

Ketogenic Diet as A Treatment Option for Different CNS Diseases

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ABSTRACT

Ketogenic diet is a replacing of carbohydrates by fats in everyday food. This approach was proposed for treatment of different brain diseases including Parkinson disease, cancer, trauma, however, currently it is approved only for curing of epilepsy and Alzheimer disease. Ketone bodies are synthesized from fats in liver. Generally they include β -hydroxybutyrate (BHB), acetoacetate and acetone. BHB and acetoacetate can permeate through blood brain barrier and are used by neurons as a fuel. It is believed that beneficial properties of ketogenic diet can be explained by moderate increase of ketone bodies plasma concentration. Potentially, ketone bodies can influence neurons on three different levels. (1) They can be energy substrates and may change several metabolic pathways; (2) They can be signaling molecules for instance due to binding to specific plasma membrane; (3) They can influence neurons on epigenetic level because BHB is recognized as a histone deacetylase inhibitor. Several molecular mechanisms were proposed for explanation of beneficial properties of ketone bodies. However, the main mechanism is still a discussible question. Most likely different metabolic and signaling pathways are involved.

Key words: Ketogenic diet; Ketone bodies; Epilepsy; Seizures; Alzheimer disease

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KETOGENIC DIET AND KETONE BODIES

The brain of human beings is a dynamic organ consuming a high amount of energy. Although the brain comprises only 2% of total body weight, it utilizes 20% of oxygen supplied to the body^[1-3]. Glucose is the main source of energy for the brain, however, under certain conditions, such as breast-feeding, prolonged fasting, and keeping on the ketogenic diet, other energy substrates such as ketone bodies (acetoacetate and β -hydroxybutyrate) can also be utilized by the brain. All of these conditions are associated with an increase in ketone bodies levels and a decrease in plasma glucose levels^[4-6]. When plasma glucose levels are low, the required amount of energy could be obtained by converting fats into ketone bodies, predominantly β -hydroxybutyrate (BHB) and acetoacetic acid, and in a lesser extent to acetone^[6]. They are byproducts of fat metabolism and formed in mitochondria in liver cells^[6]. Ketone bodies include acetoacetate which, unless oxidized with yielding useful energy, serves as a precursor for two other ketones: acetone which could not be a source of energy and BHB formally not belonging to ketones but can reversibly be synthesized from acetoacetate. The precursor for ketone bodies synthesis is acetyl-coenzyme A which is formed upon β -oxidation of fatty acids in the liver. Two important determinants for ketogenesis are the presence of acetyl-CoA and the mobilization of fatty acids released from white adipose tissue during fasting, dieting or catecholaminergic stress^[6]. Acetoacetate is the main ketone body. Acetoacetate is converted to β -hydroxybutyrate by β -hydroxybutyrate dehydrogenase in NADH-dependent reversible reaction^[6]. The yield of this reaction depends on the size of cellular NAD^+ pool^[7,8]. When this pool is greatly

reduced, all or almost all ketones are converted to BHB. The ratio between BHB and acetoacetate reflects a redox state in mitochondria^[6,8]. BHB is chemically stable. Only this ketone body is characterized by metabolic interconversion with acetoacetate^[6,8].

It would be assumed that changes in food intake may influence the course of different brain diseases associated with alterations in metabolism. The most important example of dietary treatment with proven efficacy for neurological conditions is the ketogenic diet with high fat and low carbohydrate contents which is used in patients with refractory epilepsy. This approach has also been proposed for curing other neurodegenerative diseases including Parkinson's disease and amyotrophic lateral sclerosis. Meanwhile, despite the abundance of proposed hypotheses, there is still no consensus regarding basic molecular mechanisms underlying the protective action of the ketogenic diet^[6,9-11].

In 1920-30s, epileptic conditions had been treated with relatively few anticonvulsant drugs having weak potencies. As a result, in 1921 in the Mayo clinic (USA), Wilder has developed the ketogenic diet for treating refractory forms of epilepsy in children. This diet strictly restricts the intake of carbohydrates, protein, a total amount of calories and liquid, and significantly increases fat intake to about 90% of caloric value^[12].

Therapeutic effect of this diet is based on the fact that nutrients and metabolic substrates can exert profound effects on neuroplasticity, neural network dynamics and properties of cells to improve and normalize their functioning. There are many clinical and laboratory data relating defects in energy metabolism to a broad spectrum of pathological conditions^[10].

The classical ketogenic diet comprises carbohydrates and fats in a ratio of 1:4. This sudden decrease in carbohydrates portion leads to a reduction in glucose intake. Ketone bodies (acetoacetate and β -hydroxybutyrate) formed from fatty acids entering into the liver maintain cellular metabolism instead of glucose. The major amount of energy is spent for maintaining neuronal functioning since neurons have a high rate of energy metabolism^[13].

Over the past decades, researchers have identified multiple mechanisms owing to which the ketogenic diet may have a neuroprotective action. The first characteristic feature of the ketogenic diet is an increase in plasma and cerebral ketone bodies levels. Ketone bodies were shown to have neuroprotective properties due to increasing ATP level and reducing reactive oxygen species (ROS) synthesis through enhancement of NADH oxidation and inhibition of mitochondrial pore formation^[10,14]. The ketogenic diet stabilizes synaptic functions and stimulates mitochondrial biogenesis^[15].

The second main biochemical feature of the ketogenic diet is down-regulation of glycolytic pathway. This, in turn, can result in suppression of seizures^[16]. At the same time, the relationship between caloric value reduction and ketogenic diet's mechanisms of action remains controversial^[15], obviously, the decrease in blood glucose levels is observed in both cases. In a favor of this assumption, it was shown that 2-deoxy-D-glucose, an analogue of glucose blocking glucose-6-phosphate isomerase and thereby inhibiting glycolysis, suppresses epileptogenesis in the rat model of amygdala excitation by decreasing expression of brain-derived neurotrophic factor and its primary receptor, tyrosine kinase B^[9,10,17]. Several other important mechanisms of neuroprotection mediated by caloric restriction include an improvement of mitochondrial function and reduction of oxidative stress (as do ketones and polyunsaturated fatty acids), reduction of pro-apoptotic factors activities and inhibition of inflammatory mediators such as interleukins and tumor necrosis factor alpha^[15]. Furthermore, at the level of the organism,

the caloric value reduction is known to increase lifespan in different species including primates^[15].

The ketogenic diet is widely used in patients with different epileptic syndromes, but it should be used with caution because of side effects such as dehydration, hypoglycemia, nephrolithiasis, acidosis, hyperlipidemia, and cardiomyopathy. In view of this, different modifications of the classical ketogenic diet are currently being employed^[11,12]. The modified Atkins' diet and low glycemic index treatment (LGIT) are fairly less radical and milder variants of the ketogenic diet. Using medium chain triglycerides in the ketogenic diet is thought to provide the higher ketone bodies levels in the blood as compared to low chain triglycerides^[11]. Moreover, several enterprises are manufacturing products for clinical nutrition based on caprylic acid. The mode of action for this product is believed to be almost identical to that for the diet based on medium chain triglycerides^[18,19].

ANTIEPILEPTIC EFFECTS OF THE KETOGENIC DIET

Epilepsy is a widespread disease afflicting about 1% of the population in the United States and at least 50 million people worldwide^[9,20]. Despite many antiepileptic drugs had been developed, they are not able to control seizures in 30% of patients with epilepsy^[9,21]. Some of these patients are candidates for surgical resection of the diseased tissue, however, there exist possibilities for escaping such the interventions. In 1920th, the ketogenic diet with high fat and low carbohydrate contents had been developed in order to assist curing patients with unresectable refractory epilepsy^[16,22,23]. Many clinical studies have confirmed its beneficial effects: a randomized study revealed 75% reduction in seizure frequency in children kept on this diet for three months^[9]. The diet mainly consists of fats and results in dropping plasma glucose levels and elevating ketone bodies levels through conversion of fatty acids in the liver. The ketogenic diet comprising 90% fats, 7% proteins and 2.3% carbohydrates is a valuable supplementation in the treatment of epilepsy in children and adults^[6,24]. In their study, Mack and his colleagues have shown that 53.9% of patients had more than 75% reduction in seizure frequency 1 month after diet initiation. Recent studies have demonstrated that children who kept on the ketogenic diet for more than 1 year and those who had a relevant response to the diet have exhibited positive results in the subsequent 3- and 6-year period^[6,20].

The ketogenic diet is a beneficial treatment option for patients with refractory epilepsy including certain types of epilepsy in infants and toddlers requiring expensive treatment. According to conservative estimates its effectiveness is comparable with that of pharmacological anticonvulsant drugs^[14]. It is being used for patients of all age groups. Modifications of the classical ketogenic diet allow for its broader use in patients with other neurodegenerative diseases such as Parkinson's disease, brain injury, autism, headaches, migraine, diabetes mellitus type 2^[11,14].

Investigations of the ketogenic diet keeping in mind its mechanisms of action will promote better understanding a process of epileptogenesis. Nevertheless, these mechanisms are not fully established.

Initial attempts to determine the anticonvulsant mechanisms of action of ketone bodies were unsuccessful. In electrophysiological experiments, low millimolar concentrations of β -hydroxybutyrate and acetoacetate did not influence neuronal excitability or synaptic transmission in hippocampus^[17,24]. However, more recent data have demonstrated that other subcortical structures might be crucial for

the modulation of seizure activity.

Antiseizure properties of acetoacetate were first reported by Keith in 1935th. Its administration prevented development of seizures caused by thujone in rabbits. In line with this report, Rho and his colleagues have found that intraperitoneal administration of acetoacetate and acetone, but not β -hydroxybutyrate, prevented development of seizures in juvenile mice susceptible to seizures^[9,10]. Acetone is a ketone body but not taken up by cells. Meanwhile, it could not be excluded this substance may have anticonvulsant properties. Recently it was observed that acute intraperitoneal administration of acetone in rats attenuated their susceptibility to seizures in a wide array of tests including test with maximal electroshock, subcutaneous pentylenetetrazol test, amygdala excitation test and AY-9944 test^[9,10]. Acute administration of acetone, but not its metabolites, protected juvenile mice from convulsions induced by pentylenetetrazol and 4-aminopyridine^[9,10]. However, in this study, the doses of acetone needed for significant protection from seizures have caused movement disorders in mice what significantly limits its clinical and pharmacological application. A number of evidence indicates that acute administration of acetone and acetoacetate exerts anticonvulsant effects in many standardized animal models of epilepsy. However, perspectives for its clinical use still remain unclear since no studies were conducted for investigating the anticonvulsant effects upon chronic administration of exogenous ketone bodies in models similar to those discussed above.

Although acetone demonstrated a broad spectrum of anticonvulsant properties in animal models, the ketogenic diet in the same tests does not provide a similar level of protection (in particular regarding seizures induced by pentylenetetrazol in mice). Acetone and ketogenic diet appeared to have different mechanisms of anticonvulsant action^[9,10]. Furthermore, plasma acetone levels in rats fed with high fat diet were 10-fold lower than therapeutic levels (> 2 mM), even in the presence of inhibitor of acetone metabolism^[9,17]. Conversely, the results of proton magnetic resonance spectroscopy in patients with epilepsy revealed that acetone concentration in the brain is completely controlled by the ketogenic diet and hold at approximately 0.7 mM^[9,10]. Thus, the question on involvement of acetone in antiepileptic effects of the ketogenic diet is yet to be answered.

In this stage of clinical studies, several potential mechanisms of anticonvulsive action of the ketogenic diet are identified: change in arachidonate levels, increase of GABA levels, inhibition of synaptic vesicles loading with glutamate, activation of K_{ATP} channels, and inhibition of endocytosis^[6,11,14,25-27]. Further investigation of these mechanisms will clarify the potential for clinical application of the ketogenic diet, and might identify new targets for future development of therapies.

KETOGENIC DIET IN ALZHEIMER'S DISEASE

Studies have shown the enhanced neuronal excitability in patients with Alzheimer's disease (AD)^[22]. While significant pathological processes in Alzheimer's disease include degeneration of neurons associated with accumulation of abnormal cellular products, such as fibrillar plaques and tangles, recent data point to alterations in neural network functioning and mitochondrial homeostasis^[28-30]. This point of view is supported by high frequency of attacks similar to that for epileptic seizures in patients with AD compared to the healthy population^[22]. Furthermore, it was shown that hypometabolism plays an important role in AD pathogenesis^[18]. Thus, there is a rationale for hypothesizing that the ketogenic diet can positively influence patients with AD^[31], in addition to its potential benefits in

preventing senescence.

At the present time, data from clinical studies are equivocal but promising. A randomized, double, placebo-controlled study aimed at estimating the medium chain triglycerides levels formed during the ketogenic diet has demonstrated a significant improvement in cognitive functions in APO ϵ 4-negative patients with Alzheimer's disease, but not in patients with APO ϵ 4 mutations^[10]. The significant clinical improvement is believed to be secondary relatively to the improvement of mitochondrial function because ketone bodies, in particular β -hydroxybutyrate, protect against the toxic effects of β -amyloid in neuronal culture^[10]. Ketogenic diet can actually reduce the amount of β -amyloid^[10,22]. Interestingly, other diets such as the Mediterranean diet had some encouraging results in AD possibly through reducing systemic inflammation and increasing metabolic functions^[10].

Recent studies have shown a close relationship between AD and epilepsy. For example, increased neuronal excitability and higher propensity to seizures have been detected in animal models of AD^[10,22]. These models can eventually allow for conducting the detailed analysis of the cognitive and anticonvulsant effects of the ketogenic diet or inhibition of glycolysis. Mice fed with 2-deoxy-D-glucose exhibited the improved mitochondrial functioning, decreased oxidative stress, and reduced expression of the amyloid precursor protein and β -amyloid compared to control animals^[32]. Another pathophysiological mechanism implies examining AD in terms of alteration in mitochondrial function and glucose metabolism, ie, accumulation of the main end products of glycosylation^[7,10,18]. Accumulation of these products is a normal process of aging that is accelerated during AD; proteins are subjected to non-enzymatic glycosylation which causes crosslinking and exacerbates their dysfunction. One of proposed mechanisms includes acceleration of ROS and free radicals formation which hinder the normal functioning of mitochondria. Currently, a possibility that inhibitors of the main end products of glycosylation, such as aminoguanidine, tenilsetam, carnosine, may act in concert with the ketogenic diet or antioxidants in slowing the progression of AD is actively discussed^[10,18,31].

Thus, there is growing evidence that the ketogenic diet may be effective for treatment of AD through different metabolism-induced mechanisms which reduce oxidative stress and neuroinflammation, and also improve bioenergy indicators, mainly by improving mitochondrial functioning. However, results from animal models should be very carefully extrapolated to humans because of aforementioned discrepancy in the clinical efficacy and adverse side effects. For example, adverse effects caused by caloric restriction have been reported in some rodent models^[15]. In hippocampus, abnormal morphological changes of synapses were detected in the molecular layer of CA1^[31].

NEUROPROTECTIVE PROPERTIES OF KETONE BODIES COMMON FOR DIFFERENT CNS DISEASES

It is shown that the ketogenic diet may potentially be used for treatment of quite large list of CNS diseases. Apart of epilepsy and Alzheimer's disease discussed above, this includes Parkinson's disease, amyotrophic lateral sclerosis, various types of brain cancer, autism, depression, migraine and traumatic brain injury^[10]. This suggests that ketone bodies can activate defense mechanisms that are common for various diseases. What could they be?

Firstly, BHB is a more efficient energy substrate than glucose^[6,33].

Ketone bodies can stimulate mitochondrial biogenesis by activating genes encoding mitochondrial enzymes and proteins involved in maintaining energy metabolism^[6]. Additionally, ketones increase concentrations of intermediate metabolites entering the citric acid cycle followed by 16-fold increase in acetyl-CoA levels.

Secondly, ketones protect against glutamate-mediated apoptosis and necrosis by reducing reactive oxygen species formation. Ketones can oxidize coenzyme Q resulting in reduction of free radicals formation in mitochondria^[6,10]. Metabolic changes contribute to resistance to convulsions due to reduced reactive oxygen species formation. Various studies show that the ketogenic diet strengthens the mechanisms reducing ROS formation. It is well known that reduction of ROS formation increases cell viability, but it is not completely clear whether this happens exclusively due to protection of the nervous system cells or because of direct decrease in neuronal excitability^[34]. ROS formation induced by glutamate is inhibited by ketone bodies in primary cultures of hippocampal and neocortical neurons in rats^[15,35]. The mechanisms appeared to involve rather oxidation of NADH than glutathione-mediated antioxidant effect. On the other hand, the ketogenic diet, but not ketone bodies, can change the metabolism of glutathione via transcription factor Nrf2. Ketone bodies also protected cells from cell death in cerebral cortex after exposing tissue sections to hydrogen peroxide^[9]. In addition, ketone bodies protect from damage induced by hydrogen peroxide in long-term potentiation of hippocampus^[15]. Thus, these data suggest that in addition to the effects in synapses ketone bodies have neuroprotective effects against reactive oxygen species produced during the neuropathological states^[9,15].

Thirdly, ketone bodies enhance conversion of glutamate to GABA with subsequent reinforcement of GABA-mediated inhibition^[6].

Fourthly, apoptotic cell death is attenuated upon taking ketone bodies^[6,9]. The mechanisms include a decrease of activation of caspase-3, increase in calbindin protein level and prevention of clusterin accumulation.

Fifth, cerebral metabolism of ketones improves cerebral blood flow^[6,23].

All mentioned mechanisms can be attributed to the regulation at the metabolic level. At the same time, the discovery of G protein-associated receptors for BHB on the plasma membrane of neurons^[36,37] suggests a signaling function for ketone bodies. It is therefore quite possible that BHB can act at the level of intracellular signaling. This may represent the sixth defense mechanism common for different pathologies.

Seventh, ketone bodies can act at the epigenetic level. BHB was found to be a highly effective natural inhibitor of histone deacetylase. Inhibition of histone deacetylase in turn enhances activities of antioxidant enzymes^[38].

POSSIBLE ALTERNATIVES FOR THE KETOGENIC DIET

Despite the broad spectrum of potential indications for use assigned to this treatment option, it still has a number of limitations. Adhering to ketogenic diet might be difficult for patients as it adversely impacts the liver and kidneys^[6,39-41]. Unfortunately, due to the lack of defined target and insufficient knowledge regarding mechanisms of action, replacing the ketogenic diet by any other pharmacological agent is thought to be impossible. However, ketogenic diet can be improved by other ways.

Assuming that the restriction of glycolysis and the use of non-

glycolytic energy substrates by neurons underlay the mechanism of action for the ketogenic diet, presumably, this treatment option can at least partially be replaced by pyruvate. In support of this assumption, we have shown that pyruvic acid as well as BHB inhibits endocytosis^[27]. Pyruvate was found to improve the compromised cognitive abilities in Alzheimer's disease model and displayed anti-epileptic properties^[42,43].

In the brain, lactate is a natural non-glycolytic energy substrate^[44,45]. Large amounts of lactic acid are produced during physical activity indicating that exercises may also have effects similar to those of the ketogenic diet. This hypothesis is supported by recently published results demonstrating that physical activity indeed has a neuroprotective effect^[45,46].

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