Neuroprotective and disease-modifying effects of the ketogenic diet

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Abstract

The ketogenic diet has been in clinical use for over 80 years, primarily for the symptomatic treatment of epilepsy. A recent clinical study has raised the possibility that exposure to the ketogenic diet may confer long-lasting therapeutic benefits for patients with epilepsy. Moreover, there is evidence from uncontrolled clinical trials and studies in animal models that the ketogenic diet can provide symptomatic and disease-modifying activity in a broad range of neurodegenerative disorders including Alzheimer's disease and Parkinson's disease, and may also be protective in traumatic brain injury and stroke. These observations are supported by studies in animal models and isolated cells that show that ketone bodies, especially β-hydroxybutyrate, confer neuroprotection against diverse types of cellular injury. This review summarizes the experimental, epidemiological and clinical evidence indicating that the ketogenic diet could have beneficial effects in a broad range of brain disorders characterized by the death of neurons. Although the mechanisms are not yet well defined, it is plausible that neuroprotection results from enhanced neuronal energy reserves, which improve the ability of neurons to resist metabolic challenges, and possibly through other actions including antioxidant and anti-inflammatory effects. As the underlying mechanisms become better understood, it will be possible to develop alternative strategies that produce similar or even improved therapeutic effects without the need for exposure to an unpalatable and unhealthy, high-fat diet.

Keywords

Alzheimer's disease; cellular energetics; epilepsy; ketone bodies; ketogenic diet; mitochondria; neuroprotection; Parkinson's disease; stroke; traumatic brain injury

Introduction

The ketogenic diet is a high-fat content diet in which carbohydrates are nearly eliminated so that the body has minimal dietary sources of glucose. Fatty acids are thus an obligatory source of cellular energy production by peripheral tissues and also the brain. Consumption of the ketogenic diet is characterized by elevated circulating levels of the ketone bodies acetoacetate, β-hydroxybutyrate and acetone, produced largely by the liver. During high rates of fatty acid oxidation, large amounts of acetyl-CoA are generated. These exceed the capacity of the tricarboxylic acid cycle and lead to the synthesis of the three ketone bodies within liver mitochondria. Plasma levels of ketone bodies rise, with acetoacetate and β-hydroxybutyrate increasing three-fold to four-fold from basal levels of 100 and 200 µmol/l, respectively (Musa-Veloso *et al.*, 2002). In the absence of glucose, the preferred source of energy (particularly of

the brain), the ketone bodies are used as fuel in extrahepatic tissues. The ketone bodies are oxidized, releasing acetyl-CoA, which enters the tricarboxylic acid cycle.

The ketogenic diet is an established and effective nonpharmacological treatment for epilepsy (Vining *et al.*, 1998; Stafstrom, 2004; Sinha and Kossoff, 2005). Although the diet is useful in people of all ages, clinical experience suggests that it may be more valuable in children, if only because adults have greater difficulty adhering to it. Importantly, the diet is often effective in pharmacoresistant forms of common epilepsies as well as in the difficult to treat catastrophic epilepsy syndromes of infancy and early childhood such as West Syndrome, Lennox–Gastaut Syndrome, and Dravet Syndrome (Crumrine, 2002; Trevathan, 2002; Caraballo *et al.*, 2005).

Recently, there has been interest in the potential of the ketogenic diet in the treatment of neurological disorders other than epilepsy, including Alzheimer's disease and Parkinson's disease. Studies in these neurodegenerative disorders have led to the hypothesis that the ketogenic diet may not only provide symptomatic benefit, but could have beneficial disease-modifying activity applicable to a broad range of brain disorders characterized by the death of neurons. Here, we review evidence from clinical studies and animal models that supports this concept.

Ketogenic diet

The classic ketogenic diet is a high-fat diet developed in the 1920s to mimic the biochemical changes associated with periods of limited food availability (Kossoff, 2004). The diet is composed of 80–90% fat, with carbohydrate and protein constituting the remainder of the intake. The diet provides sufficient protein for growth, but insufficient amounts of carbohydrates for the body's metabolic needs. Energy is largely derived from the utilization of body fat and by fat delivered in the diet. These fats are converted to the ketone bodies β-hydroxybutyrate, acetoacetate, and acetone, which represent an alternative energy source to glucose. In comparison with glucose, ketone bodies have a higher inherent energy (Pan *et al.*, 2002; Cahill and Veech, 2003). In adults, glucose is the preferred substrate for energy production, particularly by the brain. Ketone bodies are, however, a principal source of energy during early postnatal development (Nehlig, 2004). In addition, ketone bodies, especially acetoacetate, are preferred substrates for the synthesis of neural lipids. Ketone bodies readily cross the blood–brain barrier either by simple diffusion (acetone) or with the aid of monocarboxylic transporters (β-hydroxybutyrate, acetoacetate), whose expression is related to the level of ketosis (Pan *et al.*, 2002; Pierre and Pellerin, 2005).

Today, several types of ketogenic diets are employed for treatment purposes. The most frequently used is the traditional ketogenic diet originally developed by Wilder in 1921, which is based on long-chain fatty acids (Wilder, 1921). In the 1950s, a medium-chain triglyceride diet was introduced, which produces greater ketosis (Huttenlocher *et al.*, 1971). This modification has not been widely accepted because it is associated with bloating and abdominal discomfort and is no more efficacious than the traditional ketogenic diet. A third variation on the diet, known as the Radcliffe Infirmary diet, represents a combination of the traditional and medium-chain triglyceride diets (Schwartz *et al.*, 1989). Its efficacy is also similar to the traditional ketogenic diet.

Although the ketogenic diet was a popular treatment approach for epilepsy in the 1920s and 1930s, its medical use waned after the introduction of phenytoin in 1938. The recognition that the diet may be an effective therapeutic approach in some drug-resistant epilepsies, particularly in children, has led to a resurgence of interest in the last 15 years. The popularization of various low carbohydrate diets for weight loss, such as the Atkins diet (Acheson, 2004), probably also has increased interest in the dietary therapy of epilepsy. In fact, a modified form of the Atkins

diet, which is easier to implement than the various forms of the traditional ketogenic diet, may be an effective epilepsy treatment approach (Kossoff *et al.*, 2006).

Clinical studies

Epilepsy

At present, strong evidence exists that the ketogenic diet protects against seizures in children with difficult-to-treat epilepsy (Freeman *et al.*, 1998). Recent reports have raised the possibility that the diet may also improve the long-term outcome in such children (Hemingway *et al.*, 2001; Marsh *et al.*, 2006). In these studies, children with intractable epilepsy who remained on the ketogenic diet for more than 1 year and who experienced a good response to the diet, often had positive outcomes at long-term follow-up 3–6 years after the initiation of diet. Forty-nine percent of the children in this cohort experienced a nearly complete (≥ 90%) resolution in seizures. Surprisingly, even those children who remained on the diet for 6 months or less (most of these children terminated the diet because of an inadequate response) may have obtained a long-term benefit from exposure to the diet. Thirty-two percent of these children had a ≥ 90% decrease in their seizures and 22% became seizure free even without surgery. The diet also allowed a decrease or discontinuation of medications without a relapse in seizures. Of course, in the absence of a control group, it is not possible to be certain that the apparent good response in these children is simply the natural history of the epilepsy in the cohort studied, although these children had, by definition, intractable epilepsy before starting the diet. In any case, the results raise the possibility that the ketogenic diet, in addition to its ability to protect against seizures, may have disease-modifying activity leading to an improved long-term outcome. It is noteworthy that none of the currently marketed antiepileptic drugs has been demonstrated clinically to possess such a disease-modifying effect (Schachter, 2002; Benardo, 2003). Determining whether the ketogenic diet truly alters long-term outcome will require prospective controlled trials.

Alzheimer's disease

Recent studies have raised the possibility that the ketogenic diet could provide symptomatic benefit and might even be disease modifying in Alzheimer's disease. Thus, Reger *et al.* (2004) found that acute administration of medium-chain triglycerides improves memory performance in Alzheimer's disease patients. Further, the degree of memory improvement was positively correlated with plasma levels of β-hydroxybutyrate produced by oxidation of the medium-chain triglycerides. If β-hydroxybutyrate is responsible for the memory improvement, then the ketogenic diet, which results in elevated β-hydroxybutyrate levels, would also be expected to improve memory function. When a patient is treated for epilepsy with the ketogenic diet, a high carbohydrate meal can rapidly reverse the antiseizure effect of the diet (Huttenlocher, 1976). It is therefore of interest that high carbohydrate intake worsens cognitive performance and behavior in patients with Alzheimer's disease (Henderson, 2004; Young *et al.*, 2005).

It is also possible that the ketogenic diet could ameliorate Alzheimer's disease by providing greater amounts of essential fatty acids than normal or high carbohydrate diets (Cunnane *et al.*, 2002; Henderson, 2004). This is because consumption of foods or artificial supplements rich in essential fatty acids may decrease the risk of developing Alzheimer's disease (Ruitenberg *et al.*, 2001; Barberger-Gateau *et al.*, 2002; Morris *et al.*, 2003a, b).

Parkinson's disease

One recently published clinical study tested the effects of the ketogenic diet on symptoms of Parkinson's disease (VanItallie *et al.*, 2005). In this uncontrolled study, Parkinson's disease patients experienced a mean of 43% reduction in Unified Parkinson's Disease Rating Scale

scores after a 28-day exposure to the ketogenic diet. All participating patients reported moderate to very good improvement in symptoms. Further, as in Alzheimer's disease, consumption of foods containing increased amounts of essential fatty acids has been associated with a lower risk of developing Parkinson's disease (de Lau *et al.*, 2005).

Studies in animal models

Epilepsy

Anticonvulsant properties of the ketogenic diet have been documented in acute seizure models in rodents (Appleton and De Vivo, 1973; Huttenlocher, 1976; Hori *et al.*, 1997; Stafstrom, 1999; Likhodii *et al.*, 2000; Thavendiranathan *et al.*, 2000, 2003; Bough *et al.*, 2002). Moreover, there is accumulating evidence from studies in models of chronic epilepsy that the ketogenic diet has antiepileptogenic properties that extend beyond its anticonvulsant efficacy. Thus, in the rat kainic acid model of temporal lobe epilepsy, the development of spontaneous seizures was attenuated by the ketogenic diet and there was a reduction in the severity of the seizures that did occur (Muller-Schwarze *et al.*, 1999; Stafstrom *et al.*, 1999; Su *et al.*, 2000). In addition, animals fed the diet have reduced hippocampal excitability and decreased supragranular mossy fiber sprouting in comparison with rats fed a normal diet. Further evidence supporting the antiepileptogenic activity of the ketogenic diet is the demonstration that the development of spontaneous seizures in inbred EL/Suz mice, a genetic model of idiopathic epilepsy, is retarded by the diet (Todorova *et al.*, 2000). In other studies, caloric restriction, which often occurs with the ketogenic diet, has also been demonstrated to have antiepileptogenic effects in EL/Suz mice (Greene *et al.*, 2001; Mantis *et al.*, 2004). (Although the ketogenic diet is designed to provide calories adequate for growth, patients and animals may eat less because the diet may be unpalatable to some. Thus, the ketogenic diet may be accompanied by an unintentional caloric restriction.)

Alzheimer's disease

Epidemiological studies have implicated diets rich in saturated fat with the development of Alzheimer's disease (Kalmijn *et al.*, 1997; Grant, 1999; Morris *et al.*, 2003a, b, 2004; but see Engelhart *et al.*, 2002). Moreover, in transgenic mouse models, high-fat diets increase the deposition of amyloid β (Aβ) peptides (Levin-Allerhand *et al.*, 2002; Shie *et al.*, 2002; George *et al.*, 2004; Ho *et al.*, 2004). These studies, however, did not examine the effects of ketogenic diets rich in fats, when the high lipid content is administered along with severe carbohydrate restriction. Indeed, in a recent series of experiments using a transgenic mouse model of Alzheimer's disease, a ketogenic diet was found to improve Alzheimer's pathology. The mice used in this study, which express a human amyloid precursor protein gene containing the London mutation (APP/V717I), exhibit significant levels of soluble Aβ in the brain as early as 3 months of age and show extensive plaque deposition by 12–14 months (Van der Auwera *et al.*, 2005). They also demonstrate early behavioral deficits in an object recognition task. Exposure to a ketogenic diet for 43 days resulted in a 25% reduction in soluble Aβ(1–40) and Aβ(1–42) in brain homogenates, but did not affect performance on the object recognition task. Caloric restriction has also been demonstrated to attenuate β-amyloid depositions in mouse models of Alzheimer disease (Patel *et al.*, 2005; Wang *et al.*, 2005). How the ketogenic diet and caloric restriction affect β-amyloid levels and whether this effect could be disease modifying in Alzheimer's disease requires further study.

The ketogenic diet could have beneficial effects in Alzheimer's disease apart from effects on β-amyloid disposition. For example, essential fatty acids in the diet may have beneficial effects on learning, as demonstrated with studies of spatial recognition learning in rodent models of Alzheimer's disease (Hashimoto *et al.*, 2002, 2005; Lim *et al.*, 2005). Alternatively, the diet might protect against β-amyloid toxicity. Thus, direct application of β-hydroxybutyrate in

concentrations produced by the ketogenic diet has been found to protect hippocampal neurons from toxicity induced by Aβ(1–42) (Kashiwaya *et al.*, 2000).

Parkinson's disease

The most widely used animal model of Parkinson's disease is based on the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Exposure to MPTP causes degeneration of mesencephalic dopamine neurons, as in the human clinical condition, and is associated with parkinsonian clinical features. The ketogenic diet has not yet been studied in the MPTP or other animal models of Parkinson's disease. As in epilepsy and Alzheimer's disease models, however, caloric restriction has been found to have beneficial effects in MPTP models of Parkinson's disease. This was first demonstrated in rats fed on an alternate-day schedule so that they consume 30–40% less calories than animals with free access to food. The calorie-restricted animals were found to exhibit resistance to MPTP-induced loss of dopamine neurons and less severe motor deficits than animals on the normal diet (Duan and Mattson, 1999). More recently, it has been reported that adult male rhesus monkeys maintained chronically on a calorie-restricted diet are also resistant to MPTP neurotoxicity (Maswood *et al.*, 2004; Holmer *et al.*, 2005). These animals had less depletion of striatal dopamine and dopamine metabolites and substantially improved motor function than did animals receiving a normal diet. In other studies in mice, caloric restriction has been reported to have beneficial effects even when begun after exposure to MPTP (Holmer *et al.*, 2005).

In addition to caloric restriction, several recent reports have indicated that β-hydroxybutyrate may be neuroprotective in the MPTP model. MPTP is converted *in vivo* to 1-methyl-4-phenylpyridinium (MPP +), which is believed to be the principal neurotoxin through its action on complex 1 of the mitochondrial respiratory chain. In tissue culture, 4 mmol/l β-hydroxybutyrate protected mesencephalic neurons from MPP + toxicity (Kashiwaya *et al.*, 2000). Moreover, subcutaneous infusion by osmotic minipump of β-hydroxybutyrate for 7 days in mice conferred partial protection against MPTP-induced degeneration of dopamine neurons and parkinsonian motor deficits (Tieu *et al.*, 2003). It was proposed that the protective action is mediated by improved oxidative phosphorylation leading to enhanced ATP production. This concept was supported by experiments with the mitochondrial toxin 3-nitropropionic acid (3-NP). 3-NP inhibits oxidative phosphorylation by blocking succinate dehydrogenase, an enzyme of the tricarboxylic acid cycle that transfers electrons to the electron transport chain via its complex II function. The protective effect of β-hydroxybutyrate on MPTP-induced neurodegeneration in mice was eliminated by 3-NP. Moreover, in experiments with purified mitochondria, β-hydroxybutyrate markedly stimulated ATP production and this stimulatory effect was eliminated by 3-NP. Thus, it seems likely that β-hydroxybutyrate is protective in the MPTP model of Parkinson's disease by virtue of its ability to improve mitochondrial ATP production (Tieu *et al.*, 2003). Whether the ketogenic diet would also be protective in Parkinson's disease models as a result of increased β-hydroxybutyrate production remains to be determined. It is noteworthy that β-hydroxybutyrate is not anticonvulsant and is unlikely to directly account for the antiseizure activity of the ketogenic diet (Rho *et al.*, 2002). Whether β-hydroxybutyrate contributes in some other way to the beneficial activity of the ketogenic diet in epilepsy therapy remains to be studied.

Ischemia and traumatic brain injury

Much of the neurological dysfunction that occurs in stroke, cerebral ischemia, and acute traumatic brain injury is due to a secondary injury process involving glutamate-mediated excitotoxicity, intracellular calcium overload, mitochondrial dysfunction, and the generation of reactive oxygen species (ROS) (McIntosh *et al.*, 1998). Consequently, the underlying pathophysiological mechanisms may have features in common with those in classical neurodegenerative disorders. Recently, Prins *et al.* (2005) have reported that the ketogenic diet

can confer up to a 58% reduction in cortical contusion volume at 7 days after controlled cortical injury in rats. The beneficial effects of the diet, administered after the injury, only occurred at some postnatal ages despite similar availability of ketone bodies at all ages studied. This led the authors to conclude that differences in the ability of the brain to utilize ketones at different developmental stages may influence the protection conferred (Rafiki *et al.*, 2003; Vannucci and Simpson, 2003; Pierre and Pellerin, 2005). In a previous study, a 48-h fast, which results in similar short-term ketosis as that achieved by the ketogenic diet, was found to protect rats against neuronal loss in the striatum, neocortex, and hippocampus produced by 30-min four-vessel occlusion (Marie *et al.*, 1990). There was also a reduction in mortality and the incidence of postischemic seizures in fasted animals. Thus, there is evidence that the ketogenic diet has neuroprotective activity in both traumatic and ischemic brain injury. An additional study found that rats receiving a ketogenic diet are also resistant to cortical neuron loss occurring in the setting of insulin-induced hypoglycemia (Yamada *et al.*, 2005).

Although the mechanism whereby the ketogenic diet confers protection in these diverse injury models is not well understood, β-hydroxybutyrate could play a role. The ketone body would presumably serve as an alternative energy source to mitigate injury-induced ATP depletion. In fact, exogenous administration of β-hydroxybutyrate can reduce brain damage and improve neuronal function in models of brain hypoxia, anoxia, and ischemia (Cherian *et al.*, 1994; Dardzinski *et al.*, 2000; Suzuki *et al.*, 2001, 2002; Smith *et al.*, 2005). In addition, the other ketone bodies, acetoacetate and acetone, which are β-hydroxybutyrate metabolites and can also serve as alternative energy sources, have similar neuroprotective effects (Garcia and Massieu, 2001; Massieu *et al.*, 2001, 2003; Noh *et al.*, 2006). Interestingly, in rats receiving a ketogenic diet, neuronal uptake of β-hydroxybutyrate is increased after cortical impact injury in comparison with animals receiving a standard diet (Prins *et al.*, 2004). Thus, the ketogenic diet may promote delivery of β-hydroxybutyrate to the brain.

Cellular mechanisms underlying the neuroprotective activity of the ketogenic diet

Effects on energy metabolism

As noted above, ketone bodies, including β-hydroxybutyrate, that are produced during consumption of the ketogenic diet may serve as an alternative source of energy in states of metabolic stress, thus contributing to the neuroprotective activity of the diet. In fact, β-hydroxybutyrate may provide a more efficient source of energy for brain per unit oxygen than glucose (Veech *et al.*, 2001). Recently, using microarrays to define patterns of gene expression, Bough *et al.* (2006) made the remarkable discovery that the ketogenic diet causes a coordinated upregulation of hippocampal genes encoding energy metabolism and mitochondrial enzymes. Electron micrographs from the dentate/hilar region of the hippocampus showed a 46% increase in mitochondrial profiles in rats fed the ketogenic diet. Thus, the ketogenic diet appears to stimulate mitochondrial biogenesis. Moreover, there was a greater phosphocreatine : creatine ratio in the hippocampal tissue, indicating an increase in cellular energy reserves, as expected from the greater abundance of mitochondria. In sum, during consumption of the ketogenic diet, two factors may contribute to the ability of neurons to resist metabolic stress: a larger mitochondrial load and a more energy-efficient fuel. In combination, these factors may account for the enhanced ability of neurons to withstand metabolic challenges of a degree that would ordinarily exhaust the resilience of the neurons and result in cellular demise.

Effects on glutamate-mediated toxicity

Interference with glutamate-mediated toxicity, a major mechanism underlying neuronal injury, is an alternative way in which the ketogenic diet could confer neuroprotection, although the available evidence supporting this concept is scant. Thus, acetoacetate has been shown to

protect against glutamate-mediated toxicity in both primary hippocampal neuron cell cultures; however, a similar effect occurred in an immortalized hippocampal cell line (HT22) lacking ionotropic glutamate receptors (Noh *et al.*, 2006). Acetoacetate also decreased the formation of early cellular markers of glutamate-induced apoptosis and necrosis, probably through the attenuation of glutamate-induced formation of ROS, as discussed below.

Effects on γ-aminobutyric acid systems

Another possible way in which the ketogenic diet may confer neuroprotection is through enhancement of γ-aminobutyric acid (GABA) levels, with a consequent increase in GABA-mediated inhibition (Yudkoff *et al.*, 2001). Thus, ketone bodies have been demonstrated to increase the GABA content in rat brain synaptosomes (Erecinska *et al.*, 1996), and, using in-vivo proton two-dimensional double-quantum spin-echo spectroscopy, the ketogenic diet was associated with elevated levels of GABA in some but not all human subjects studied (Wang *et al.*, 2003). Rats fed a ketogenic diet did not, however, show increases in cerebral GABA (al-Mudallal *et al.*, 1996).

Antioxidant mechanisms

Enhancement of antioxidant mechanisms represents an additional potential mechanism of neuroprotection. For example, ketone bodies have been shown to reduce the amount of coenzyme Q semiquinone, thereby decreasing free radical production (Veech, 2004).

A key enzyme in the control of ROS formation is glutathione peroxidase, a peroxidase found in erythrocytes that prevents lipid peroxidation by reducing lipid hydroperoxides to their corresponding alcohols and reducing free hydrogen peroxide to water. The ketogenic diet induces glutathione peroxidase activity in the rat hippocampus (Ziegler *et al.*, 2003).

The ketogenic diet also increases production of specific mitochondrial uncoupling proteins (UCPs) (Sullivan *et al.*, 2004). For example, in mice fed a ketogenic diet, UCP2, UCP4, and UCP5 were increased, particularly in the dentate gyrus. UCPs serve to dissipate the mitochondrial membrane potential, which, in turn, decreases the formation of ROS. Thus, juvenile mice fed a ketogenic diet had higher maximum mitochondrial respiration rates than those fed a control diet. Oligomycin-induced ROS production was also lower in the ketogenic diet-fed group. The ketogenic diet likely induces UCP production via fatty acids (Freeman *et al.*, 2006). Levels of many polyunsaturated fatty acids are elevated in human patients on the ketogenic diet (Fraser *et al.*, 2003). In fact, in patients with epilepsy, levels of one polyunsaturated fatty acid, arachidonate, were found to correlate with seizure control, although it has not yet been shown that arachidonate induces UCP production.

Effects on programmed cell death

The ketogenic diet may also protect against various forms of cell death. For example, the diet was protective against apoptotic cell death in mice induced by the glutamate receptor agonist and excitotoxin kainate, as evidenced by reductions of markers of apoptosis, including terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick-end labeling and caspase-3 staining, in neurons in the CA1 and CA3 regions of the hippocampus (Noh *et al.*, 2003). Activation of caspase-3, a member of a larger family of cysteine proteases, has been implicated in neuronal cell death produced by different brain insults including seizures and ischemia (Gillardon *et al.*, 1997; Chen *et al.*, 1998). Apoptosis in seizure models can proceed via a number of molecular pathways (McIntosh *et al.*, 1998; Fujikawa, 2005). One molecule that may play a role is calbindin, which is increased in mice on the ketogenic diet (McIntosh *et al.*, 1998; Noh *et al.*, 2005a). Calbindin is believed to have neuroprotective activity through its capacity to buffer intracellular calcium, which is a mediator of cell death (Mattson *et al.*, 1995; Bellido *et al.*, 2000). Further, protection by the ketogenic diet may be mediated by the

prevention of kainic acid-induced accumulation of the protein clusterin (Noh *et al.*, 2005b), which can act as a prodeath signal (Jones and Jomary, 2002).

Anti-inflammatory effects

It is well recognized that inflammatory mechanisms play a role in the pathophysiology of acute and chronic neurodegenerative disorders (Neuroinflammation Working Group, 2000; Pratico and Trojanowski, 2000; Chamorro and Hallenbeck, 2006). Inflammation has also been hypothesized to contribute to the development of chronic epilepsy (Vezzani and Granata, 2005). It is therefore of interest that fasting (a state associated with ketonemia, as in the ketogenic diet) or a high-fat diet has been associated with effects on inflammatory mechanisms (Palmblad *et al.*, 1991; Stamp *et al.*, 2005). A link between the ketogenic diet, anti-inflammatory mechanisms, and disease modification of neurological disease is still highly tentative. It is, however, noteworthy that intermittently fasted rats have increased expression of the cytokine interferon-γ in the hippocampus, and it was further shown that the cytokine conferred protection against excitotoxic cell death (Lee *et al.*, 2006). The high fatty acid load of the ketogenic diet may also activate anti-inflammatory mechanisms. For example, it has been shown that fatty acids activate peroxisome proliferator-activated receptor α, which may, in turn, have inhibitory effects on the proinflammatory transcription factors nuclear factor-κB and activation protein-1 (Cullingford, 2004).

Carbohydrate restriction as a protective mechanism

A key aspect of the ketogenic diet is carbohydrate restriction. The role of decreased carbohydrates in neuroprotection has been investigated through the use of 2-deoxy-D-glucose (2-DG), a glucose analog that is not metabolized by glycolysis. Lee *et al.* (1999) found that administration of 2-DG to adult rats at a nontoxic dose (200 mg/kg) for 7 consecutive days produced dramatic protection against hippocampal damage and functional neurological deficits induced by the seizure-inducing excitotoxin kainate. In addition, 2-DG was protective against glutamate-induced and oxidative stress-induced neuronal death in cell culture. The authors also found that reduced glucose availability induces stress proteins, including GRP78 and HSP70, which they proposed act to suppress ROS production, stabilize intracellular calcium, and maintain mitochondrial function.

Conclusions

A wide variety of evidence suggests that the ketogenic diet could have beneficial disease-modifying effects in epilepsy and also in a broad range of neurological disorders characterized by death of neurons. Although the mechanism by which the diet confers neuroprotection is not fully understood, effects on cellular energetics are likely to play a key role. It has long been recognized that the ketogenic diet is associated with increased circulating levels of ketone bodies, which represent a more efficient fuel in the brain, and there may also be increased numbers of brain mitochondria. It is plausible that the enhanced energy production capacity resulting from these effects would confer neurons with greater ability to resist metabolic challenges. Additionally, biochemical changes induced by the diet – including the ketosis, high serum fat levels, and low serum glucose levels – could contribute to protection against neuronal death by apoptosis and necrosis through a multitude of additional mechanisms, including antioxidant and antiinflammatory actions. Theoretically, the ketogenic diet might have greater efficacy in children than in adults, inasmuch as younger brains have greater capacity to transport and utilize ketone bodies as an energy source (Rafiki *et al.*, 2003; Vannucci and Simpson, 2003; Pierre and Pellerin, 2005).

Controlled clinical trials are required to confirm the utility of the diet as a disease-modifying approach in any of the conditions in which it has been proposed to be effective. A greater

understanding of the underlying mechanisms, however, should allow the diet to be more appropriately studied. Indeed, there are many as yet unanswered questions about the use of the diet. For example, in epilepsy, how long an exposure to the diet is necessary? Do short periods of exposure to the diet confer long-term benefit? Why can the protective effects of the diet be readily reversed by exposure to carbohydrates in some but not all patients? In situations of acute neuronal injury, can the diet be administered after the neuronal injury, and if so, what time window is available? Does monitoring the diet through measurements of biochemical parameters improve efficacy and, if so, what is the best marker to monitor? Finally, the most fundamental research questions are what role ketosis plays, if any, in the therapeutic effects of the diet, and whether low glucose levels contribute to or are necessary for its symptomatic or proposed disease-modifying activity.

Moreover, a better understanding of the mechanisms may provide insights into ketogenic diet-inspired therapeutic approaches that eliminate the need for strict adherence to the diet, which is unpalatable, difficult to maintain, and is associated with side effects such as hyperuricemia and nephrolithiasis, and adverse effects on bone health and the liver (Freeman *et al.*, 2006). A variety of approaches have been devised that allow ketosis to be obtained without the need to consume a high fat, low carbohydrate diet. The simplest is the direct administration of ketone bodies, such as through the use of the sodium salt form of β-hydroxybutyrate. Toxicological studies in animals have demonstrated that β-hydroxybutyrate sodium is well tolerated, and that theoretical risks such as acidosis and sodium and osmotic overload can be avoided by careful monitoring of blood parameters (Smith *et al.*, 2005). Intravenous β-hydroxybutyrate has the potential to provide neuroprotection against ischemia during some surgical procedures, such as cardiopulmonary bypass. Owing to its short half-life, β-hydroxybutyrate sodium is, however, not suitable for long-term therapy in the treatment of chronic neurodegenerative disorders. In these circumstances, orally bioavailable polymers of β-hydroxybutyrate and its derivatives with improved pharmacokinetic properties may be of utility (Veech, 2004; Smith *et al.*, 2005). Another interesting alternative to the ketogenic diet is the administration of metabolic precursors of ketone bodies. Among potential precursor molecules, 1,3-butanediol and 1,3-butanediol acetoacetate esters have been most extensively studied. These compounds are metabolized in a chain of enzymatic reactions in the plasma and liver to the same ketone bodies that are produced during the ketogenic diet (Desrochers *et al.*, 1992, 1995; Ciraolo *et al.*, 1995). Although each of the aforementioned alternatives is still early in development, the idea of developing the ketogenic diet in a 'pill' is very attractive and may be approachable.

References

Acheson KJ. Carbohydrate and weight control: where do we stand? Curr Opin Clin Nutr Metab Care 2004;7:485–492. [PubMed: 15192454]

al-Mudallal AS, LaManna JC, Lust WD, Harik SI. Diet-induced ketosis does not cause cerebral acidosis. Epilepsia 1996;37:258–261. [PubMed: 8598184]

Appleton DB, De Vivo DC. An experimental animal model for the effect of ketogenic diet on epilepsy. Proc Aust Assoc Neurol 1973;10:75–80. [PubMed: 4792164]

Barberger-Gateau P, Letenneur L, Deschamps V, Peres K, Dartigues JF, Renaud S. Fish, meat, and risk of dementia: cohort study. BMJ 2002;325:932–933. [PubMed: 12399342]

Bellido T, Huening M, Raval-Pandya M, Manolagas SC, Christakos S. Calbindin-D28k is expressed in osteoblastic cells and suppresses their apoptosis by inhibiting caspase-3 activity. J Biol Chem 2000;275:26328–26332. [PubMed: 10835428]

Benardo LS. Prevention of epilepsy after head trauma: do we need new drugs or a new approach? Epilepsia 2003;44:27–33. [PubMed: 14511392]

Bough KJ, Gudi K, Han FT, Rathod AH, Eagles DA. An anticonvulsant profile of the ketogenic diet in the rat. Epilepsy Res 2002;50:313–325. [PubMed: 12200222]

Bough KJ, Wetherington J, Hassel B, Pare JF, Gawryluk JW, Greene JG, et al. Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. Ann Neurol 2006;60

Cahill GF Jr, Veech RL. Ketoacids? Good medicine? Trans Am Clin Climatol Assoc 2003;114:149–161. [PubMed: 12813917]

Caraballo RH, Cersosimo RO, Sakr D, Cresta A, Escobal N, Fejerman N. Ketogenic diet in patients with Dravet syndrome. Epilepsia 2005;46:1539–1544. [PubMed: 16146451]

Chamorro A, Hallenbeck J. The harms and benefits of inflammatory and immune responses in vascular disease. Stroke 2006;37:291–293. [PubMed: 16410468]

Chen J, Nagayama T, Jin K, Stetler RA, Zhu RL, Graham SH, Simon RP. Induction of caspase-3-like protease may mediate delayed neuronal death in the hippocampus after transient cerebral ischemia. J Neurosci 1998;18:4914–4928. [PubMed: 9634557]

Cherian L, Peek K, Robertson CS, Goodman JC, Grossman RG. Calorie sources and recovery from central nervous system ischemia. Crit Care Med 1994;22:1841–1850. [PubMed: 7956290]

Ciraolo ST, Previs SF, Fernandez CA, Agarwal KC, David F, Koshy J, et al. Model of extreme hypoglycemia in dogs made ketotic with (*R,S*)-1, 3-butanediol acetoacetate esters. Am J Physiol 1995;269:E67–E75. [PubMed: 7631780]

Crumrine PK. Lennox-Gastaut syndrome. J Child Neurol 2002;17:S70–S75. [PubMed: 11918467]

Cullingford TE. The ketogenic diet; fatty acids, fatty acid-activated receptors and neurological disorders. Prostaglandins Leukot Essent Fatty Acids 2004;70:253–264. [PubMed: 14769484]

Cunnane SC, Musa K, Ryan MA, Whiting S, Fraser DD. Potential role of polyunsaturates in seizure protection achieved with the ketogenic diet. Prostaglandins Leukot Essent Fatty Acids 2002;67:131–135. [PubMed: 12324231]

Dardzinski BJ, Smith SL, Towfighi J, Williams GD, Vannucci RC, Smith MB. Increased plasma beta-hydroxybutyrate, preserved cerebral energy metabolism, and amelioration of brain damage during neonatal hypoxia ischemia with dexamethasone pretreatment. Pediatr Res 2000;48:248–255. [PubMed: 10926303]

Desrochers S, David F, Garneau M, Jetté M, Brunengraber H. Metabolism of R- and S-1,3-butanediol in perfused livers from meal-fed and starved rats. Biochem J 1992;285:647–653. [PubMed: 1637355]

Desrochers S, Dubreuil P, Brunet J, Jetté M, David F, Landau BR, Brunengraber H. Metabolism of (*R,S*)-1,3-butanediol acetoacetate esters, potential parenteral and enteral nutrients in conscious pigs. Am J Physiol 1995;268:E660–E667. [PubMed: 7733265]

de Lau LM, Bornebroek M, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Dietary fatty acids and the risk of Parkinson disease: the Rotterdam study. Neurology 2005;64:2040–2045. [PubMed: 15985568]

Duan W, Mattson MP. Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease. J Neurosci Res 1999;57:195–206. [PubMed: 10398297]

Engelhart MJ, Geerlings MI, Ruitenberg A, van Swieten JC, Hofman A, Witteman JC, Breteler MM. Diet and risk of dementia: does fat matter? The Rotterdam Study. Neurology 2002;59:1915–1921. [PubMed: 12499483]

Erecinska M, Nelson D, Daikhin Y, Yudkoff M. Regulation of GABA level in rat brain synaptosomes: fluxes through enzymes of the GABA shunt and effects of glutamate, calcium, and ketone bodies. J Neurochem 1996;67:2325–2334. [PubMed: 8931464]

Fraser DD, Whiting S, Andrew RD, Macdonald EA, Musa-Veloso K, Cunnane SC. Elevated polyunsaturated fatty acids in blood serum obtained from children on the ketogenic diet. Neurology 2003;60:1026–1029. [PubMed: 12654976]

Freeman J, Veggiotti P, Lanzi G, Tagliabue A, Perucca E. The ketogenic diet: from molecular mechanisms to clinical effects. Epilepsy Res 2006;68:145–180. [PubMed: 16523530]

Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, Kelly LM. The efficacy of the ketogenic diet – 1998: a prospective evaluation of intervention in 150 children. Pediatrics 1998;102:1358–1363. [PubMed: 9832569]

Fujikawa DG. Prolonged seizures and cellular injury: understanding the connection. Epilepsy Behav 2005;7:S3–S11. [PubMed: 16278099]

Garcia O, Massieu L. Strategies for neuroprotection against l-trans-2, 4-pyrrolidine dicarboxylate-induced neuronal damage during energy impairment *in vitro*. J Neurosci Res 2001;64:418–428. [PubMed: 11340649]

George AJ, Holsinger RMD, McLean CA, Laughton KM, Beyreuther K, Evin G, et al. APP intracellular domain is increased and soluble A β is reduced with diet-induced hypercholesterolemia in a transgenic mouse model of Alzheimer disease. Neurobiol Dis 2004;16:124–132. [PubMed: 15207269]

Gillardon F, Bottiger B, Schmitz B, Zimmermann M, Hossmann KA. Activation of CPP-32 protease in hippocampal neurons following ischemia and epilepsy. Brain Res Mol Brain Res 1997;50:16–22. [PubMed: 9406913]

Grant WB. Dietary links to Alzheimer's disease: 1999 update. J Alzheimers Dis 1999;1:197–201. [PubMed: 12214118]

Greene AE, Todorova MT, McGowan R, Seyfried TN. Caloric restriction inhibits seizure susceptibility in epileptic EL mice by reducing blood glucose. Epilepsia 2001;42:1371–1378. [PubMed: 11879337]

Hashimoto M, Hossain S, Shimada T, Sugioka K, Yamasaki H, Fujii Y, et al. Docosahexaenoic acid provides protection from impairment of learning ability in Alzheimer's disease model rats. J Neurochem 2002;81:1084–1091. [PubMed: 12065621]

Hashimoto M, Tanabe Y, Fujii Y, Kikuta T, Shibata H, Shido O. Chronic administration of docosahexaenoic acid ameliorates the impairment of spatial cognition learning ability in amyloid β-infused rats. J Nutr 2005;135:549–555. [PubMed: 15735092]

Hemingway C, Freeman JM, Pillas DJ, Pyzik PL. The ketogenic diet: a 3- to 6- year follow-up of 150 children enrolled prospectively. Pediatrics 2001;108:898–905. [PubMed: 11581442]

Henderson ST. High carbohydrate diets and Alzheimer's disease. Med Hypotheses 2004;62:689–700. [PubMed: 15082091]

Ho L, Qin W, Pompl PN, Xiang Z, Wang J, Zhao Z, et al. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. FASEB J 2004;18:902–904. [PubMed: 15033922]

Holmer HK, Keyghobadi M, Moore C, Menashe RA, Meshul CK. Dietary restriction affects striatal glutamate in the MPTP-induced mouse model of nigrostriatal degeneration. Synapse 2005;57:100–112. [PubMed: 15906381]

Hori A, Tandon P, Holmes GL, Stafstrom CE. Ketogenic diet: effects on expression of kindled seizures and behavior in adult rats. Epilepsia 1997;38:750–758. [PubMed: 9579901]

Huttenlocher PR. Ketonemia and seizures: metabolic and anticonvulsant effects of two ketogenic diets in childhood epilepsy. Pediatr Res 1976;10:536–540. [PubMed: 934725]

Huttenlocher PR, Wilbourn AJ, Signore JM. Medium-chain triglycerides as a therapy for intractable childhood epilepsy. Neurology 1971;21:1097–1103. [PubMed: 5166216]

Jones SE, Jomary C. Clusterin. Int J Biochem Cell Biol 2002;34:427–431. [PubMed: 11906815]

Kalmijn S, Launer LJ, Ott A, Witteman JC, Hofman A, Breteler MM. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol 1997;42:776–782. [PubMed: 9392577]

Kashiwaya Y, Takeshima T, Mori N, Nakashima K, Clarke K, Veech RL. d-β-hydroxybutyrate protects neurons in models of Alzheimer's and Parkinson's disease. Proc Natl Acad Sci USA 2000;97:5440–5444. [PubMed: 10805800]

Kossoff EH. More fat and fewer seizures: dietary therapies for epilepsy. Lancet Neurol 2004;3:415–420. [PubMed: 15207798]

Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP. A modified atkins diet is effective for the treatment of intractable pediatric epilepsy. Epilepsia 2006;47:421–424. [PubMed: 16499770]

Lee J, Bruce-Keller AJ, Kruman Y, Chan SL, Mattson MP. 2-Deoxy-d-glucose protects hippocampal neurons against excitotoxic and oxidative injury: evidence for the involvement of stress proteins. J Neurosci Res 1999;57:48–61. [PubMed: 10397635]

Lee J, Kim SJ, Son TG, Chan SL, Mattson MP. Interferon-gamma is upregulated in the hippocampus in response to intermittent fasting and protects hippocampal neurons against excitotoxicity. J Neurosci Res 2006;83:1552–1557. [PubMed: 16521127]

Levin-Allerhand JA, Lominska CE, Smith JD. Increased amyloid-levels in APPSWE transgenic mice treated chronically with a physiological high-fat high-cholesterol diet. J Nutr Health Aging 2002;6:315–319. [PubMed: 12474021]

Likhodii SS, Musa K, Mendonca A, Dell C, Burnham WM, Cunnane SC. Dietary fat, ketosis, and seizure resistance in rats on the ketogenic diet. Epilepsia 2000;41:1400–1410. [PubMed: 11077453]

Lim GP, Calon F, Morihara T, Yang F, Teter B, Ubeda O, et al. A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. J Neurosci 2005;25:3032–3040. [PubMed: 15788759]

Mantis JG, Centeno NA, Todorova MT, McGowan R, Seyfried TN. Management of multifactorial idiopathic epilepsy in EL mice with caloric restriction and the ketogenic diet: role of glucose and ketone bodies. Nutr Metab (London) 2004;1:11.

Marie C, Bralet AM, Gueldry S, Bralet J. Fasting prior to transient cerebral ischemia reduces delayed neuronal necrosis. Metab Brain Dis 1990;5:65–75. [PubMed: 2385215]

Marsh EB, Freeman JM, Kossoff EH, Vining EP, Rubenstein JE, Pyzik PL, Hemingway C. The outcome of children with intractable seizures: a 3- to 6-year follow-up of 67 children who remained on the ketogenic diet less than one year. Epilepsia 2006;47:425–430. [PubMed: 16499771]

Massieu L, Del RP, Montiel T. Neurotoxicity of glutamate uptake inhibition in vivo: correlation with succinate dehydrogenase activity and prevention by energy substrates. Neuroscience 2001;106:669–677. [PubMed: 11682154]

Massieu L, Haces ML, Montiel T, Hernandez-Fonseca K. Acetoacetate protects hippocampal neurons against glutamate-mediated neuronal damage during glycolysis inhibition. Neuroscience 2003;120:365–378. [PubMed: 12890508]

Maswood N, Young J, Tilmont E, Zhang Z, Gash DM, Gerhardt GA, et al. Caloric restriction increases neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease. Proc Natl Acad Sci USA 2004;101:18171–18176. [PubMed: 15604149]

Mattson MP, Cheng B, Baldwin SA, Smith-Swintosky VL, Keller J, Geddes JW, et al. Brain injury and tumor necrosis factors induce calbindin D-28k in astrocytes: evidence for a cytoprotective response. J Neurosci Res 1995;42:357–370. [PubMed: 8583504]

McIntosh TK, Saatman KE, Raghupathi R, Graham DI, Smith DH, Lee VM, Trojanowski JQ. The Dorothy Russell Memorial Lecture. The molecular and cellular sequelae of experimental traumatic brain injury: pathogenetic mechanisms. Neuropathol Appl Neurobiol 1998;24:251–267. [PubMed: 9775390]

Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, et al. Dietary fats and the risk of incident Alzheimer disease. Arch Neurol 2003a;60:194–200. [PubMed: 12580703]

Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 2003b;60:940–946. [PubMed: 12873849]

Morris MC, Evans DA, Bienias JL, Tangney CC, Wilson RS. Dietary fat intake and 6-year cognitive change in an older biracial community population. Neurology 2004;62:1573–1579. [PubMed: 15136684]

Muller-Schwarze AB, Tandon P, Liu Z, Yang Y, Holmes GL, Stafstrom CE. Ketogenic diet reduces spontaneous seizures and mossy fiber sprouting in the kainic acid model. Neuroreport 1999;10:1517–1522. [PubMed: 10380973]

Musa-Veloso K, Likhodii SS, Cunnane SC. Breath acetone is a reliable indicator of ketosis in adults consuming ketogenic meals. Am J Clin Nutr 2002;76:65–70. [PubMed: 12081817]

Nehlig A. Brain uptake and metabolism of ketone bodies in animal models. Prostaglandins Leukot Essent Fatty Acids 2004;70:265–275. [PubMed: 14769485]

Neuroinflammation Working Group. Inflammation and Alzheimer's disease. Neurobiol Aging 2000;21:383–421. [PubMed: 10858586]

Noh HS, Kim YS, Lee HP, Chung KM, Kim DW, Kang SS, et al. The protective effect of a ketogenic diet on kainic acid-induced hippocampal cell death in the male ICR mice. Epilepsy Res 2003;53:119–128. [PubMed: 12576173]

Noh HS, Kang SS, Kim DW, Kim YH, Park CH, Han JY, et al. Ketogenic diet increases calbindin-D28k in the hippocampi of male ICR mice with kainic acid seizures. Epilepsy Res 2005a;65:153–159. [PubMed: 16046100]

Noh HS, Kim DW, Kang SS, Cho GJ, Choi WS. Ketogenic diet prevents clusterin accumulation induced by kainic acid in the hippocampus of male ICR mice. Brain Res 2005b;1042:114–118. [PubMed: 15823260]

Noh HS, Hah YS, Nilufar R, Han J, Bong JH, Kang SS, et al. Acetoacetate protects neuronal cells from oxidative glutamate toxicity. J Neurosci Res 2006;83:702–709. [PubMed: 16435389]

Palmblad J, Hafstrom I, Ringertz B. Antirheumatic effects of fasting. Rheum Dis Clin North Am 1991;17:351–362. [PubMed: 1862244]

Pan JW, de Graaf RA, Petersen KF, Shulman GI, Hetherington HP, Rothman DL. [2,4-^{13}C$_2$]-β-Hydroxybutyrate metabolism in human brain. J Cereb Blood Flow Metab 2002;22:890–898. [PubMed: 12142574]

Patel NV, Gordon MN, Connor KE, Good RA, Engelman RW, Mason J, et al. Caloric restriction attenuates Aβ-deposition in Alzheimer transgenic models. Neurobiol Aging 2005;26:995–1000. [PubMed: 15748777]

Pierre K, Pellerin L. Monocarboxylate transporters in the central nervous system: distribution, regulation and function. J Neurochem 2005;94:1–14. [PubMed: 15953344]

Pratico D, Trojanowski JQ. Inflammatory hypotheses: novel mechanisms of Alzheimer's neurodegeneration and new therapeutic targets? Neurobiol Aging 2000;21:441–445. [PubMed: 10858591]

Prins ML, Lee SM, Fujima LS, Hovda DA. Increased cerebral uptake and oxidation of exogenous βHB improves ATP following traumatic brain injury in adult rats. J Neurochem 2004;90:666–672. [PubMed: 15255945]

Prins ML, Fujima LS, Hovda DA. Age-dependent reduction of cortical contusion volume by ketones after traumatic brain injury. J Neurosci Res 2005;82:413–420. [PubMed: 16180224]

Rafiki A, Boulland JL, Halestrap AP, Ottersen OP, Bergersen L. Highly differential expression of the monocarboxylate transporters MCT2 and MCT4 in the developing rat brain. Neuroscience 2003;122:677–688. [PubMed: 14622911]

Reger MA, Henderson ST, Hale C, Cholerton B, Baker LD, Watson GS, et al. Effects of β-hydroxybutyrate on cognition in memory-impaired adults. Neurobiol Aging 2004;25:311–314. [PubMed: 15123336]

Rho JM, Anderson GD, Donevan SD, White HS. Acetoacetate, acetone, and dibenzylamine (a contaminant in L-(+)-β-hydroxybutyrate) exhibit direct anticonvulsant actions *in vivo*. Epilepsia 2002;43:358–361. [PubMed: 11952765]

Ruitenberg A, Kalmijn S, de Ridder MA, Redekop WK, van HF, Hofman A, et al. Prognosis of Alzheimer's disease: the Rotterdam Study. Neuroepidemiology 2001;20:188–195. [PubMed: 11490165]

Schachter SC. Current evidence indicates that antiepileptic drugs are anti-ictal, not antiepileptic. Epilepsy Res 2002;50:67–70. [PubMed: 12151118]

Schwartz RH, Eaton J, Bower BD, ynsley-Green A. Ketogenic diets in the treatment of epilepsy: short-term clinical effects. Dev Med Child Neurol 1989;31:145–151. [PubMed: 2786822]

Shie FS, Jin LW, Cook DG, Leverenz JB, LeBoeuf RC. Diet-induced hypercholesterolemia enhances brain Aβ accumulation in transgenic mice. Neuroreport 2002;13:455–459. [PubMed: 11930160]

Sinha SR, Kossoff EH. The ketogenic diet. Neurologist 2005;11:161–170. [PubMed: 15860138]

Smith SL, Heal DJ, Martin KF. KTX 0101: a potential metabolic approach to cytoprotection in major surgery and neurological disorders. CNS Drug Rev 2005;11:113–140. [PubMed: 16007235]

Stafstrom CE. Animal models of the ketogenic diet: what have we learned, what can we learn? Epilepsy Res 1999;37:241–259. [PubMed: 10584974]

Stafstrom CE. Dietary approaches to epilepsy treatment: old and new options on the menu. Epilepsy Curr 2004;4:215–222. [PubMed: 16059506]

Stafstrom CE, Wang C, Jensen FE. Electrophysiological observations in hippocampal slices from rats treated with the ketogenic diet. Dev Neurosci 1999;21:393–399. [PubMed: 10575263]

Stamp LK, James MJ, Cleland LG. Diet and rheumatoid arthritis: a review of the literature. Semin Arthritis Rheum 2005;35:77–94. [PubMed: 16194694]

Su SW, Cilio MR, Sogawa Y, Silveira DC, Holmes GL, Stafstrom CE. Timing of ketogenic diet initiation in an experimental epilepsy model. Brain Res Dev Brain Res 2000;125:131–138.

Sullivan PG, Rippy NA, Dorenbos K, Concepcion RC, Agarwal AK, Rho JM. The ketogenic diet increases mitochondrial uncoupling protein levels and activity. Ann Neurol 2004;55:576–580. [PubMed: 15048898]

Suzuki M, Suzuki M, Sato K, Dohi S, Sato T, Matsuura A, Hiraide A. Effect of β-hydroxybutyrate, a cerebral function improving agent, on cerebral hypoxia, anoxia and ischemia in mice and rats. Jpn J Pharmacol 2001;87:143–150. [PubMed: 11700013]

Suzuki M, Suzuki M, Kitamura Y, Mori S, Sato K, Dohi S, et al. β-hydroxybutyrate, a cerebral function improving agent, protects rat brain against ischemic damage caused by permanent and transient focal cerebral ischemia. Jpn J Pharmacol 2002;89:36–43. [PubMed: 12083741]

Thavendiranathan P, Mendonca A, Dell C, Likhodii SS, Musa K, Iracleous C, et al. The MCT ketogenic diet: effects on animal seizure models. Exp Neurol 2000;161:696–703. [PubMed: 10686088]

Thavendiranathan P, Chow C, Cunnane S, McIntyre BW. The effect of the 'classic' ketogenic diet on animal seizure models. Brain Res 2003;959:206–213. [PubMed: 12493608]

Tieu K, Perier C, Caspersen C, Teismann P, Wu DC, Yan SD, et al. d-β-hydroxybutyrate rescues mitochondrial respiration and mitigates features of Parkinson disease. J Clin Invest 2003;112:892–901. [PubMed: 12975474]

Todorova MT, Tandon P, Madore RA, Stafstrom CE, Seyfried TN. The ketogenic diet inhibits epileptogenesis in EL mice: a genetic model for idiopathic epilepsy. Epilepsia 2000;41:933–940. [PubMed: 10961617]

Trevathan E. Infantile spasms and Lennox-Gastaut syndrome. J Child Neurol 2002;17:2S9–2S22. [PubMed: 11952036]

Van der Auwera I, Wera S, Van LF, Henderson ST. A ketogenic diet reduces amyloid beta 40 and 42 in a mouse model of Alzheimer's disease. Nutr Metab (London) 2005;2:28.

VanItallie TB, Nonas C, Di RA, Boyar K, Hyams K, Heymsfield SB. Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. Neurology 2005;64:728–730. [PubMed: 15728303]

Vannucci SJ, Simpson IA. Developmental switch in brain nutrient transporter expression in the rat. Am J Physiol Endocrinol Metab 2003;285:E1127–E1134. [PubMed: 14534079]

Veech RL. The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. Prostaglandins Leukot Essent Fatty Acids 2004;70:309–319. [PubMed: 14769489]

Veech RL, Chance B, Kashiwaya Y, Lardy HA, Cahill GF Jr. Ketone bodies, potential therapeutic uses. IUBMB Life 2001;51:241–247. [PubMed: 11569918]

Vezzani A, Granata T. Brain inflammation in epilepsy: experimental and clinical evidence. Epilepsia 2005;46:1724–1743. [PubMed: 16302852]

Vining EP, Freeman JM, Ballaban-Gil K, Camfield CS, Camfield PR, Holmes GL, et al. A multicenter study of the efficacy of the ketogenic diet. Arch Neurol 1998;55:1433–1437. [PubMed: 9823827]

Wang ZJ, Bergqvist C, Hunter JV, Jin D, Wang DJ, Wehrli S, Zimmerman RA. *In vivo* measurement of brain metabolites using two-dimensional double-quantum MR spectroscopy: exploration of GABA levels in a ketogenic diet. Magn Reson Med 2003;49:615–619. [PubMed: 12652530]

Wang J, Ho L, Qin W, Rocher AB, Seror I, Humala N, et al. Caloric restriction attenuates β-amyloid neuropathology in a mouse model of Alzheimer's disease. FASEB J 2005;19:659–661. [PubMed: 15650008]

Wilder RM. The effects of ketonemia on the course of epilepsy. Mayo Clin Proc 1921;2:307–308.

Yamada KA, Rensing N, Thio LL. Ketogenic diet reduces hypoglycemia-induced neuronal death in young rats. Neurosci Lett 2005;385:210–214. [PubMed: 15975714]

Young KW, Greenwood CE, van RR, Binns MA. A randomized, crossover trial of high-carbohydrate foods in nursing home residents with Alzheimer's disease: associations among intervention response, body mass index, and behavioral and cognitive function. J Gerontol A Biol Sci Med Sci 2005;60:1039–1045. [PubMed: 16127110]

Yudkoff M, Daikhin Y, Nissim I, Lazarow A, Nissim I. Ketogenic diet, amino acid metabolism, and seizure control. J Neurosci Res 2001;66:931–940. [PubMed: 11746421]

Ziegler DR, Ribeiro LC, Hagenn M, Siqueira IR, Araujo E, Torres IL, et al. Ketogenic diet increases glutathione peroxidase activity in rat hippocampus. Neurochem Res 2003;28:1793–1797. [PubMed: 14649719]