

Nutritional therapy for epilepsy

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Abstract

Extensive studies have been done to understand the patho-physiology of epilepsy. In spite of large number of antiepileptic drugs being available in the market, 30% of patients still suffer from epilepsy. Various experiments have been done to explore the association of dietary supplements in relieving symptoms of epilepsy and it suggests that dietary therapy shows important adjunct to the available antiepileptic drugs (AEDs). Therefore, this review discusses current status of various dietary supplements (amino acids, minerals, antioxidants, vitamins, ketogenic diet, Atkin diet and herbal therapy) and the probable mechanisms of their efficacies. This would be helpful in their development as future nutritional therapy for the treatment of intractable epileptic disorders.

Keywords: *Epilepsy, amino acids, minerals, vitamins, antioxidants, ketogenic diet, Atkins diet, herbal therapies*

INTRODUCTION

Epilepsy is a collective term for a group of chronic seizure disorders having in common sudden and transient episodes of seizures with loss or disturbance of consciousness, usually but not always with a characteristic body movement (convulsion) and sometimes with automatic hyperactivity[1]. Seizures result from episodic neuronal discharges. The form of seizure depends on part of the brain affected [1]. Epilepsy is the third most common neurological disorder with an estimation of about 50 million people suffering from epilepsy. About four fifth of these are thought to be in developing countries. At least 2.4 million new cases of epilepsy occur each year. In India alone there are about 8-10 million people suffering from epilepsy with prevalence rate of 5.59 per 1000 [2,3,4].

Available treatment

The most widely accepted treatment for epilepsy currently is drug treatment. These drug may be of older generation like carbamazepine, phenobarbital, phenytoin, primidone, and valproic acid while the newer generations include lamotrigine, levetiracetam,

oxcarbazepine, topiramate and zonisamide [5]. The other method of treating epilepsy is vagus stimulation in which small pulses of electrical energy are sent to brain via vagal nerve [5,6]. Alternatively the excision of epileptogenic zone to remove the site of seizure onset to inhibit initial seizure propagation helps in alleviating the episodes [7].

Limitations

Problems associated with drug treatment are adverse effects due to use of antiepileptic drugs like blood dyscrasia, decreased cognitive abilities, psychiatric complications, hepatic toxicity, severe and cutaneous reactions [8-10]. The pre-marketing clinical trials are of shorter duration and cannot correctly predict or identify the long term adverse effects of antiepileptic drugs prescribed for several years in patients suffering from epilepsy chronically. These trials also exclude pregnant females, children and elderly patients thus making it difficult to predict the adverse effects of antiepileptic drugs in such population [9,10]. Surgery is highly effective and safe for selected patients with treatment resistant focal epilepsy, but at the same time a single

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site of origin cannot be localized or identified in many patients, complicating the therapeutic outcome of the surgery [8]. Also vagus stimulation cannot be recommended for treating all cases of epilepsy.

Need for nutritional therapy

The limitations associated with the current available treatment of epilepsy with none of these being able to treat the root cause of the disorder; nutritional therapy could be an economical and promising option to treat epilepsy. Adverse effects associated with nutritional therapy are not so severe and minimal most of time. Nutritional therapy especially ketogenic diet is effective across wide variety of ages, seizure types and severities.

Nutritional therapy

Amino acids

Taurine

Taurine is an inhibitory amino acid in the brain and causes hyperpolarization of neuron and inhibition of neuronal firing. Increase in level of taurine is associated with reduced seizure susceptibility while decrease in level with more spontaneous seizure activity. The mechanism by which taurine could decrease seizure susceptibility may/could be by (i) inhibiting the release of D-aspartate (analogue of L-glutamate) (ii) decreasing the intracellular level of free Ca^{2+} (iii) by its effect on chloride channels (activating GABA_A receptors). It has been found that about one-third of human beings suffering from epilepsy have shown significant alleviation of seizure by taurine administration. However, the major issue with taurine treatment is decreased efficacy with time as body adapts to the therapy by causing its excretion through urine. Numbers of taurine derivatives have been developed so far but none of them were proved to be very effective. Hence systemic study of taurine derivatives in future could be an arsenal of antiepileptic drugs in future [11,12].

Carnosine

Carnosine is an amino acid found in the brain involved in GABA activity. It is normally found as homocarnosine, a dipeptide metabolite of histidine and GABA [13, 14]. The

findings regarding the role of homocarnosine have contradictory results, a study claims increase in homocarnosine levels in children with febrile seizures and uncontrolled epilepsy whereas other study claims increase in homocarnosine levels in epilepsy patient treated with AED therapy [15]. In this study the homocarnosine levels were increased along with increase in GABA levels [15]. Therefore further studies are required to confirm the role of homocarnosine in the treatment of epilepsy.

Carnitine

Carnitine is a transport molecule that helps the cells to make their energy available, it also helps the cells to remove their waste products. Most of our requirement of carnitine is obtained with meat and dairy products [15]. It was reported that supplementation of carnitine to mice could reduce the seizure episodes when exposed to seizure provoking agent. However human studies did not support this observation [16]. It has been found that the patients treated with valproic acid (VPA) have the tendency to develop carnitine deficiency as VPA decreases concentration of α -ketoglutarate required in the synthesis of Carnitine. Also, carnitine supplementation increases the β -oxidation of VPA thereby decreasing the production of toxic metabolite involved in the liver toxicity and ammonia accumulation. Hence further studies are required to establish the role of Carnitine in management of epilepsy and VPA therapy [15].

Minerals

Manganese

Manganese is an essential trace element required for proper development and functioning of the central nervous system. It has been reported that manganese is required for activity of glutamine synthetase which converts glutamate to glutamine, however deficiency of manganese causes accumulation of glutamate and therefore leads to generation of seizure. An old Anglo Saxon preparation Lupine was used in the treatment of epilepsy, its anticonvulsant activity could be because of exceptionally high concentration of manganese [17-20].

Carl et al (1986) carried out a study in which he compared 44 epilepsy patients with 44 controls and found that manganese blood levels were significantly lower in the patients than in the control group [21]. However at the same time manganese toxicity is associated with tremors and seizures which quickly resolve on withdrawal from supplementation [16,18]. Therefore, the alteration in the concentration of manganese; either increase or decrease can be accompanied by seizures.

Magnesium

Magnesium is the fourth most common mineral in the human body and plays an important role in enzyme activities and membrane properties. Recent studies have shown that people with epilepsy have lower Mg levels than that of people without epilepsy. Also, various in vitro studies have shown that lower magnesium concentration is associated with seizures (spontaneous epileptic discharge and tonic-clonic like events) [22]. Studies in rats have shown that, deficiency of Mg in diet can lead to decrease in seizure threshold whereas its subsequent oral supplementation can increase the seizure threshold. Magnesium is also important in body's utilization of vitamin B6, which is a cofactor required for GABA synthesis [23,24]. The anti-seizure effect of magnesium could also be because of its property to inhibit NMDA receptor. Therefore magnesium supplementation can be considered for the management of patients with refractory epilepsy.

Zinc and Copper

Zinc and Copper are micronutrients that play essential role in several cellular functions. They are present in high concentration in brain regions such as hippocampus, olfactory bulb and hypothalamus. These trace elements accumulate in the synaptic vesicles, especially in areas like glutamatergic neurons and are co-released with neurotransmitters during normal synaptic events [25]. It has been suggested that alteration in the homeostasis of zinc in the brain may be associated with epilepsy although it is not confirmed whether this is responsible for the seizure episode. Clinical studies correlating

epileptic episodes, AEDs and zinc levels report contradictory results and hence it is difficult to establish direct correlation of zinc levels with epilepsy [26]. Copper deficiency may cause seizures and its levels are higher when treated with AEDs probably due to formation of copper complexes by activation of AEDs. Though the correlation of zinc-copper ratio is not fully understood still some research theorize that seizure occurs when the ratio fall suddenly in the absence of taurine [15,24,26].

Vitamins

Vitamin B6 (Vitamin B6)

Vitamin B6 is a coenzyme necessary for the synthesis and metabolism of various amino acids and also in an important factor for hormonal modulation, gluconeogenesis, neurotransmitter formation and immune functioning. The active form of Vitamin B6 used by human being is pyridoxal 5'-phosphate (PLP). Vitamin B6 is especially important in epilepsy as it is essential factor in the functioning of glutamate decarboxylase which converts glutamate to GABA, an important inhibitory neurotransmitter in the brain. Deficiency of Vitamin B6 leads to decrease GABA synthesis in the brain, therefore increasing the risk of convulsions. The most common cause of Vitamin B6 deficiency is found in tuberculosis patient treated with isoniazid. Overdose of isoniazide is associated with inhibition of pyridoxal phosphate kinase, an enzyme required for synthesis of PLP, which in turn decreases GABA levels in the brain and lowering the seizure threshold. Thus patient with isoniazid shows seizures which are refractory to conventional AED but respond to pyridoxine treatment [27]. A rare genetic disorder with deficiency of Vitamin B6 causes severe neonatal seizures and mental disability which requires lifelong supplementation of Vitamin B6 [20,21]. However, the excessive amount of Vitamin B6 supplementation can cause sensory nerve damage resulting in numbness in hands and feet [28,29]. Therefore more studies are required to optimize the therapeutic efficacy of Vitamin B6 in the treatment of epilepsy.

Antioxidants

Oxidative stress is a contributing factor for various neurological disorders including acquired epilepsies such as temporal lobe epilepsy (TLE). Acquired epilepsy is initiated with brain injury followed by “latent period”. During this period lot of molecular, biochemical changes associated with oxidative stress take place in the brain leading to chronic epilepsy. Therefore, antioxidant therapies have received considerable importance for the treatment of epilepsy [30]. Antioxidants are endogenous or exogenous redox active compounds that limit the oxidative stress by reacting with a reactive oxidant. These antioxidants are majorly categorized into two viz. enzymes (Super Oxide Dismutase (SOD), catalase and peroxidase) and low molecular weight antioxidant (LMWA). LMWA can further be classified into directly acting antioxidant (e.g scavenger and chain breaking antioxidant) and indirectly acting antioxidant (chelating agents). The former category contains compounds like polyphenols, carotenoids, ascorbic acid etc [31]. Endogenous hormone melatonin (pineal gland hormone) is well known free radical scavenger. Melatonin has proved to be anticonvulsive agent in range of animal models like kainic acid (KA), pentylenetetrazole (PTZ) and pilocarpine. Another endogenous antioxidant ‘lipid acid’ though present in small quantity in body showed potent antiepileptic effect in both in vivo & in vitro conditions when supplied externally. A reduced form of lipoic acid i.e. dihydrolipoic acid has been proved to be more active than lipoic acid. α -Tocopherol is a lipophilic antioxidant proved to be effective against PTZ and pilocarpine induced seizure but not against kainic acid and amygdala induced kindling. Thus, the detailed pharmacological investigation and mechanism of action of these antioxidants is desirable before their clinical application [30,32].

Ketogenic Diet (KD)

In the early 1920s, it was found that a calorie-restricted diet high in fats, with sufficient protein (1 g/kg) and limited carbohydrates (5-10 g/day) could mimic the biochemical changes of starvation and could preserve its

beneficial effects on the seizures. In modified form this has become today’s ketogenic diet. Though it was found to be very beneficial in treating epilepsy its use reduced with invention of phenytoin and other antiepileptic drugs [33]. It is difficult to follow strict diet plan with ketogenic diet as meals are prepared strictly adhering to the prescribed substances. For some children even small quantity of carbohydrate can lead to seizure. However, considering limitations of other therapies and multiple studies confirming its efficacy with very limited side effects, it is very effective in treating children with difficult-to-control seizures and thus interest in ketogenic diet has been reawakened [33]. The “classic” ketogenic diet, developed at John Hopkins Institute contains a 4:1 ratio of fats to carbohydrates. The quantity of protein in formulation would be such that, approximately 90% of calorie would be derived from the fat. Whereas, total calories is restricted to 75% of the required daily allowance [34,35]. During this process large amount of acetyl-CoA is generated, leading to formation of ketone bodies like β -hydroxy butyrate – BHB, acetoacetate and acetone [36,37]. These ketone bodies are utilized as an energy source in various tissues including brain.

Role of Ketone Bodies

Initially β -hydroxy butyrate was considered to be responsible for anticonvulsant effect of ketone bodies. However studies carried out reveal that there is significant correlation between acetone and seizure control [33,34]. A proposed mechanism by which ketone bodies like acetoacetate & acetone may act by activation of K_{2p} channels. K_{2p} channels hyperpolarize cell membranes and regulate membrane excitability. [34].

Role of Glucose Restriction

Some studies have suggested that along with ketosis in KD, glucose restriction could be the other feature to prevent seizure. Calorie (glucose) restriction reduces the energy production through glycolysis, limiting the ability of the neuron to achieve high level of synaptic activity required for seizure generation. Other hypothesis suggests that glucose restriction leads to ATP release

through pannexin hemichannels localized in neurons. This increased level of extracellular ATP would be rapidly degraded to adenosine by ectonucleotidases. The increased level of adenosine further activates A1 receptors which in turn will activate ATP sensitive potassium (K_{ATP}) channels. These channels then hyperpolarize neuronal membrane [38]. KD induced increase in ATP concentration may prolong the activation of Na^+/K^+ -ATPase, however there is no direct correlation of this pump to antiepileptic activity [38].

Role of Neurotransmitter and Neuropeptide System

All ketone bodies produce acetyl CoA which enters TCA cycle at the citrate synthetase step. This step involves consumption of oxaloacetate; hence oxaloacetate is not available for conversion of glutamate to aspartate. As a result more glutamate is available for synthesis of GABA (through glutamic acid decarboxylase) which being inhibitory has anticonvulsant effect. Also less production of aspartate means reduction in excitatory neurotransmitters [33,34]. In general, increase in noradrenergic tone is associated with anticonvulsant effect. Several lines of evidences support the hypothesis that the anticonvulsant activity of KD may result in part from enhancement in release of norepinephrine (NE) [38]. Peptides like leptin may play important role in antiepileptic effect of KD. Leptin helps in regulating the energy homeostasis of the body. It also has modulatory effect on neuronal excitability and seizure activity. It has been reported that leptin attenuates focal or generalized seizures in rodent models possibly through modulation of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptors. As KD causes increase in leptin levels hence enhancement of leptin level could also be one of the mechanisms of antiepileptic effect of KD [38].

Role of Fatty Acids

It mainly includes polyunsaturated fatty acids (PUFAs) such as docosahexanoic acid (DHA), arachidonic acid(AA), eicosapentanoic acid(EPA). PUFAs were found to inhibit fast voltage gated Na channels, L-type Ca channels[33,34] and can activate potassium channels (K_{2P}) this dampens

neuronal excitability[33,34,38]. The PUFAs are shown to activate of peroxisome proliferator activated receptors (PPARs) and activation of PPARs in turn inhibit the pro-inflammatory transcription factors. As the inflammation is considered to be a core contributor of epileptogenesis PUFAs may be considered as rational approach to prevent epileptogenesis [38]. PUFAs have to property to induce the expression of mitochondrial uncoupling protein (UCPs). These are homodimer protein that span the inner mitochondrial membrane and help in proton leak from the inter-membrane space of mitochondria. This uncoupling effect though in small quantity reduces the proton motive force and thereby uncouples the electron transport from ATP production. This process also inhibits the reactive oxygen species (ROS) production. It has been reported by Dian et al., (2003) that chronic expression of of UCP in neuronal tissue increased the ATP levels through mitochondrial biogenesis and did not inhibit the cellular energy production as hypothesized. KD follows the same process and decrease the seizure induced mitochondrial dysfunction and ROS production [33,39,40,41].

Triheptanoin

According to a hypothesis, seizure is associated with increased neurotransmission (Glutamate, Aspartate and GABA). As all the mentioned neurotransmitters are synthesized from α -ketogluatarate; seizure is associated with depletion of α -ketogluatarate. This α -ketogluatarate is also an intermediate of TCA cycle. Hence there is direct correlation between increased neurotransmission (seizure episode) with decreased TCA cycle and energy production. Therefore refilling these metabolites (Anaplerosis i.e. formation of intermediates of metabolic pathways) could produce antiepileptic effect [42]. Triheptanoin is a medium chain triglyceride (three odd carbon atom chain fatty acid heptanoate connected to glycerol).It act as an anaplerotic agent in addition to ketogenic diet and hence shows better activity when compared against ketogenic diet without triheptanoin. Hence Triheptanoin has the great potential in the treatment of epilepsy in refractory patients.

Alongwith beneficial effects some side effects like propionic acidemia, needs to be carefully monitored during therapy [42].

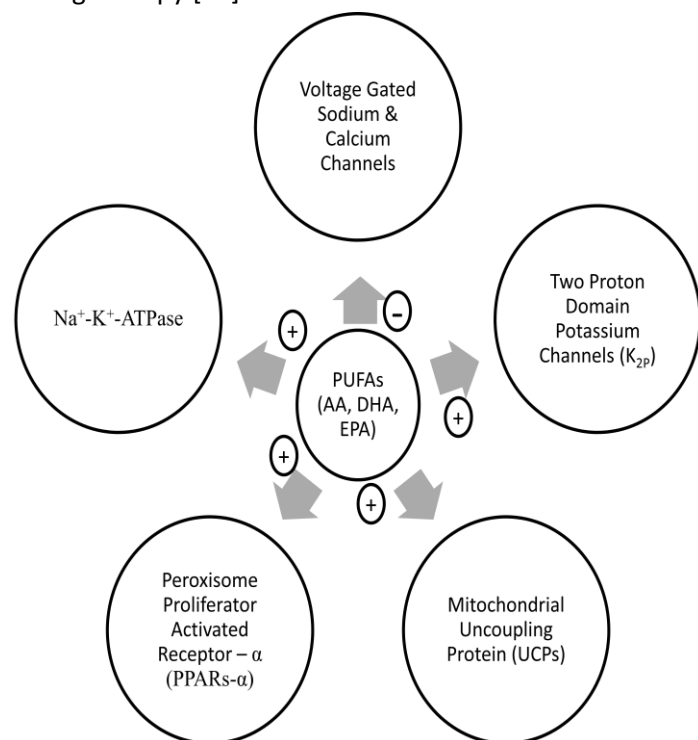


Figure 1: Mechanism of anticonvulsant effect of Poly Unsaturated Fatty Acids (PUFAs).

The Atkins Diet

The Atkins diet is an alternative to ketogenic diet for epilepsy treatment and was prepared by Dr. Rober Atkins in 1970 to combat obesity like that of ketogenic diet. The ketogenic diet comprises of 80% fat, 15% protein and 5% carbohydrate, whereas, the Atkins diet comprises of 60% fat, 30% protein and 10% carbohydrate. Published reports on the efficacy of Atkins diet says that 45% of patients taking Atkins diet have seizure reduction upto 50-90% and 28% patients have seizure reduction >90% which is very much similar to that of traditional ketogenic diet. The Atkins diet have additional benefit of being effective in both children as well as adults and patients are more comfortable with Atkins diet as compared to the restrictions of KD [36,43].

Herbal therapies for epilepsy

In developing countries, herbal therapies to treat epilepsy have evolved over the centuries (as early as

6000 BC in India and 3000 BC in China, Peru and Africa), in conjugation with system of health care and level of education. Ayurveda contains dietary therapies recommended for epilepsy and it includes plant preparations such as, *Centella asiatica* and *Bacopa species* (Brahmi) with honey, old pure *desi ghee* (clarified butter), and *Asparagus racemosus* with milk. Other herbs recommended for treatment of epilepsy in Ayurveda are *Acacia nilotica*, *Acorus calamus*, *Bacopa monnieri*, *Clitorea ternatea*, *Celastrus paniculatus*, *Convolvulus pluricaulis*, *Phyllanthus emblica*, *Withania somnifera*. Various other herbs like *Eclipta alba* and *Semecarpus anacardium* have been traditionally used in the treatment of epilepsy [44,45,46]. The Chinese system of medicine also includes formulations like Chai-Hu-Long-Ku-Mu-Li-Tan (formulation of more than 13 different plants) and many others having neuroprotective properties. However, despite their extensive use in epileptic patients, there is still lack of scientific evidence in support of their use. Although some herbal therapies may pose safety risk to the people consuming it, they still provide new inexpensive treatment strategies to the patient suffering from intractable epilepsy [44].

CONCLUSION

Nutritional treatment comprises a fascinating approach for the treatment of epileptic patients. It includes the treatment with amino acids, antioxidants, vitamins, mineral, ketogenic diet and Atkins diet. However, our knowledge about the correlation between epilepsy and its treatment with nutrition is in its infancy. The treatment strategy would depend on the type of epilepsy and hence a detailed diagnostic examination is required before the initiation of the treatment. It is also extremely important to understand the molecular and biochemical aspect of nutritional therapies on different types of epilepsies and their probable interactions with the current available AEDs.

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