Published in final edited form as:

Brain Res. 2019 January 15; 1703: 26–30. doi:10.1016/j.brainres.2018.05.049.

Metabolism and Epilepsy: Ketogenic Diets as a Homeostatic Link

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Abstract

Metabolic dysfunction can underlie seizure disorders, and metabolism-based treatments can afford seizure control and promote homeostasis. This relationship between metabolism and the risk of sporadic seizures was observed historically with the clinical success of a low-carbohydrate, high-fat, ketosis-inducing ketogenic diet – a treatment that remains relevant today, and one that has been shown to be effective against medically refractory epilepsy. Mechanisms underlying the success of the ketogenic diet are a topic of intense research efforts – not only because of proven success in arresting treatment-resistant seizures, but also because recent evidence suggests that altering metabolism with a ketogenic diet enables a homeostatic state in the brain that is less excitable, and hence raises the threshold for seizure genesis. Metabolic therapy with a ketogenic diet has been shown to normalize a range of abnormal physiological and behavioral parameters and may also make the central nervous system more resilient to other insults or physiological stresses. Because the therapeutic ability of such a diet may be more limited than a drug because of a dose “ceiling”, investigations are underway to develop and test analogous or supplemental approaches. In addition, significant efforts have been made to demonstrate broader applications of metabolic therapy in promoting health and preventing disease, including conditions where epileptic seizures manifest in a comorbid fashion.

Keywords

epilepsy; seizures; metabolism; ketogenic diet; ketosis; homeostasis

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Overview/Introduction

The excessive synchronous neuronal activity that defines an epileptic seizure is an exaggeration of obligate ion channel activity associated with normal brain function. Thus, some epilepsies are caused directly by mutations in genes encoding cellular membrane-bound ion channel proteins. The aberrant function of such channels (a manifestation of so-called *channelopathies*) can causally lead to electro-clinical seizure activity. Unremitting seizures due to dysregulated ion channels can also cause significant brain damage and can even be lethal. This concept is simple and intuitive, especially since epilepsy has been considered traditionally as a disorder of abnormal cellular membrane excitability. Yet why are patients with known epilepsy-related channelopathies not in a constant state of seizure activity?

While there is no straightforward answer to this question, it reveals that there must be other factors that critically influence the distinct ictal and interictal states (and transitions between the two) that have been observed consistently in both humans and laboratory animal models of epilepsy. Indeed, epileptic seizures are defined as spontaneous (i.e., unpredictable) and recurrent. A better characterization, regardless of underlying etiology, is that seizure events are sporadic. Seizures appear spontaneous when precipitating factors are unknown, not monitored and/or not quantifiable.

The brain comprises a vast dynamic network of tens of billions of cells, which responds to fluctuating changes in the environment, and is susceptible to innumerable internal and external factors that can collectively generate a seizure – or prevent one from occurring. In some instances, a specific acute stimulus can trigger a seizure – e.g. flashing lights. However, in general, excessive neuronal activity arises from a complex, probabilistic, and largely occult set of variables. Some of these factors could come together to precipitate intermittent recurrent seizures in a susceptible and unstable network. Within this framework, identification and mitigation of the important dynamic physiological factors that increase seizure propensity, and leverage those that decrease probability, could reduce their episodic recurrence. Importantly, such an approach may potentially reduce co-morbidities, the need for aggressive medical treatment, or other disease symptomologies.

One of the physiological factors known to influence seizure susceptibility is cellular metabolism. Local metabolic dysregulation is a hallmark of the epileptic brain, and clinical evidence dating back to the 1920s demonstrates that metabolism-based therapies (namely, the traditional high-fat, low-carbohydrate ketogenic diet; KD) can arrest or reduce seizures even when drugs fail (Wilder, 1921a; Wilder, 1921b). More recent evidence suggests that a metabolic therapy can also either prevent or reverse seizure progression (Freeman et al., 2006; Lusardi et al., 2015; Masino and Rho, 2012) and thus influence the disease process itself. Consistently, clinical investigators have reported that ~50% of patients with medically intractable epilepsy experience a 50% reduction in seizures while on the KD, and 10–20% of such patients – typically children – can maintain seizure freedom even after weaning from anti-seizure drugs and dietary restrictions (Caraballo et al., 2011; Freeman et al., 2006; Weimer-Kreul et al., 2017).

Clearly, metabolism is a major physiological variable that exerts direct control over cellular homeostasis and can play a pivotal role in the balance between seizure generation and seizure abatement. Here, we highlight promising mechanisms and the translational potential of metabolic therapies for reducing the probability of sporadic seizure activity and promoting brain health and stability.

Metabolic Therapy – Long Established Yet Still Emerging Treatment for Epilepsy

The link between metabolism and neuronal activity is well established, yet the relationships are complex and still poorly understood. Targeting metabolism per se has not yet been incorporated as an explicit mechanistic strategy in epilepsy experimental therapeutics. However, despite many decades of relative obscurity, clinical use of and research into mechanisms of the KD have experienced a major resurgence worldwide during the past ~20 years (Kossoff and McGrogan, 2005; Kossoff et al., 2015). In the epilepsy field, this shift is likely due to a combination of continued inadequacy of available therapies for up to 30% of patients who remain medically intractable, the rising popularity of diet-based approaches, new insights into underlying mechanisms of KD action, and increasing recognition that the KD and related metabolic therapies have clinical relevance and untapped potential in neurological disorders extending beyond epilepsy (Ruskin and Masino, 2012; Stafstrom and Rho, 2012).

The resurgence of interest in the KD was catalyzed initially by a remarkably successful case of pediatric epilepsy that received significant media attention. This spurred the formation of the Charlie Foundation for Ketogenic Therapies. The Charlie Foundation was a major sponsor of the first large-scale international symposium on the KD (held in Phoenix, AZ, 2008), and since then, a highly motivated group of international healthcare providers, clinical and basic researchers, clinical nutritionists and other stakeholders have gathered on a biennial basis to promote research, education and awareness of ketogenic therapies. These biennial meetings have catalyzed the steady growth of metabolic and ketogenic therapies, and while epilepsy is still the most common indication, emerging treatment opportunities include brain tumors, Parkinson's disease, Alzheimer's disease, traumatic brain & spinal cord injury, pain, multiple sclerosis, and autism spectrum disorder, among other medical conditions (Gasior et al., 2006; Kim et al., 2012; Prins et al., 2005; Ruskin et al., 2013, 2017a; Stafstrom and Rho, 2012; Streijger et al., 2013; Van der Auwera et al., 2005; Zhao et al., 2006; Zhou et al., 2007).

Currently, identifying treatments or supplements that promote or mirror the key mechanistic changes induced by the KD and its variants is an increasingly active area of investigation. It is well established that many patients have their seizures reduced or resolved very quickly – within days – and the majority show a clear clinical response within two weeks (Kossoff et al., 2008). It is remarkable that a change in metabolism reduces the risk of a sporadic seizure in a majority of patients who were refractory to other treatments. Further, it is intriguing to speculate that the KD may be more efficacious than anti-seizure drugs in patients with newly diagnosed epilepsy, but there are currently no informative data in this regard due the rarity of

first-line use of KD (Wang and Lin, 2013). Nevertheless, there is a credible rationale for metabolic therapy being at least as effective as drugs in this non-refractory population. All of this underscores the notion that metabolic factors can reduce the occurrence of sporadic and apparently “spontaneous” seizures in the clear majority of patients with epilepsy.

Mechanisms Underlying Metabolic Therapy for Epilepsy: Basic Science

Indeed, strong research collaborations are necessary to achieve a deeper understanding of how metabolic therapies can benefit epilepsy and potentially a broad range of neurological (and non-neurological) conditions. Substantial progress has been made in our understanding of the acute and chronic mechanisms underlying the efficacy of the KD since its clinical and scientific resurgence in the mid-1990's. Given clinical and experimental observations that the KD can block spontaneous recurrent seizures (and may even possess anti-epileptogenic activity), the myriad system-wide changes induced by a metabolic therapy, and the emerging evidence that the KD can impact a broad range of neurological and non-neurological conditions (Augustin et al., 2018; Gasior et al., 2006), it is no surprise that a plethora of mechanisms have been invoked by investigators worldwide. It is important to consider that key mechanisms may differ depending on the seizure condition itself, and may vary based on the clinical protocol or duration of diet administration. In this light, initial acute anti-seizure mechanisms may or may not overlap with those contributing to the lasting effects of metabolic therapy – whether solely neuroprotective and/or anti-epileptogenic (Lusardi et al., 2015). Evidence suggests that the acute metabolic effects occur rapidly, whereas in some cases seizure control and behavioral effects develop over time. This diversity of mechanisms and the potential for lasting benefits are increasingly appreciated as major strengths of a metabolic approach, and recent reviews provide comprehensive overviews of mechanisms underlying KD's effect in seizures and other disorders (Augustin et al., 2018; Boison, 2017; Gano et al., 2014; Rogawski et al., 2016).

Here, we focus on acute links between metabolism and excitability that can influence the spontaneous generation of seizures. Multiple postulated mechanisms mobilized by the KD have their roots in the immediate and hallmark effects of the KD: increased ketone bodies and reduced glucose in blood and cerebrospinal fluid (Courchesne-Loyer et al., 2017; Wang et al., 2017). Evidence also indicates that the KD increases levels or actions of ATP and adenosine – purines that are critical for metabolic stability (Deng-Bryant et al., 2011; DeVivo et al., 1978; Nakazawa et al., 1983; Zhao et al., 2006) and that act as endogenous anti-seizure agents (Kawamura et al., 2010; Kawamura et al., 2014; Masino et al., 2011), respectively. Other studies have shown increased levels of GABA following KD administration (Calderón et al., 2017; Dahlin et al., 2005; Nylen et al., 2008; Roy et al., 2015).

Elevated blood ketone levels represent the most consistent metabolic biomarker of adherence to the KD. Yet, there has been an enduring perception – founded on conflicting clinical and experimental data – that ketone levels do not correlate with clinical efficacy (Gilbert et al., 2000; Kossoff and Rho, 2009; van Delft et al., 2010). Indeed, dietary formulations designed to avert ketosis appear equally effective in seizure models as those that do (Dallérac et al., 2017). In contrast, ketosis has been shown to be necessary and sufficient for an anti-seizure

effect in a clinically relevant animal model of epilepsy (Kim et al., 2015), and has recently been shown in a prospective study to be inversely related to seizure activity in pediatric patients with medically intractable epilepsy (Buchhalter et al., 2017).

The mixed experimental and clinical results for direct effects of ketone bodies may be due to the inadequacy of focusing on one mechanism and/or the diversity of experimental and clinical conditions that have attempted to validate the role of ketone bodies in reducing seizures. The dynamics of ketone body levels *in vivo* – and what may be a non-linear relationship between blood ketone bodies and seizure suppression (Fraser et al., 2003; Karimzadeh et al., 2014; Kossoff et al., 2006) – further complicate a straightforward relationship between ketone body metabolism and seizure propensity. One suggestion is that the ratio of glucose to ketones may be a key factor (Meidenbauer et al., 2015), at least with respect to KD effects against malignant glioma, and an initial metabolomics analysis of cerebrospinal fluid from children with refractory epilepsy suggests that those who achieved complete seizure cessation had both higher ketones and lower glucose levels (Ruskin et al., 2017b).

At present, the long-standing question of whether ketone bodies, either alone or in combination, contribute mechanistically to KD actions remains unresolved. However, recent data support the growing recognition that ketone bodies are not merely substrates for energy production but also possess pleiotropic mechanistic properties that collectively may yield a net anti-seizure effect (Puchalska and Crawford, 2017; Simeone et al., 2018). Indeed, the most prominent ketone body augmented by the KD, β -hydroxybutyrate (BHB), has been shown to interact with multiple novel molecular targets such as the mitochondrial permeability transition pore, histone deacetylases, hydroxycarboxylic acid receptors on immune cells, and the NLRP3 inflammasome (Simeone et al., 2018). Taken together, there is growing clinical and experimental evidence that ketone bodies may in part mediate the anti-seizure effects of the KD.

The role of glucose in influencing brain activity and plasticity, and in preventing or promoting a seizure has been demonstrated clinically and experimentally. Evidence that a low or stable glucose level reduces seizure susceptibility is demonstrated clinically: a low-glycemic index treatment can be effective in reducing seizures without producing ketosis (for instance, Karimzadeh et al., 2014), and increased glucose levels can precipitate seizures (Huttenlocher, 1976; Masino et al., 2011). The impact of glucose is also observed experimentally whereby seizures are shown to vary with glucose levels (Huttenlocher, 1976; Meidenbauer and Roberts, 2014; Muzykewicz et al., 2009; Schwechter et al., 2003), and a low or stable glucose level may be necessary to reveal anti-seizure effects of a KD in some *in vitro* models (Kawamura et al., 2014). These findings suggest that high glucose levels commonly used *in vitro* may be masking some metabolic effects of the diet, and that clinically a low-glycemic index treatment may reduce spontaneous seizures even in patients who are not prescribed a special metabolic therapy.

Adenosine has long been a clear link between metabolism and neuronal excitability. It is well known to be neuroprotective, to promote homeostasis and to hyperpolarize and stabilize the cellular membrane potential. Evidence suggests that a KD promotes activation of

inhibitory adenosine A₁ receptors (A₁Rs), likely via adenosine derived from dephosphorylation of extracellular ATP (Dunwiddie et al., 1997). The link between A₁Rs and activation of G protein-coupled inwardly-rectifying K⁺ channels (GIRKs) is well established. A KD may also link A₁Rs with ATP-sensitive potassium (K_{ATP}) channel activation (Kawamura et al., 2010; Kawamura et al., 2014). It is important to note that conditions associated with altered adenosine levels – such as exercise and changes in circadian rhythms – are also associated with changes in the disposition for epileptic seizures.

There is an additional mechanistic path linking the KD to increases GABA levels and activates K_{ATP} channels via GABA_B receptors is another. Other studies have shown a more direct activation of K_{ATP} channels (Ma et al., 2007). Regardless of the mechanism(s) involved, increased K_{ATP} channel activity in seizure-prone areas of the brain (e.g. hippocampus) will reduce the risk of sporadic seizure activity.

Important features of the KD and metabolic therapies are that: 1) the effects do not significantly impair ongoing normal brain function or behavior; and 2) some effects can outlast the administration of the treatment – and thus suggesting an enduring or perhaps a permanent decrease in seizure propensity. For example, in recordings from awake behaving animals, the impact of a KD on synaptic function was only revealed during tetanic or high-intensity stimulation (Blaise et al., 2015; Koranda et al., 2011). Under these conditions, a KD limited excitability and reduced the magnitude of (but did not prevent) long-term potentiation, without affecting input-output excitability or paired-pulse, stimulation-induced plasticity. Regarding lasting mechanisms, and the potential for disease modification, continued seizure suppression after discontinuing KD therapy has been observed anecdotally and in clinical case seizures for decades (Caraballo et al., 2011; Martinez et al., 2007), and has now been confirmed in experimental models (Hu et al., 2011; Jiang et al., 2012; Lusardi et al., 2015; Muller-Schwarze et al., 1999; Su et al., 2000; Todorova et al., 2000). While not the focus herein, this disease-modifying potential of the KD is relevant to the current discussion in that it is reasonable to expect that a shift away from a state of spontaneous seizure generation may take time to evolve. In this context, the KD and adenosine have each been shown to have epigenetic effects that may underlie a permanent reduction in seizure risk due to a shift away from the threshold for seizure generation (Benjamin et al., 2017; Williams-Karnesky et al., 2013). It is also intriguing to note that the ketogenic diet has been shown to mitigate DNA methylation-mediated changes in gene expression seen in an experimental model of temporal lobe epilepsy (Kobow et al., 2013). Further, BHB has been shown to inhibit histone deacetylases (Shimazu et al., 2013). So while the full delineation of KD-induced epigenetic effects in various tissues has not yet been forthcoming, early evidence points to a not altogether surprising concept that metabolic factors can profoundly influence epigenetic changes in epileptic brain (Kobow and Blümcke, 2018).

Metabolic therapy for epilepsy: translational potential and practical advice

Metabolism influences seizures in fundamental and distinct ways compared to traditional pharmacological approaches (wherein typical targets are transmembrane ion channels, receptors and transporters). It is now also appreciated that metabolic dysfunction is a common feature among neurological disorders – and seizures (sometimes subclinical) are

recognized increasingly as a common comorbidity – for example, in autism spectrum disorder and Alzheimer’s disease (Cai et al., 2012; Cheng et al., 2017). In some cases, seizures could be considered the canary in the coal mine for abnormal brain function: a sporadic expression of a pathological state, and even an attempt to use ongoing dynamics to reset brain function – at least temporarily. Clearly, a diverse set of causes and symptoms are associated with a developmental disorder that is diagnosed behaviorally (i.e., autism spectrum disorder) and a neurodegenerative disorder found solely in the adult, aging brain (i.e., Alzheimer’s disease). Regardless of the specific dysfunction or pathology, metabolic support at the mitochondrial and cellular levels can improve the overall metabolic health of the brain.

Ironically, one of the most vexing ongoing issues for research into metabolic therapy with a diet (or an analogous supplement) is that it mobilizes many pathways and mechanisms. Yet this range of mechanisms aligns with the conceptual framework that many diverse triggers and physiological variables precipitate sporadic seizures. Without an appreciation or understanding of key physiological variables (and an inability to monitor or measure them) each seizure can indeed appear spontaneous. Recognizing the unparalleled success of and many mechanisms mobilized by metabolic therapy highlights the benefits of a multi-faceted resilience and a broad-based buffer against excitability. The focus of such a buffer would be to enable normal function and augment mechanisms associated with network stability – thus preventing spontaneous combinations of physiological fluctuations from pushing network activity into a range where sporadic seizure generation is more likely or inevitable.

Promoting stability and resilience aligns with clinical data indicating that complex factors such as dehydration, sleep deprivation, and stress – and combinations of these and other factors – can combine to shift the balance away from the normal degrees of inhibition and excitation to seizure generation (van Campen et al., 2014). In contrast, a ketogenic or low-glycemic index treatment, regular exercise, and an absence of these physiological stresses reduces the risk of a seizure. While the mechanisms that ultimately trigger a sporadic seizure remains unknown, the probability can be reduced by a promoting a metabolic buffer that stabilizes physiology and optimizes metabolic health.

Conclusions

There is a clear therapeutic link between metabolism and neuronal activity, one that can reveal important mechanistic underpinnings of the epileptic brain. Metabolic therapy with the KD enhances mitochondrial function, increases inhibition, and reduces the probability that neuronal excitability will reach a critical seizure threshold. Metabolism-based treatments enable a homeostatic state that is less excitable – by raising the seizure threshold – and is potentially more resilient to other insults or physiological stresses. That said, we realize that this metabolic approach is not helpful or sufficient for some epileptic conditions – and with diet alone there is a limited opportunity to escalate the “dose” as would be possible with a drug. Supplements may provide this “increased dose” opportunity and intense efforts are underway to develop and test analogous approaches that do not rely on such strict dietary control. Furthermore, there is rapidly expanding research into broader applications of metabolic therapy in promoting health and preventing disease. The

acknowledgment of the scientific community regarding the diversity of disorders where metabolic therapy can have an impact underscores the fundamental role of metabolism as a primary mechanism in brain function and brain health. It sits alongside the implicit recognition that (unlike seizures) these diverse conditions cannot be distilled solely into ion-channel based pathologies, and that there is a spectrum of conditions (with or without seizures as a comorbidity) that could benefit from metabolic treatments. For now, we know that a more stable and robust metabolic phenotype is a foundation for the increased probability of normal brain function and a significant shift away from unpredictable and sporadic seizure activity.

Acknowledgments

This work was supported by the National Institutes of Health [NS066392, SAM], Trinity College [SAM], the Canadian Institutes of Health Research [JMR], and the Alberta Children's Hospital Research Institute [JMR].

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Seizures appear spontaneous because precipitating factors are typically unknown, not monitored and/or not quantifiable.

Identifying dynamic physiological factors that increase seizure propensity, and leveraging those that decrease probability, could reduce their episodic recurrence.

Metabolism influences seizure susceptibility, and metabolic therapy with a ketogenic diet reduces seizures susceptibility and promotes stability and homeostasis of the neuronal network.

A more stable and robust metabolic phenotype is a foundation for increasing the probability of normal brain function and decreasing unpredictable and sporadic seizure activity.