Review Article

Int. J. Biopharm. Res.
ISSN: 2287-6898
OPEN ACCESS
www.ijbpr.net

The hidden role of Vitamin D in Epilepsy

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Received for publication: April 10th 2014; Accepted: April 21st 2014

Abstract: Vitamin D plays an important role in variety of biological processes like calcium, mineral and bone homeostasis. Beside this, Vitamin D plays an important role in Neurological disorders like Epilepsy, Parkinson's disease, Schizophrenia, Dementia and Multiple sclerosis. To highlight the role of Vitamin D induced neuronal apoptosis and increased expression of Cytochrome C in Epilepsy prevention hes been discussed in this review.

Key Words: Vitamin D, Epilepsy.

Introduction

Vitamin D is a steroid hormone that plays a vital role in calcium and phosphorous absorption. Vitamin D is mainly found in the body in two forms that is Vitamin D_2 and Vitamin D_3. Vitamin D_3 or Cholecalciferol is formed in the skin after exposure to sunlight or UV radiation. Vitamin D_2 or Ergocalciferol, is obtained from various food sources including milk and fish.[1] These two forms of Vitamin D are metabolized in the liver and stored as 25-hydroxy vitamin D. Before biological use the storage, form must be converted into an active form. One such active form is 1, 25-dihydroxy Vitamin D.[2]

Hypovitaminosis D is described as any deficiency of Vitamin D. Recently researchers have considered below 30ng/mL to be an insufficient concentration of Vitamin D.[3] Subnormal levels of Vitamin D are usually caused by poor nutrition or a lack of sunlight exposure. Risk factors include premature birth, darker skin pigmentation, living at high altitude, obesity, malnutrition and older age.[4] Hypovitaminosis D is linked to neuropsychiatric disorders which include Alzheimer's disease, Parkinson's disease, Multiple sclerosis, Schizophrenia and last but not the least that is Epilepsy.[5]

What is Epilepsy?

The term Epilepsy is derived from the Ancient Greek verb meaning "to seize, possess, or afflict"[6] is a group of long term neurological disorders characterized by epileptic seizures.[7] These seizures are episodes that can vary from nearly undetectable to long periods of vigorous shaking.[8] In epilepsy, seizures recur due to no immediate underline cause while those which occur due to a specific reason do not represent epilepsy.

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Epilepsy is characterized by long term risk of recurrent seizures. The most common type of seizures are convulsive while two-thirds begin as focal seizures while rest one-third begin as generalized seizures.[9] Some people can also develop epilepsy due to brain injury, stroke, brain tumor and drug or alcohol misuse. Epileptic seizures are the result of excessive and abnormal cortical nerve cell activity in the brain.[10] Epilepsy can be confirmed with an electroencephalogram (EEG).

Treatment options

Neurostimulation is preferable treatment in candidates who are not preferable for surgery and those who don't respond to medications. This includes vagus nerve stimulation and anterior thalamic stimulation.[11] When our body fat burns it produces ketones which may cause change in metabolism leading to strong anticonvulsant effect. Thus, a ketogenic diet (high fat, low carbohydrate and adequate protein) appears to be helpful in decreasing the number of seizures by about 30-40% in children, but the exact reason is still not known.[12]

Vitamin D and Epilepsy

The brain uses many neurosteroids to develop and function properly. Several Vitamin D metabolites are found in cerebrospinal fluid and have the ability to cross the blood brain barrier. These Vitamin D metabolites include 25-hydroxy Vitamin D_3, 1, 25 di-hydroxy Vitamin D_3 and 24, 25 di-hydroxy Vitamin D_3. Derivatives of these metabolites are highly expressed in substantia nigra and the hypothalamus. These two brain structures are responsible for motor function and thus link the nervous system to endocrine system. The expression of these metabolites in the brain suggests

that these structures have the ability to synthesize these products from vitamin D.[5]

In addition to Vitamin D metabolites, Vitamin D receptor (VDR) proteins are also found in the cerebellum, thalamus, hypothalamus, basal ganglia and hippocampus.[5]The highest density of VDR is present in the primary areas of dopamine production. Also, significant content is also found in the supra optic and para ventricular nuclei and in lower densities in the hippocampus.[13]

Vitamin D may function as modular in brain development and as a neuroprotectant.[5] Vitamin D has exhibited an association with the regulation of Nerve growth factor (NGF) synthesis. NGF is responsible for the growth and survival of neurons.[14]This relationship has also been studied in embryonic and neonatal rats. Developmental Vitamin D Deficient (DVD) rats have decreased levels of neurotropic factors, increased mitosis and decreased apoptosis. These findings suggest that Vitamin D potentially affect the development of neurons as well as their maintenance and survival. Vitamin D is a factor contributing to normal brain functioning. Hypovitaminosis D may impact neuropsychiatric disorders like Dementia, Parkinson's disease, Multiple sclerosis, Schizophrenia and Epilepsy.

Medications for Epilepsy Causes Vitamin D Deficiency

Mostly the drugs used to treat epilepsy are known as anticonvulsants. These drugs function by suppressing the abnormal brain activity. Since Epileptic seizures are caused by neurons with in the brain sending out unusual electrical signals, these anticonvulsants decrease the frequency with which epileptic patients experience seizures. Mostly multiple anticonvulsants are also used to control the seizures.[15]

One of the drawbacks of using anticonvulsants is that they can lead to a deficiency in Vitamin D. Two commonly used anticonvulsants medications, phenytoin and phenobarbital decrease the activity of Vitamin D in the body when these are used for extended periods of time. These medications increase the activity of enzymes in the liver, which causes Vitamin D to be more rapidly broken down into inactive forms. Vitamin D is essential for body to properly utilize and metabolize calcium, therefore long-term use of anticonvulsants can cause conditions such as rickets in children and osteomalacia in adults as the bones become brittle due to lack of calcium because of Vitamin D deficiency caused by these anticonvulsive drugs.[15]

Mechanisms of Vitamin D in Pathology of Epilepsy

One of the plausible mechanisms is through neuronal apoptosis which is programmed death of neurons. Hypo-vitaminosis D decreases this specific apoptosis by lowering the expression of Cytochrome C and decreasing the cell cycle of neurons. Cytochrome C is a protein that can promote the activation of pro-apoptopic factors.[16] Thus the lowered expression of Cytochrome C due to Vitamin D deficiency may cause epileptic seizures.

Second plausible mechanism is by the association of neurotropic factors like Nerve Growth factor, Brain derived neurotropic factor, Glial cell line derived neurotropic factor. These neurotropic factors are the proteins that are involved in the growth and survival of developing neurons and they are involved in the maintenance of mature neurons.[17]

Role of Vitamin D in Epilepsy and Seizures

Seizures are caused by disturbances in brain activities when neurons fire abnormally. In one small pilot study conducted by Christiansen in 1974 Vitamin D supplementation, but not placebo treatment was associated with decreased seizures. Vitamin D can regulate pro-convulsant and anti-convulsant factors. Vitamin D decreases the concentration of IL-6, which is a potent proconvulsant.[13] Vitamin D is also associated with the up regulation of anticonvulsant neurotropic factors, GDNF and TN-3. In order to maintain proper homeostasis pro-convulsant must be down regulated and anticonvulsant should be upregulated to prevent epileptic seizures. It is hypothesized that this disturbance of homeostasis may lower the threshold for convulsive activity leading to Epilepsy. Vitamin D has also shown to promote the expression of calcium binding proteins that are known to possess anti-epileptic properties.[18]

Summary and Conclusions

From the above review it can be postulated that Vitamin D deficiency can also be the

underlying cause of epilepsy due to decreased neuronal apoptosis and decreased neurotropic factors. Secondly treatment with anticonvulsants can also lead to Vitamin D deficiency. Now there are two available options for the treatment from the above review, one is to supplement with Vitamin D in order to increase neuronal apoptosis and neurotropic factors so that there is decrease in epileptic seizures and the other is to supplement Vitamin D with antiepileptic drugs so that Vitamin D deficiency does not occur along with the treatment of epilepsy.

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Source of support: Nil
Conflict of interest: None Declared