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Personal view/review

THE USE OF FATTY ACID SUPPLEMENTATION FOR SEIZURE MANAGEMENT

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Impressive research demonstrates the importance of essential fatty acids (FA) for many physiological and behavioral mechanisms, in both humans and animals. In humans, essential fatty acids must be supplied via the diet. The genesis, maintenance, exacerbation, and treatment for many chronic health conditions are often related to deficiencies in omega-6 (linoleic acid) and omega-3 (alpha-linolenic acid), and their derivatives. In animal studies, providing supplementation of these FA changes chemical, immune, and structural properties of the brain, including the fluidity of the neuronal membrane. Of particular interest to epilepsy, pre-treatment of a ratio of the FA omega-3 / omega-6 resulted in altering the threshold for seizures following administration of convulsant agents that reliably induce epileptic activity. This report reviews the human and animal clinical and experimental data and theoretical considerations that support the promise for FA supplementation for use by seizure patients.

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All anticonvulsant medications share a common feature, that is, they supply specially designed

chemicals to the brain that are able to change the neurophysiology of the brain and thereby control the bioelectrical discharges that cause seizures. The need to control seizures is self evident. In addition to the clinical and observable behavior changes that define an epileptic seizure, animal studies have shown that seizures cause a reduction in important operation of the hippocampus (a brain structure that is involved with memory, execution of logical tasks, and emotion, among other functions [see below]) as well as disturbances in learning on how to avoid and escape from an unpleasant environment.¹⁻⁴ At the cellular and biochemical level, functional changes in the hippocampus following a seizure include a decrease in both the short and in the persisting electrical activity of the cell,³⁻⁷ as well as structural changes such as loss of neuronal cells in critical areas of the hippocampus.²

Anticonvulsant medications are imperfect and their effects are not uniform for every patient.⁵ Often, no single chemical preparation is adequate to provide satisfactory clinical control. Moreover, the more one has to add to the cocktail of anticonvulsant medications to better control seizures, the more likely a patient will suffer from the treatment side-effects. The less serious side effects may take the form of drowsiness, clouded learning and cognitive ability, stomach upset, and hyperactivity.⁸⁻⁹ Sometimes seizures turn out to be especially resistant to conventional treatment¹⁰⁻¹¹ and the frustration by the patients and their caregivers leads them to consider unconventional therapies, many of which have little or no sound scientific basis or

credibility. But not everything that is unconventional is necessarily useless or fraudulent.

Among the more popular proposed epilepsy "alternative treatments" having certain degree of support, are the use of behavior modification, hypnosis, exercise, and, EEG biofeedback.¹²⁻¹³ These activities have been shown to help numerous patients, but true randomized clinical trials (the only ones that serious critics of any experiment are prepared to accept and be convinced) remain to be conducted. Currently, the existing data are largely based on small sample studies and anecdotal reports.

One exception to the widespread criticism of "alternative treatment" is the use of the "ketogenic diet" (see below for details). For all other techniques, however, rigorous clinical trial methodologies (to convincingly demonstrate the benefits of such alternative or complementary treatments) are not available yet. In contrast to the pharmacological attempts at seizure control, the theoretical rationale for alternative or complementary techniques is limited at best. Historically, however, it happened that many of the significant advances in medicine have resulted from accidental discoveries of "things that work", with an understanding of "why" they work, coming much later (if coming at all).

CONCLUSIONS TO DRAW

In this personal viewpoint article we wish to propose yet another epilepsy "treatment alternative" based on dietary intake. We have to note that considerable research with human subjects is due before we can comfortably conclude that our approach has beaten a new and clinically significant path that has been overlooked. We will advocate the use of a special dietary supplementation, not necessarily as the primary or sole treatment of choice, but more likely in the form of an adjunct or add-on therapy. Even in the absence of large scale human studies, however, we are currently able to provide a scientific rationale for our proposal and to back up our enthusiasm with data from laboratory experiments that we and others have conducted over a number of years, with animal subjects. Furthermore, we can assure the reader that the risk of side effects for most patients is minimal, and that the cost of following such a program is economically acceptable. In a sense we are suggesting a chemical supplementation of a somewhat different type, and one that is not usually associated with the world of anticonvulsants. The chemical preparation under discussion is available in nature, in some of the foods humans commonly

eat. These specific chemical formulations are known as "essential fatty acids"; "essential" because, as opposed to many animals who can manufacture these chemicals, the only way human body receives the needed supply is via the diet. Interested reader may find a description of fatty acid biochemistry in a number of web resources (ex <http://www.indstate.edu/thcme/mwking/lipids.html>), biochemistry textbooks or even well written books for lay audience.¹⁴

The promising relationships between epilepsy and seizure on one hand and fatty acids on the other hand are complex and not obvious. This is especially true for a class of fatty acids known as polyunsaturated fatty acids (PUFA), that serve as neuroprotectors and neural stabilizers.¹⁵ The PUFA directly affect the flow of brain chemicals through the neuronal membrane that can be quantified and expressed by the "membrane fluidity index".¹⁵ Because of the pivotal role in regulating neuronal functions, PUFA affect many complex activities in human brain, and are involved in the management of epileptic seizures.¹⁵

The aim of this viewpoint article is (1) to provide the evidence that essential fatty acids play major role in epilepsy and in seizures, (2) to demonstrate that essential fatty acid treatment may be helpful in preventing or limiting the number and severity of seizures, and (3) to present the hypothesis explaining such property of the essential fatty acids..

ESSENTIAL FATTY ACIDS

Few topics in nutrition cause as much controversy and concern, and are as frequently misunderstood, as fats.¹⁶ The repeated cautionary warnings from the medical profession has been to dramatically reduce the amount of fat one eats, so as to minimize the risks associated with cardiovascular diseases, diabetes, and other chronic disorders. However, deficiencies in fat intake are equally likely to contribute to health hazards, including increased risk of infection, dysregulation of cyclic and rhythmic activity, and impaired cognitive and sensory functions (especially in infants).¹²⁻¹⁴ Symptoms of essential fatty acid deficiency may include fatigue, skin problems, immune weakness, gastrointestinal disorders, heart and circulatory problems, growth retardation, and sterility. In addition to these symptoms, a lack of dietary essential fatty acids has been implicated in many disorders including (but not limited to) the development or aggravation of breast cancer, prostate cancer, rheumatoid arthritis, asthma,

preeclampsia, depression, schizophrenia and ADHD (attention deficit/hyperactivity disorder).^{17,18}

A consensus has emerged from recent research that it is not so much the amount of fat we eat as it is the balance of the different types of fats.¹⁹⁻²⁰ The type of dietary fat we consume affects the biology of each cell, and determines how well it can perform its vital function and its ability to resist diseases. Within the class of essential fatty acids, two polyunsaturated fatty acids (PUFA), linoleic acid and alpha-linolenic acid, are necessary for good health. These "essential fatty acids" (EFA) must be provided by nutritional intake, and have beneficial effects when available in moderation. Excess of these otherwise beneficial fatty acids should, however, be avoided. In contrast to PUFA, high intake of saturated and hydrogenated fats are being linked to an increase in the number of health risks, including degenerative diseases, cardiovascular disease, cancer and diabetes.

PUFA: OMEGA-6 and OMEGA-3 FATTY ACIDS (n-6 AND n-3 FA)

Linoleic acid is a member of the family of omega-6 (omega-6 or n-6) fatty acids and alpha-linolenic acid is an omega-3 (omega-3 or n-3) fatty acid. These terms refer to characteristics in the chemical

structure of the fatty acids. Other omega-6 fatty acids can be manufactured in the body using linoleic acids as a starting point. These include gamma-linoleic acid (GLA), dihomo-gamma-linoleic acid (DHGLA) and arachidonic acid (AA). Similarly, other omega-3 fatty acids (that are manufactured in the body using alpha linolenic acid as a starting point) include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Many fatty acids are sold as supplements in nature food and health stores, and are commonly featured on a product label.

It is important to remember that there are two sources for all n-3 and n-6 acids in the brain. These PUFAs are the fatty acids that are comprised of more than 18 carbons in their chain. One source is the elongation process of linoleic acid (LA) and alpha-linolenic acid (ALA), which takes place in the blood-brain barrier (BBB) and in most cells in the brain. The other source of PUFA is from the diet itself. The fatty acids that come from the diet must cross the blood brain barrier, although, at this stage we do not know how most of the PUFA is able to accomplish the crossing. A better understanding of this issue is very important in order to understand the pathological processes that occur in aging and in other pathological states. A more detailed review and discussion of this problem and its ramifications can be found elsewhere.²¹

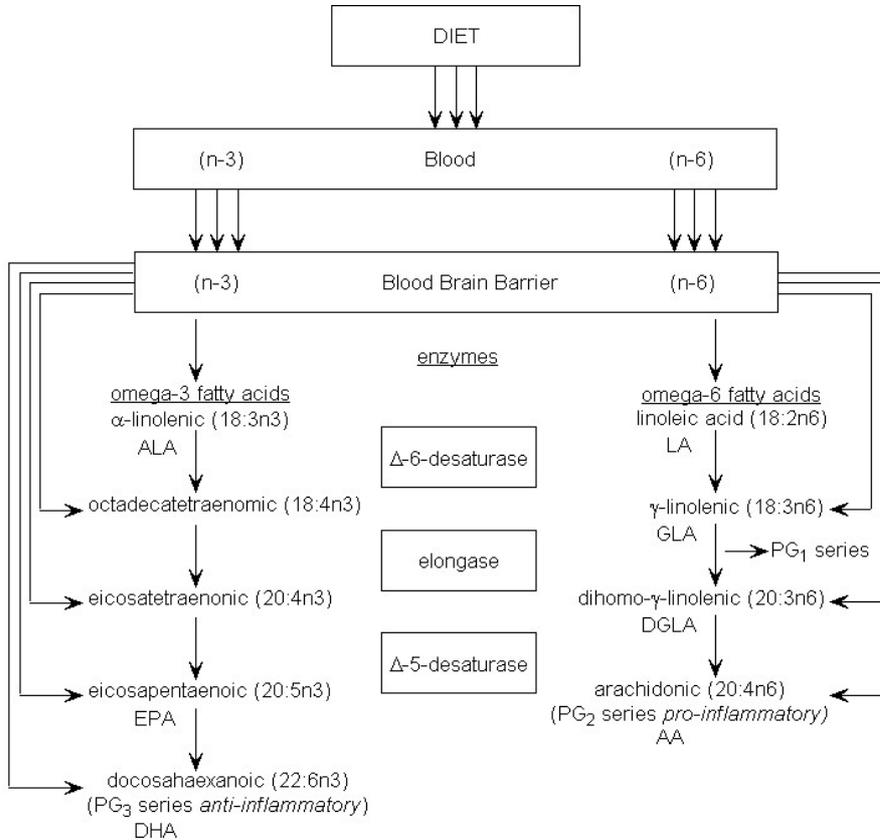


Figure 1. Some of the major essential fatty acids (Fas) and their metabolites.

Note that following dietary intake, the derivative fatty acids from both linoleic acid (LA) and alpha-linolenic (ALA) acid can be supplied to the body directly from the blood. Alternatively, they may first have to cross the blood brain barrier (BBB).

Essential fatty acids are necessary for energy production, the transfer of oxygen from the air to the bloodstream, and the manufacture of hemoglobin. They are also involved in growth, cell division and nerve function. Essential fatty acids are found in high concentrations in the brain and are essential for normal neurotransmission and brain function.

Among the significant components of cell membranes are the phospholipids, which contain fatty acids. The type of fatty acids in the diet determines the type of fatty acids that is available to the composition of cell membranes. A phospholipid made from a saturated fat has a different structure, and is less fluid, than one that incorporates an unsaturated and essential fatty acid. Linoleic and alpha-linolenic acids are able to decrease the cholesterol level in the membrane, and thereby increase the membrane fluidity index. Poor membrane fluidity would make it difficult for the cell to carry out its normal functions and would increase the cell's susceptibility to injury and death. These consequences for cell function are not restricted to absolute levels of FAs, but rather depend on the relative amounts of omega-3 fatty acids and omega-6 fatty acids in cell membranes.¹⁹

We have previously proposed that common to the different brain effects are five categories of PUFA function, namely: modifications of (a) neural membranes fluidity; (b) activity of enzymes bound to the membrane that break down FA into other forms of FA; (c) number and properties of receptors that are able to make use of the incoming chemicals; (d) function of ion channels that allow molecules of a chemical to flow through the cell; and (e) production and activity of neurotransmitters (chemicals responsible for the passage of nerve impulse progress/stimulation) that block or activate other chemicals and interfere with electrical activity.^{15,22} Numerous studies of the neurobiological properties of essential fatty acids confirm their important role in a variety of CNS activities in both health and disease.^{20,23} These FA are involved in retinal function, learning and memory mechanisms, thermoregulation, pain, stress and sleep. We have previously demonstrated that a specific mixture of alpha-linolenic acid (n-3) and linoleic acid (n-6) in a ratio of 1:4 had significant effect on both humans and lab animals.¹⁹ This compound improved the quality of life of Alzheimer's patients²⁴ and exerted beneficial effects in naive aged rats, as well as in rats that were experimentally rendered learning deficient. It improved the memory, thermoregulation and sleep in humans and in rats, and rehabilitated symptoms of induced multiple sclerosis in rats (for review, see Refs. 20, 22, 25-27). Furthermore, we were able to

demonstrate that this FA formulation was an effective protective agent in rats who were injected with a convulsant that usually produced seizures.²⁸

In case of epilepsy, seizures are understood to occur when there is a sudden change in the brain functioning, and a "storm" of uncontrolled neuronal firing occurs. Such changes in neuronal firing apparently result from temporary changes in the neuronal membrane, which senses the activity of fatty acids.

The relationship between lipids and fatty acid metabolism on the one hand, and epilepsy on the other, has previously been described.^{22,29} The global category of the PUFAs and n-3 fatty acids in particular, are regarded as "neuroprotectors" insofar as they protect the brain from insults such as ischemia. They are also considered "membrane stabilizers", as can be seen in their beneficial effects on cardiac tissue and in raising the seizure threshold.³⁰ The biochemical relationships between lipids and acid levels or fatty acid metabolism during and after experimentally induced epilepsy, have been reported elsewhere.³¹ The major finding is that seizures cause a gross disturbance in the fatty acid metabolism and inhibition of the biochemical pathway.³²⁻³⁷ One of the effects of a seizure is the disruption of the blood-brain barrier,^{38,39} which is critical for the production of some PUFAs. Treatment with n-3 fatty acid alleviates symptoms of convulsions in epileptic patients,^{20,25,40} and possible due to the preservation of the status of the biochemicals that are necessary for normal brain function.

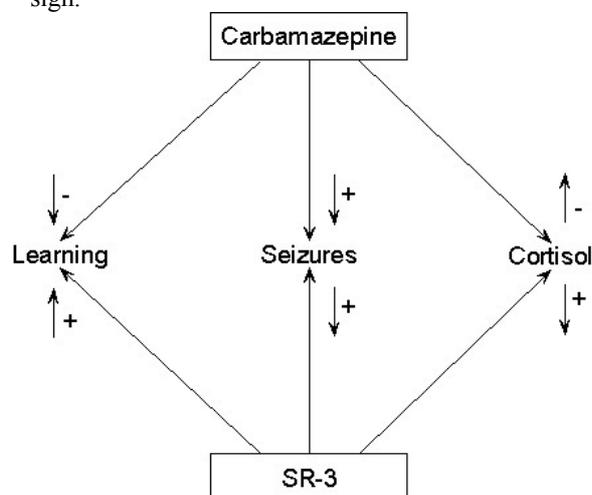
A well-known application of fatty acids for treating epilepsy is the ketogenic diet. It is based on a specially prepared high lipid diet, that has been beneficial in children with refractory seizures.⁴¹⁻⁴⁴ The powerful and dramatic therapeutic results of the ketogenic diets were reaffirmed by several clinical investigations.^{5,45-47} Although ketogenic diet has been developed independent of theoretical considerations of PUFA biochemistry,⁴⁴ "PUFA diet" was hypothesized to have effects similar to a ketogenic diet.

POSSIBLE MODE OF ACTION OF FATTY ACIDS

We have previously itemized the possible mode of action of lipids and fatty acids in the brain:^{15,20}

1. Lipids are important constituents of the neuronal membrane and changes in lipid composition may alter membrane activities.

Figure 2. The separate effects of carbamazepine (CBZ) and SR-3 on learning, seizures, and cortisol level. A favorable effect is noted by a plus (+) sign. An adverse effect is indicated by a minus (-) sign.



2. Lipids may offset the deleterious effects of substances that induce epilepsy, such as iron, that has been shown to increase other lipid peroxidation.

3. Lipids may offer stability in the membrane fluidity (that may be beneficial for controlling epilepsy).

4. Lipids may control the change in neuronal membrane phospholipid metabolism. The change in phospholipid metabolism may be due to the high level of excitatory amino acid receptors in the epileptic focus of the brain, and lead to frequent and uncontrolled electrical firing.

5. Although a genetic link may exist between epilepsy and PUFA deficit, associated lipids may provide certain measure of correction.

6. Some of the essential fatty acids may serve as neuroprotectors, similar to effects observed in the heart. As shown in a recent study alpha-linolenic acid (but not palmitic acid or GLA (a form of LA)) was found to protect against ischemia-induced neuronal death, could prevent seizures induced by a powerful convulsant agent (kainic acid) and kainate-induced neuronal death,^{36,49} thus serving as neuroprotector.

EPILEPSY, LEARNING, MEMORY AND THE HIPPOCAMPUS

A potentially significant advantage of adapting the FA treatment program for seizure control in human patients would be an offset of undesired properties

of standard anticonvulsant preparations that are accompanied by a number of side effects, such as tremors, gastrointestinal distress, effects on the bone, auditory hallucinations, and demyelination⁵⁰⁻⁵². Another consequence of the anticonvulsant medications is the frequently reported impairment of cognitive performance.⁵³ It is still not clear, however, whether seizures per se induce cognitive deficits, or if they result from the effects of the anti-epileptic drugs. Several studies have indicated the general tendency of anti-epileptic drugs to induce cognitive decline.^{45,47,53-55} Similar results were found for both epileptic patients and healthy volunteers who were administered anti-epileptic drugs.⁵⁶ In humans, anti-epileptic drugs have been particularly implicated in causing a decrease in declarative memory⁴⁷ and long-term memory,⁵⁷ suggesting an insult to the hippocampus and perhaps other brain areas.

In view of the cognitive decline in some epileptic patients, it is of interest to consider the role of the hippocampus in epilepsy. As noted earlier/elsewhere, the hippocampus, which is important for several forms of learning and memory, undergoes changes following a seizure. Among the biochemical changes are the decrease in the serotonin level,⁵⁸ acetylcholine level,⁵⁹ brain derived factors,⁶⁰ amino acid and energy metabolism,⁶¹ and enzymatic changes.⁶² The biochemical changes apparently trigger mood changes (including depression), sexual functioning, and maintaining a balance for many normal activities of the body's systems. Furthermore, induced seizures increase the arachidonic acid (AA) and platelet-derived factors;³³ the latter being a potent biologically active phospholipid in the adaptive properties of the synapse, that is critical for the transmission of the CNS signals.

Recently we experimentally compared the anti-seizure effects and the cognitive effects of carbamazepine (CBZ or CMP) and developed by us FA compound SR-3.²⁵ While both drugs were effective in antagonizing the pentylenetetrazol (PTZ) induced seizure activity, only the FA was able to rehabilitate the PTZ induced learning deficits. In addition, we found that the administration of CBZ leads to an increase in cortisol level. The beneficial effects of the FA preparation correlated with its ability to decrease the cortisol level. In that report we formulated a theoretical description to account for the interacting effects and multiple pathways that involve seizures, cognitive performance, and cortisol following either CBZ or SR-3. Both compounds reduced seizure frequency or severity. However, among the

undesirable side effects of CBZ is a decrease in learning performance and an increase in cortisol.^{63,64} On the other hand, SR-3 provided a protection in Morris Water Maze performance and control of cortisol level elevation.^{25,65}

POSSIBLE EXPLANATION

The possible explanation of our results is rather complicated. Several variables play a role in this situation. One variable is the blood-brain-barrier (BBB) during and after seizure attacks. Cornfield and Oldendorf³⁸ demonstrated that seizures cause disturbances in BBB functions, especially in glucose transport which is an energy source required for healthy cellular function. In addition, recent studies found evidence for changes in the rates of penetration of glucose and oxygen as well as structural changes in the BBB tissue itself during a seizure, with vast amount of arachidonic acid (AA) (20:4n6) being released.⁶³ The importance of the increased AA level is twofold. First, AA is one of the most powerful generators of free radicals, known to be destructive in brain chemistry. Thus AA initiates a vicious cycle, such that a seizure induces an increase in AA level, that leads to an increase in the free radical level, that causes damage to brain areas (frontal cortex and hippocampus) that may intensify the next seizure. Recently, Farooqui *et al.* described the role of AA in kainic acid induced neurotoxicity⁶⁶ where stimulation of kainic acid receptors causes a rapid release of AA. This increased level of AA, modifies the membrane fluidity index and membrane permeability. Second, AA may prolong the period required for complete recovery from a seizure.⁶⁷ Pretreatment and treatment with n-3 fatty acids may protect the brain from the damaging effects of the excessive level of AA. It has previously been demonstrated that the effects of n-3 fatty acids are opposite to n-6 fatty acids activity, and that n-3 fatty acids may inhibit n-6 fatty acids activity.²⁵

The role of cortisol in seizures needs further clarification. A seizure can be considered a stressful situation. Indeed immunological markers of stress can be detected immediately after seizure⁶⁸ along with the increase in the level of cortisol produced in response to stress.⁶⁹⁻⁷⁰ Since a seizure is a sudden electrical activity storm in the brain, the involvement of ionic channels (and hence the role of cortisol) in the neurophysiology of seizures is apparent. However, a discussion concerning the particular ion channels (K⁺, Na⁺ or Ca²⁺) and their role in epilepsy is beyond the scope of this review, but can be found elsewhere.⁷²⁻⁷⁴

SUMMARY

The possible protective effects against seizures provided by polyunsaturated fatty acids, especially fatty acids of the n-3 group (EPA and DHA) have been previously reported in the literature. Some additional support can be found in a recent review on the beneficial effects of a ketogenic diet.⁷⁵ Similarly, the role of fatty acids in increasing the threshold for electrically induced seizures has been established in a series of meticulously executed *in vitro* research studies.⁷⁶ Confirmatory *in vivo* research using the mouse has shown that n-3 fatty acids are able to block PTZ induced unhealthy brain excitation and stimulation that produces convulsions in various hippocampal neurons.⁴⁹

While it seems that essential fatty acids are neuroprotective, the relative potency of the separate FAs is not known. From our laboratory findings, and from the work of others,¹⁹ we believe that a ratio of 1:4 of alpha-linolenic (ALA) to linoleic acid (LA) is the optimal neuroprotective combination. Some investigators, however, have proposed that even with an adequate LA and ALA levels, seizure patients may lack sufficient enzymatic activity necessary to metabolize these FAs, and that supplementation with EPA and/or DHA could be more attractive clinical design for near term clinical experimentation. We believe that even without waiting for the results of formal designs of randomized clinical trials the safety of dietary PUFA supplementation (when taken in the recommended dosages) is significant to warrant implementation at this time, on a case by case basis.

ACKNOWLEDGEMENT

The viewpoint presented in this viewpoint review article is the authors' view. It is provided for educational purpose only, and should not be relied upon when undertaking a seizures' therapy. Always consult your doctor and nutritionist before undertaking a seizures' therapy and FA food supplementation, respectively.

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COMPETING INTEREST DECLARATION

The authors report no competing financial interest. The compound described earlier in the related US Patent 5,599,840 (Feb. 4, 1997) and The Wall Street Journal article (Aug. 25, 1992) is not available commercially and currently is not under commercialization.^{77,78}

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