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The effects of the ketogenic diet on behavior and cognition

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Abstract

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.

Keywords

Cognition; Memory; Learning; Sleep; Children; Dietary treatment

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

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to delineate 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 nonrandomized 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 (SWS), are involved in memory formation and cognitive performance. Recent studies have shown that sleep after learning enhances consolidation of declarative, procedural, and emotional memories. SWS particularly enhances declarative memories, whereas REM sleep preferentially supports procedural and emotional memory aspects (Smith and Wong, 1991; Smith et al., 2004; Gais et al., 2002;

Huber, 2004). This relationship between cognition and sleep appears to be far more complicated in epilepsy patients, as their disease pathology enters into the equation as well. Indeed, it has been found that sleep and sleep deprivation are potent activators of seizures and epileptiform discharges, (Shouse et al., 1996; Crespel et al., 2000; Bazil, 2003) and affect behavior in epileptic children (Méndez and Radtke, 2001). Similarly, epilepsy during sleep adversely affects sleep quality (Touchon et al., 1991; Ohayon et al., 2004). The present cumulative evidence suggests that sleep deprivation and epilepsy during sleep can affect memory, learning, and behavior in children. Interictal epileptiform discharges (IED) may affect cognition and sleep, even in the absence of clinical or subclinical seizures. Sleep deprivation and / or sleep disruption not only affect the neurophysiological and neurochemical mechanisms important for the memory formation and learning process, but also influence the expression of epileptiform discharges and seizures. Learning and memory consolidation can take place over extended periods, and sleep has been demonstrated to play a fundamental role in these processes through neuroplastic remodeling of neural networks (Pasiri et al., 2010). Hence, variations in sleep patterns could account for both the learning impairment and other typical symptoms in children with epilepsy, such as the interictal epileptiform discharges in electroencephalography (EEG) and persistence and circadian distribution of seizures.

The degree of synchronization and antigravity tone during sleep are also critical factors impacting seizure-propagation and expression. REM is presented with a desynchronized EEG and absent postural tone, and hence, seizures rarely occur during REM sleep. However, non REM sleep is presented with a synchronized EEG and preserved antigravity tone, which suggests that sleep of this type is most likely to be responsible for seizure occurrence. In support of the notion that sleep plays an important role in epilepsy, polysomnographic studies available have shown alterations in sleep structure in individuals with epilepsy. In children with different types of epilepsy, deviations from normal sleep patterns such as reduction in total sleep time, reduced sleep efficiency, decreased REM sleep, an increase in stage shifts, greater number of arousals, and sudden waking after sleep onset is commonly found. In children with refractory epilepsy, a decrease in stage 2 sleep and an increase in SWS has also been reported (Bazil and Walczak, 1997; Nunes et al., 2003; Baxter, 2005; Kaleyias et al., 2008). Moreover, specific sleep disorders such as obstructive sleep apnea syndrome, restless leg syndrome, and periodic limb movements are commonly reported in children with epilepsy (Miano et al., 2009; Tezer et al., 2009; Foldvary-Schaefer, 2003; Oliveira et al., 2000). Sleep behavior problems are seen in more than 50% of children with epilepsy. Based on parental reports, sleep problems such as reduced sleep efficiency, longer sleep latency, shorter sleep time, more awakenings, daytime sleepiness, anxiety over their night-time sleep, reluctance to go to sleep, need for parental presence at bedtime, and an increased tendency to fall asleep in places other than bed appear to be quite common in children with epilepsy (Kohrman and Carney, 2000; Becker et al., 2003; Dunn, 2002; Maganti et al., 2006; Batista and Nunes, 2007). These data indicate that there is a strong sleep component to epilepsy pathology that previously has not gained much attention.

Ketogenic diet and changes in sleep structures

A few studies have implicated the benefits of KD in providing better sleeping patterns and improved cognitive function in patients with epilepsy. In one study, sleep structures and possible correlations with changes in clinical effects, seizure reduction, seizure severity, quality of life (QOL), and behavior during KD treatment in children with therapy-resistant epilepsy were evaluated. Eighteen children were examined with ambulatory polysomnographic recordings initially and after 3 months of KD treatment. Eleven children continued with the KD and were also evaluated after 12 months. KD induced a significant decrease in total sleep ($p = 0.05$) and total night sleep ($p = 0.006$). Slow wave sleep was preserved, rapid eye movement (REM) sleep increased ($p = 0.01$), sleep stage 2 decreased ($p = 0.004$), and sleep stage 1 was unchanged. Attention behavior was found to be improved significantly ($p = 0.003$). Despite the reduction of total amount of sleep time, there was a strong correlation between increased REM sleep and improvement in QOL, suggesting that the quality of sleep was improved with the KD (Spearman $r = 0.6$, $p = 0.01$). Eleven children continued with the KD and were evaluated after 12 months. They showed a significant decrease in daytime sleep ($p = 0.01$) and a further increase in REM sleep ($p = 0.06$). Seizure frequency ($p = 0.001$, $p = 0.003$), seizure severity ($p < 0.001$, $p = 0.005$), and QOL ($p < 0.001$, $p = 0.005$) were significantly improved at both 3 and 12 months of KD treatment. In this study, it was observed that KD decreases total sleep, total night sleep, and daytime sleep, but improves sleep quality in children with therapy-resistant epilepsy. This improvement in sleep quality, potentially through increased REM sleep, seems to contribute to the improvement in QOL (Hallböök et al., 2007). While the mechanism behind the enhanced sleep through KD treatment is presently unclear, it is likely that that the KD therapy involves some action through the hypothalamus. The hypothalamus and the ventro-lateral preoptic nucleus (VLPO) withhold sub-regions that are specialized for the control of REM versus non-REM sleep via locus coeruleus, pedunculo-pontin tegmental- and latero-dorsal tegmental nucleus. Since the VLPO contains γ-aminobutyric acid (GABA) and galanin, one could speculate that, besides the anti-convulsing effects, the increase in REM sleep of KD is induced by changes in GABAergic and galaninergic functioning (Sherin et al., 1998; Saper et al., 2001,2005). In children with therapy-resistant epilepsy we have previously obtained data on cognitive function at baseline and after 3 and 12 months of KD. The children who were clinically diagnosed as mentally retarded (IQ < 70) were placed on KD and subsequently tested using various methods of testing protocols; six children were tested with Wechsler Preschool and Primary Scale of Intelligence (WPPSI), ten with Bayley Scale of Infant Development (BSID) and one with Wechsler Intelligence Scale for Children (WISC). The data from the subjects who completed the KD treatment and performed the cognitive task revealed that for most children, there were no differences in cognitive functioning before and after introduction of KD, but the regimen did not cause any decrease in cognitive performance either. However, a few subjects displayed small improvements during the diet while two children improved one standard deviation in the Full Scale Intelligence Quotient (FSIQ) test (Hallbook and Stjernqvist, unpublished data). Thus, while the KD did not offer cognitive enhancements to all study participants, it did not appear to lower cognitive capacity. Considering that cognitive assessment in children is age dependent because of development, lack of cognitive decline could indicate an improvement. While mechanisms behind improvements in cognitive functions and enhancements in sleep quality

through KD currently unclear, there is evidence that supports the notion that the KD is an effective treatment for some epilepsy patients (addressing both aspects — the mental impact and sleep deprivation - of epilepsy pathology), and merits further studies in order to elucidate its potential effects further.

Potential KD therapeutic mechanisms

Due to the complexity inherent in altering a diet regimen, the elucidation of discrete and definitive therapeutic mechanisms is often problematical. The current pace of investigation is increasing and therefore our mechanistic appreciation is likely to increase exponentially in the next decade. However, it is likely that KD therapeutic activities may involve the inter-play between neurophysiological, electrohysiological and endocrinological systems and therefore concerted experimental and clinical data management and scrutiny will be vital to bring together diverse pieces of evidence. The current KD mechanistic literature has shown that alterations in diets exert multifactorial direct, indirect and adaptive physiological effects in multiple physiological systems such as somatic energy management, diverse hormonal changes and alterations in the genomic output of different cells in different tissues of the body (Martin et al., 2007,2008,2009). As discussed previously, the KD appears to exert a neuroprotective effect in neurological diseases that involve some degree of oxidative damage and therefore it is not surprising that one mechanistic conclusion may be that KD, in-part, acts through an antioxidant effect (Maalouf et al., 2009; Bough and Rho, 2007). Several studies have shown that the KD improves mitochondrial function by increasing metabolic efficiency, while lowering the production of reactive oxygen species (ROS), which then protects the brain from oxidative stress (Sullivan et al., 2004; DeVivo et al., 1978; Bough et al., 2006). This hypothesis is therefore highly consistent with some of the animal and clinical findings. Excessive accumulation of ROS has been suggested to be one of the major hallmarks of the aging process (Martin et al., 2010a) and it is therefore not surprising that KD seems to protect against age-related neurodegenerative diseases (Reger et al., 2004; Xu et al., 2010; Maalouf et al., 2009). It is clear from many lines of research that aberrant glucose metabolism plays a profound role in the development of drug-resistant epilepsy (Pumain et al., 2008; Yellen, 2008) and that bypassing this pathophysiology with the KD non-glucose energy sources presents another viable mechanism of action of KD in cognitive health. In addition to avoiding pathological metabolic pathways, the KD also appears to attenuate programmed cell death-related signaling events. Studies have suggested that the neuroprotective activity of the KD is due to an anti-apoptotic activity (Maalouf et al., 2009). KDs can suppress the expression of pro-apoptosis factors such as clusterin and caspase-3, which coordinate strongly with the enhanced rates of recovery from seizure episodes and acute ischemic events of patients on the KD regimen (Noh et al., 2003,2005a; Maalouf et al., 2009; Tai and Truong, 2007; Tai et al., 2008). As multiple components of classical apoptotic cascades are controlled by excessive calcium entry into neurons it is likely that KDs also may control cellular survival by increasing intracellular calcium buffering capacity, *e.g.* by increasing the hippocampal expression of the calcium binding protein calbindin (Noh et al., 2005b). In accordance with its ability to modulate calcium levels, the KD has also been found to actively limit neuronal hyperexcitability induced by seizures (Maalouf et al., 2009), however the mechanism(s) by which this is achieved is still a matter of debate. One factor in this aspect of excitability may be that the ability of the KD

to increase the levels of the γ-aminobutyric acid (GABA), which upon activating $GABA_A$-receptor chloride channels, causes neuronal cellular hyperpolarization through rapid influx of negative chloride ions (Cheng et al., 2004). Neuronal hyperpolarization can then curtail the activation of voltage-gated sodium and calcium channels, whose activity is required for neuronal excitation. In addition to alterations in GABA, the KD may also limit neuronal hyperexcitability by affecting noradrenergic receptor signaling and norepinephrine levels, both of which are correlated to the anticonvulsant effect of the KD (Szot et al., 2001; Martillotti et al., 2006).

As we have stated previously, dietary alterations can also induce profound changes in living organisms at both the physiological and genomic levels (Martin et al., 2007,2009), and it is highly likely that multiple mechanisms beyond the ones covered in this review are collaboratively involved in producing the overall antiepileptic and neuroprotective effects of the KD. These hypotheses are just several, of likely many, nodes in the complex physiological networks through which the KD exerts its undoubted therapeutic actions. While further and more in-depth analysis is required to fully appreciate the molecular nature of action of the KD, this effort is likely to be fruitful with respect to the refinement of the KD(s), say to specific patient populations, or with respect to the ability to recapitulate the effects of the KD in a simple drug-like formulation.

Future perspectives

At the present time our understanding of the effect of ketosis on behavior and cognition is still rudimentary, despite the clear reproducibility of its therapeutic efficacy. While the available literature suggests the ability of the KD to improve neuronal health and cognition, its precise mechanism(s) of action and its applicability is limited for multiple reasons. The lack of diverse, double-blind randomized control studies that accurately measure the effect of the KD and its effect on cognitive function is certainly a crucial factor. In addition to this, our ability to understand the precise effects of the KD is marred by the variety of different methods and models that have been employed in recent years that often lead to the generation of contradictory findings (Zhao et al., 2004; Maalouf et al., 2009; Xu et al., 2010; Thio et al., 2010; Cunnane and Likhodii, 2004). One of the most important considerations for future studies is the potential standardization of both human protocols as well as consistent use of the most appropriate animal models (Martin et al., 2010b). At the present time, the KD is often only employed as a last treatment method for epilepsy after drug resistance is encountered. Most standard treatments for epilepsy have highly adverse side effects, which are not, as far as we know today present with the KD, yet, the regimen is still avoided, perhaps due to the minimal number of standardized and ‘drug study-like’ clinical studies reported. In order to provide both patients and clinicians with the confidence necessary to employ the KD as a viable first-line therapy, further studies documenting the behavioral and cognitive effects of the diet are necessary in order to achieve greater understanding of the regimen. In conclusion, while further research is needed, the available evidence suggests that the KD is a regimen that merits attention as a potential primary therapy for epilepsy, and in the future potentially also for other neurodegenerative disorders.

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