as well as to impair antioxidant system (6). For instance valproic can declines mitochondrial coenzyme A and affects the oxidation of fatty acids and ATP synthesis in the mitochondria (7). Also following a seizure, the antioxidant defense decreases in epileptics brains (8).

Although it is estimated that up to 70% of epileptic patients can become seizure-free with monotherapy (single drug treatment), alternative treatments like a combination therapy with brain stimulation, plant oils, antioxidants and so forth might be required for improving its efficacy as well as tolerability. Therefore, it is reasonable to propose that treatment with vitamins as antioxidants during the epileptic process could inhibit sever neuronal damages produced by seizure and the burden of adverse effects of antiepileptic drugs (9, 10, 11, 12).To support mentioned theory, some researchers have evaluated the influence of kinds of vitamins on neuroprotection against epilepsy.

Material and methods: this review summarized several studies which reported use of vitamins alone or add-on therapy for modulating seizure and oxidative stress in epilepsy. For this purpose electronic databases including PubMed and Google Scholar were searched for each of monotherapy and polytherapy of antiepileptic drugs and vitamins. The searched terms were epilepsy, seizure, antiepileptic drug and several kinds of vitamins.

Results

Several dietary supplements may reduce seizures or improve deficiencies resulting from anticonvulsant drugs (13). The anticonvulsive effects of types of vitamins are supported by evidences coming from animal experiments as well as clinical studies (13,14,15). Here, we reviewed the evidences which have studied the efficacy of vitamins in seizures.

Animal studies:

Vitamin A:

Vitamin A (retinol) is a fat-soluble micronutrient and its recommended daily dose to maintain well-being for men and women is 900 and 700 μg retinol activity equivalents /day, respectively (16). The major sources of vitamin A are animal-derived foods as well as its provitamin A (carotenoids) in darkly colored fruits and vegetables. (16). It is converted into retinoic acid in body and has variety of biological actions including mature of central nervous system (17), vision, immune function and reproduction (18). It regulates numerous of genes in different tissues and is involved in neurogenesis, neuronal survival and synaptic plasticity (18,19). It has been reported that a vitamin A deprivation diet caused convulsions in the steers (15,20). Also vit A can depress clonic seizures, tonic seizures and lethality during kindling induced by PTZ as a model for epileptogenesis (15). Additionally it has been demonstrated that β-Carotene as a main source of vit A inhibits the tonic seizures and lethality without affecting to clonic seizures during kindling and delays the hyperoxia- induced seizures (15).

Vit A may play a role in seizure development through retinoid nuclear receptors and changes in gene transcription (21). Another possible mechanism of vit A might be due to regulation gap junctions by retinoic acid and to a less extent it can directly reduce the gap junction conductance. Besides the synaptic contacts, the neuronal gap junctions are supposed to be involved in seizure generation (22, 23). The opened gap junctions can increase duration of seizures and closed gap junctions can reduce the epileptiform activity (24).

Vitamins B:

There are eight B vitamins (a class of water soluble complexes) which collectively called B complex vitamins including thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folate (B9) and cobalamin (B12) (25). It was reported that B vitamins (B1, B6 and B12) attenuated degenerating processes in the nervous system and counteracted abnormal genomic DNA methylation reactions (26). Vitamin B12 plays a key role in the synthesis and maintenance of the myelin sheath and cell growth (27). Thiamine can modify cognitive function and thiamine deficiency provokes epileptic phenomena in people with epilepsy (14, 28).

It was shown that B1, B6 and B12 pre-treatment of mice, prior to kainate (a model of epilepsy induced by kainate) which acts as neurodegenerative stimulus, might lead to high expression of anti-apoptotic factor (Bcl-2) and a protective effect against degenerative cellular induced by kainic acid (26). There is some evidence that B1-vitamin develops their protective properties by a decrease in kainate binding sites (26, 29). Some studies have shown that vitamin B6 as antioxidant can lower damage due to oxidative stress and contributes to attenuate of the consequences of neurodegenerative disorders (30).

Use of some antiepileptic drugs can reduce serum level of vitamin B6 in patients as well as leads to hyperhomocysteinemia (31,32). Production of homocysteine is accompanied by generation of free radical and oxidative stress (33). Homocysteine stimulates strongly the *N*-methyl-d-aspartate (NMDA)-type glutamate receptors, which are key receptors in epileptogenesis (34). Furthermore, homocysteine reduces the seizure threshold by arresting endogenous anti-convulsants like adenosine (35). It has been reported that an upregulation of cytokines and growth factors such as tumor necrosis factor (TNF) or nerve growth factor were observed following both epilepsy and deficiency of vitamin B12 (36, 37, 38). TNF is involved in inducing apoptosis (39). These data indicate that B12 might attenuate the upregulation of TNF and subsequently the consequences of seizures (40).

Vitamin C:

Vitamin C, a group of water-soluble vitamins, as an antioxidant and electron donor accumulates in central nervous system. Humans are not capable of synthesizing vit C and dependent on dietary intake (41, 42, 43) and its recommended daily dose should be 75 (women) and 90 (men) mg per day (44, 45, 46). It can transport through the blood-brain barrier via the sodium dependent vitamin C transporter from blood into cerebral spinal fluid and extracellular fluid into neurons (47). Vitamin C deficiency contributes to several neurodegenerative and psychiatric disorders like Alzheimer, Parkinson, Huntington, multiple sclerosis, amyotrophic sclerosis, depression, anxiety disorders and schizophrenia (48).

Some studies demonstrated that ascorbic acid (the reduced form of vitamin C) pretreatment prior to pilocarpine-induced seizure caused a 60% reduction in the frequency of hippocampal brain damage induced by seizures and 5-fold decrease in the area of hippocampal damage in animals (49). Additionally, ascorbic acid can decrease epileptic seizures induced by FeCl3 (50) or penicillin administration (51). Moreover vitamin C treatment by increasing basal progesterone concentrations can produce a significant anticonvulsant effect against seizure in animals injected with pentylenetetrazole-induced seizures (52). Also it was reported that co-treatment of low dose of sodium valproate (conventional antiepileptic drug) with vitamins C increased the anticonvulsant activity of the drug on seizure induced by strychnine in adult rat (12). Also a study has reported that concomitant administration of ascorbic acid with sodium valproate produced a synergistic anticonvulsive by increase in the latency of seizure and reduction in seizure duration in pentylenetetrazole-induced seizures in male mice (53).

Ascorbate has multiple functions of action and plays substantial role as a neuromodulator and scavenges reactive oxygen species which can reduce harmful oxidants (54). It is crucial for recycling vitamin E and lipoic acid (55). This vitamin as a neuroprotective factor by consolidating cell membranes and decreasing lipid

peroxidation and diminishing reactions of oxidative stress in brain and cooperate with other antioxidants like alpha-tocopherol reduces injury in during seizures (47). Pre-treatment by ascorbate can cause an increase in hippocampal superoxide dismutase and catalase activities, increase in the latency to first seizures, suppression of behavioral seizure episodes, decrease in lipid peroxidation, nitrite content, severity of hippocampal lesions and mortality of rats (55,56,57).

It was showed that vitamin C exert its anticonvulsant effects via activation of inhibitory receptors GABA (58) and expression of several glutamate transporter genes (59) which can play strong therapeutic roles in epilepsy. Moreover Vitamin C by decreasing Bax, increasing Bcl-2 expression and inhibition of caspase-3 can attenuate detrimental effects induced by PTZ in adult rats (59).Bax (an apoptosis promoter) and caspase enzymes stimulate programmed cell death and play an significant role in the process of apoptosis while Bcl-2 is an antiapoptotic member of the Bcl-2 family, which play important roles in the regulation of the apoptotic pathway (59).

Vitamin D:

Vitamin D (a group of fat-soluble seco-sterols) is a steroid which can be considered as a hormone when is released into the blood circulation. Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), as two major forms of vitamin D, are acquired respectively from plants and animals sources. But the major source of vitamin D is from ultraviolet irradiation of sunlight on human epithelial cells results in conversion 7-dehydrocholesterol to vitamin D3 which is biologically inert and by two separate hydroxylation (P450 enzymes 25-hydroxylase and 1a-hydroxylase) in liver and kidneys would be active (60).

Vitamin D acts via two types of receptors: the nuclear vitamin D receptor which induce changes in gene expression and the membrane receptor which is located at the cell surface and initiates non-genomic effects such the regulation of calcium homeostasis and bone metabolism (61). Apart from this, One of most its functions is regulation of nervous system development and function by influencing on neurotrophin production and release, neuromediator synthesis, intracellular calcium homeostasis, and prevention of oxidative damage to nervous tissue (62).

Besides its well-known importance in bone health, due to widespread expression of its receptors, its reductions may be implicated in the pathogenesis a number of diseases like cardiovascular diseases, infections, diabetes, dementias, parkinson's disease (63,64,65). Animal studies suggest that vitamin D3 raises the threshold of chemically induced seizures and reduces the deleterious effect of seizures (66). Similarly, administration of pentylenetetrazole to mice with a deficiency in vitamin D receptors induces less latency to the seizure beginning and increases seizure susceptibility (67). It has been demonstrated that vitamin D receptors increased within the hippocampus after pilocarpine-induced seizures (68). In some studies were described that vitamin D enhanced anticonvulsant effects of lamotrigine (69), phenytoin and valproate as well as elevates the electroconvulsive threshold (70).

Vitamin E:

Vitamin E (α-tocopherol) is a lipophilic antioxidant which is able to penetrate the blood-brain barrier and the root of wheat and vegetable oils are its original source (71). Composition α is the most important part of vitamin E which forms 90% of the tocopherol of animal tissues. The major physiological effects proposed for vitamin E are stabilization of membrane, acting as enzyme enhancer and repressor of the effect of Vitamin A. This substance has the ability to absorb free radicals of oxygen and attenuate the negative effects of lipid peroxidation in the brain tissue (72).

Some studies have claimed that vitamin E has an anticonvulsant effect and can be considered in add-on epilepsy therapy (72, 73, 74). In animal researches has been shown that Vitamin E can increase catalase activity and decline lipid peroxidation after seizures induced by pilocarpine (74). Moreover, vitamin E can attenuate blood-brain barrier disruption (75) after chemical-induced seizures as well as can reduce seizure activity in other epileptic animal's models including ferrous

chloride seizures (76), hyperbaric oxygen seizures (77) and penicillin-induced seizures (78). On the contrary, it was showed that Vitamin E cannot be effective in seizures induced by amygdala kindling, kainite models as well as maximal electroshock (76). This contrast may be due to the wide dosage and treatment duration of vitamin E in various experiments. Vitamin E has been used in a different dose ranges from 100 IU/d (79) or 200 IU/d (80) to high doses such as 1200 IU/d (81) across studies.

Vitamin K:

Vitamin K as a family of fat-soluble vitamins with a naphthoquinone compound and isoprenylacyl side chains acts as a cofactor for gamma-glutamyl carboxylase and play significant role in carboxylation of glutamic acid in vitamin K–dependent proteins. This carboxylase is expressed in the central nervous system during embryogenesis (82). It is well known that vitamin K is important in the maintenance of normal biosynthesis of CNS myelin (83). In addition, exposure to the vitamin K antagonist warfarin in utero induces CNS deformity and mental retardation (84). These observations suggest a possible role of vitamin K in the developing brain (82).

Some studies have been shown anticonvulsant activity of vitamin K in the minimal clonic seizure (6 Hz) and corneal-kindled as mouse models of epilepsy (85). It was reported vitamin K_3 declined swim activity induced by pentylenetetrazol in zebrafish at lower concentrations than valproate (2-n-propylpentanoic acid). Pentylenetetrazol stimulates a rapid increase in swimming behavior as an indicator for seizures in zebrafish. It seems the potential mechanism of vitamin K analogs for the prevention of seizures may lie in the ability of these compounds to affect ATP metabolism and increase total cellular ATP (85).

Moreover, in an animal study was reported a protective action of vitamin K in preventing oxidative stress as a cause of cell death in neurological disorder which showed vitamin K_1 and K_2 strongly prevented glutathione depletion in primary cultures of neurons exposed to oxidative cell death (82).

Clinical studies:

Experimental experiences on the use of antiepileptic drugs in combination with various vitamins may provide valuable clues regarding their clinical significance or adverse effects. However, the results of animal's studies should be practically tested in human.

Substantial evidences have proven the effect of various antioxidants like vitamins as useful adjuncts to antiepileptic drugs in clinical studies. It was shown that parameters of oxidative stress including lipid peroxidation, glutathione peroxidase in epileptic patients are higher and suggesting that free radicals may be involved in epilepsy. Furthermore, the prevalence of vitamin deficiency is high in epilepsy patients. Numerous effects of several antioxidants like vitamins were reported in patients with epilepsy (86, 87).

The most common used antiepileptic drugs impact on vitamins. Currently a large body of evidences indicates that several antiepileptic drugs lower vitamins in epileptic patients (31,32,88,89). It was displayed that anticonvulsant therapy (phenytoin, primidone, carbamazepine or phenobarbital) is associated with reduced thiamine (14), B6 (89), folate (88), biotin (90) and B12 (88) serum levels as well as hyperhomocysteinemia (91) in epileptic patients (14,31,32,88,89). Treatment with phenobarbital caused an increase in plasma concentrations of vitamins A and E and C (86), but it is associated with a decline in vitamin B12 serum levels in patients (88). Contrast, in valproate treatment, vitamin B12 levels is higher compared with untreated patients (88). Moreover, serum folate levels in patient taking carbamazepine, gabapentin, oxcarbazepine, phenytoin, primidone, or valproate lower (88).

Additionally, enzyme inducer drugs such as carbamazepine and phenytoin, phenobarbital and primidone lower vitamin D levels because of its catabolism (92, 93). It seems that the newer drugs including lamotrigine, levetiracetam which are non-enzyme inducer have minimal impact on vitamin D levels (92,94,95). Concerning valproate treatment, which considers as a non-inducer enzyme, shows no or

less reduction in 25(OH) D levels in epileptic patients (94, 96).

Add on therapy by vitamins revealed a significant seizure reduction in epilepsy patients. B vitamins accompany by antiepileptic drugs can produce more seizure control after stroke (97). Also, it was reported that carbamazepine with vitamin B12 can reduce levels of TNF-α (tumor necrosis factor alpha) in the serum (40). TNFα modulates glutamate receptor and increases excitatory synaptic transmission and induces seizures (39).

Regarding vitamin C, a depleted level of vitamin C has been reported in epileptic patients (98). There weren't any clinical studies about role of vitamin C in epileptic patient but some evidences suggest that vitamin C administration may have a variety of beneficial effects in patients with diabetes mellitus and cancer. It seems that vitamin C by decreasing serum fibrinogen has positive effect in patient with cardiovascular risk (99).

Clinical experiences indicated that vitamin D deficiency ranges from 4 to 75% in children with epilepsy (100). Some evidences suggested that serum 25-hydroxyvitamin D levels may decrease in epilepsy patients taking oxcarbazepine or carbamazepine due to an increase in vitamin D metabolism (101). In addition, an increase expression of vitamin D-binding protein within the cerebrospinal fluid from patients with temporal lobe epilepsy has been observed (102). However, little clinical data exist which support that correcting vitamin D in epileptic patient can relieve seizures (65,103).

Despite conflicting reports, some clinical data have shown beneficial effects of vitamin E as adjunctive therapy on the frequency of seizures as well as its capacity in raising antioxidant capacity in patients with uncontrolled epilepsy (72,104). These differences can be explained in regard to kind of antiepileptic drugs, the dosage and treatment duration of vitamins across several studies (72,79,80).

Only few clinical data exist to support the efficacy of the vitamin K in epilepsy. Enzyme- inducer drugs, such as phenobarbital, carbamazepine and phenytoin, cross the placenta (105). These drugs induce degradation in vitamin K metabolism and cause vitamin K deficiency as well as bleeding in neonates with maternal anticonvulsant therapy (106,107).

There are few clinical studies toward the proconvulsive effects of vitamins. It was reported that high-dose of folic acid may be epileptogenic. Administration of large doses of folic acid may decrease blood levels of phenytoin, phenobarbital, and carbamazepine as well as can decrease seizure control in some, but not all (108,109,110,111). Also, in one study was displayed that high-dose vitamin B6 reduced serum phenytoin and phenobarbitone levels in epileptic children (112,113). Overall, although conflicting between several studies on efficacy of vitamins in patients and vitamin therapy is not a substitute for antiepileptic drugs but add on therapy by them may relieve drugs- induced deficiencies as well as more researches are needed to evaluate the effectiveness of vitamins in epileptic humans (14).

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Conflict of interest

The authors declare that they have no conflict of interest.

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