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Harnessing the Power of Metabolism for Seizure Prevention: Focus on Dietary Treatments

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Abstract

The continued occurrence of refractory seizures in at least one-third of children and adults with epilepsy, despite the availability of almost 15 conventional and novel anticonvulsant drugs, speaks to a dire need to develop novel therapeutic approaches. Cellular metabolism, the critical pathways by which cells access and utilize energy, is critical for normal neuronal function. Furthermore, mounting evidence suggests direct links between energy metabolism and cellular excitability. The high-fat, low-carbohydrate ketogenic diet has been used as a treatment for drug-refractory epilepsy for almost a century. Yet, the multitude of alternative therapies to target aspects of cellular metabolism and hyperexcitability is almost untapped. Approaches discussed in this review offer a wide diversity of therapeutic targets that might be exploited by investigators in the search for safer and more effective epilepsy treatments.

Keywords

epilepsy; metabolism; dietary treatments; ketogenic diet; calorie restriction; 2-deoxy-D-glucose; mTOR; anaplerosis

1. Introduction

Epilepsy is one of the most common neurological diseases but despite major advances in drug development, 20-30% of patients have seizures that are not controlled by the first two medications prescribed [1-4]. This gap in medication efficacy is a significant challenge in clinical epilepsy care and indicates the need for new strategies to better treat the underlying pathological process of epilepsy [5]. For patients who do not have a lesion that can be resected surgically (i.e., multifocal epilepsy or certain epilepsy syndromes of childhood), dietary therapy remains an underutilized but highly effective option.

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The beneficial effect of fasting on seizure control was noted at the time of Hippocrates [6]. In order to mimic the beneficial effects of fasting on seizures, a high-fat, low-carbohydrate ketogenic diet was developed at the beginning of the last century [6]. To this day, the ketogenic diet still is used to treat patients with epilepsy that is refractory to medicines (i.e., "drug-resistant" or "medically intractable"). Despite its clinical success (discussed below), there remains a lack of a clear mechanistic understanding of how metabolism can be manipulated to prevent recurrent unprovoked seizures. Over time, a number of other dietary and pharmacologically-based metabolism interventions have been developed in an attempt to mimic the effects of the ketogenic diet while providing an easier regimen for patients and their families to follow. A mechanistic understanding of how the ketogenic diet works also would allow clinicians to optimize the diet's efficacy while minimizing adverse consequences (Table 1). Implementation and maintenance of the ketogenic diet require the involvement of a dietician familiar with its management, and such expertise may not be available in some medical centers. Increasing the ease of use of the diet also might increase its accessibility to patients. From a scientific perspective, elucidating these mechanisms also would likely improve our understanding of the role of how seizures recur and may provide key insights into neuronal pathophysiology. Finally, mechanism-based studies also may identify new pharmacological antiseizure targets.

2. Specific metabolic treatments for epilepsy

2.1 Ketogenic diet

2.1.1. Background—Patients consuming a high-fat, low-carbohydrate diet metabolize the fats via mitochondrial fatty acid oxidation into the main ketone bodies (i.e., β-hydroxybutyrate, acetoacetate, and acetone), which then are filtered by the kidneys, resulting in ketonuria [7]. Blood-borne ketone bodies circulate to regions of high energy demand (e.g., brain, muscle), supplying these tissues with an alternative energy source to carbohydrates. Despite the ketogenic diet's name, ketone bodies are not necessarily the primary mechanism of its antiseizure action (see below) [6].

2.1.2. Clinical efficacy—There are three main indications for clinical use of the ketogenic diet. First, patients with mutations in the SLC2A1 gene have a decreased ability to transport glucose from the blood into the cerebrospinal fluid (i.e., GLUT-1 deficiency), resulting in seizures, movement disorders, and developmental delays of varying severity [8]. The ketogenic diet is thought to circumvent this 'block' by providing 2-carbon equivalents to the tricarboxylic acid (TCA) or Krebs cycle, allowing nonglycolytic production of ATP [9]. Second, patients with pyruvate dehydrogenase deficiency can have seizures and benefit from the ketogenic diet for analogous reasons [10]. Third, as a treatment for epilepsy, the ketogenic diet has been used for nearly a century in patients with medically intractable seizures but reports of its efficacy for this indication were largely anecdotal until approximately 20 years ago. Case series (some prospectively assembled) were summarized in a series of meta-analyses demonstrating the efficacy of a ketogenic diet. Methodological concerns about case series have been outlined elsewhere; it is particularly challenging to blind observers involved in ketogenic diet clinical studies [11]. The first meta-analysis showed that 16% of children had a complete cessation of seizures and 56% of children had a >50% reduction in seizures, comparable to most standard medicines (keeping in mind that most patients consuming a ketogenic diet have failed >5 medications before trying the diet) [12]. A different meta-analysis showed an odds ratio of 2.25 (95% confidence interval 1.69-2.98) for a >50% reduction in seizures [13]. The most convincing data demonstrating the efficacy of the ketogenic diet come from a randomized controlled study that showed a >50% reduction in seizures in 38% of children on the ketogenic diet vs. 6% in the control group (who continued their anticonvulsants) over a 3-month period [14]. Most of these

studies were based on ketogenic diets using primarily long-chain fatty acids but diets based on highly ketogenic medium chain triglycerides have shown similar efficacy [15-17]. The main difference between long-chain and medium-chain fat diets is the occurrence of gastrointestinal-related side effects, with constipation being especially common with long-chain fat diets and diarrhea a frequent adverse effect of medium-chain fat diets [11]. To summarize, the clinical antiseizure efficacy of ketogenic diets has been established. Another trial used a novel strategy (reversal of ketosis with an oral glucose solution) in a randomized, blinded controlled study [18]. The primary outcome measure, seizure frequency, did not achieve significance, probably due to an underestimation of the amount of glucose needed to reverse ketosis.

While the ketogenic diet is effective in a broad spectrum of drug-resistant epilepsies, the question has arisen as to whether it might afford particular benefit in specific epilepsy syndromes, which could then lead to mechanistic hypotheses about the how the diet works [19]. One relevant example is Dravet syndrome [20-23]. Most cases of Dravet syndrome are associated with mutations in the SCN1A gene, which encodes a subunit of the sodium channel [24]. The mutation seems to preferentially affect inhibitory interneurons, leading to reduction of inhibition in neuronal circuits prone to seizure generation [25]. Clinically, Dravet syndrome typically begins with a prolonged febrile seizure in the first year of life, followed later in childhood by medically intractable seizures, developmental delays, and movement disorders including myoclonus, with further neurological deterioration into adulthood [26]. In case series, a ketogenic diet led to improved seizure control in slightly over half of patients with Dravet syndrome, with some patients becoming seizure-free [20, 21, 23]. Similar findings have been shown in mice harboring mutations in *SCN1A,* in which two weeks of ketogenic diet treatment led to an increased latency to onset of generalized convulsions induced by flurothyl [27]. These experiments create an opportunity for mechanism-based studies in Dravet syndrome.

2.1.3. Putative mechanisms

2.1.3.1. Approaches to studying mechanisms: A wide variety of experimental approaches have been utilized to study how the ketogenic diet and other dietary therapies work. Broadly, these can be divided into in vitro systems using brain slices, cultured neurons or other reduced preparations, and whole animals. In vitro systems allow investigation of direct effects of compounds on cellular excitability, while whole animals are used to assess the effect of ingested or administered agents on seizure threshold as well as safety issues. Each approach has advantages and disadvantages, depending on the specific information sought [28]. In the sections that follow, studies of epilepsy diet mechanism that employ both approaches are considered, but first, we discuss an alternative test of seizure susceptibility to address the question: Does the ketogenic diet have a similar profile to standard anticonvulsant drugs on acute seizure tests [7]?

Currently, candidate anticonvulsants currently are tested in a panel of tests in the Anticonvulsant Screening Program (ASP) at the National Institutes of Health (NIH) [29]. Until recently, the initial screen consisted of the $GABA_A$ receptor antagonist pentylenetetrazol (PTZ) and the maximal electroshock test (MES). The PTZ and MES tests are used to screen anticonvulsant compounds against generalized tonic-clonic and myoclonic seizure susceptibility, via chemical and electrical means, respectively. Generally speaking, drugs with similar mechanisms of action have a similar pattern of protection against certain convulsants and lack of protection against others (i.e., comparable acute seizure test profiles). For example, phenytoin and lamotrigine inhibit activity of voltage-gated sodium channels; both work in the MES test but not in the PTZ test [30-32].

In a series of experiments designed to test the effects of the ketogenic diet in rodents, mice (rather than rats) were chosen as the experimental subjects based on the goal of eventually testing the paradigm using genetically-modified animals. Although the ketogenic diet protects against seizures induced by PTZ in rats, it does not protect against PTZ-induced convulsions in mice [33-36]. Results using MES have been mixed, partly because this test is performed differently with a dietary treatment (i.e., with a limited dose range), versus an injectable drug (i.e., in which doses are widely varied in order to determine an ED_{50}). Thus, there was a need for an easily-administered screening test with the capability of rapid throughput that would demonstrate the ketogenic diet's anticonvulsant effects in mice – an effect that has been already demonstrated clinically. The 6 Hz electroshock test was used in the 1950s but lost favor as a screening tool because of its inability to demonstrate the anticonvulsant effects of phenytoin [32]. Nonetheless, the 6 Hz electroshock test was recently re-introduced into the ASP because it demonstrated anticonvulsant effects of levetiracetam, whereas this drug did not exert protective effects in the PTZ or MES tests [29, 32]. The 6 Hz electroshock test also demonstrated the anticonvulsant effects of a ketogenic diet in mice [37], a finding that has been confirmed by other investigators [34]. Furthermore, the ketogenic diet had an acute seizure test profile that was distinct from other anticonvulsants, suggesting that its mechanism of action is unique.

2.1.3.2. Inhibitory neurotransmission: Ultimately, changes in neuronal excitability are due to alterations in excitatory or inhibitory neurotransmission, which is the rationale for investigating the role of neurotransmitters in ketogenic diet mechanisms. Ketogenic diets may exert their antiseizure effects by increasing neuronal inhibition. This effect may occur via a variety of mechanisms, including alteration of synaptic γ-aminobutyric acid (GABA) levels, GABA metabolism, GABA receptors, or some other alteration in GABAergic neuron function. One study of children with epilepsy consuming a ketogenic diet showed an increase in cerebrospinal fluid levels of the inhibitory neurotransmitter GABA [38]. Interestingly, patients who responded best to the ketogenic diet had higher cerebrospinal fluid (CSF) levels of GABA at baseline, which raises the possibility that CSF GABA levels may serve as a biomarker that would predict successful treatment with the diet. Ketone bodies increase the GABA content in rat brain synaptosomes [39]. However, differences in GABA levels in rodent brains have not been demonstrated during ketogenic diet treatment [40-44]. Measurement of regional GABA concentrations might mask more subtle increases in GABA synthesis during ketogenic diet consumption; such increases in GABA synthesis were demonstrated using isotope-labeled amino acids [42]. However, ketone bodies do not appear to change GABA receptor currents in cultured neurons and magnetic resonance spectroscopy studies of brain GABA in patients have been inconclusive [45-47]. Direct application of ketone bodies at physiologically relevant concentrations did not alter GABA-evoked inhibitory currents in cultured hippocampal neurons [45]. $GABA_A$ receptors expressed in *Xenopus* oocytes show increased activity when incubated with 10 mM β–hydroxybutyrate or 50 mM acetone but not at lower ketone body concentrations seen typically in children on a ketogenic diet [32, 33]. In one study, rats consuming a ketogenic diet showed elevated levels of the GABA-synthesizing enzyme glutamic acid decarboxylase (both mRNA and protein) but the translational relevance of this finding is unclear because the increase was noted only in regions not thought to be involved in the generation of seizures [48]. Given their importance in neonatal brain metabolism [49], ketone bodies may play a role in neonatal GABA-mediated neurotransmission. However, the specifics of such an interaction and their applicability to ketogenic diets in older children are debated (discussed in [50]). The role of GABA neurotransmission in the ketogenic diet remains an area of active investigation.

Another way in which ketone bodies may directly dampen neuronal excitability is by activation of inwardly rectifying ATP-sensitive potassium (K_{ATP}) channels. These channels

contribute to neuronal hyperpolarization when intracellular ATP levels fall. In GABAergic neurons of the substantia nigra pars reticulata, considered to be a “gate” that prevents seizure generalization, application of ketone bodies slowed neuronal firing rate, an effect reversed by $GABA_B$ receptor antagonists [32, 33]. Therefore, it is possible that ketone bodies exert inhibitory effects by altering $GABA_B$ receptor function. Other factors that influence metabolism may affect K_{ATP} channels, as well. Dentate granule neuron K_{ATP} channel activity is increased when the protein BAD (Bcl-2-associated death promoting protein), which plays roles in both apoptosis and metabolism, is modified or deleted, resulting in decreased glucose metabolism [51]. Metabolism of β-hydroxybutyrate is increased in neurons and astrocytes in these genetically modified mice. The same modifications of BAD increase resistance to seizures induced by pentylenetetrazol and kainic acid. K_{ATP} channels also are an attractive target to study because they serve as a link between metabolism (via ATP levels) and neuronal firing. Data on brain ATP levels have been somewhat conflicting, with some studies showing no change after ketogenic diet treatment and other studies demonstrating an increase in levels [44, 52-55]. Importantly, K_{ATP} channels usually are thought to be activated by low, rather than high, levels of ATP [56]. However, in hippocampal CA3 neurons cultured in low glucose media, K_{ATP} channels may be activated via adenosine A_1 receptors, which in turn are activated by adenosine released from the dephosphorylation of ATP released by pannexin-1 hemichannels [57]. The translational relevance of pannexin-1 hemichannel-mediated K_{ATP} activity is somewhat unclear because patients consuming a ketogenic diet have normal fasting morning blood glucose levels, while blood glucose levels in rodent models have shown varied results levels [34, 58, 59]. Nonetheless, adenosine receptors appear to be necessary for the ability of the ketogenic diet to inhibit spontaneous electrographic seizures in adenosine A_1 receptor knockout mice [60]. Similarly, mice lacking dopamine-β-hydroxylase (i.e., an enzyme in the inhibitory norepinephrine synthesis pathway) are not protected from seizures induced by the volatile convulsant flurothyl [61]. The necessity of norepinephrine synthesis also has been seen with other anticonvulsants such as phenobarbital[62]. Although multiple inhibitory neurotransmitters appear to be necessary for seizure protection during a ketogenic diet, the specific contribution made by each neurotransmitter system (and possibly, an interaction between them) remains unclear.

2.1.3.3. Excitatory neurotransmission: Patients in the study of cerebrospinal fluid neurotransmitters did not have significantly lower cerebrospinal fluid levels of aspartate and glutamate (compared to the pre-diet baseline), although these levels were significant in children under the age of 5.5 years [38]. Decreased levels of excitatory amino acids are unlikely to be the sole mechanism of the ketogenic diet’s anticonvulsant action, since only some rodent studies have shown decreases in aspartate or glutamate [41, 42, 55, 63]. Ketone bodies did not exert an effect on NMDA or AMPA receptor synaptic currents in hippocampal slices or cultured cortical neurons [45, 47]. The ketogenic diet does not alter levels of the glutamate transporter EAAC1 in rat neocortex or hippocampus, making it less likely that increased glutamate clearance decreases seizures in rodents consuming the diet [64]. A novel potential mechanism for the effect of ketone bodies on excitatory neurotransmission was shown by the ability of acetoacetate to compete with chloride ions for allosteric regulation of glutamate uptake into synaptic vesicles (mediated by the glutamate transporter, VGLUT) [65]; therefore, ketone bodies might alter the metabolic state of the neuron and thus its ability to release glutamate. Acetoacetate also inhibited glutamate release in cultured neurons and hippocampal slices, as well as in rats exposed to the potassium channel blocker 4-aminopyridine. However, the concentration of acetoacetate found to be most effective in the animal experiments was 10 mM, which is nearly two orders of magnitude higher than cerebrospinal fluid levels of acetoacetate in children consuming a ketogenic diet (*in vitro* data showed that submillimolar concentrations of acetoacetate

altered neuronal firing, however) [66]. In summary, ketogenic diets do not appear to directly induce a significant decrease in levels of excitatory neurotransmitters but ketone bodies at high concentrations may decrease glutamate levels in the synaptic cleft. The effects of the ketogenic diet on excitatory neurotransmitter receptor subunit expression, trafficking, and physiology remain underexplored.

2.1.3.4. Mitochondria and metabolism: Changes in metabolism pathways that reside in the mitochondrial matrix (i.e., TCA or Krebs cycle) may serve as a link between metabolism and neurotransmitters [67]. Metabolism of fats to ketone bodies may increase activity in the initial reactions of the Krebs cycle, which may in turn increase levels of α–ketoglutarate [54]. In turn, increased α–ketoglutarate should increase glutamate synthesis (catalyzed by aspartate transaminase), which has been demonstrated experimentally [42]. Interestingly, levels of total brain glutamate are not elevated, implying that glutamate metabolism is increased [42, 55]. Therefore, mitochondria may provide a link between ketogenic diet effects on both excitatory and inhibitory neurotransmission [68].

In specific disease models associated with mitochondrial degeneration or depletion, ketogenic diets increase mitochondrial biomass or function [52, 69]. Ketogenic diets also increase the transcription of subunits involved in oxidative phosphorylation (OXPHOS), although it is unclear whether this directly leads to an increase in ATP production [55]. In considering mitochondrial electron flow through OXPHOS proteins, it is interesting to note that ketogenic diets also increase the expression of brain mitochondrial uncoupling proteins [70], implying that an electron “leak” may be an alternative explanation in studies showing no difference in ATP levels (discussed previously).

2.2 Intermittent fasting and calorie restriction

As noted previously, the ketogenic diet was designed to mimic the beneficial effects of fasting on seizure control. This has led to the commonly-held belief that calorie restriction and ketogenic diets have identical anticonvulsant mechanisms [71, 72]. Daily calorie restriction protects against seizures in one mixed genetic/environmental model of epilepsy, EL mice [73]. Another form of calorie restriction, intermittent fasting (i.e., alternating *ad lib* feeding days with fasting days), protects against cell death after exposure to systemic or intrahippocampally-delivered kainic acid [74-76]. The efficacy of the ketogenic diet requires some degree of calorie restriction in some rodent models [77, 78] and there is no difference in the expression of glutamic acid decarboxylase (-65 & -67 isoforms) between rats fed a ketogenic diet and those that had calories restricted [48]. However, differences were noted between a calorie-restricted ketogenic diet and calorie-restricted normal rodent chow in the maximal dentate activation test (an electrophysiological test that assesses the excitability or burst-firing propensity of dentate granule neurons) [79, 80]. Importantly, both of those diets involved some form of calorie restriction. Thus, it was unclear whether the antiseizure effect of the ketogenic diet was simply due to restriction of calorie intake. To address this question, the ketogenic diet was compared to intermittent fasting (for 11-14 days) in a battery of acute seizure tests based on those used in the ASP. If the two treatments had identical mechanisms of action, it would be predicted that the treatments would protective in the same tests. Surprisingly, the two interventions had opposite effects in the acute seizure tests. On the 6 Hz electroshock test, mice that were fasted intermittently had lower seizure thresholds than those treated with the ketogenic diet. Upon exposure to kainic acid to induce status epilepticus, mice fasted intermittently had lower overall seizure scores than mice fed normal chow *ad lib* or a ketogenic diet, despite being matched for body weight [81]. These data challenge the assumption that the ketogenic diet and intermittent fasting share identical anticonvulsant mechanisms and suggest that while both exert anticonvulsant actions, the two

dietary protocols need to be considered as distinct entities. We are not aware of any modern literature examining the clinical efficacy of intermittent fasting.

2.3 Modified Atkins Diet and Low Glycemic Index Treatment

The modified Atkins diet (MAD) and low glycemic index treatment (LGIT) are alternative dietary regimens that have proven useful in the management of refractory seizures in patients in whom the classic ketogenic diet is not feasible. The MAD differs from the classic ketogenic diet in that it is less restrictive with regard to protein and calorie limitations, with its efficacy thought to be related to the high-fat intake and more modest carbohydrate restriction. The LGIT employs foods that raise blood glucose less abruptly and to a lesser degree than a typical diet. Further details about the clinical use and efficacy of these regimens are available elsewhere [82, 83]. As of this writing, the MAD and LGIT have not been studied in animal models, though additional mechanistic insights could be obtained by examining the effect of increasing protein content (i.e., similar to MAD) or altering the carbohydrate content in a more conventional diet to mimic the LGIT.

2.4 Glycolytic Inhibition (2-deoxy-D-glucose and fructose-1,6-bisphosphate) and Anaplerosis

Since ingestion of a small amount of carbohydrate by a patient on the ketogenic diet results in rapid reversal of seizure control [84], the hypothesis arose that carbohydrate restriction could protect against seizures [85, 86]. The ketogenic diet bypasses glycolysis by utilizing ketones as the main energy source. Therefore, it was hypothesized that glycolytic inhibition might protect against seizures.

2-Deoxy-D-glucose (2DG) is a glucose analog that differs from glucose only by substitution of a single oxygen atom in the 2′-position. 2DG cannot be metabolized and inhibits glycolysis by blocking the enzyme phosphoglucose isomerase, thereby preventing the conversion of glucose-6-phosphate to fructose-6-phosphate. 2DG has potent anticonvulsant and antiepileptic actions in several animal models, including kindling, audiogenic seizures in Fring's mice, and the 6 Hz electroshock test [87, 88]. *In vitro,* 2DG reduces hyperexcitability in hippocampal CA3 neurons in slices exposed to elevated extracellular K^+, bicuculline, 4-aminopyridine or metabotropic Group 1 agonists [89].

Both acute and chronic anticonvulsant effects of 2DG have been documented. Acute anticonvulsant effects of 2DG *in vitro* and *in vivo* against both ictal and interictal activity suggest that 2DG may act directly at the synaptic or membrane levels through mechanisms independent of altered gene expression [88]. Acute effects of 2DG could be related to rapid-onset metabolic or electrophysiological consequences of glycolytic inhibition leading to reduction of network synchronization. For example, 2DG could influence neuronal excitability by alteration of systemic lipid metabolism, mitochondrial function, or the phosphorylation state of $GABA_A$ receptor subunits [90]. In whole-cell recordings of hippocampal CA3 neurons, acute application of 2DG suppressed spontaneous excitatory postsynaptic currents (EPSCs) after transient epileptic activity induced by elevated extracellular potassium or metabotropic Group 1 agonists, but not in normal slices, suggesting activity-dependent effects of glycolytic inhibition [91]. These and other potential acute mechanisms are currently under study.

Chronic antiepileptic effects of 2DG are related to the molecular regulation of genes for brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine kinase B (trkB). Repression of both BDNF and trkB expression are required for kindling progression [92]. 2DG suppresses seizure-induced increases in BDNF and trkB, mediated by the transcriptional repressor neuron restrictive silencing factor (NRSF) and its nicotinamide

adenine dinucleotide (NADH)-sensitive co-repressor carboxy-terminal binding protein (CtBP). NRSF and CtBP act at the promoter regions of BDNF and trkB genes [87]. Glycolysis and glucose production are increased during seizures, leading to elevated levels of NADH. NADH elevation causes dissociation of CtBP from NRSF, decreasing transcriptional repression and resulting in increased expression of BDNF and trkB. In the presence of 2DG, which reduces NADH levels as a consequence of glycolytic inhibition, the NRSF-CtBP complex maintains repression of BDNF and trkB, and kindling progression is slowed [87, 93]. It is likely that the ketogenic diet and 2DG work by different mechanisms, since the ketogenic diet retards kindling development in mice with NRSF conditionally knocked out [94].

These chronic anticonvulsant and antiepileptic effects of 2DG make it a viable candidate for clinical trials with the potential for modification of both seizure susceptibility and disease progression, assuming 2DG can be shown to be nontoxic. A favorable safety profile has been reported with regard to cognitive performance [86, 92], though a recent pathological evaluation of chronic oral 2DG ingestion in two rat strains reported cardiotoxic effects with vacuolization of cardiac myocytes and reduced lifespans [95]. While it is difficult to compare oral and parenteral 2DG doses, as well as interspecies differences, further studies are needed to assess reversibility of histological effects observed with 2DG treatment.

Another glycolytic intermediate, fructose-1,6-bisphosphate (FBP), exerts acute anticonvulsant activity in several seizure models in adult rats including kainate, pilocarpine, pentylenetetrazol, and kindling [96, 97]. In fact, FBP exhibited greater anticonvulsant efficacy than 2DG, KD, and valproate. FBP increases glucose flux from glycolysis into the pentose phosphate pathway (PPP). NADPH generated in the PPP reduces glutathione, which possesses anticonvulsant activity. Thus, FBP may exert an endogenous anticonvulsant (and perhaps anti-oxidant) action [98], though the precise mechanism has not yet been determined.

A final dietary approach to epilepsy relates to the observation that seizures cause a deficiency in TCA intermediates (particularly α-ketoglutarate and oxaloacetate), leading to increased excitability and possibly to further seizures. It has been conjectured that “refilling” these deficient compounds, a process called “anaplerosis”, might oppose seizure generation. An example of an anaplerotic compound is triheptanoin, which has recently been investigated in both acute and chronic seizure models [99]. Mice fed triheptanoin exhibited resistance to development of seizures by corneal kindling, and triheptanoin feeding increased PTZ seizure threshold in chronically epileptic mice that had undergone status epilepticus 3 weeks before PTZ testing [99]. Therefore, like 2DG, anaplerotic compounds alter both acute and chronic seizure susceptibility. Anaplerosis represents a novel approach that expands the potential metabolic modifications that could be anticonvulsant or antiepileptic. Together, results from studies of the KD, 2DG, FBP, and anaplerosis suggest that modification of metabolic pathways such as glycolysis could represent a novel mechanism for epilepsy management.

2.5 mTOR Inhibition

2.5.1. Clinical efficacy—Tuberous sclerosis complex is a genetic disorder of cell growth and differentiation that involves dysplasia or benign tumor formation in several organs including kidney, heart, and brain. Specific neuropathological findings include cortical tubers, which are hamartomatous collections of abnormal neurons and glia and subependymal giant cell nodules that have a propensity to become astrocytomas. Neurological consequences of tuberous sclerosis complex include seizures (frequently medically intractable), autism and related behavior problems, and intellectual disability [100-103]. Tuberous sclerosis complex is caused by mutations in the TSC1 or TSC2 gene,

which encode key proteins upstream of the serine-threonine protein kinase mammalian target of rapamycin (mTOR) [102]. This pathway is one of the master integrators of metabolic signaling, with upstream regulation by the insulin receptor and glucose levels (via adenosine monophosphate kinase) and downstream effects on translation and lipid metabolism [104]. Patients with mutations in *TSC1* or *TSC2* have increased mTOR activity, leading to decreased constraint on cell growth and tumor formation in multiple tissues. Everolimus, an inhibitor of mTOR activity, decreases seizure frequency in patients with tuberous sclerosis and limits progression of the size of subependymal giant cell astrocytomas [105]. The ketogenic diet is another effective treatment for intractable epilepsy in patients with tuberous sclerosis [103].

2.5.2. Putative mechanisms—Rapamycin, the canonical mTOR inhibitor, inhibits seizures in a mouse model of tuberous sclerosis [106]. Rapamycin also inhibits recurrent seizures after status epilepticus induced by kainic acid or pilocarpine in rats that do not harbor mutations in the mTOR pathway [107, 108]. Rapamycin treatment also suppressed behavioral spasms in the doxorubicin/lipopolysaccharide/p-chlorophenylalanine model of infantile spasms [109] and decreased susceptibility to kainic acid-induced seizures in a juvenile rat hypoxia model [110]. These data raise the possibility that mTOR plays a wider role in seizure perpetuation, beyond tuberous sclerosis complex. However, mTOR's effect may not be universal because rapamycin (or other rapamycin analogs, known as "rapalogs") does not prevent recurrent seizures after pilocarpine-induced status epilepticus in mice, nor does it prevent acute seizures in the rat hypoxia model (without kainic acid exposure) [110, 111].

The specific mechanism by which mTOR inhibitors prevent seizures is not entirely clear because *in vitro* studies of rapamycin have not shown a consistent decrease in baseline or provoked neuronal firing [112, 113]. However, mTOR activity is necessary for synaptic plasticity, including long term potentiation and long term depression [114-117]. This requirement may be a reflection of the role played by mTOR activity in the development and maintenance of dendrite morphology [112, 118-121].

Interestingly, ketogenic diets decrease mTOR activity in rats [122]. Ketogenic diets differ from rapamycin in their acute antiseizure test profiles but it is unknown whether they have similar antiseizure mechanisms in models of chronic epilepsy [123]. Nonetheless, the studies outlined here suggest that the role of mTOR inhibition in seizure prevention deserves further study.

3. Concluding thoughts

Despite the availability of at least ten new anticonvulsant medications in the past two decades, the percentage of patients with medically refractory epilepsy has not changed. Even in the present day, up to one-third of epilepsy sufferers continue to have seizures as well as disabling co-morbidities such as cognitive dysfunction and neuropsychiatric disorders. Therefore, the need for alternative and effective epilepsy treatments is dire. The metabolic approach to seizure management represents is both novel and compelling, with several such therapies providing seizure control as well as improved quality of life and fewer side effects (Fig. 1). These considerations make understanding of the mechanisms by which dietary and metabolic approaches work a major research priority [124]. Studies such as those outlined above are just beginning to touch the surface of the panoply of mechanisms that could improve epilepsy through alteration of energy utilization.

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Highlights for review

1. New data suggest direct links between energy metabolism and neuronal excitability.
2. Therapy targeting cellular metabolism and hyperexcitability is relatively untapped.
3. Approaches discussed here offer a variety of potential therapeutic targets.

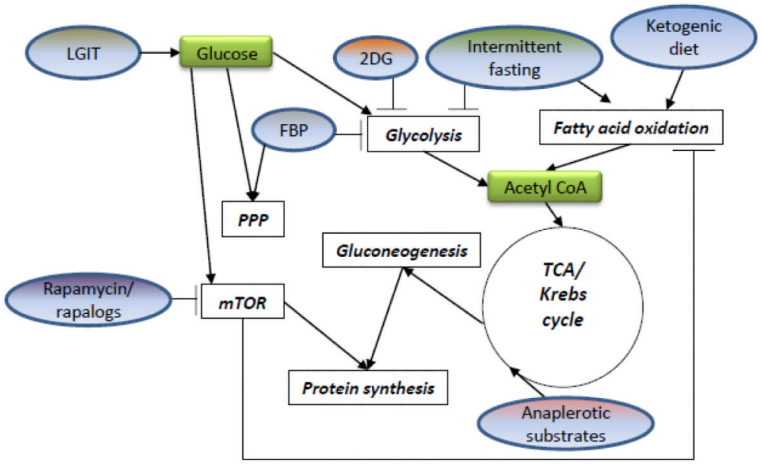

Figure 1. Summary of metabolism-based therapies and their sites of action

Different types of metabolism-based antiseizure treatments (dietary and pharmacological) affect metabolic pathways at different sites. Some processes are affected by more than one type of treatment (i.e., glycolysis, fatty acid oxidation). “Rapalogs” are analogs of rapamycin, modified to decrease toxicity and/or increase specific activity. Specific interventions are shown in ovals; metabolic processes are shown in clear rectangles; and specific metabolites are shown in green rectangles. FBP, fructose-1,6-bisphosphate; LGIT, low glycemic index treatment; mTOR, mammalian target of rapamycin; PPP, pentose phosphate pathway; TCA, tricarboxylic acid cycle; 2DG, 2-deoxy-D-glucose.

Table 1

Reasons to explore the mechanism of metabolism-based antiseizure therapies

Optimize efficacy
Minimize adverse consequences Increase convenience
Increase accessibility
Improve understanding of epilepsy
Identify new anticonvulsant targets