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New insights into the mechanisms of the ketogenic diet

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Abstract

Purpose of review—High-fat, low-carbohydrate ketogenic diets (KDs) have been used for almost a century for the treatment of epilepsy. Used traditionally for the treatment of refractory pediatric epilepsies, in recent years the use of KDs has experienced a revival to include the treatment of adulthood epilepsies as well as conditions ranging from autism to chronic pain and cancer. Despite the ability of KD therapy to suppress seizures refractory to antiepileptic drugs and reports of lasting seizure freedom, the underlying mechanisms are poorly understood. This review explores new insights into mechanisms mobilized by KD therapies.

Recent findings—KDs act through a combination of mechanisms, which are linked to the effects of ketones and glucose restriction, and to interactions with receptors, channels, and metabolic enzymes. Decanoic acid, a component of medium chain triclycerides, contributes to seizure control through direct AMPA receptor inhibition, whereas drugs targeting lactate dehydrogenase reduce seizures through inhibition of a metabolic pathway. KD therapy also affects DNA methylation, a novel epigenetic mechanism of the diet.

Summary—KD therapy combines several beneficial mechanisms that provide broad benefits for the treatment of epilepsy with the potential to not only suppress seizures but also to modify the course of the epilepsy.

Keywords

metabolism; ketones; seizure suppression; epileptogenesis; epigenetics

Introduction

Since ancient times it was known that sustained fasting or a ‘water diet’ can be used to control seizures in epilepsy. In the 1920s it was found that a diet composed mostly of fats, i.e. a high-fat low-carbohydrate ‘ketogenic diet’, could replicate the effects of fasting, and those beneficial effects were ascribed to the production of ketones, such as β-hydroxybutyrate (BHB), acetoacetate, and acetone in the liver [1]. Despite early successes of KD therapies, the advent of antiepileptic drugs (AEDs) in the 1940s pushed KD therapy to

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Conflicts of interest

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the sidelines. However, the clinical use of KD therapies received increased attention in the 1990s, and KD therapy is now an established therapy for difficult-to-treat epilepsies in addition to a wider use in a variety of neurological disorders [2]. Seizure freedom during KD treatment is a clinical reality with one study reporting a 24% rate of seizure freedom, however there is still a risk of breakthrough seizures [3]. Core mechanisms of the diet have been covered in excellent recent reviews [4–6]. This review focuses on new mechanistic findings, which support the concept that the broad success of KD therapy is based on a combination of multiple beneficial mechanisms. The purpose of this review is not to provide a comprehensive overview of all potential mechanisms, but to guide the reader to areas of current research interest.

Clinical associations

Clinical studies can be used to associate metabolites or neurotransmitters/modulators mobilized by KD therapy with treatment success and to identify predictors for successful therapeutic outcomes. For example, it is well known that high blood BHB levels correlate with positive treatment outcome. Similarly, an increase in cholecystokinin-8, a peptide with antiepileptic properties, and a decrease in leptin associated with seizure suppression in patients with refractory epilepsy [7]. On the amino acid level it was found that changes in cerebrospinal fluid (CSF) lysine and arginine associated with >50% seizure reduction in a study involving 60 children [8]. On the genomic level single nucleotide polymorphisms (SNPs) can be used to associate gene variants with treatment success. However, variants in KCNJ11 and Bcl-2-associated death promoter (BAD), two key metabolic regulators, were recently shown to not predict response to KD therapy [9].

Ketosis and ketone bodies

Ketone bodies, such as BHB, and their derivatives have received most attention as mediators of the anti-seizure, neuroprotective, and anti-inflammatory effects of KD therapy [1,10,11]. In neurons BHB can compete with glucose for energy generation by inhibiting glycolytic flux upstream of pyruvate kinase [12•]. KDs can thereby shunt ketones into oxidative metabolism in the brain, which also enhances the capacity to produce amino acids such as GABA [13]. BHB levels in plasma are generally taken as indicator for ketosis but interactions with conventional antiepileptic drugs may exist [14]. Traditionally, BHB has been considered as the main effector of the therapeutic benefits of KD therapy. BHB in turn appears to have pleiotropic effects. In one mechanistic study BHB was shown to support synaptic vesicle recycling with a net effect of endocytosis exceeding exocytosis, a mechanism with possible anticonvulsant outcome [15]. BHB can also have direct effects by acting as endogenous ligand of the hydroxyl-carboxylic acid receptor 2 (HCA2) [11]. Activation of HCA2 on a subset of macrophages induces a neuroprotective phenotype depending on prostaglandin D2 production, whereas the genetic ablation of HCA2 abolished BHB-induced neuroprotection in a murine stroke model [11]. One therapeutic goal is to replace the KD, and its strict requirements for adherence, with dietary supplements that can produce sustained ketosis. Ketone esters, such as R,S-1,3-butanediol acetoacetate diester (BD-AcAc2) are currently considered as a substitute to KD therapy in efforts to develop a ‘ketogenic diet in a pill’. In support of therapeutic efficacy BD-AcAc2 was shown to

increase the thresholds for pentylenetetrazole induced seizures in the rat [16] and to ameliorate seizures in a mouse model of Angelman syndrome [17].

Medium-chain fatty acids

The medium chain triglyceride (MCT) KD is commonly used for the treatment of refractory childhood epilepsy. Importantly, one on one comparisons of a variety of medium chain fatty acids with valproic acid (VPA), a conventional AED, showed enhanced anti-seizure efficacy of medium chain fatty acids with reduced toxicities compared to VPA in a panel of *in vitro* and *in vivo* assays [18]. Medium chain fatty acids, such as heptanoic acid, octanoic acid, or decanoic acid, exert pleiotropic anti-seizure effects and have therefore been considered as add-ons to KDs or to regular non-KDs. Heptanoic acid can supply the tricarboxylic acid cycle with both acetyl-CoA for energy production and propionyl-CoA to replenish the cycle. It has been shown that heptanoic acid can lead to increased levels of glutamine in the brains of glucose transporter I deficient mice suggesting a role for glial metabolism of heptanoate [19]. A small scale open-label case series tested the effects of triheptanoin-supplemented diets in 14 patients with inborn glucose transporter type I deficiency. The authors of this study reported a modest improvement in ictal events, but the underlying mechanisms were not further evaluated [20]. Branched octanoic acid compounds have been generated that show promising antiseizure activity in *in vitro* and *in vivo* seizure models, without affecting histone deacetylase activity [21]. Chronic feeding of diet with 35% of the calories derived from tridecanoin but not from trioctanoin was anticonvulsant in two mouse models in the absence of increased plasma and brain BHB [22•]. Only tridecanoin but not trioctanoin improved mitochondrial metabolic functions and antioxidant capacity [22]. Specifically, decanoic acid but not octanoic acid improved mitochondrial biogenesis as well as mitochondrial numbers through a PPARγ-mediated mechanism in neuronal cell culture systems [23,24]; decanoic acid led to an increase in the transcription of genes related to fatty acid metabolism, while downregulating genes involved in glucose metabolism [23]. Using single-cell imaging in pluripotent stem cell-derived human astrocytes and neurons it was found that decanoic acid promoted astrocytic but not neuronal glycolysis and lactate formation, whereas octanoic acid did not affect glycolysis but increased astroglial ketogenesis [25]. The authors of this study concluded that medium chain fatty acids modulate astrocyte metabolism by providing lactate and ketones as fuel for neighboring neurons via the glial/neuronal shuttle system [25•]. Medium chain fatty acids were also shown to affect amino acid metabolism, with an increase of tryptophan in the brain associated with reduced hippocampal excitability [26]. Finally, a recent seminal study from Chang et al., identified an exciting novel mechanism, by which decanoic acid directly reduces neuronal excitability by inhibition of AMPA receptor activity; importantly, it was shown that decanoic acid, acts as a non-competetive AMPA receptor antagonist binding to a site that is distinct from the perampanel binding site of the receptor [27••]. These findings suggest the existence of a powerful anticonvulsant mechanism of medium chain triglyceride ketogenic diets, which is based on the direct inhibition of excitatory neurotransmission by decanoic acid.

Polyunsaturated fatty acids (PUFAs)

A classic KD consists mostly of long-chain saturated triglycerides; however, polyunsaturated fatty acids (PUFAs) may also decrease neuronal excitation and provide neuroprotection by inducing the opening of voltage-gated potassium channels through binding to a newly identified PUFA binding site in the open state of the channel [28]. However, a recent study suggests that a PUFA diet, or a KD supplemented with PUFA did not reduce spontaneous recurrent seizures (SRS) in a kainic acid (KA)-induced rat model of epileptogenesis compared to control diet or KD, respectively [29•].

PPARs and inflammatory pathways

Inflammatory pathways and oxidative stress play a major role in the pathophysiology of epilepsy. Of interest, KD therapy exerts a major inherent anti-inflammatory activity, which appears to be independent of PUFA's [30•]. The metabolically regulated transcription factors of the family of peroxisome proliferator activated receptors (PPAR) are involved in mitochondrial biogenesis and the control of genes involved in anti-inflammatory and anti-oxidant pathways. PPARα is activated by X-box binding protein 1 (XBP1), which is activated by hepatic serine/threonine-protein kinase/endoribonuclease inositol-requiring enzyme 1 (IRE1), which in turn functions as a nutrient sensor that regulates metabolic adaptation to fasting [31]. PPARγ is activated by fatty acids, such as decanoic acid, and might therefore mediate anti-inflammatory and anti-oxidant properties of the KD. A PPARγ antagonist abrogated KD-induced seizure protection in Kv1.1 knockout mice, a spontaneously epileptic mouse strain responsive to KD therapy [32], whereas an PPARγ agonist conferred seizure protection; in line with these findings KD therapy was ineffective in preventing seizures in PPARγ knockout mice [33•]. Since seizure suppression was associated with a PPARγ induced increase in PPARγ$_2$ expression, the authors of this study concluded that PPARγ$_2$ contributes to the anti-seizure effects of KD therapy.

K_{ATP} Channels

The ATP-sensitive potassium (K_{ATP}) channel is a sensor for the energy state of the cell and acts as a feedback system to restrict neuronal firing, when energy levels are low. K_{ATP} activity is determined by phosphoregulation of BAD, a protein with dual functions in apoptosis and glucose metabolism. Genetic manipulation of BAD designed to reduce glucose metabolism produced an increase in the activity of neuronal K_{ATP} channels and resistance to seizures *in vivo* [34]. In line with those findings, pharmacological inhibition or genetic manipulation of K_{ATP} function abrogated or attenuated ketone-induced neuroprotection and seizure resistance [34,35•]. In the substantia nigra K_{ATP} channels are activated under conditions that favor decreased mitochondrial respiration [36]. Together these findings suggest a tight mechanistic link between metabolism, BAD, K_{ATP} channel function and the control of neuronal excitation.

Neurotrophic factors

The neurotrophin brain derived neurotrophic factor (BDNF) is linked to both AMP kinase (AMPK) and mammalian target of rapamycin (mTOR signaling) and thought to be implicated in epileptogenesis. A KD, but not a high fat or a low fat diet, led to a circadian shift in the expression of brain and liver BDNF, suggesting that a KD might impact *(i)* circadian activities, and *(ii)* the expression of BDNF [37]. However, the significance of neurotrophic factors as possible mediators of KD therapy are not yet clear, because in healthy rats a KD reduced BDNF levels in striatum, but not hippocampus, whereas the astrocyte neurotrophic cytokine S100β was not affected in the brain [38].

Increased mitochondrial function and biogenesis

Mitochondrial function is crucial for brain function and several inborn metabolic disorders compromise mitochondrial function and trigger complex clinical phenotypes with seizures. KD therapy is known to improve mitochondrial function and is therefore considered for the treatment of metabolic seizure disorders. One of those conditions is brain aspartate-glutamate carrier (AGC1) deficiency, which affects a transporter that shuttles aspartate from mitochondria to the cytosol and indirectly promotes the transfer of nicotinamide adenine dinucleotide (NADH)-reducing equivalents into mitochondria, and which causes hypotonia, impaired psychomotor development, and seizures. A recent case report demonstrated that KD treatment was able to compensate for the metabolic defects with major improvement of clinical symptoms [39•]. Glucose and mitochondrial hypometabolism contributes to the pathology a Dravet Syndrome (DS), a catastrophic form of childhood epilepsy. A KD formulation rescued mitochondrial respiration and restored glucose metabolism in a zebrafish model of DS [40•]. The underlying molecular mechanism through which a KD in general, and ketone bodies in particular, improve mitochondrial function has been unraveled in a recent study that investigated the effects of ketone bodies on acutely isolated brain mitochondria from Kcna1 knockout mice [41••]. The authors of this study demonstrated that ketone bodies alone suppressed seizures in spontaneously epileptic Kcna1-null mice, restored impaired hippocampal long-term potentiation and learning in those mutants, and raised the threshold for calcium-induced mitochondrial permeability transition (mPT). Importantly, the targeted deletion of the cyclophilin D subunit of the mPT complex uncoupled the effects of ketone bodies on mPT, while mPT was directly related to the antiseizure effects of ketone bodies; therefore, the direct link between ketone bodies, mPT, and seizure control indicates a mechanistic explanation for the antiseizure effects of KD therapy [41].

Oxidative stress

Among a multitude of detrimental downstream pathways, oxidative stress leads to the formation of reactive lipid fragments that can further aggravate tissue damage. Isotope labelling experiments have shown that KD therapy induces cytochrome P450 4A-dependent ω- and ω-1-hydroxylation of reactive lipid species, a novel mechanism that might contribute to the anti-inflammatory properties of KD therapy [42].

Protein restriction

It needs to be kept in mind that a strict KD regimen not only restricts the supply of carbohydrates, but also of proteins. Protein restriction itself has been shown to enhance the production of the endocrine signal fibroblast growth factor 21 (FGF21) in the liver [43]. FGF21 in turn can increase glucose uptake by adipocytes and reduce blood glucose levels, an additional beneficial effect that might be attributable to low protein content in certain KDs.

Lactate dehydrogenase

The astrocyte to neuron lactate shuttle is a major component of a metabolic route that supplies the neuron with alternate sources of energy. Lactate dehydrogenase (LDH) is a metabolic enzyme mediating this lactate shuttle and needed to supply neurons with glucose-derived energy (via lactate). In a seminal landmark study Tsuyoshi Inoue's group demonstrated that the inhibition of LDH hyperpolarizes neurons and suppresses seizures [44••]. Remarkably, this enzyme was also found to be a molecular target of stiripentol, a clinically-used antiepileptic drug for Dravet syndrome [44••]. These findings are remarkable and suggest that inhibition of this metabolic pathway can mimic the effects of KD therapy, and might lead to the development of a 'KD in a pill'.

Disease modifying and epigenetic mechanisms

A series of recent data suggests that KD therapy exerts disease modifying effects in epilepsy and that epigenetic mechanisms might be involved. Strikingly, KD therapy was found to postpone disease progression, delay the onset of severe seizures and to increase the lifespan of Kcna1-null mice, a model of progressive epilepsy and sudden unexpected death in epilepsy (SUDEP) [45••]. A disease modifying epigenetic mechanism of KD therapy is supported by findings that a predominant increase of DNA methylation is associated with chronic epilepsy in the rat and that KD therapy attenuated seizure progression and ameliorated DNA methylation mediated changes in gene expression [46]. A subsequent study showed that a transient KD therapy restored normal adenosine levels and global DNA methylation levels in epileptic rats that were otherwise adenosine deficient and hypermethylated; importantly, transient KD therapy reduced seizure activity long-term, even after diet reversal to control diet [47••]. Because KD therapy increases adenosine [47,48] and because adenosine blocks DNA methylation [49] it is likely that the KD exerts its disease modifying effects through an adenosine-dependent epigenetic mechanism.

Gut microbiome

The gut microbiome is increasingly recognized to play a major role for brain health. A recent study found that KD feeding in the BTBR mouse model of autism resulted in anti-microbial effects and a compositional remodeling of the gut microbiome [50••]. Although the underlying mechanisms remain enigmatic, this is a significant finding suggesting a much broader systemic effect of KD therapy.

Conclusion

The ketogenic diet combines several mechanisms that together reduce neuronal excitability. The identification of specific mechanisms may lead to the development of treatments in which a strict ketogenic diet might be replaced by dietary supplements. The identification of disease-modifying properties of KD therapy may offer hope for long-lasting therapeutic outcomes even after discontinuation of the diet.

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Key points

- The antiepileptic effects of ketogenic diet therapy are based on a combination of multiple beneficial mechanisms.
- Certain lipids, such as medium chain fatty acids, have their own independent anticonvulsant effects that may boost the efficacy of KD therapy, or that may lead to replacement therapies.
- Decanoic acid controls seizures through direct AMPA receptor inhibition.
- Drugs targeting lactate dehydrogenase reduce seizures through inhibition of a metabolic pathway.
- KD therapy exerts disease modifying, antiepileptogenic effects that are based on an epigenetic mechanism.