Ketogenic Diet as a Treatment for Refractory Epilepsy

Nam Phan

Abstract

Recent advances in the understanding of the causes of epilepsy have resulted in an increased interest in treatment of this disorder in the past 30 years. With the introduction of more effective anti-epileptic drugs (AED), and genetic, molecular and imaging innovations, epilepsy can be treated effectively in the majority of cases. Although dietary therapy as a means to treat epilepsy has become less popular nowadays with the advent of new AEDs, it is still widely used for children with refractory seizures who are not responding to other treatment or who have serious adverse reactions to AEDs. The most popular diet in the treatment of epilepsy is the ketogenic diet, which has been used for more than 80 years. Even though there are not clearly defined guidelines as to how the diet is to be administered and sustained, there is no doubt as to the efficacy of this treatment. Despite the fact that there has been a long history of its use, much remains to be learned about the diet, including mechanisms of action and the biochemical basis of its therapeutic affects. Understanding why the diet is effective may allow for the development of new therapies.

Epilepsy is a general term used for a group of disorders and is typically characterized by the occurrence of at least two unprovoked seizures (Hauser, Rich, Lee, Annegers, & Anderson, 1998). Seizures result from abnormal discharge of neurons in the brain. The type of seizure and its clinical manifestations are dependent on the extent of abnormal cortical neuronal discharge and the location of the discharge. Depending on the part of the brain that is affected, the surge of neuronal impulses may have an effect on a person's state of consciousness and cause intractable movements of the body, or other symptoms. For example, if the burst of electrical energy were located in the visual cortex, patients would experience symptoms involving visual experiences. Epilepsy affects 1% of the general population and is the most common neurological disorder in children (Persad, Thompson, & Percy, 2005).

Anecdotal evidence from the past couple of millennia describes secondarily generalized tonic-clonic seizures over 3000 years ago in Mesopotamia. Epileptic seizures have been described in several ancient writings, including China, Egypt, and India. Hippocrates also wrote the first book about epilepsy almost 2500 years ago, where he detailed cases of epileptic patients being treated with diets consisting mainly of fasting (Kossof, 2004). During biblical times, treatment of epilepsy relied on a diet very similar to starvation (often referred to as the "water diet"). This method of handling severe seizures was reportedly used in the early 20th century in France and subsequently became widely accepted as an effective treatment for epilepsy (Barborka, 1930). The problem with this treatment was due to the fact that seizure control would only last as long as the fasting was continued and it was not feasible to sustain this diet indefinitely. As a result, researchers attempted to discover a method to induce ketosis associated with starvation, while allowing for proper nutritional consumption. Dr. R.M. Wilder (1921) developed a diet that mimicked the biochemical changes that were observed during fasting and referred to it as the ketogenic diet. This diet prescribes foods with high-fat, low-carbohydrate content. As the body starts to metabolize fat as its primary source of energy, ketones build up as a by-product of fatty-acid breakdown. When excess ketone bodies accumulate, the state is referred to as ketosis and this is believed to alleviate epileptic seizures. Several publications and reports started to demonstrate the efficacy of the ketogenic diet and the popularity of the diet started to spread. However, the introduction of more effective AEDs, such as diphenylhdantoin (phenytoin) made the ketogenic diet obsolete. For many decades, the diet was only an afterthought, with minimal research and use until interest was rekindled in the early 1990s. At Johns Hopkins Hospital, a boy named Charlie was treated for intractable seizures with the ketogenic diet after no response to drugs or surgery (Abrahams, 1994). It was highly effective and led to resurgence in public and clinical interest. Over 200 studies and reports have been published about the ketogenic diet since then.

Typically, the ketogenic diet begins with a period of fasting and relative dehydration aimed at achieving ketosis, which is then monitored by measuring levels of ketones in the urine, with a high level being indicative of the state of ketosis (Bailey, Pfeife, & Thiele, 2005). It is then followed with a strict and regimented high-fat, low protein and very low-carbohydrate diet. This is all predicated on the idea that the body can be forced into ketosis by depriving carbohydrates and glucose, thus shifting the body's metabolism to fat breakdown, resulting in the creation of ketones and fatty acids as a source of energy (Veech, 2004). The initiation of the diet is normally accomplished in a controlled environment like a hospital or specialized

clinic. The meals are specially prepared, as any deviation from carbohydrate withdrawal can lead to more seizures. The diet consists of meal portions with a ratio of four to one of fats to proteins and carbohydrates (Kossof, 2004). A standard dish usually contains several portions of vegetables or fruit, a protein source, while whipping cream and vegetable oils are used to provide the necessary fat. Standard foods like bread, cereal, pasta and rice are excluded. A popular variation on the ketogenic diet involves the use of medium chain triglycerides (MCT) oil derived from coconuts as a supplement. This MCT diet limits carbohydrates as well, but because the oil is more quickly metabolized than most other fats, it allows for more regular eating regimens and a more normal lifestyle. The ketogenic diet and the MCT variant both attempt to decrease total calories and fluid intake to prevent fat from being flushed from the system in favor of carbohydrates (Nebling & Lerner, 1995).

Although the ketogenic diet is obviously not the first choice among current epileptic treatments, in instances where surgery and medications have proved ineffective, or the side effects are intolerable, it is a safe alternative that has proven its efficacy over many centuries. Since the diet makes use of natural processes in the body as opposed to the influx of foreign chemicals in AEDs, the side effects that result are less severe. As research discovers more about the physiology of the brain, we may be able to understand the underlying mechanisms that make the ketogenic diet effective in treating seizures and possibly devise treatments that allow for a normal lifestyle.

Classification of Epileptic Seizures

Seizures are classified into two categories based upon the origin of the neuronal disturbance (The National Society of Epilepy, 2003). Partial seizures usually have electrical discharges focused on a single cortical area and are often preceded by an aura which warns subjects of an impending seizure. On the other hand, generalized seizures originate from uncharacteristic neural discharges in both hemispheres of the brain. Subjects lose consciousness and as a result experience no aura. Although each seizure has its own distinct clinical manifestations, they are further classified based upon observed symptoms.

Partial-onset seizure classifications are based upon levels of consciousness. A seizure where there is complete preservation of consciousness is referred to as a simple partial seizure (Chabolla, 2002). Simple partial seizures involve the cerebral cortex and can include sensory events such as occipital seizures. The seizures may last a few seconds to a few minutes and if the

aura lasts longer than 30 minutes, it is referred to as a simple partial status epilepticus. In cases where the patient experiences impairment in their consciousness during the seizure, it becomes classified as a complex partial seizure. During these seizures, the patient stares ahead, while chewing, lip smacking, mumbling, and fumbling with the hands, followed by a brief period of confusion. They may remember an aura, but have no memory of the actions following it. Complex partial seizure last approximately 60-90 seconds. However, generalized weakness and fatigue may last for a few days. Finally, seizures that start with an aura evolving into complex partial seizures and continue onto generalized tonic-clonic seizures are called secondarily generalized seizures. Although it is often hard to diagnose, amnesia of the seizure event is very indicative of secondary generalized seizures.

Generalized-onset seizures are separated into categories based upon differing clinical manifestations (Benbadis & Luders, 1996; Chabolla, 2002). The most common type of generalized-onset seizure is the tonic-clonic seizure (previously referred to as a 'grand mal' seizure). Similar to simple partial seizures, the patient experiences rhythmic shaking of the extremities. It may also be associated with respiratory arrest and reflex emptying of the bladder and bowels followed by loss of consciousness. The only clinical difference between these tonic-clonic seizures and secondarily generalized tonic-clonic seizures is that these seizures lack an aura. Another form of generalized-onset seizure is myoclonic seizures; this consist of rapid arrhythmic twitching of the body lasting less than a second. If the twitching evolves into rhythmic jerking movements, they are classified as clonic seizures. A less conspicuous form of generalized-onset seizures is known as absence seizures, which typically begin during childhood or adolescence. These seizures involve a momentary impairment of consciousness, where the patient loses all signs of awareness of their surroundings. During the seizure, the patient will have facial ticks and/or rapidly blink, which is often followed by hyperventilation. In children, absence seizures are often unrecognized until generalized-onset seizures develop. Finally, patients with severe neuronal abnormalities may experience atonic seizures, where all muscle control is lost, resulting in falls and accidents.

Molecular Basis of Epileptic Seizures

Two of the most important and ubiquitous neurotransmitters in the nervous system are gamma-aminobutyric acid (GABA) and glutamate, which control, respectively, the inhibition and excitation of neuronal impulses necessary for proper functioning of the brain (Johnston, 1996). Regular brain function is thought to occur when there is an equilibrium between excitation and

inhibition; an imbalance occurs when excitation forces exceed inhibition forces can lead to brain hyper-excitability and low seizure threshold (i.e., facilitate seizures). This disparity in forces may be a result of too little inhibition from the GABA-ergic neurons or too much excitation from the glutamate system. Although understanding of the molecular basis of epilepsy is limited, much research in epilepsy has been focused on the hypothesis that GABA and glutamate play major roles in epileptic physiology.

GABA

GABA is the main inhibitory neurotransmitter in the brain. It binds mainly to three classes of receptors: GABAA, GABAB and GABAC. The GABAA and GABAC receptors produce inhibitory hyperpolarizing responses on neurons through chloride channels and they are one of the main targets of many anti-epileptic drugs on the market (Chebib & Johnston, 1996). The hyperpolarizing response is due to an increase in the chloride conductance of the neuronal membrane allowing chloride ions to flow down their electrochemical gradient into the cell, making it more difficult for a neuron to reach the threshold membrane potential that is needed to transmit an action potential. The release of GABA into the synaptic cleft allows for postsynaptic activation of GABAA receptors and consequently propagation of inhibitory postsynaptic potentials (IPSP). GABAA and GABAC receptors are structurally similar and are composed of five subunits that arrange together to form an ion channel. GABAA receptors are made up of a mixture of six different alpha units and three different beta and gamma units (Macdonald & Olsen, 1994). As a result, a vast number of combinations exist resulting in numerous receptor subtypes. Still, only 20 different receptor subtypes have been found in the human brain and in recent animal models it has been found that mutations in some of these subunits may be responsible for certain forms of epilepsies, as the ability to produce IPSPs are reduced by mutated receptors (Meisler, Kearney, Ottman, & Escayg, 2001).

The GABAB receptor consists of seven transmembrane domains that are coupled to potassium channels (Jones et al., 1998). A G protein mediates coupling to the potassium channel via a second messenger system that includes phopholipase C and adenylyl cyclase (Chebib & Johnston, 1996). These in turn activate potassium and calcium channels, inducing IPSPs. GABAB receptors can also be found pre-synaptically and may inhibit the release of excitatory neurotransmitters in the synaptic cleft. As a result of the coupling of the potassium channel to a G-protein, there is a relatively long duration of action in comparison to the fast acting action potential evoked by activation of the GABAA and GABAC receptors (Chebib &

Johnston, 1996). Alterations in the conformation of the GABAB receptor are thought to possibly play a major role in the transition between a brain wave abnormality and a partial-onset seizure. It is also believed that mutations in the different subunits of the GABAB receptors may affect seizure threshold or susceptibility for refractory seizures (Hosford et al, 1992).

Glutamate

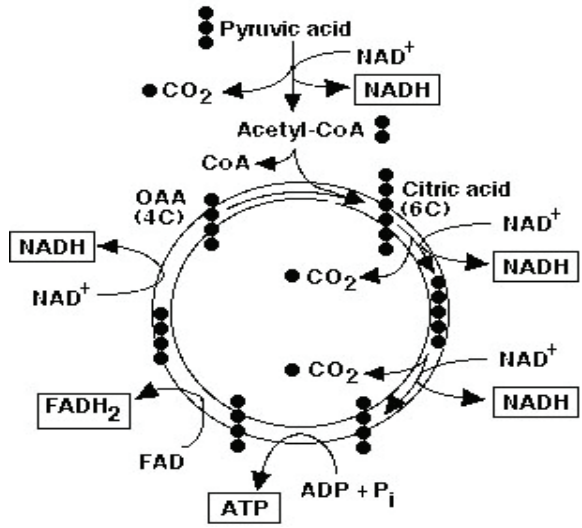
Glutamate is the major excitatory neurotransmitter in the brain and it causes membrane depolarization and subsequently an excitatory post synaptic potential (EPSP) in the postsynaptic neuron via activation of glutaminergic receptors. The receptors are grouped as AMPA/kainate, NMDA, or metabotropic receptors (Johnston, Chebib, Hanrahan, & Mewett, 2003). (The acronyms AMPA and NMDA refer, respectively, to alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid and N-methyl-D-aspartate. Metabotropic receptors are a type of receptor that is linked to intracellular production of 1,2-diacylglycerol and inositol 1,4,5-trisphosphate. Kainate receptors are a type of glutamate receptor that participates in excitatory neurotransmission.) Fast neurotransmission occurs via excitation of either the AMPA/kainate or NMDA receptors. The metabotropic receptor alters cellular excitability through a second messenger system, which results in later onset of the EPSP signal, but with a longer duration. The difference between the two fast receptor types lies within their functionality. AMPA/kainate receptors open channels that primarily allow passage of monovalent cations (i.e., sodium and potassium), whereas the NMDA type is coupled to channels that also allow passage of divalent cations (i.e., calcium). Patients with epilepsy may have faster or longer-lasting NMDA channels and as a result may have altered seizure thresholds (Meldrum, Akbar, & Chapman 1999). Glutamate levels have been observed to markedly increase in the hippocampus during spontaneous seizures (During & Spencer 1993; Wilson et al. 1996) and have been associated with evoked seizures during surgery (Ronne-Engström, Hillered, Flink, Spännare, Ungerstedt, & Carlson, 1992).

Ketogenic Diet

The ketogenic diet (KD) is a high-fat, low-carbohydrate, adequate-protein diet. It is essentially a form of starvation, which forces the body to start metabolizing fat (albeit incompletely) in lieu of glucose. The mechanism by which the ketogenic diet suppresses seizures is still controversial, but the most likely reason is the increase in production of ketone bodies during ketosis (Sinha & Kossof, 2005).

As the body is deprived of glucose, glycogen reserves are rapidly depleted and the body begins to metabolize reserves of fat and protein. In the absence of glucose (which is converted into pyruvate for the Krebs cycle), fat is used as another source of acetyl-CoA that is needed for the tricarboxylic acid (TCA) cycle (Fig. 1). This cycle is the main source of adenosine triphosphate (ATP), which serves as the major energy source within a cell (Krebs, 1960).

Figure 1. Krebs cycle following normal glycolysis



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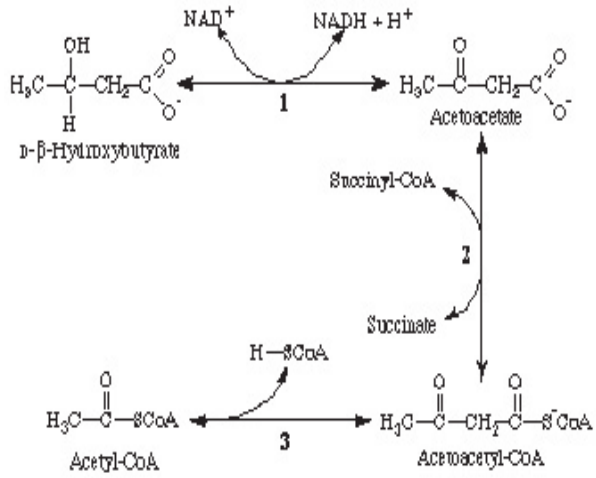
When fat metabolization outstrips carbohydrate breakdown as a result of the ketogenic diet, ketone bodies are produced by liver mitochondria. This is a result of the large amount of acetyl-CoA produced by fat metobolization, which overloads the TCA cycle (limited carbohydrate means that citric acid intermediates will be depleted – there is not enough oxaloacetate (OAA) to condense with all the acetyl-CoA). As a consequence, excess acetyl-CoA is converted in the liver into acetoacetate (essentially two acetyl groups covalently linked). Acetoacetate can be further reduced to form β-hydroxybutyrate. These two compounds are referred to as ketone bodies.

Figure 2. Conversion of Ketone bodies to Acetyl-CoA and vice versa



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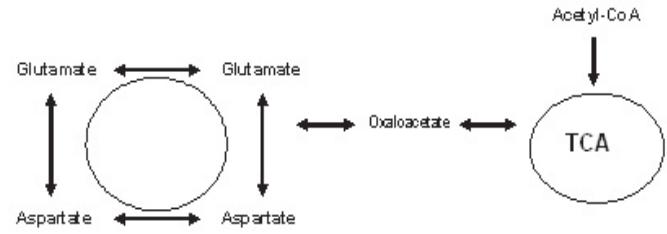
After synthesis in the liver, the ketone bodies diffuse into the circulatory system to be used as fuels by several tissues including heart muscle and the renal cortex, which often use acetoacetate in preference to glucose (Sato et al., 1995). In contrast, glucose is the major fuel for the brain and erythrocytes in a human. Still, the brain has the capacity to adapt to the use of acetoacetate, as it meets more than 70% of the energy needs of the brain in the absence of sufficient glucose (Owen, Morgan, Kemp, Sullivan, Herrera, & Cahill, 1967). It is vital that the brain is able to metabolize acetoacetate as energy since regular fatty acids cannot enter the neural tissue through the blood brain barrier. The amount of ATP produced from oxidation of fatty acids via formation of ketone bodies during ketosis is approximately the same as the production of ATP via normal metabolism of glucose, as there is no penalty to the body in converting acetyl-CoA to acetoacetate and then back to acetyl-CoA. (ATP, or adenosine triphosphate, is the major energy source in the body; energy derived from the breakdown of ATP drives many important reactions in the body.)

Mechanisms of Action

Although there are many theories and hypotheses involving the biochemical basis behind the effectiveness of the ketogenic diet, one of the main possibilities lies with the idea that the diet leads to an alteration in the metabolism of glutamate.

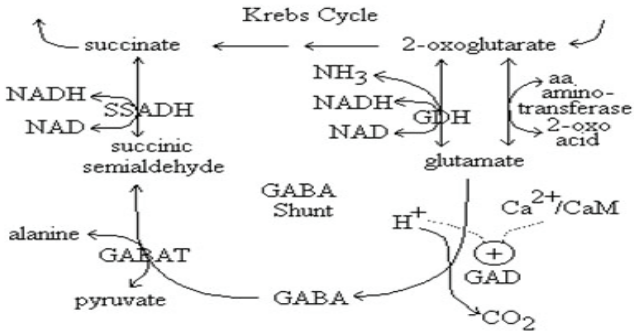
Glutamate metabolism is in constant flux with aspartate within the aspartate aminotransferase reaction (Yudkoff, Daikhin, Nissim, Lazarow, & Nissim, 2001). This pool depends on a ready supply of oxaloacetate to keep equilibrium between the production of glutamate to aspartate (Fig. 3). However, during periods of ketosis brought upon by the ketogenic diet, the brain's consumption of energy proceeds through the metabolization of acetyl-CoA almost exclusively as the availability of glucose declines. As more acetyl-CoA is produced during ketosis through the increased production of the ketone body acetoacetate, more oxaloacetate is being consumed through the TCA cycle and less becomes available as an intermediate for the asparate aminotransferase reaction (Yudkoff, Daikhin, Nissim, Lazarow, & Nissim, 2004). Another effect ketosis has is a decline in co-enzyme A, which is necessary for oxaloacetate production, further shifting the equilibrium between glutamate and aspartate (Yudkoff et al, 2001). As a consequence, we see the flux from glutamate to aspartate diminish, increasing the pool of readily available glutamate and decreasing the pool of aspartate. Researchers have found this to be true in rat models injected with ketone bodies (Thurston, Hauhart, & Schiro, 1986) and in rats that have been raised on high-fat diets (DeVivo, Leckie, Ferrendelli, & McDougal, 1978). A similar relationship is also observed in the human heart, where an increased use of ketone bodies as energy results in an expanded pool of acetyl-CoA and a reduction in pools of oxaloacetate and aspartate (Sato et al., 1995).

Figure 3. The aminotransferase reaction



Ordinarily, the aminotransferase reaction is the main outlet for glutamate metabolism. However, with diminished oxaloacetate, glutamate becomes more available to other pathways, including glutamate decarboxylase, which allows for the synthesis of GABA and glutamine, a precursor of GABA (Fig. 4). It has been found that even a small change in intraneuronal glutamate can favor GABA production in the glutamate decarboxylase pathway (Paulsen & Fonnum, 1988). It is possible that ketone bodies may be responsible for directly altering the properties of glutamate decarboxylase-67, a major enzyme in the pathway (Kaufman, Houser, & Tobin, 1991). It is also believed that the ketone bodies created during the ketogenic diet may be directly involved in the production of glutamine, as increased levels of acetate in the brain have been linked with an increase in production of glutamine in glial cells (Sinha & Kossoff, 2005).

Figure 4. Glutamate decarboxylase pathway



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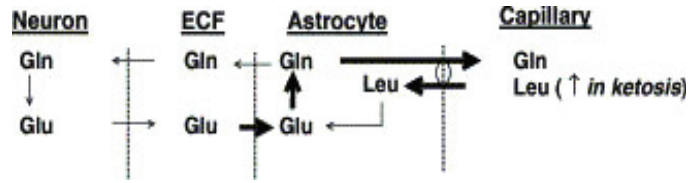
Given that GABA is the main inhibitory neurotransmitter, augmentation of GABA synthesis theoretically might have a positive effect and reduce or prevent epileptic seizures. The relationship between GABA and seizure prevention has been widely documented. Animal models of epilepsy have documented abnormalities in GABA receptors as well as in the synthesis of GABA (Homanics et al, 1997; Lasley & Yan, 1994). It has also been reported that GABA levels in the brains of epileptics are less then those of control groups (Petroff, Rothman, Behar, & Mattson, 1996).

Another amino acid, leucine, which increases a great deal during ketosis, may play a role in the uptake of glutamate (Yudkoff et al, 2004). Under

normal conditions, glutamate, upon being released from nerve endings into extra cellular fluid and then taken into astrocytes and converted to glutamine, is reconverted to glutamate in neurons (Fig. 5). During ketosis, leucine levels increase and as a result, there is an increased level of leucine entering the brain, which is mediated by counter-exchange with glutamine. As levels of glutamine in the astrocyte decline, excess glutamate in the synaptic cleft is taken up in the astrocyte and converted back to glutamine. In essence, the exchange of glutamine for leucine allows for another mechanism of glutamate disposal via the astrocyte. Given that glutamate is the main excitatory neurotransmitter, any reduction might help ease seizures associated with excess neuronal firing.

Figure 5. Leucine (Leu) counter-exchange with glutamine (Gln) opens room for glutamate (Glu) uptake in the astrocyte



From "Ketogenic diet, brain glutamate metabolism and seizure control," by M. Yudkoff , Y. Daikhin, I. Nissim, A. Lazarow, & I. Nissim, 2004, Prostaglandins, Leukotrienes, and Essential Fatty Acids, p. 277-285. Reprinted with permission of the author

It has also been proposed that the serum acidosis (a lowering of pH of the serum) caused by ketosis may be responsible for anticonvulsant action (Giffard, Monyer, Christine, & Choi, 1990). Acidosis has been linked to diminishment in seizure susceptibility via its actions on NMDA and glutamate receptors by decreasing sensitivity to ligands that may bind to them.

Increase in GABA production may not be the only by-product of the ketogenic diet that can affect seizure control. It is possible that the attenuation of aspartate synthesis during ketosis may be involved in the anti-epileptic effect. Many studies have implicated aspartate as a primary agent in epilepsy (Flavin, Wieraszko, & Seyfried, 1991; Millan, Chapman, & Meldrum, 1993), with increases in extracellular aspartate observed during the onset of seizures. Another hypothesis involves changes in energy states of the brain and its neurons. During ketosis, the ratio of ATP to ADP increases (Sinha & Kossoff, 2005). As a result, one would expect the activity to increase in ATP-dependent sodium pumps found in the neurons and glial cells. Consequently, this would lead to hyperpolarization and a decrease in excitability.

In a similar vein, a new line of research has focused on ATP-sensitive potassium (KATP) channels (Vamecq, Vallee, Lesage, Gressens, & Stables, 2005). These potassium channels provide a physiological link between metabolic activity and membrane potential and regulate insulin levels in the pancreas. During periods of regular food intake, the high intracellular level of ATP inhibits KATP channels, which in turn lowers membrane potential and depolarizes membranes. In the pancreas, the resulting influx in calcium stimulates secretion. In instances of low glucose (ketogenic state), lower levels of ATP cause the opening of KATP channels, causing membrane hyperpolarization. This subsequently blocks membrane depolarization, preventing insulin secretion. Although these KATP channels have been mainly studied in the pancreas, it is believed the same scenario of membrane hyperpolarization occurs in the brain. As a result, KATP channels have been targeted for pharmalogical protection against seizures (Lauritzen, De Weille, & Lazdunski, 1997).

Efficacy of the Ketogenic Diet

The ketogenic diet has been proven effective in suppressing seizures in animal models well before humans. With the recent increase in awareness of this diet, research has increased exponentially in human patients. A meta-analysis of studies ranging from 1925 to 1998 showed that 37% of patients have at least a 90% reduction in seizures, while 30% experience between a 50 and 90% reduction (Thiele, 2003). Young children and adolescents appear to benefit the most from the diet, although this fact may reflect limited data on young adults and the elderly (Vining, 2003). In a recent prospective study, 150 children were observed while on the ketogenic diet (Vining et al, 1998). It was observed that 55% had more then a 50% reduction in seizures after 6 months of treatment. Some believe the efficacy in children lies with a higher level of ketosis in children compared to adults (Nehlig & Vasconcelos, 1993). Although a great deal of evidence has been collected supporting the efficacy of the diet, a double-blind, placebo-controlled study has never been done.

Conclusion

Much of the data collected on the ketogenic diet involves short-term studies. This is due to the fact that keeping a child on the diet for an extended period of time is an extremely hard task. The reliance on prospective clinical trials and experiments on animal models can only go so far in providing proper evidence for the mechanism of the ketogenic diet. As a result, even after 80 or so years of studies, many questions are still left unanswered. At the

clinical level, it has not yet been determined which patients are the best candidates for the diet. The long-term goal of research on the ketogenic diet is to characterize the mechanisms underlying the effectiveness of the diet in treating seizures. With this knowledge, new treatments may be developed that will prevent seizures with the same efficacy as the ketogenic diet, while allowing for a normal lifestyle and eating regimen.

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Correspondence

Nam Phan
801 Bay St. Apt. 905
Toronto, ON, M5S-1Y9

nphan@uhnres.utoronto.ca