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Review

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 pathway by which cells access and utilize energy, is essential 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.

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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 an epileptogenic 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.

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 who is 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 and 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].

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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

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 the children had a complete cessation of seizures, and 56% of the children had a >50% reduction in seizures, comparable to most standard medicines (keeping in mind that seizures in most patients consuming a ketogenic diet have failed to substantially improve with >5 medications before the diet is tried) [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 the 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 are tested in a panel of tests in the Anticonvulsant Screening Program (ASP) through 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 the 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