EPILEPSY CURRENTS

Current Review
in Basic Science

Epilepsy Currents
2024, Vol. 24(2) 117-122

DOI: 10.1177/15357597231216916
journals.sagepub.com/home/epi
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The Unconventional Effects of the Ketogenic Diet (KD) in Preclinical Epilepsy

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Abstract

The integration of metabolic therapeutics in the available clinical armory is becoming more commonplace in health care as our understanding about the dependence of disease on metabolism continues to deepen and evolve. In the epilepsy field, we often think about the ketogenic diet (KD, high fat: carbohydrate ratio) in terms of its anti-seizure efficacy. The aim of this article is to review what we've learned from preclinical studies about the KD's more unconventional effects, including its neuroprotective effects, anti-epileptogenic and disease-modifying effects, and how the KD influences comorbidities associated with epilepsy. As time moves us into the future and metabolic therapies become more common place, the effects of the KD considered *unconventional* herein, may end up being referred to as *traditional*.

Keywords

ketogenic diet, epilepsy, cognitive dysfunction, sleep problems, comorbidity, autism, depression, anxiety, metabolic therapy, preclinical

Introduction

The integration of metabolic therapeutics in the available clinical armamentarium is becoming more commonplace in health care as our understanding about the dependence of disease on metabolism continues to deepen and evolve. The ketogenic diet (KD) has a high fat: carbohydrate ratio and its anti-seizure efficacy in epilepsy is well established both clinically and preclinically. The aim of this article is to review what we've learned from preclinical studies about the KD's more unconventional effects. We'll highlight the KD's neuroprotective effects, its anti-epileptogenic and disease modifying effects, and how the KD influences comorbidities associated with epilepsy.

Neuroprotective Effects

Neuroprotection is the attenuation or prevention of cell injury or death, and the preservation of neuronal function during pathologic challenges. Preclinical histological studies in mice and rats have shown that hippocampal regions which typically experience cell death and mossy fiber sprouting following status epilepticus (SE)-induced epilepsy are protected in cohorts treated with KD, irrespective of treatment beginning prior to or following SE.[1-4] Similarly, KD treatment protects against hippocampal cell loss in genetic models of spontaneous recurrent seizures (SRS).[5]

Mitochondria have a prominent role in cell injury and death in epilepsy. Under conditions of hyperexcitability, there is a higher probability that electrons, which are pulled from substrates and passed along the mitochondrial electron transport chain at a faster rate (to ensure sufficient ATP concentrations), spin off and bind to molecular oxygen. The resultant reactive species injure local proteins, membranes, RNA, and DNA and can reduce ATP production by post-translationally inhibiting mitochondrial respiration.[6,7] In addition, mitochondria sequester cytosolic calcium to aid in maintaining homeostatic levels in the soma and at synaptic sites. Reactive species lower mitochondrial calcium buffering capacities, which dysregulates synaptic activity and lowers the threshold for mitochondrial

permeability transition resulting in the release of additional signals, such as caspases, that further promote cell injury and death.

Numerous preclinical studies have found that KD treatment multi-mechanistically improves mitochondrial function in preclinical epilepsy. KD treatment increases the fidelity of successful electron transport, thereby reducing reactive species formation. Specifically, the fatty acid products of the KD act as chaperones to translocate protons back into the mitochondria via uncoupling proteins.[8] This frees the electron transport from the limitations imposed by the ATP synthase. Thus, KD also protects proteins, membranes, and nucleotide sequences from reactive species injury and prevents post-translational inhibition of mitochondrial respiration, thus restoring ATP generation.[7] The fatty acid products of the KD also activate transcription factors including PPARgamma and NRF2, which further promote neuroprotection by regulating the expression of pro-mitochondrial, antioxidant, and anti-inflammatory signals.[9-11] In addition, the KD attenuates mitochondrial permeability transition and reduces caspase release (as well as other injurious and cell death signals) in epilepsy models.[4,8,9,12] These KD effects are thought to provide functional protection by preserving synaptic activity during insults and reducing synaptic, cellular, and network hyperexcitability in epilepsy.[13,14]

The impact of the KD on mitochondria may not only underlie its neuroprotective effect but may also contribute to its anti-seizure effect and its effects on epileptogenesis, disease modification, and comorbid disorders as described in later sections. However, numerous and diverse mechanisms of the KD (and its ketone body and fatty acid byproducts) have been identified and likely also contribute. These include but are not limited to direct effects on ion channels by ketone bodies and fatty acids, gut microbiome alterations, epigenetic influences, and anti-inflammatory signaling. To learn more the reader is referred to previous detailed reviews.[15-21]

Antiepileptogenic and Disease Modifying Effects

Anti-epileptogenic and disease-modifying effects may be distinguished by the timing of treatment initiation relative to disease onset. In preclinical acquired epilepsy models, the period of epileptogenesis occurs after an initial insult such as SE, traumatic brain injury, viral infection, and so on,. until SRS develop. A treatment is deemed antiepileptogenic if it (i) delays the development of SRS. In the pilocarpine-SE model of acquired epilepsy, KD treatment (either initiated 3 weeks before SE or immediately after SE) did not delay the latency to the first SRS,[1,22] thus the authors of one study concluded KD was not antiepileptogenic.[1] However, a treatment can also be considered antiepileptogenic if it (ii) prevents the development of SRS or (iii) reduces the severity of the resultant epilepsy. Indeed, KD treatment prevented SRS development in 12% of rats, and seizure frequency was reduced by 50% to 70% in the rats that did develop SRS compared to animals fed a standard diet.[1,22] Using these 2 metrics, the KD exerts antiepileptogenic effects. Electrical kindling is another preclinical model of epileptogenesis involving administration of electrical stimulations at low intensities that initially elicit short, mild seizures. After multiple days of stimulations, the animal's seizure threshold is lowered, and the same low intensity stimulation induces severe behavioral seizures. When a plateau is reached, the animal is considered kindled. In this model, KD treatment slowed the development of severe seizures to the sub-threshold stimuli. This effect occurred irrespective of whether treatment began before or soon after the start of the kindling protocol.[23-25] Taken together these data indicate that the KD has antiepileptogenic effects.

A disease-modifying treatment begins after onset of the disease and differs from a symptomatic treatment. A symptomatic intervention attenuates symptoms without interfering with the disease process; thus, symptoms will return quickly after the treatment is discontinued.[26] Current anti-seizure medications are considered symptomatic interventions. In contrast, in addition to treatment beginning after disease onset, the concept of treatment-induced disease modification necessitates that the symptoms are attenuated by targeting disease-promoting mechanisms; functionally relevant biomarkers of disease may be attenuated; and following treatment discontinuation, either the symptoms re-emerge more slowly because of the impact on disease progression, or, in the best-case scenario, the symptoms resolve, and the disease is "cured." In the context of epilepsy, three metrics that can be used to identify whether the KD is a disease-modifying treatment are whether (i) seizures are attenuated, (ii) progression of epilepsy is slowed, and (iii) the effects are long-lasting after treatment discontinuation.[26] When assessing the preclinical literature, it is important to keep in mind that these endpoints are rarely examined within the same study, and laboratories differ in use of preclinical models, KD composition, and experimental design, making it difficult to identify comparable data. Nevertheless, preclinical data suggest the KD does exert disease-modifying effects. KD treatment slowed disease progression (ie, delayed seizure worsening) and postponed death in genetic models of SRS and early mortality, such as *Aldh5a1*-null, *Kcna1*-null, and El mice; however, treatment discontinuation was not examined in these studies.[27-30] In a pivotal study, Bough et al (2006)[13] found that a KD raised the threshold of pentylenetetrazol (PTZ)-induced seizures which was maintained 1-month after cessation of KD treatment, and long after blood ketones (beta-hydroxybutyrate) and glucose returned to normal levels. More recently, in the pilocarpine-SE model of acquired epilepsy (in which the spontaneous seizures become more frequent and severe) two groups demonstrated that KD treatment reduced SRS and delayed progression, an effect which persisted for up to 2 months after KD discontinuation.[2,31]

Collectively, these studies support the notion the KD can exert neuroprotective, anti-seizure, anti-epileptogenic, and disease-modifying effects. Some effects are dependent on the timing of treatment initiation and duration. Whether these effects involve similar or different mechanisms is not entirely clear and merit continued investigation.

Comorbidities

In addition to exerting anti-seizure, neuroprotective, and disease-modifying effects, the KD also influences comorbidities associated with epilepsy. Here, we'll review the preclinical data concerning the KD's effects on sleep disorders, cognitive deficits, depression, anxiety, and autism.

Sleep Disorders

KD treatment improves sleep in epilepsy. While there are preclinical studies looking at how the KD influences *seizures* (that occur during specific stages of sleep), there are few examining the effects of the KD on *sleep and sleep architecture*. *Kcna1*-null mice model SRS with a comorbid sleep disorder.[32,33] Two weeks of KD treatment improved sleep-wake diurnal rhythmicity.[32] Further assessment of sleep architecture using electroencephalography indicated that SRS mice have increased latency to sleep onset and fragmented sleep, as well as reduced rapid eye movement (REM) and non-REM (NREM) sleep.[33] KD treatment restored normal sleep architecture as well (Simeone et al., unpublished). *Kcna1*-null mice are also a model of sudden unexpected death in epilepsy. Sleep deficiency is associated with early mortality. It was found that sleep-deficiency worsened prior to sudden death in a *Kcna1*-null mice.[32] In addition to restoring sleep, KD treatment also increased longevity of *Kcna1*-null mice.[32,34] Of note, preclinical studies have found KD treatment also improves sleep and sleep architecture in models of Alzheimer's disease and Huntington's disease.[35,36]

Cognitive Deficits

Preclinical treatment with KD improves cognitive processes in epilepsy models. *In vivo*, preclinical experiments assess memory acquisition by measuring how quickly and efficiently a task is learned. Depending on the interval between training and testing, short-term or long-term memory is measured. The hippocampus is critical for multiple types of learning and memory processes. Synapses at different relay points in the hippocampal circuitry are tested for synaptic excitability, strength, and the ability to potentiate after stimulation. Long-term potentiation (LTP) is considered a physiological correlate of memory. It is well-established that synaptic potentiation, learning, and/or memory are impaired in multiple preclinical epilepsy models. In a majority of studies, KD improves cognitive processing. In a genetic model of SRS, 2 weeks of KD treatment normalized spatial learning and memory and restored LTP.[12] In a model of PTZ-induced SE acquired SRS, KD-treated rats spent more time exploring novel objects and less time exploring a familiar location, both indicative of improved recognition memory.[37] Interestingly, learning and memory improvements were still measurable after cessation of KD treatment. Following pilocarpine-induced SE (60 min SE), subjects were treated with KD for 4 weeks, then standard diet for 2 weeks. Both learning and memory performance in the Morris Water Maze were improved despite being off KD treatment for 2 weeks.[2] While improvement in cognitive processes should be celebrated, it is not possible to determine whether the benefits reported in these studies were directly or indirectly a result of seizure reduction and/or attenuated neuropathology, which also occurred. KD treatment also improved hippocampal LTP, learning and memory in preclinical models of multiple sclerosis, Alzheimer's Disease, and sleep-deprivation-induced cognitive dysfunction.[35,38,39] These studies further support the beneficial effects of KD on cognitive processes.

Depression and Anxiety

There is only one preclinical report about KD impacts on depression or anxiety in a preclinical model of epilepsy. A 6-month prospective, randomized, double-blinded, placebo-controlled, crossover dietary trial reported that after 3 months of KD treatment, anxiety and ADHD-like behaviors were reduced in canines with idiopathic epilepsy.[40] However, numerous studies have reported anti-depressive and anti-anxiety effects of the KD in preclinical models of stress, traumatic brain injury, and Rett syndrome.[41-46]

Autism

Preclinical autistic behavioral tests include the 3-chamber sociability test, preference for social novelty and evaluating passive communication, and self-directed repetitive behaviors. KD improved sociability, social communication, and ameliorated self-directed repetitive behavior in multiple models of autism with reduced seizure threshold (including Black and Tan BRachyury [BTBR] mice, offspring from prenatal maternal immune activation, and offspring from prenatal valproic acid exposure) and models of autism with epilepsy (including EL mice).[47-50]

Conclusion

In the epilepsy field, we often think about the KD in terms of its anti-seizure efficacy; and the research into this effect has been foundational in the translation of its use for people with other neurological disorders including Alzheimer's disease, Parkinson's disease, and multiple sclerosis, for people with cancer, and for elite athletes to further advance their performance. As time moves us into the future and metabolic therapies become more common place, the effects of the KD considered *unconventional* herein may end up being referred to as *traditional*.

Acknowledgments

The author wishes to thank Shruthi H. Iyer for her scientific insight and discussions.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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