

## From the Ancient Diets to the Recent Acquisitions on the Role of Brain Inflammation in Epilepsy, Are there Any Links?

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Received date: June 30, 2015; Accepted date: July 28, 2015; Published date: August 03, 2015

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### Abstract

Recent studies put in evidence the role of brain inflammation in the pathogenetic mechanisms of seizures. It has been reported that an intestinal inflammation may be able to migrate to the brain, thus an intestinal inflammation could be the original cause of epilepsy, as osteopaths believed in the '20s. We attempted to demonstrate the role of gut-brain axis in epilepsy on the basis of recent acquisitions.

**Keywords:** Ketogenic diet; Inflammation; Intestine; Gut-brain axis

### Manuscript

Surely, the diet is the oldest form of medicine, used to treat diseases since ancient times. According to Hippocrates (460 BC) "every patient requires a diet." Early as 300 BC, Erasistratus put in evidence a connection between epilepsy, intestine and digestive organs. In the second century, Galen referred to diet and purges to control crisis. In the eighteenth century, Arnold of Villanova considered the diet as the most important aspect in the treatment of epilepsy. In the twenties, fasting was widely used to control seizures [1], and its efficacy was linked to ketosis. Later, in 1866, a diet rich in fats and poor in carbohydrates was proved to produce ketosis, hence it was suggested to control seizures, and named ketogenic diet (KD).

A recently published meta-analysis [2] on a total of 38 studies shows that the success rate of the patients following the KD was 58,4% at 3 months and 42,8% at 6 months. However, it must be kept into consideration that about 50% of patients dropped out at 6 months, mainly for its scarce palatability.

Major limitation to evaluate the diet's efficacy by gold standard protocols is that it cannot be administered to patients following the double-blind, crossover vs. placebo studies. For this reason the diet is nowadays largely considered as non-conventional medicine.

However, in 2008 Helen Cross conducted a pseudo-controlled study on the KD, through random enrollment of about 100 children: half of them received drug treatment, using drugs available in 2008, the second half were put on KD. At six months of treatment, the result of this study showed a 30% average worsening in the number of seizures in pharmacologically treated patients, while the group treated with KD had achieved a seizure average reduction of about 30% [3].

Today, we know that ketones are not responsible for anticonvulsant action [4]. In fact, the hypoglycemic diet, which does not produce

ketosis, already proposed by Lennox in 1928 [5], produces results similar to those of KD [6].

Unveiling KD's mechanism of action could be helpful to understand the pathogenesis of epilepsy. In particular, its large spectrum of action on different types of seizures [7] has to be considered and compared with the high specificity of the drugs, which may even be pro-convulsive in epileptic types different from those on which they are proposed [8,9].

Thus, KD's large spectrum of action could be linked to an increase of epileptogenic threshold, rather than blowing out the seizures.

KD, along with starvation, is reported not only to induce ketosis, but also to increase brain norepinephrine (from  $100 \pm 15$  to  $250 \pm 15$  pg/ml in the hippocampus) [10], which has both anticonvulsant and antidepressant effects [11]. Furthermore, an increase of norepinephrine is reported to potentiate the anticonvulsant action of both KD [12] and drugs [13].

Even more importantly, KD is capable of increasing brain NPY level [14], and the same action is reported for valproic acid [15,16] and topiramate [17]. Being NPY an endogenous anticonvulsant, increasing its level must be considered among their anticonvulsant mechanisms [18,19].

Interestingly, KD has been proposed to treat several different clinical conditions: it decreases beta-amyloid plaques in Alzheimer's disease [20], it slows the progression of disease in ALS [21], on rheumatoid arthritis, where an intestinal origin of the pathology has been suggested [22,23], an improvement of 43% in the rating scales has been reported in Parkinson's [24]. It produces interesting results not only in clinical trials, but also in experimental models of epilepsy [25,26] of ischemia and head trauma [27].

All in all, results have led to put in evidence a neuroprotective role of KD [28], even without being able to link it to some precise mechanisms.

We suggest that such a role might be specifically related to the increase of NPY, since it is known to control the brain's self-reparative mechanisms [29]. NPY has been recognized as pivotal in the ILs expression mechanisms [30] involved in inflammation responses, as much as in intestinal inflammation [31] and in immune-modulation [32]. Furthermore it is co-released with norepinephrine and it is fundamental in the gut-brain communication (gut-brain axis) [33]. Such a wide spectrum of action suggests a possible interaction between different districts of the body: therapeutic action on the central nervous system (CNS) could be a reflex induced by an action on the intestinal mucosa.

In the twenties, even without being able to understand the mechanisms, American osteopaths were certain of the role of intestinal inflammation in the pathogenic mechanisms of seizures [34], and at that time, to control seizures, intestinal resections were suggested too [35-37].

Recent studies show that brain inflammation is the pathogenic cause of the seizures [38], it is not simply a predisposing factor, and constitutes a biomarker [39]. Thus, reducing brain inflammation can counteract epileptogenesis [40], and it might be an interesting, innovative tool for seizure control [41,42].

Today, it has been demonstrated that chronic intestinal inflammation migrates to other organs, including the brain [43], and decreases the epileptogenic threshold [44], providing the missing scientific evidence to the osteopaths' theory.

Furthermore, systemic inflammation has been reported to trigger brain inflammation [45], if BBB permeability resulted increased, but it is controlled by intestinal microbiota [46], then our microbe control all inflammation process, in the brain, too.

Thus, lowering the intestinal inflammation can result in a reduction of seizures.

In agreement with this, the anti-epileptic effect of Vagus nerve stimulation (VNS) has been linked with the stimulation of the cholinergic anti-inflammatory pathway [47]. Thus, VNS confirms the role of gut-brain axis and inflammation in seizure controls.

In support to these findings, it has been reported that acetylsalicylic acid is able to control seizures in drug resistant experimental models, apparently by stimulation of self-healing mechanisms [48]. Again, on experimental models, N-palmitoylethanolamine (PEA) has been reported to have an anticonvulsant action [49,50]. It has been demonstrated that PEA exerts a great variety of biological functions related to chronic pain and inflammation, it is proven to have anti-inflammatory [51], anti-nociceptive [52] properties and to play a neuroprotective role [53].

Curcumin is another agent reported to be neuroprotective [54] on the basis of results obtained in Parkinson, Alzheimer, epilepsy, stroke, depression and neurodegenerative disorders. Interestingly, it is known to fail to reach the brain for its scarce bio-availability [55]. One more time, evidence demonstrates curcumin to be an intestinal anti-inflammatory agent [56].

Curiously, Valproic acid, serendipity discovered to be anti-convulsive, was synthesized from Valeric acid, a component of valerian, used in the past for seizure control. Valeric acid is a short chain fatty acid (SCFA), one of the intestinal cells main nutrients.

SCFAs are obtained by fermentation processes of indigestible fibers (from C2 to C4). The C6 to C12 fatty acids (known as Medium Chain

Triglycerides - MCT), obtained through the same processes, are used in seizures control, alone or together with KD. Both SCFAs and MCTs have a clear role in decreasing the intestinal inflammation [57].

Moreover, VPA has been reported to be a histone deacetylase (HDAC) inhibitor able to significantly improve hemodynamics, intestinal perfusion, and the survival rate after lethal burn shock [58].

These small molecules, inhibitors of HDACs, have been found to trigger both pro- and anti-inflammatory effects, and they are therapeutic promises in inflammatory diseases such as: arthritis, inflammatory bowel diseases, septic shock, ischemia-reperfusion injury, airways inflammation and asthma, diabetes, age-related macular degeneration, cardiovascular diseases, multiple sclerosis and other CNS and neurodegenerative diseases [59].

Again, referring to health of the intestinal mucosa, Alpha-lactalbumin (ALAC), is a highly effective prebiotic agent of the human intestine, which, through colostrum, activates the newborns' intestine. Several intestinal actions are reported on this whey protein [60-62].

ALACs' efficacy has been reported in several experimental models of epilepsy, in particular it is able to control both types of seizure induced by Pilocarpine [63]. Furthermore, after a period of time of daily ALAC administrations, audiogenic mice continue to be protected by seizures for at least one month from the treatment discontinuation [64]. This evidence suggests that ALAC does not blow out the seizures, but rather decreases the epileptogenic threshold. Surely, ALAC decreases intestinal inflammation, that, once chronic, can migrate to the brain.

Taking in account the role of peripheral inflammation on the pathogenetic mechanisms of seizures, the intestinal actions of anti-epileptic drugs has to be considered, since they are orally administrated. Moreover, it is not always possible to know the exact drug's amount able to reach the brain, and if it is comparable with the amount reported to be able to act on neuronal ionic channels by patch clamp experiments. Lacking to know these data, it has been suggested that drug-resistance is due to the expression in the brain of drug-resistant proteins that throw the drugs outside the brain [65].

## Conclusion

The recent acquisitions on the role of brain inflammation in the pathogenetic mechanisms of seizures, allow us to re-evaluate the anti-epileptic effect of ancient diets.

As a clear consequence to this possibility, we have to consider the intestinal actions of orally administrated drugs, especially taking into account that, for many of them, data on brain intake is unavailable.

Taking in consideration the intestinal action of the drugs allow us to better understand not only their mechanisms of action, but the pathogenetic causes of epilepsy, too. Since, the main action is to decrease intestinal inflammation, the diet becomes pivotal in seizure control.

Potential inflammatory foods could also affect the anti-inflammatory action of drugs, resulting in a decrease of the epileptogenic threshold.

All the aforementioned evidences show that reducing intestinal inflammation increase seizure control by controlling the inflammation process, which triggers seizures.

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