KETOCGENIC DIET IN THE TREATMENT OF REFRACOTRY EPILEPSY

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Abstract

Epilepsy is a chronic neurological disease which affects around 50 million people worldwide. Approximately 30% of all patients treated are resistant to anti-epileptic drugs. The ketogenic diet is a high-fat, low carbohydrate and adequate protein diet. It has been used for treating epilepsy, especially refractory childhood epilepsy, for more than 90 years. Possible mechanisms through which ketogenic diet suppresses seizures in epilepsy will be described and both short and long-term effects of the diet will be shown.

KEYWORDS: anticonvulsant, epileptogenesis, epilepsy, ketogenic diet, seizures

INTRODUCTION

Epilepsy is a chronic disorder that originates in the brain and is characterized by increased seizure predisposition. It is caused by excessive electrical discharges in nerve cells in different parts of the brain. Depending on which neurons are affected it can cause different signs and symptoms. They include loss of awareness or consciousness and disturbances of movement, sensation, mood or other cognitive functions. It is one of the most common neurological diseases, affecting approximately 50 million people worldwide with 2.4 million newly diagnosed patients each year. An emerging problem in treating epilepsy is the resistance to anti-epileptic drugs (AEDS). It is estimated that around 30 to 35% of all cases are pharmacoresistant. This shows a need for developing new kinds of treatment. Over the years numerous rodent and human studies had shown efficiency of the ketogenic diet in treating refractory (drug resistant) epilepsy.

THE KETOGENIC DIET

The ketogenic diet (KD) is a high-fat, low carbohydrate and adequate protein diet. KD includes 80% fat, 15% protein and 5% carbohydrate in ratio from 2:1 to 4:1 (the ratio of fat to carbohydrate plus protein), with higher ratios being more effective although more restrictive. This radical reduction in carbohydrates causes metabolic shift from glucose to ketone bodies, beta-hydroxybutyrate (BHB) and acetoacetate, which replace glucose as the main energy source for the brain cells.

Although KD might seem to be a new approach in treating epilepsy it was actually first used in 1920s as the only way of controlling epileptic seizures. With development of first anti-epileptic drugs, diphenylhydantoin (Dilantin), in 1938, its use was diminished with research focus turning to drug development. Since 1990s KD has seen continuous rise in the use, especially for children with refractory epilepsy, who have proven resistance to more than 2 or 3 anti-epileptic drugs. Ketogenic diet has proven efficiency not only for drug resistant pediatric epilepsy but for all types of epilepsy with best results shown in patients with Lennox-Gastaut syndrome, West syndrome, Dravet syndrome and infantile spasms.

POTENTIAL MECHANISMS OF THE KETOGENIC DIET

In the last two decades there has been many researches focusing on potential mechanisms (Figure 1) in which ketogenic diet affects epilepsy. The main focus has been whether ketone bodies themselves reduce neuronal excitability or is it a consequence of reduced glucose utilization. One of the proposed mechanisms is a decrease of glycolysis and an increase in mitochondrial metabolism of ketone bodies. Ketone bodies enter nerve cells using monocarboxylate transporter (MCT) and are then directly metabolized by mitochondria in neurons (Figure 1, A1). Mitochondria then use ketone bodies to produce ATP as a source of energy for brain. In his research Kristopher Bough had shown that KD treatment causes an increase in energy metabolism in mitochondria of hippocampal tissue and elevation of energy reserves in hippocampus.
This metabolic shift from glycolysis to mitochondrial ketone metabolism causes a decrease in glucose levels as ketone bodies become the main energy fuel in the brain (Figure 1, A2).

One of the candidates for the tie between changes in metabolism and neuronal excitability are \( \text{ATP} \)-sensitive potassium (\( \text{ATP} \)-sensitive \( \text{K} \)) channels. \( \text{ATP} \)-sensitive \( \text{K} \) channels are widely distributed in the brain and their increased activity has been connected with rushes of action potentials in hippocampal dentate granule neurons. Action of \( \text{ATP} \)-sensitive \( \text{K} \) channels is closely connected with ion pumps. Ion pumps such as \( \text{Na}^+ / \text{K}^+ \) channel use \( \text{ATP} \) and in doing so free \( \text{ATP} \) channels from \( \text{ATP} \) inhibition. The activity of \( \text{ATP} \)-sensitive \( \text{K} \) channels might also be increased by elevated \( \beta\)-hydroxybutyrate (\( \beta\text{HB} \)) levels in dentate granule neurons caused by decrease in glycolysis and production of glycolytic \( \text{ATP} \).

The purine ribonucleoside adenosine had first been recognized as endogenous modulator of neuronal excitability in late 1960s by Fredholm and Dunwiddie. Since then there had been numerous researches that support hypothesis about the role of adenosine as anticonvulsant and neuroprotector. Glial cells of the brain, astrocytes have a major role in keeping adenosine levels in homeostasis via releasing \( \text{ATP} \), main precursor of adenosine. Masino and co. have proven that ketogenic diet has anticonvulsant effect in mice via activation of adenosine \( \text{A1} \) receptors (\( \text{A1R} \)) and that adenosine deficiency may be one of the underlining mechanisms of epileptic seizures. In this study day used three groups of transgenic mice; \( \text{A1R} \)-/- mice lacking both \( \text{A1R} \) alleles, \( \text{A1R} \)-/+ mice lacking just one allele and Adk-Tg mice based on Adk-Tg gene leading to adenosine kinase (\( \text{ADK} \)) overexpression in brain. All three lines of mice showed seizures as a result of adenosine deficiency or reduced \( \text{A1R} \) signaling (\( \text{A1R} \)-/- and \( \text{A1R} \)-/+/). To prove the effects of ketogenic diet they fed mice according to ketogenic diet or control diet (\( \text{CD} \)) — standard rodent diet. After 3 weeks of KD, seizures were almost completely terminated in mice with intact \( \text{A1R} \) (Adk-Tg mice), reduced in \( \text{A1R} \)-/+ mice (approximately 50%) and remained the same in \( \text{A1R} \)-/- mice lacking adenosine \( \text{A1} \) receptors. This study shows that KD suppresses seizures in adenosine deficiency or in signaling reduction, but is ineffective in the absence of adenosine \( \text{A1} \) receptors. This shows that an increase in levels of adenosine, acting through \( \text{A1} \) receptors, is one of...
the mechanisms of ketogenic diet’s anticonvulsant effect (Figure 1, A).\(^5\) Masino and co. also proved that KD reduces adenosine kinase (ADK) expression. ADK is an astrocyte based enzyme which plays a major role in extracellular adenosine homeostasis by transferring gamma-phosphate from ATP to adenosine.\(^6\) After first part of the experiment was over they sacrificed both KD and CD-fed mice. Western blot analysis showed substantial decrease of this enzyme in KD-fed group.\(^7\)

So far, we have shown how ketone bodies can suppress neuronal excitability themselves, but some studies have shown that the decrease in glucose metabolism might be more important.\(^5\) In the previous study, Masion and co., had proven that single glucose injection can restore seizures within 30-90 min in thus backing hypothesis of importance of reduced glucose usage. Recent Boston study used transgenic mice lacking the protein BAD (Bcl-2 associated death promoter) which is involved in initiating cell death, apoptosis.\(^8\) They used real-time mitochondrial oxygen consumption rate to measure mitochondrial metabolism of glucose in cultured hippocampal cortical neurons and astrocytes from BAD-/- mice. Their research showed a decline in glucose oxidation and an increase of beta-hydroxybutyrate metabolism. This is consistent with earlier mentioned metabolic shift from glycolysis to ketone body metabolism in the ketogenic diet. They have also examined the activity of KATP channels from dentate granule neurons in BAD knockout mice hippocampal slices. Activity of this channels was notably higher in BAD mutant slices indicating that metabolic shift from glucose utilization to ketone body metabolism results in increase KATP channel activity and reduced neuron excitability (Figure 1, D).\(^5,8\)

Reduction in glucose levels and rise of ketone body levels in the ketogenic diet are connected with a decline in glycolysis. This fact leads to hypothesis that reduction in glycolysis or its inhibition may reduce seizures.\(^5\) 2-deoxy-glucose (2DG) is glucose analog which reduces uptake of glucose and thus inhibits glycolysis. It has been shown to slow seizure kindling in mice. This effect was suggested to origin from decreased expression of bdnf (brain-derived neurotrophic factor) and its receptor, TrkB.\(^4\) The repression of bdnf may result from a decrease in cytosolic NADH caused by reduced glycolysis (Figure 1, B).\(^4\) This possibly proves the hypothesis that bdnf is a proconvulsant and that its decrease through TrkB receptor decreases seizure occurrence.

**SHORT AND LONG-TERM EFFECTS OF THE KETOGENIC DIET**

The use of ketogenic diet for treatment of epilepsy, especially childhood refractory epilepsy has been, off-and-on, in use since 1921. KD and its effects have been well studied on the point of short-term effects, but long-term effect studies, especially human ones, need to be further investigated.\(^7\) Multiple human studies of short-term efficiency of the ketogenic diet over the span of 3 to 6 months have shown similar results with approximately 50% of the children having 50% or higher reduction in seizures and 24% having seizure improvement higher than 90%.\(^7\)

Despite lack of human studies and clinical data confirming long-term effects of ketogenic diet and it neuroprotective and anti-epileptogenic effect, there has been a significant rise in animal and in vitro studies supporting both theories.\(^7\) Most recent American study done by Lusardi and co. proves that ketogenic diet is not only anticonvulsant but can also prevent epileptogenesis and disease progression in rodent models.\(^8\) Epileptogenesis ("birth of epilepsy" or "beginning of epilepsy") is a complex process resulting in normal brain becoming epileptic.\(^8\) Lusardi and co. used kindling rodent models to present effect of the ketogenic diet on development of epilepsy. They used 3 groups of adult mice, one group (control group) was fed with normal rodent diet (CD) and other two were fed according to ketogenic diet (KD-I and KD-II). Eight weeks after introduction of KD all three groups were started on pentylentetrazole (PTZ) kindling of epileptogenesis, and beginning of kindling was marked as Day 1. During kindling period seizures gradually become more severe in all groups and Day 29 marked and of PTZ kindling. On that day KD fed group KD-II received single glucose injection which caused termination of KD effects momentarily and diet was reversed to normal diet (CD). Four days later, on Day 33, all groups were submitted to PTZ challenge (Figure 2, A). The results of the study showed attenuation in kindling epileptogenesis in mice fed KD 8 weeks before onset of PTZ kindling. Starting at day 19, a significant decrease can be seen in the average seizure score in the KD-fed groups in comparison to control (Figure 2, B). On the day 33 all groups (CD, KD-I and KD-II, diet reversed group) were injected with a single dose of PTZ (PTZ challenge). Kindling suppression in both KD groups continued in day 33, even after diet reversal. Seizures in control group remained constant during both day 29 and day 33 (Figure 2, C). Body weight increased and stayed constant in all 3 groups, with no minimal differences between CD and KD-fed groups (Figure 2, D). Blood ketone levels were measured on day 38 and were elevated as expected in both KD groups and low in CD group (Figure 2, E). Their findings show that KD prevents progression of epilepsy and that its effect doesn’t diminish even after reversal of the diet. This research confirmed the role of the ketogenic diet in preventing epileptogenesis.\(^8\) Jiang and Yang had come to similar discovery. Using model of amygdaloid-kindling seizures they confirmed that KD delays seizure progression.\(^8\) They also had proven that KD has neuroprotective effects on hippocampal neurons. After 4 weeks of KD diet regime and 20 days of one-sided kindling stimulation in amygdala, all animals were sacrificed and researchers then measured the neuronal density in hippocampus and parahippocampal cortices. Mice that were fed with a normal diet showed notable loss in neuronal density of these regions, while KD fed mice showed attenuation in neuronal loss, only in the ipsilateral hippocampal CA1 region, but not in the other areas.\(^8\)

Although a still significant lack in controlled human studies supporting neuroprotective and anti-epileptogenic effect of the ketogenic diet exists; there are some
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follow-up clinical studies in the treatment of refractory epilepsy. One of those follow-up studies confirming long lasting seizure protection even after discontinuation of the ketogenic diet is an Argentinean multicenter study of pediatric patients. The study included 216 pediatric patients with different types of epilepsy in the period between 1990 and 2010. Eighteen months after the initiation of the ketogenic diet, 65% of the initial patients remained on the diet. Of those 65%, 22% were seizure free, 34.5% had a decrease in seizures greater than 75%, 10% had a decrease in seizures between 50 and 75% and the remaining 33.5% had decrease lower than 50%. After returning to normal diet, 75% of patients from seizure free group hadn’t had seizures recurrence. Of the 40 patients who had a decrease in seizures higher than 50%, seizures recurred in 10 after the diet was discontinued. Another follow-up study was done by Austrian doctors in drug-resistant childhood epilepsy. They evaluated data from 50 children who were treated between 1999 and 2008. 50% children were responders (seizure reduction higher than 50%) of which 24% become seizure free. Seven patients remained seizure free for more over a year after conclusion of the ketogenic diet.

The longest use of the ketogenic diet in treatment of epilepsy was reported in the paper by Kossoff and co. in 2007. It was a case report of 26-year-old man with tuberous sclerosis complex who had been started on the ketogenic diet at the age of 6 years. Even though he hadn’t been controlled by a neurologist, he exhibits excellent seizure control without any serious side effects (only side effect was poor growth). At the time of the report he was continuously on the ketogenic diet for over 20 years. He still brings specially prepared meals daily to work and continuous to have approximately 1-2 seizures a year without any tolerability issues.

Figure 2. Suppression of PTZ kindling epileptogenesis by a KD in adult mice.
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CONCLUSION

Epilepsy is a serious chronic brain disorder, the symptoms of which can be successfully treated in most patients with one or more antiepileptic drug. Yet about 30% of patients continue to experience seizures despite all available drug options and are candidates for other treatment options. Numerous researches of the ketogenic diet and its mechanisms in treating epilepsy have proven not only short-term anticonvulsant effect of the diet but also long-term anti-epileptogenic and neuroprotective roles. Even though the number of animal studies supporting this statement is increasing, additional studies are required, especially human controlled clinical studies.

References:

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KETOGENA DIJETA U LIJEČENJU REFRAKTORNE EPILEPSIJE

Sažetak

Epilepsija je kronična neurološka bolest koja zahvaća oko 50 milijuna ljudi diljem svijeta. Otpričeklo 30% oboljelih je rezistentno na antiepileptike. Ketogena dijeta sadrži visoki postotak masti, mali postotak ugljikohidrata i zadovoljavajući postotak proteina. Koristi se u liječenju farmakorezistentne epilepsije i to poglavito u dječjoj dobi više od 90 godina. U ovom radu su opisani mogući mehanizmi putem kojih ketogena dijeta suprimira epileptičke napadaje te su prikazani kratkoročni i dugoročni učinci dijete.

Ključne riječi: antikonvulziv, epileptogeneza, epilepsija, ketogena dijeta, napadaji

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