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The effects of the ketogenic diet on behavior and cognition

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Summary Multiple forms of the ketogenic diet (KD) have been successfully used to treat drug-resistant epilepsy, however its mainstream use as a first-line therapy is still limited. Further investigation into its clinical efficacy as well as the molecular basis of activity is likely to assist in the reversal of any resistance to its implementation. In this review we shall attempt to elucidate the current state of experimental and clinical data concerning the neuroprotective and cognitive effects of the KD in both humans and animals. Generally, it has been shown by many research groups that effective implementation of KD exerts strong neuroprotective effects with respect to social behavior and cognition. We will also elucidate the role of KD in the interesting relationship between sleep, epilepsy and memory. Currently available evidence also indicates that, under appropriate control, and with further studies investigating any potential long-term side effects, the KD is also a relatively safe intervention, especially when compared to traditional anti-epileptic pharmacotherapeutics. In addition, due to its neuroprotective capacity, the KD may also hold potential benefit for the treatment of other neurological or neurodegenerative disorders.

Ketogenic diet

The ketogenic diet (KD) is a regimen that constitutes a food supply of high-fat, medium-protein, and low-carbohydrates. The KD is so-termed, as maintenance on this diet induces and sustains a ketotic state in the body. The KD has been used to treat various forms of drug-resistant epilepsy. In the clinical setting, patients are usually given 1 g of protein per 1 kg of bodyweight, 5—10 g of carbohydrates, and the remainder of the necessary daily calories is given in the form of fat (Kossoff, 2004). The KD minimizes somatic glucose levels (55-75 mg/dl serum glucose) (Zupec-Kania and Spellman, 2009) in the body without causing caloric restriction or malnutrition. While many studies have demonstrated KD efficacy in treating epilepsy (Cross and Neal, 2008; Kossoff, 2004; Maalouf et al., 2009), it is often not considered a potential first-line therapeutic despite the presence of long-term KD therapeutic outcomes (Patel et al., 2010; Neal et al., 2008). In this review our primary goal is to delineate

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the scientific and clinical evidence and potential mechanisms of action of the KD, with a special focus on some of its effects on cognitive function in epilepsy.

Experimental animal findings

Ketogenic diet and seizure models

Application of the KD to multiple animal epilepsy models has demonstrated therapeutic effects, *e.g.* KDs can increase induced-seizure threshold, delay seizure development, attenuate seizure risk and decrease the seizure severity (Maalouf et al., 2009; Todorova et al., 2000; Xu et al., 2006; Mantis et al., 2004). While careful attention has been paid to the effects of KD upon seizure activity, less is known about its effects upon cognition.

Neuroprotective capacity of the ketogenic diet

Data are available that suggest that the KD has neuroprotective effects that could be applied beyond its treatment for epileptic conditions. Several studies have demonstrated that KDs can enhance cognitive function in both pathophysiological and normal healthy experimental animal systems (Appelberg et al., 2009; Xu et al., 2010). For example, KDs were able to improve the motor coordination and cognition recovery in young rats suffering from traumatic brain injury (Appelberg et al., 2009). Pro-cognitive and memory enhancement effects of KDs have been demonstrated in normal, healthy, aged rats and to a lesser extent in young rats, suggesting that age may not be a confound for KD use (Xu et al., 2010). In a murine model of Alzheimer's disease (AD) in which mice express a mutated human amyloid precursor protein (APP) transgene, KDs have been shown to attenuate the production and accumulation of the cytotoxic proteolytic products of APP, *i.e.* amyloid-β 40/42, that are thought to underlie the etiology of AD (Van dA et al., 2005). Amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease), like AD, is a neurodegenerative disorder often linked to oxidative stress of neurons. Murine models of ALS, in which transgenic mice possess a human mutation of an enzyme that protects from oxidative damage (superoxide dismutase 1), KDs can delay the onset of motor coordination loss and reduce motor neuron loss in the spinal cord (Zhao et al., 2006). KDs have also been demonstrated to reduce neuronal cell death and the generation of seizure activity in experimental models of stroke and cerebral ischemia (Tai and Truong, 2007; Tai et al., 2008). While animal studies have demonstrated many beneficial effects of KDs, due to variation in animal husbandry and experimental design, conflicting data can be obtained. For example, KD has been implicated in deficiencies in spatial learning and memory, as well as impaired brain growth (Zhao et al., 2004), although it is possible that these negative effects may be due to uncontrolled malnutrition in the KD regimen (Cunnane and Likhodii, 2004). Even with this caveat however, overall, the findings presented by various research groups certainly encourages the therapeutic use of the KD beyond epilepsy, as it offers neuroprotective effects in normal animals, and has beneficial effects in multiple murine models of neurological disorders.

Clinical findings

Ketogenic diet and seizure activity

There is now a considerable body of human clinical study data that demonstrates the efficacy of the KD regimen. The KD has been demonstrated clinically to significantly reduce seizure incidence in children in both randomized and non-randomized acute studies (Zupec-Kania and Spellman, 2009; Neal et al., 2008), as well as providing long-term seizure prophylaxis (Patel et al., 2010).

Ketogenic diet and cognitive function

Although no prospective studies of developmental or behavioral outcomes have been performed so far, anecdotal evidence and parental report measures have indicated that children treated with the KD show increased alertness and better cognitive functioning, as well as improved behavior (Kinsman et al., 1992; Nordli et al., 2001; Pulsifer et al., 2001). In addition to the dietary regimen itself, and with specific attention to pediatric cases, it has been shown that there is considerable therapeutic synergism between social behavioral support and the KD itself, perhaps suggesting that involvement of emotional neurological pathways may be a crucial factor in KD efficacy (Farasat et al., 2006).

Ketogenic diet and cognition beyond epilepsy

Beyond its potential as an epilepsy therapy, the regimen has been shown to hold potential as a treatment for a variety of other neurological disorders and certain metabolic disorders (Maalouf et al., 2009). In addition to exerting beneficial cognitive effects in epileptic backgrounds the KD has, as in mouse models, demonstrated an ability to ameliorate neurodegenerative processes and conditions in which cognitive deficits and excitotoxicity may be present. For example, KD implementation can enhance cognitive activity in patients with Alzheimer's (Reger et al., 2004) and Parkinson's disease (Vanitallie et al., 2005). In a pilot study involving autistic children, the KD has also shown encouraging signs that this regimen can ameliorate some of the behavioral, social communication and cognitive deficits in this patient group (Evangeliou et al., 2003). These findings from multiple and diversely structured studies support the concept that the KD offers broad-ranging neuroprotective benefits, and that the regimen merits attention as a therapeutic option for other neurodegenerative, cognitive and behavioral diseases beyond epilepsy.

The complex interactions between sleep, epilepsy and memory

Sleep is a complex system of internally generated oscillations involving the cortex, thalamus and brainstem, regulated by circadian influences and homeostatic pressure. These oscillations are also important for learning, memory and behavior in children. There is growing evidence that sleep in general and specific sleep stages, such as Rapid Eye Movement (REM) and/or slow-wave sleep