The Common Allergic Mechanism of Rhinitis and Asthma

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Abstract

Allergic rhinitis and asthma are closely linked diseases which are very prevalent within the population, affecting millions. They are both characterized by chronic airway inflammation. They are often present in the same patients and rhinitis is even considered an independent risk factor for asthma. Treating allergic rhinitis can reduce the severity of asthma. Mechanisms connecting the two have been researched for many years. Studies show that they have a similar allergic mechanism that is mediated by the same cells. The allergic inflammation is characterized by the presence of eosinophils and is mediated by T-helper type 2 lymphocytes. The circulation of Th2 cells and the cytokines it releases, including IL-4 and IL-5, are important factors in airway inflammation. When their levels are reduced, the condition is improved. Controlling the production and circulation of these cells can potentially help treat allergic rhinitis and asthma.

Introduction

Allergic rhinitis is a common disorder, affecting over 600 million people worldwide. The disease involves an IgE mediated inflammation of the nasal membranes due to allergen exposure. Allergic rhinitis negatively impacts the patient's sleep, work, cognitive abilities and social life. Allergic rhinitis is also noted as a risk factor for asthma. (Bousquet,et. al. 2008) The association between the two disorders has been studied for many years. Numerous studies have been done to identify the mechanism and strength of the connection. In a survey done by the European Community Respiratory Health Survey, 13.4% of participants with rhinitis reported asthma and 71% of subjects with asthma reported rhinitis. (Leynaert, 2004) In a study done on college students, 56%-86% of asthma cases were associated with allergic rhinitis. Eighteen to twenty-one percent of the students with allergic rhinitis also had asthma. In a 12 year follow-up of college students without asthma, 10.5% of those originally diagnosed with allergic rhinitis later developed asthma. Only 3.6% of students without allergic rhinitis developed new asthma. (Settipane and Settipane, 2000) It has also been shown that treating allergic rhinitis can improve asthma symptoms. In one study, patients treated for allergic rhinitis were seen to have a significantly lower incidence of emergency room visits or hospitalizations than the asthmatics whose rhinitis symptoms were not treated at all. (Crystal-Peters, et. al. 2002) Another study treated asthma patients with medications directed at the nose, such as nasal steroids and antihistamines. The number of emergency department visits decreased among these patients compared to the control group. (Adams, et. al. 2002) It can be concluded that asthma and allergic rhinitis are intrinsically connected and should be considered one syndrome within the united airway. Much work has been done to determine the mechanism in which the two affect each other. Knowledge of how they are linked can help in the prevention, diagnosis and treatment of these airway disorders. Several hypotheses have been proposed, yet none have been conclusively proven.

Methods

The NCBI PubMedCentral database, the Touro College library database, and Google Scholar were the search engines used to find information. A search for articles containing the key words "asthma" and "allergic rhinitis" resulted in several review articles discussing this topic. The review articles provided an idea of what the current hypotheses and research are. Their references were used to find original research papers. In addition, more key words important to the topic were discovered in the review articles. A search for "epidemiology" with the words "allergic rhinitis" or "asthma" was conducted to find information regarding the prevalence of the disease. In order to find out about the common allergic mechanism, several searches were tried varying the terms "asthma", "allergic rhinitis", "mechanism", "Th2", "allergic response", "cytokines", "upper airway", "lower airway" and "unified airway". Articles that were marked as similar to the ones found in searches and articles that cited or were cited by pertinent articles were also used.

Results

Many of the researchers on the topic of asthma and allergic rhinitis discuss the allergic response mechanism involved in allergy. Exposure to an allergen leads to a series of cellular events concluding in an inflammatory response. (Benson, et. al. 2001) When a person is first exposed to an allergen, the allergen is recognized by T-helper lymphocytes (TH). The TH lymphocytes cause the B-cells to produce IgE that is specific to that allergen and primed to respond to it. The IgE then binds to the surface of mast cells. The next time the immune system is exposed to the same substance, the allergen is recognized by the IgE already on the surface of the mast cells. The mast cells are activated, releasing mediators like histamine and leukotrienes. The mast cells also release cytokines that can recruit other leukocytes like eosinophils, neutrophils and Th2 lymphocytes. This cascade ultimately leads to typical allergic symptoms, including sneezing, runny nose, nasal obstruction or airway constriction. (Cirillo, et. al. 2009)

The upper and lower airways share many anatomical and physiological properties. The majority of both the upper and lower respiratory tract is covered in ciliated epithelial cells. There are also many goblet cells associated with the epithelium, although their presence decreases closer to the lungs. The entire airway is also characterized by a dense network of blood vessels and nerves. Although each portion of the respiratory tract has its own task to fulfill, like humidification, filtration,

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warming, olfaction and gas exchange, the airways are united by a common purpose: the passage of air. (Ciprandi, et. al. 2012) Furthermore, the nose and lungs are susceptible to the same irritants and have similar reactions to them. Some agents that can trigger a response in the upper and lower airways are infections, viruses, pollutants, certain drugs, cigarette smoke, allergens, and sometimes physical exercise. (Caimmi, et. al. 2012) Allergic rhinitis and asthma are two common respiratory disorders. Although they affect different parts of the airway, they have similar causes and inflammatory processes and are characterized by chronic airway inflammation.

Allergic mucosal inflammation is identifiable by high levels of eosinophils in body tissue. (Braunstahl, 2001) This characteristic is often used to judge reaction levels in allergic subjects. A study was done to compare inflammation in the upper and lower airways in asthma and allergic rhinitis. The results showed increased eosinophil and mast cell levels in the mucosa of the bronchi and the nose. Surprisingly, the subjects with allergic rhinitis and asthma showed similar levels of inflammatory cells in the upper and lower airways as the patients with allergic rhinitis only. Although the rhinitis subjects exhibited no clinical signs of asthma, their lower airways showed the presence of inflammatory cells. (Braunstahl, et. al. 2003) The inflammation was present all along the airway, regardless of asthmatic symptoms. This supports the idea of a unified airway, the hypothesis that the upper and lower airways are connected and should be considered as one entity.

Lymphocytes are white blood cells that play a significant role in allergy and immunity. There are two categories of lymphocytes, T-cells and B-cells. The T-cells are divided into killer T-cells and T-helper cells. There are two types of T-helper cells. Type 1 T-helper cells (Th1 cells) are "infection fighters" and type 2 T-helper cells (Th2 cells) are "allergy promoters". Th2 cells and Th1 cells can inhibit each other's functions. Th1 reactions lead to a delayed immune response by activating macrophages. (Settipane and Settipane, 2000) A Th2 reaction releases certain key cytokines involved in inflammation; particularly interleukins (IL) 4 and 5. The cytokine IL-4 causes an overproduction of IgE. IL-5 causes an influx of eosinophils. The allergic reactions in rhinitis and asthma have been attributed to an immune pathway mediated by Th2 cells (Benson, et. al. 2001).

To determine the role of Th2, one study used Glucan, an immunomodulator that stimulates a Th1-mediated anti-tumor response. The study was completed using 24 subjects with allergic rhinitis. The test subjects received a treatment of Glucan pills and the control group was given a placebo. Under the influence of Glucan, allergens that normally would stimulate Th2 cells activate Th1 cells. Levels of cytokines in nasal lavage fluid were tested before and after nasal allergen challenge. Due to the decrease of Th2 mediated reactions caused by the Glucan, levels of the Th2 secreted cytokines IL-4, IL-5 were significantly decreased in the nasal fluid of the test subjects compared to the controls. The Th1 secreted cytokine IL-12 was found to be increased in the experimental group. The higher than usual Th1 levels inhibited the Th2 cells, lowering the concentration of the cells and cytokines responsible for the inflammatory response. (Kirmaz,et. al. 2005) This supports the idea that it is specifically the Th2 cells that are involved in allergic rhinitis.

In asthma, Th2 is thought to be very important in regulating the disease. The levels of theTh2 triggered cytokines IL-4 and IL-13 were found to be elevated in the lungs of asthmatic patients. A study comparing the bronchioalveolar lavage fluid of asthma patients to control subjects found a significantly greater concentration of Th2 associated cytokines in the lungs of the asthmatic subjects. (Robinson, 1992) One study used Toll-like receptor ligands to bias the immune system toward a Th2 response. The results in the test subjects showed that Th2 cells can aggravate asthma. (Redecke, et. al. 2004) Th2 is clearly a common factor in asthma and allergic rhinitis and is highly involved in allergic response.

A 2010 study set out to determine the mechanism in which the upper and lower airways interact. Using mice, they created a model of allergic rhinitis. OVA sensitized mice were used as controls. Controlling for Th2 cells allowed the researchers to determine its role. When the mice were subjected to a lower airway challenge of the allergen, the allergic rhinitis group showed a much higher concentration of eosinophils in the brochoalveolar lavage fluid than the control group. Using anti-CD3 antibodies to deplete Th2 cells before airway challenge significantly reduced lower airway inflammation, as shown by reduced numbers of eosinophils, dendritic cells and Th2 cells. The researchers then injected cultured Th2 cells into mice before the airway challenge. The mice that had received the OVA specific Th2 cells exhibited much higher levels of IL-5 and eosinophils than the controls. The presence of these Th2 cells was sufficient to induce inflammation upon challenge. Next, while developing allergic rhinitis in the mice, they were treated with FTY720, which prevents recirculation of lymphocytes. This did not stop the mice from developing allergic rhinitis. Later, when challenged with the allergen OVA, the AR mice treated with FTY720 did not display the eosinophilic inflammation that was expected and had very reduced levels of T cells in the bronchoalveolar lavage fluid. This suggests that blocking the Th2 cells from circulating prevents lung inflammation upon challenge, even in the presence of allergic rhinitis. This study concludes that allergic rhinitis models are much more susceptible to lower airway inflammation than controls and that circulating Th2 cells are necessary for the interaction of the upper and lower airway during allergic inflammation. (Kleinjan, et. al. 2009)

Discussion

The connection between asthma and rhinitis is well known and accepted. (Caimmi, et. al. 2012) Studies have been conducted for many years in an attempt to elucidate the mechanism in which they relate to each other. Several hypotheses have been proposed over the years. Researchers suggested a possible nasal-bronchial reflex involving sensory nerve endings. Although this reflex can be observed in animals there is no conclusive data proving its existence in humans.

Another hypothesis is that mouth breathing due to nasal blockages in people with allergic rhinitis impaired nasal humidification and filtration of air. Unconditioned air would enter the lungs and cause problems there (Togias, 1998). However, the most tested and observable connection is the similarity of the allergic response. Inflammation of the upper and lower airways share many features and are characterized by the prevalence of specific cells.

Allergic rhinitis and asthma have many similarities. One frequently studied factor in inflammatory airway diseases is the role of Th2 lymphocytes. Several studies have been conducted to bring evidence that the cytokines released in a Th2 mediated immune response are greatly involved in inflammation in both allergic rhinitis and asthma. Experiments that reduced the levels of Th2 and its associated cytokines by a variety of methods had similar results. Most importantly, reducing Th2 was enough to lower inflammation. Increasing Th2 and its cytokines aggravated the disease. Another important discovery was the fact that airway inflammation is not localized to only the nose or only the lungs. Patients with allergic rhinitis or asthma have shown signs of allergy in the opposite parts of their respiratory tract. The lungs in people with allergic rhinitis are also much more easily affected by allergen challenge than people without any airway inflammation at all. Once present in the airways, inflammatory cells evidently circulate, potentially affecting the entire tract. Blocking the Th2 cells in the nose from reaching the lungs reduces the sensitivity of the lungs to allergens. This may mean that if scientists can find a way to target Th2 or specific cytokines that lead to allergic reactions, allergic diseases like rhinitis or asthma can be controlled or even prevented. In many cases, allergic rhinitis seems to be leading to asthma. It is possible that through blocking Th2 cell recirculation in allergic rhinitis, the inflammatory cells can be contained within the upper airway and not spread to the lungs.

Conclusion

The inflammatory response in allergic rhinitis and asthma is important to understand in order to prevent and treat these common and debilitating diseases. The upper and lower airways make up a continuum and should be treated as one entity. Disorders in both areas should be treated by the same specialists. When diagnosing one, the physician should check for the other. The airway must be considered as a whole, with the realization that they share an allergic mechanism that can affect the entire respiratory tract. Additional research must be done to determine a course of treatment that could practically and effectively control the inflammatory cells. This could prevent people with allergic rhinitis from developing asthma; a phenomenon that is very widespread. It could also help in the treatment and diagnosis of these diseases and perhaps enable sufferers to lead more pleasant lives.

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Is There an Alternative Way of Treating Drug Resistant Epilepsy? The Effects of the Ketogenic Diet in Children with Intractable Epilepsy

Chaya M. Weinberg

Abstract

Many children with epilepsy experience seizures that cannot be resolved with medication. Since surgical intervention is not always an option, the ketogenic diet (KD), a high fat, low carbohydrate and protein diet, offers a chance for seizure reduction and in some cases freedom from seizures and medication. Side effects do exist, although none are serious. Efficacy has been proven through many studies. The mechanism of the KD's effectiveness is still unknown, although several hypotheses exist, including the theory that ketone bodies themselves are anticonvulsant, and the hypothesis that glucose restriction stops seizures. Adenosine A1 receptors are also thought to have a role in seizure reduction. Additionally, some researchers believe that ketone bodies provide the brain with energy to withstand seizures, although there are contradictions to this theory. Finally, the KD may play a neuroprotective role in the treatment of epilepsy.

Introduction

Epilepsy is a disorder characterized by recurrent seizures (Greenberg et al., 2012) which are caused by transitory disturbances of cerebral function due to abnormal paroxysmal firings by neurons in the brain (Aminoff, Kerchner, 2013). In the United States alone, over 300,000 children under the age of fifteen are affected by the disorder (epilepsyfoundation.org). Epilepsy has a great impact on a child's quality of life, psychosocial functioning, and cognitive functioning. These children experience social stigmatization and isolation from their peers. Standard treatment of seizures involves anti-epileptic drugs, of which many are available today, as are infinite ways in which drugs and dosages can be combined. Many children suffer from intractable epilepsy, which is defined by seizures that cannot be treated adequately despite optimal efforts using anti-epileptic drugs (Papandreou et al., 2006). Medical treatment options for intractable epilepsy are scant; in fact, the only choices are implantation of a vagus nerve stimulator or brain surgery (PubMed Health).

The Ketogenic Diet, a high-fat, adequate protein, and low carbohydrate diet that aims to biologically mimic the fasting state (Huffman, Kossoff, 2006) by producing a controlled ketonemia, is a non-invasive way of treating epileptic seizures (Papandreou, et al., 2006). Contrary to popular belief, the KD is not a "holistic" or "alternative" therapy; rather, it is a medical treatment which has been carefully studied and proven to be successful (Freeman et al., 2007a). The present paper will review the ketogenic diet and its effects on children with epilepsy as well as some proposed mechanisms of the diet's actions.

Seizures: A Brief Overview

A seizure is caused by abnormal excitation of neurons in the brain. Hyperexcitability can occur due to increased excitatory synaptic neurotransmission, decreased inhibitory neurotransmission, or alterations in ion flow or voltage-gated ion channels (Bromfield, et al.,2006).

Poor compliance with an anti-epileptic drug can lead to status epilepticus, a medical emergency classified by an occurrence of two or more convulsions without recovery of consciousness between attacks, or a seizure that lasts over 30 minutes. Status epilepticus can result in mental impairment or death (Papadakis, McPhee). It is therefore of utmost importance that seizures be controlled. When two medications fail, the KD should be considered. It should not be used as a last resort (Freeman et al., 2007a).

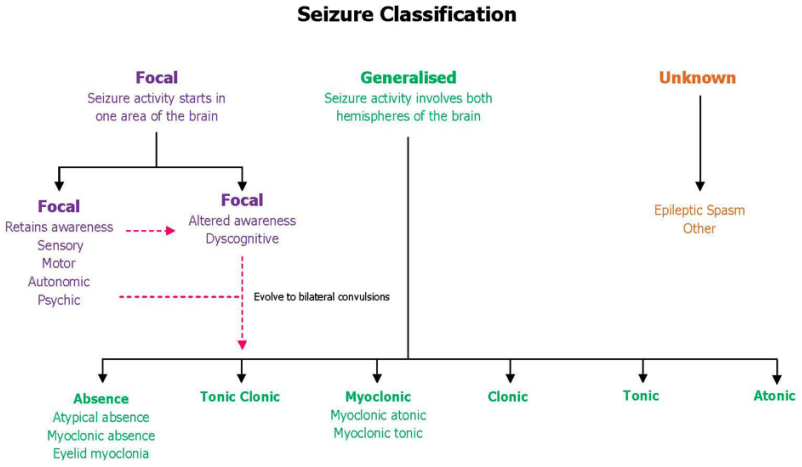

Figure 1: Classification of seizures
Source: http://www.epilepsy.org.au/about-epilepsy/understanding-epilepsy/seizure-types-classification

History of the Ketogenic Diet

Fasting as a cure for epilepsy can be traced back to as far as Hippocrates, who prescribed it to an epileptic patient as a means of purging the body of "polluted humors" (Huffman, Kossoff, 2006). Although not commonly known to many, the KD has been in use since its inception in 1921 (Martinez et al., 2007). The KD retained its novelty until 1938, when the anti-epileptic drug phenytoin (Dilantin) was discovered. Until then, pharmacological treatment of epilepsy could only be achieved with phenobarbital and bromides, both of which had severe sedative adverse effects. Thus the KD was lost in the sea of emerging anti-epileptic drugs, and encouraged by drug companies, physicians looked toward drugs as a primary method of treatment for epilepsy (Freeman, et al., 2007b). However, regardless of increased availability of new drugs, approximately one third of patients have seizures that resist

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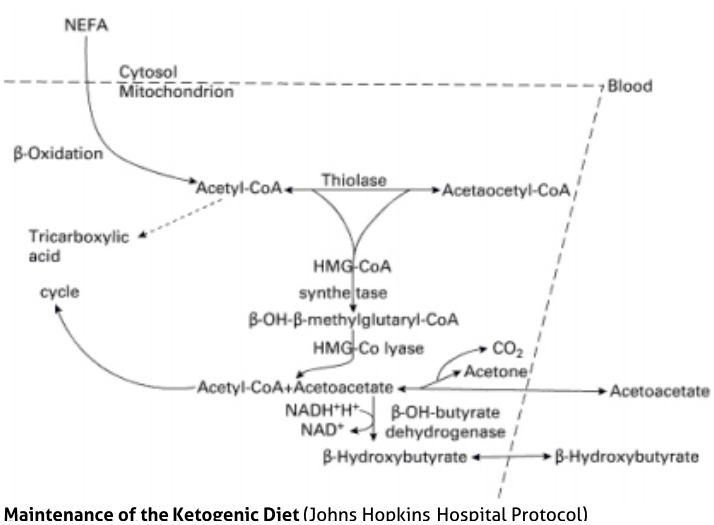
even these anticonvulsants (Noh, et al., 2008). The resurgence of the KD occurred in the mid-1990's, largely due to attention from the media. Since then, there has been a significant worldwide increase in the KD's use (Freeman, et al., 2007b).

Methods

Research for this paper was conducted by evaluating a variety of peer-reviewed journal articles from online databases. Databases include Proquest, Medline, and Pubmed. Access Medicine was used for medical information. In addition to journal articles, diet information was obtained from a book written by Johns Hopkins Hospital M.D.s and dietitians.

The Diet

The KD is so named due to the ketonemia it causes in patients. The diet is comprised mostly of fat and is low in carbohydrates and protein, usually in a 4:1 or 3:1 ratio of fat to carbohydrates and protein (Hartman, Vining, 2007). Calories are restricted to 75-80% of the recommended daily allowance and fluid intake is reduced to 80% of usual amount. This deviation from a normal diet leads to production of ATP from fatty acid metabolism rather than from the usual glucose metabolism. Essentially, the KD has the same physiological effects as starvation. Under normal conditions, aerobic oxidation of glucose yields energy for the brain. In the absence of glucose, fatty acids are ß-oxidized in the liver, generating ketone bodies which can be used as an alternative energy source (Papandreou, et al., 2006). Ketone body levels in blood are usually maintained at ~0.3 mM, but can rise up to ~10 mM with the diet (Juge, et al., 2010). The main ketone bodies are ß-hydroxybutyrate and acetoacetate. Decarboxylation of acetoacetate yields acetone, a minor volatile ketone body (Papandreou, et al., 2006) which vaporizes in the lungs and gives the characteristic "ketone breath" odor (Wheless et al., 2001). Figure 2 shows the steps of ketogenesis in the liver.



Maintenance of the Ketogenic Diet (Johns Hopkins Hospital Protocol)

Figure 2: Ketogenesis in the liver. NEFA, non-esterfied fatty acids. HMG, β-hydroxy- β-methylglutaryl. NAD, nicotinamide adenine dinuclueotide. Source: Papandreou et al., 2006

It is of utmost importance that the KD be administered under close medical supervision (Freeman, et al., 2007a). Initiation of the diet typically occurs in a hospital setting, where the patient can be closely monitored in the event that there are complications. Patients must be accepted into the program to ensure that they are proper candidates (Casey, et al., 1999).

Initiation of the diet involves a 4-day hospital stay (Casey, et al., 1999). The KD normally begins with a fast of 36-48 hours (Freeman, et al., 2007a). Blood glucose is monitored and checked every 6 hours. Although glucose levels may fall very low (25-40mg/dL), they need not be treated unless the patient is hyperemetic or is extremely lethargic (Hartman, Vining, 2007). Introduction of substantial nutrition begins when ketone bodies begin to appear in the urine (Papandreou, et al., 2006). Calories are administered gradually in the form of "eggnog"; 1/3 of planned caloric intake is given on day 1 of feeding, followed by 2/3 and full caloric intake on days 2 and 3 respectively (Hartman, Vining, 2007). During the fasting period, parents attend daily classes on diet management.

After the initiation period, the child begins the actual ketogenic diet. Each child's diet is created to provide optimum seizure control while maintaining adequate nutrition for growth. Anthropometric measurements, activity status, and present medications are considered when calculating a diet. The diet is fine-tuned to give the child a high level of ketosis. A sample KD is shown in Table 1.

A Sample Ketogenic Diet for a 3-Year-Old Boy With No Medical Problems Other Than Intractable Epilepsy

Wt. 15.9 kg.	1035 calories daily/ 4:1 ketogenic ratio	19 grams protein daily
Ht. 42.5 in.	3 meals daily: 305 calories per meal	7 grams carbohydrate daily
65 cal/kg	1 snack daily: 120 calories	103.35 grams fat daily

Breakfast	**Snack**
22 grams egg	Peanut butter cup:
10 grams of applesauce	7 grams creamy Peanut butter
18 grams of butter	10 grams butter
30 grams of 36% cream	(mix together, roll into a ball and chill)
5 grams of bacon	
Lunch	**Dinner**
18 grams American cheese	14 grams chicken
28 grams cucumber	15 grams green beans
15 grams butter	22 grams butter
35 grams 35% cream	35 grams 36% cream

Table 1: Source Casey, et al., 1999

Breakthrough seizures can occur if the diet is not strictly maintained. Since the calorie restriction of the diet causes a loss of almost all body fat, seizures can occur when the body has no fat to burn and begins to break down protein to obtain glucose. Therefore, a snack should be given before bedtime, when the body will not have sufficient fat to metabolize for a prolonged period of time (Casey, et al., 1999). Parents must also be aware of hidden carbohydrates, as they may cause seizures. Even sugar alcohols such as sorbitol can cause seizures and can

be hidden in products such as suntan lotion and toothpaste. Certain medications can also contain starches which can cause breakthrough seizures (Freeman et al., 2007a).

Efficacy of the Ketogenic Diet

The KD offers a greater chance for seizure control than any of the anti-epileptic drugs developed recently (Freeman, et al., 2007a).There have been many studies that prove the efficacy of the diet. Effectiveness is generally not correlated with seizure type (Murphy 2005). Overall, about 10% of children become seizure-free on the KD (Martinez, et al., 2007) and about 50% have a 50% or greater improvement (Neal, et al., 2008). Freeman, et al., (2007a) prospectively studied 150 children on the KD. Before starting the diet, these children averaged over 600 seizures a month and had been on an average of 6 medications. After a year on the KD, 27% of children had a >90% reduction in seizures (Table 2). In a prospective study,

Number initiating And diet status	Seizure control	Time After Starting the Diet 3 Months	6 Months	12 Months	3-6 Years
Total N=150	Seizure-free	4 (3%)	5 (3%)	11 (7%)	20 (13%)
	>90% seizure reduction	46 (31%)	43 (29%)	30 (20%)	21 (14%)
	50-90%	39 (26%)	29 (19%)	34 (23%)	24 (16%)
	<50%	36 (24%)	29 (19%)	8 (5%)	18 (16%)
Continued on Diet		125 (83%)	106 (71%)	83 (55%)	83 (55%)

Table 2. Outcomes of the Ketogenic Diet-Johns Hopkins 1998 (Adapted from Freeman et al., 2007a)

150 children with medically refractory epilepsy who averaged 410 seizures a month were treated with the KD. After a year, 83 children remained on the diet, and almost all had a >50% reduction in seizures. Forty-one (27%) of the 150 had a >90% reduction in seizures. After 3-6 years on the diet, 13% of the original 150 were seizure free and an additional 14% had a >90% improvement (Hemingway, et al., 2001).

A more recent randomized controlled trial (Neal, et al., 2008) studied 145 children between the ages of 2 and 16. These children had daily seizures that had failed to respond to at least two medications. Seventy-three children were assigned to the KD group, and 72 to the control group. In both groups, seizure frequency was recorded during a 4 week baseline period. The diet group then started the KD for 3 months while the control group underwent no changes in epilepsy treatment (the control group had the opportunity to initiate the diet after the 3 month period was over). Data for 103 patients were available for analysis; 54 on the KD and 49 in the control group. Results showed a 62% mean drop in seizures in the KD group, and a 137% increase in seizures in the control group. This surprising increase in seizures was due to 3 outliers; when their data were removed, the percent of seizure increase in the control group went down to 12. Although these results are not as drastic as those of other studies, they are still very significant as they show a direct comparison between children on the diet and children being treated unsuccessfully with medication (Table 3).

	Diet Group (n=73)	Control Group (n=72)
>90% reduction in seizures	5 (7%)	0 (0%)
>50% reduction in seizures*	28 (38%)	4 (6%)
<50% reduction in seizures†	45 (62%)	68 (94%)

Percentages based on numbers allocated to each intervention.
* Includes patients who reported >90% reduction.
† Includes 71 patients with data and 42 unknown (16 did not receive treatment, 16 with no data)
Table 3: Number of children in each group who achieved 50% and 90% seizure reduction at 3 months. (adapted from Neal et al., 2008)

Along with reducing seizure frequency, the KD also has been shown to slightly improve overall developmental functioning and motor skills, as well as attention and social problems in children who remained on the diet for at least a year (Pulsifer, et al., 2001). Additionally, medications can be lowered in dosage or in some cases eliminated completely. Although there are side effects to the KD (see below), most parents preferred these consequences to the sedation and cognitive dulling that result from anti-epileptic drugs (Groesbeck, et al., 2006).

Children who benefit from the diet usually remain on it for 2 years, or until they have successfully stopped medication for a year. They are then slowly weaned off the diet, going from a 4:1 ratio to a 3:1 ratio for 6 months. If a child remains seizure free, the ratio can be lowered to 2:1 for another 6 months, after which the child can return to a normal diet (Freeman et al., 2007a). A retrospective study (Martinez, et al., 2007), reviewed 557 children who were treated at Johns Hopkins Hospital. Sixty-six (12%) discontinued the diet after becoming seizure-free. Ninety-two percent of these 66 children were also medication-free. Thirteen (20%) children had their seizures recur after about 2.4 years off the diet, yet 7 of the 13 became free of seizures their second time on the KD, 4 with anticonvulsant therapy. Thus, children who are seizure-free on the KD have a 20% chance of recurrence. This is significantly lower than the 30-50% rate of seizure recurrence in children who stop medication. However, it is important to note that this is the only study of its kind.

Side Effects and Disadvantages of the Ketogenic Diet

Kidney Stones

As with all medical treatments, the KD has some side effects and disadvantages. In a retrospective study of 195 children on the KD for a median of 12 months, 13 (6.7%) developed kidney stones. Fortunately, this did not result in termination of the diet for any of these children. A few factors put children on the diet at risk of nephrolithiasis. The KD causes a general acidosis which can lead to bone demineralization and hypercalciuria. It also causes hypocitraturia; since citrate usually solubilizes free calcium in the urine, a shortage of it will leave more calcium available to form stones. Uric acid is also less soluble at a low pH and can form crystals that attract

calcium. Stones can form due to the fluid restriction of the diet (Sampath, et al., 2007). Family history of nephrolithiasis is taken before initiation of the KD. Patients at risk are treated prophylactically with oral citrate salts (Hartman, Vining, 2007).

Dyslipidemia

Dyslipidemia (abnormal amounts of lipid in the blood) due to the high fat content of the diet was also found in children on the KD. Interestingly, total cholesterol levels were found to decrease in patients over time, suggesting that eventually, their bodies can better metabolize cholesterol and fat (Nizamuddin, et al., 2008). Additionally, since the high fat is accompanied by an overall restriction of calories, changes in blood levels of lipids, cholesterol, LDL, and lipoproteins are slight (Freeman, et al., 2007a, 117).

Lack of Growth

The KD seems to have an effect on long term growth in children. In a study of 28 children on the diet, 14 were below the 10th percentile for height before initiation. Follow-up measurements showed that this number had increased to 23. Height and weight percentiles remained proportionate to each other (Groesbeck, et. al., 2006). Other studies have also confirmed the KD's slowing effect on growth (Kim, et al., 2013, Williams et al., 2002). A child's growth is constantly monitored on the KD. If the child is not growing normally, the diet ratio can be lowered to allow more protein (Freeman, et al., 2007a, 116).

Noncompliance

The KD is a very stringent diet. Food must be weighed for every meal and the child must eat everything on the plate to ensure that a correct ratio of fat to carbohydrates and protein is received. Many children discontinue the diet for non-medical reasons. In a study of 46 children on the KD, there were 9 such cases. Non-compliance was more common in older children (Lightstone, et al., 2001). Reasons for discontinuation in this study are shown in table 4.

Table 4. Reasons for Discontinuation of the Ketogenic Diet

	All		Neurological Status		SES[a]		Age (years)		
	Number	Percentage	Normal	Abnormal	Low	High	<6	6-12	>12
Total Number of Children Initiating Diet	46		8	38	7	39	25	15	6
Number Remaining on the Diet at 6 Months	27	59%	5	22	2	25	14	11	2
Medical Reasons for Discontinuing Diet	10	22%	1	9	2	8	9[b]	1[b]	0[b]
Lack of efficacy	8	17%	1	7	2	6	7	1	0
Complications	1	2%	0	1	0	1	1	0	0
Acute hospitalization (unrelated)	1	2%	0	1	0	1	1	0	0
Nonmedical Reasons for Discontinuing Diet	9	20%	2	7	3	6	2[c]	3[c]	4[c]
Caregiver issues	5	11%	0	5	2	3	2	1	2
Too regimented/ could not prepare diet in a timely fashion	2	4%	0	2	1	1	0	0	2
Overwhelming anxiety re: food preparation and measurement	1	2%	0	1	0	1	1	0	0
Perception of too little	1	2%	0	1	1	0	0	1	0
Refusal of caregiver to follow the diet	1	2%	0	1	0	1	1	0	0
Patient Issues	4	9%	2	2	1	3	0[b]	2[b]	2[b]
Patient refused to eat diet foods	2	4%	0	2	1	1	0	2	0
Patient cheated on the diet	2	4%	2	0	0	2	0	0	2

[a]SES= socioeconomic status
[b] $p < .05$
[c] $p < .01$

Table 4: Reasons for discontinuation of the Ketogenic Diet. Source: Lightstone, et. al, 2001

Mechanisms of the Ketogenic Diet

Although many studies prove KD's efficacy, its exact mechanism of action remains unknown. However, many theories have been hypothesized as a result of experimentation using animal models. The following are the some of the proposed mechanisms of the KD.

Ketone Body Hypothesis

It seems evident that a high concentration of ketones in the blood is responsible for the anticonvulsant effects of the KD. After comprehensive research on the subject, it is not yet clear as to whether this is the case. Still, there have been some significant correlations between ketone bodies and seizure reduction (Masino, Rho, 2011). In humans on the KD, seizure control often does not peak until after 2 weeks, when ketone levels are at their highest (Bough, Rho, 2007). Moreover, blood levels of ß-hydroxybutyrate seem to be related to the degree of seizure control in children on the KD (Masino, Rho, 2011). However, when carbohydrates are abruptly reintroduced to the diet, breakthrough seizures and loss of ketosis can occur. Yet, overall seizure resistance waned gradually in patients who discontinued the diet. This indicates that a breakthrough seizure does not reflect complete loss of ketosis; ketone levels are still high after introduction of carbohydrates. Thus a certain degree of ketosis is necessary, but is not sufficient to control seizures (Bough, Rho, 2007).

Although the KD has been successful in many age groups, it seems to be more effective in infants and children. This is another reason why ketones are thought to have an anticonvulsant effect (Wheless, et al., 2001). Ketones pass across the blood-brain barrier by means of monocarboxylate transporters. Studies have indicated that a KD can increase the expression of monocarboxylate transporters in the brain of adult rats. However, this enhancement was found to be far greater in suckling rats (Papandreou, et al., 2006). Prior to weaning, a rat's blood level of ketone bodies is high due to the fatty composition of rat milk (Morris, 2005), and young rats' brains are more accustomed to using ketones as an energy source (Papandreou, et al., 2006). In fact, the blood-brain barrier's permeability to ß-hydroxybutyrate has been shown to increase by a factor of 7 during the suckling period in rats, and decrease after weaning (Morris, 2005). A child is able to extract ketones from the blood and transport them to the brain four to five times as efficiently as in adults. (Wheless, et al., 2001). However, some studies have indicated that the KD is as effective in adults as it is in children (Morris, 2005).

ß-hydroxybutyrate is the most prevalent ketone body in the blood. Although levels of plasma ß-hydroxybutyrate are raised in a KD patient, it has not been proven to have anticonvulsant effects (Masino, Rho, 2011). However, when cultured glutamatergic neurons metabolized

ß-hydroxybutyrate, their glutamate content decreased (Lund, et al., 2009). Metabolism of this ketone body in the place of glucose may reduce the availability of glutamate, an excitatory neurotransmitter, and thereby have an indirect anticonvulsant effect (Masino, Rho, 2011). ß-hydroxybutyrate also has structural similarities to gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter (Morris, 2005).

The other ketone bodies, acetoacetate and its decarboxylated product, acetone, have prevented seizures in animal models. In one study, acetoacetate was found to inhibit vesicular glutamate transporters, which are needed for exocytotic release of glutamate (Masino, Rho, 2011). Cl^- acts as an allosteric activator and regulates these transporters. When neurons derived from rat hippocampus were stimulated with KCl, considerable amounts of glutamate were released. Addition of acetoacetate to the culture medium inhibited glutamate exocytosis, and this inhibition was fully reversed upon removal of acetoacetate. (Juge, et al., 2010). Acetoacetate competes with an anion-dependent regulatory site on presynaptic vesicles, thus decreasing the amount of glutamate and excitatory neurotransmission (Masino, Rho, 2011). This may explain why sudden ingestion of carbohydrates can cause an immediate seizure. Ketosis suppresses glutamatergic neurotransmission through inhibition of vesicular glutamate storage (Figure 3). Acetoacetate levels decrease upon introduction of carbohydrates, and vesicular glutamate transporter action is turned on, leading to an influx of glutamate into synaptic vesicles (Juge, et al., 2010). However, this still does not explain why seizures occur despite the fact that ketone levels remain high after carbohydrate introduction. Acetone may also contribute to the KD's anticonvulsant properties. In one study, magnetic resonance spectroscopy showed the presence of acetone in the brains of five out of seven patients successfully treated by the KD (Bough, Rho, 2007). There was no evidence of ß-hydroxybutyrate or acetoacetate in the spectra even though they were present in these patients' urine. Acetone may be the principle intracerebral intracellular ketone amassed in response to the KD (Seymour, et al., 1999).

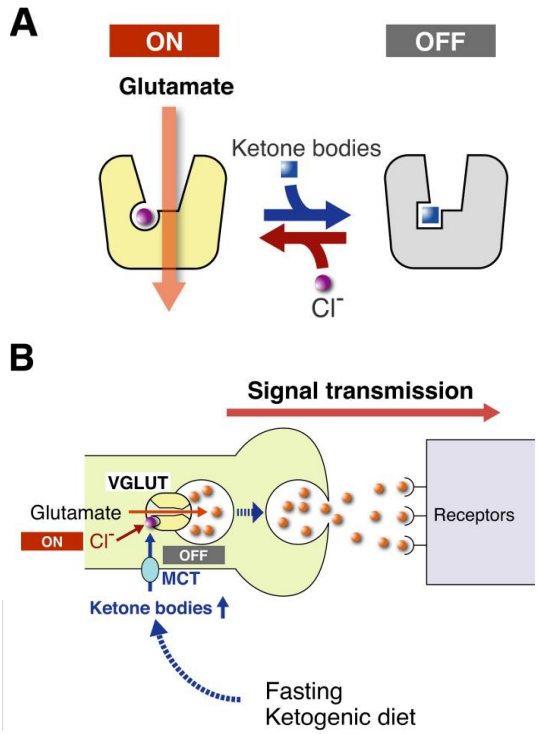


Figure 3: Proposed mode of action of ketone bodies on VGLUT-mediated suppression of glutamatergic neurotransmission.
VGLUT: vesicular glutamate transporter
MCT: monocarboxylate transporter
Source: Juge et al., 2010

Additionally, Increased amounts of ketone bodies lead to increased levels of α-ketoglutarate, part of the tricarboxylic acid cycle. α-ketoglutarate is also a component of the GABA shunt; if elevated, increased input into the GABA shunt may occur. This may have an increasing effect on GABA, an inhibitory neurotransmitter, in local areas of the brain (Wheless, et al., 2001). In humans, cerebrospinal fluid levels of GABA were found to be higher during the KD than before the diet, and the best responders to the diet had the highest levels (Hartman, et al., 2007).

Glucose Restriction Hypothesis

The flip-side to the ketone body hypothesis is that glucose restriction is responsible for the anticonvulsant effects of the KD. As ketonemia develops, glucose levels in the blood are reduced simultaneously. The hypoglycemia may just work to stabilize ketosis, but some studies suggest that the lack of glucose itself can reduce seizures (Bough, Rho, 2007). One study reported that during epileptic seizures, uptake of glucose is high and lactate, the precursor to glucose is also increased (Papandreou, et al., 2006). Greene, et al. (2001) hypothesized that calorie restriction reduces the amount of energy from glycolysis and restricts a neuron's ability to obtain the high levels of energy needed for epileptogenesis.

Another hypothesis involves the effect of low glucose on ATP-sensitive potassium (KATP) channels. KATP channels are ligand gated receptors found in neurons and glia throughout the central nervous system. These channels sense fluctuating levels of ADP and ATP and cell membrane excitability changes accordingly (Bough, Rho, 2007). Although overall levels of ATP in the brain are elevated during the KD, the oxidative metabolism of ketone bodies causes a reduction in brain glucose utilization. ATP derived from glycolysis may play a prioritized role in controlling processes at the cell membrane, including regulation of KATP channels and fueling of ATP-driven sodium pumps (Yellen, 2008). As intracellular glycolytic ATP concentration falls during the KD, KATP channels open to hyperpolarize the cell. When ATP levels rise in the presence of glucose, KATP channels close. As such, KATP channels may regulate seizure threshold (Bough, Rho, 2007). These channels are predominant in the GABAergic projection neurons of the substantia nigra pars reticulata, the region of the brain thought to be responsible for regulating seizure threshold; (Yellen, 2008) therefore, they are in the ideal position to regulate many

threshold; (Yellen, 2008) therefore, they are in the ideal position to regulate many different types of seizures. Genetically engineered mice that exhibited an overexpression of the sulfonylurea subunit of the KATP channel were substantially more resistant to seizures than wild type mice. (Bough, Rho, 2007). Similarly, KATP channel knockout mice exhibited grand mal seizures and death following brief hypoxia, while wild-type mice all recovered from the same stimulus (Yamada, et al., 2001).

Other Hypotheses

There are several other theories as to why the KD works. A recent study showed that increased activation of adenosine A1 receptors suppresses seizures in mice. Adenosine has been found to be a powerful anticonvulsant, and the KD elevates its levels in the brain by reducing expression of adenosine kinase. Overexpression of adenosine kinase has been linked to seizures, and can reduce adenosine A1 receptor activation. In transgenic mice, the KD stopped spontaneous seizures caused by deficiencies in adenosine metabolism if adenosine A1 receptors were intact. Seizure activity was reduced by 50% in mice that had half the amount of receptors, and unaltered in mice that lacked adenosine A1 receptors. Western blot analysis showed that the KD reduced amounts of adenosine kinase. Likewise, brain tissue of humans with intractable epilepsy showed increased levels of adenosine kinase, signifying possible adenosine deficiency (Masino, et al., 2011).

Others say that ketone bodies provide more energy per unit of oxygen to the brain. This may help to enhance a neuron's ability to endure metabolic challenges (Hartman, et al., 2007) and resist hyperexcitability (Rho, Sankar, 2008). However, this contradicts the hypothesis that glucose restriction results in reduced availability of energy for epileptogenesis.

Other hypotheses include the KD playing a neuroprotective role by reducing the amounts of reactive oxygen species in mitochondria, and enhancing glutathione, an antioxidant (Rho, Sankar, 2008).

Conclusion

Many parents of children with medically refractory epilepsy have given up hope of their child becoming seizure-free and leading a normal life. However, when medication and surgery are not options, the KD can effectively reduce seizures in many cases. The KD has shown its success both in studies and in individual patients. It is both a cheaper and less toxic treatment than drugs or surgery. It can increase mental clarity and improve motor functioning in children. As with all medical treatments, the KD has side effects, although not as severe as those of medications.

The diet's mechanism of action is still unknown, but scientists are still researching the possibilities. Many hypotheses currently exist, yet most of these are based on animal models. Further research may need to be done on human subjects for scientists to discover the real mechanism. However, this may be impossible as many of the animal studies would be considered inhumane if implemented in humans. Discovery of a mechanism may eventually lead to a drug that works differently than those that are currently available. Still, the fact that so many hypotheses exist may indicate that the real mechanism is a combination of many of the possibilities. Regardless of what is known about the KD, it is still a miracle cure for many patients who suffer from epilepsy.

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