



Dietary Therapies for Epilepsy and Other Neurological Disorders: Highlights of the 3rd International Symposium

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The 3rd International Symposium on Dietary Therapies for Epilepsy was held in Chicago from September 19–21, 2012. The symposium was primarily sponsored and coordinated by The Charlie Foundation to Help Cure Pediatric Epilepsy with major support from Nutricia. The conference, which drew 420 attendees from 30 countries, generated broad appeal among physicians, scientists, dietitians, nurses, pharmacists, and other allied health professionals, as well as interested families. This article briefly reviews some of the scientific advances highlighted at the meeting in the field of dietary therapy for epilepsy since the prior international symposium in 2010. A more comprehensive review of the proceedings will appear in a special issue of the *Journal of Child Neurology* in 2013, edited by Eric Kossoff, Liu Lin Thio, and Elizabeth Thiele.

The keynote address was given by Gary Taubes, science writer and author of *Good Calories, Bad Calories*. Taubes traced the correlation between dietary practices and disease incidence across cultures and historical eras. The overall conclusion: Societies that eat fewer carbohydrates are healthier, exhibit less obesity, and develop fewer diseases; in essence, “a calorie is not just a calorie” but depends upon its source (1). The findings that a diet high in fat and low in carbohydrates not only can be tolerated but is also healthier supports the use of the ketogenic diet as an epilepsy therapy with beneficial overall health implications, rather than a bizarre, unhealthy alternative, as previously thought. Subsequent symposium sessions dealt with specific dietary formulations and practices, clinical updates on dietary therapies for epilepsy and other disorders, and scientific advances in understanding the mechanisms of dietary therapies.

Clinical Advances

The effectiveness of the high-fat, low-carbohydrate ketogenic diet for medically refractory childhood epilepsy has been recognized throughout its 90-year history, and now evidence-based efficacy is established by a randomized clinical trial (2). More than 38% of patients who started on a ketogenic diet experienced a 50% or greater reduction in seizures at 3 months, a response largely maintained at 1 year. As reviewed by Helen Cross, four randomized clinical trials have now been published, with an updated Cochrane review concluding that compared to a prior review in 2003, the ketogenic diet results in short- to medium-term benefits in seizure control, comparable to modern antiepileptic drugs (3). This exciting evidence validates observations of clinicians who have been using the diet for decades; this evidence-based data infuses the field with tremendous energy as we move forward to optimize the ketogenic diet and establish its place in the treatment of epilepsy and other disorders. From this conference, it is clear that the ketogenic diet is now considered an essentially mainstream treatment for children with refractory epilepsy—a remarkable change compared to 1994 when The Charlie Foundation was founded.

A related clinical advance is the recent effort to determine the responsiveness of different seizure subtypes and epilepsy syndromes to the ketogenic diet. Also reviewed by Dr. Cross, data are accumulating to support the use of the ketogenic diet in such intractable epilepsy syndromes as infantile spasms and Lennox-Gastaut syndrome (4–8). Other epilepsy syndromes that appear to respond well to the ketogenic diet include Dravet syndrome, myoclonic astatic epilepsy (Doose syndrome), GLUT1 deficiency (reviewed by Joerg Klepper), status epilepticus (9), and other generalized genetic epilepsies (7). In addition, evidence suggests that the ketogenic diet and its variants are effective across the age spectrum, not just in young children but also in infants, adults, and elderly individuals (as discussed by several speakers).



As indicated by the conference's title, dietary therapies are now expanding beyond epilepsy (10, 11). Other neurologic disorders that may be amenable to ketogenic diet therapy include pain (discussed by Susan Massino) (12), Alzheimer disease (discussed by Marwan Maalouf) (13, 14), amyotrophic lateral sclerosis (discussed by Anne Marie Willis) (15), autism (discussed by Patricia Murphy and Julie Buckley) (16), traumatic brain injury (discussed by Mayumi Prins) (17), cancer (discussed by Joseph Maroon) (18, 19), and many others. Data suggesting a beneficial effect of the ketogenic diet in those conditions remains preliminary and anecdotal; however, collectively, they raise the possibility that neurologic disorders with diverse etiologies can respond to dietary manipulation—not only diseases of abnormal excitability but also chronic neurodegenerative diseases and those with undetermined etiologies. As discussed by several speakers, neuroprotection and anti-inflammation may be common underlying mechanistic themes as to why dietary therapy might be beneficial in these diverse conditions. Further clinical trials and laboratory investigations will proceed in parallel to optimize dietary approaches to these disorders.

An underlying goal is to formulate a regimen that is better tolerated and has equal or better efficacy than the classic ketogenic diet. Several speakers, including Eric Kossoff, Elizabeth Neal and Elizabeth Thiele, updated the clinical use of alternative ketogenic diets (20). While evidence for ketogenic diet variants—such as the medium chain triglyceride (MCT) diet, modified Atkins diet (MAD), and low glycemic index treatment (LGIT)—has been accumulating for several years, new data presented at this symposium confirms the effectiveness of these diets, with an expanding number of patients and wider applications in terms of age (21–25). The MAD and LGIT appear to have excellent efficacy in a spectrum of epilepsies very similar to the classic ketogenic diet and with better tolerability, especially for older children and adults able to make dietary choices. Furthermore, a variety of specific syndrome-based applications are emerging, with studies showing efficacy in Angelman syndrome, tuberous sclerosis, and infantile spasms (26–28). Obviously, use of these promising alternative diets in specific patient populations and for specific epilepsy syndromes needs to be validated.

A unique breakout session dealt with the expanding use of dietary therapy for adults with epilepsy. Speakers from the United States, United Kingdom, and India reported their early experience in setting up adult epilepsy diet centers in their countries. Two adults with epilepsy shared their personal insights and challenges in maintaining a restrictive diet, which was very enlightening for dietitians and neurologists present. Jeff Volek, a dietitian and exercise specialist, educated the group about his research into maintaining optimal health of adults on low carbohydrate diets.

Basic Science Advances

Basic science presentations complemented clinical advances and delved into emerging mechanisms by which diets might work. Further understanding of dietary mechanisms will aid our ability to devise even more effective therapies. Several speakers presented new information about the mechanisms of dietary treatments, with a focus on alterations in energy metabolism or utilization.

The mechanism by which the ketogenic diet exerts an anticonvulsant effect remains elusive. Bioenergetic considerations lie at the heart of theories as to how the ketogenic diet works. Concepts about energy metabolism at the cellular level were reviewed by Matthew Vander Heiden, who introduced the perspective that different cells utilize different energetic control mechanisms (29). For example, cancer cells differ from normal cells in having high metabolic needs for the purpose of proliferation, using aerobic glycolysis—the Warburg effect—whereby glucose is metabolized into lactate for energy, regardless of oxygen availability. This concept has been previously invoked to link a beneficial effect of the ketogenic diet or calorie restriction to slow the growth of brain tumors (30). Given the great diversity of cell types and functions in the CNS and their varying energy requirements, this idea has fundamental implications as to how we attempt to unravel the energetic principles by which dietary therapies work.

The relative contribution of increased fat versus decreased carbohydrate availability in ketogenic diets was discussed by Carl Stafstrom. The glucose analog 2-deoxy-D-glucose (2DG) partially inhibits glycolysis by impeding the flux of glucose at the level of the enzyme phosphoglucose isomerase; 2DG has been shown to exert both acute anticonvulsant and chronic antiepileptic actions in several experimental models including kindling, corneal electroshock, and audiogenic seizures in Fring's mice, as well as in hippocampal slices exposed to a variety of convulsant agents (elevated K^+ , bicuculline, 4-aminopyridine) (31). However, 2DG does not suppress acute seizures evoked by the maximum electroshock test. The mechanism of chronic antiepileptic action of 2DG may involve suppression of seizure-induced upregulation of genes for brain-derived neurotrophic factor (BDNF) and its receptor *trkB* (32). The acute anticonvulsant mechanism of 2DG is not fully established, but its effects are activity-dependent; preliminary data suggest that it acts presynaptically. When administered to animals either before or after seizures, 2DG has beneficial actions. Altogether, 2DG manifests a unique spectrum of action unlike any current antiepileptic drug and may modify disease progression, posing this compound as a novel treatment approach for seizures and epilepsy. Preclinical studies are underway to support an investigational new drug (IND) application.

Ketones must somehow regulate neuronal excitability, although a direct inhibitory effect on cell membrane ion channels or synaptic currents has not been demonstrated (33). As glutamate neurotransmission is affected by ketone bodies, another potential target of ketones could be the loading of glutamate into presynaptic vesicles. Theoretically, reduced glutamate transport into vesicles (via the transport protein VGLUT) and its release machinery might reduce glutamate release and lower its availability at the synapse, ameliorating synaptic excitation. Yoshinori Moriyama presented data showing that glutamate uptake into presynaptic vesicles—normally dependent on Cl^- —is reduced by ketones (34, 35). The ketone body, acetoacetate, suppressed seizures induced by direct infusion of the convulsant 4-aminopyridine into mouse brain and decreased glutamate release in a dose-dependent manner. Therefore, the KD diet may work, at least partially, via regulation of the availability of glutamate for synaptic release.



A further link between alternative fuel utilization and neuronal excitability comes from studies of the Bcl-2-associated agonist of cell death (BAD), a unique protein with multiple functions: It both promotes apoptosis and controls mitochondrial fuel utilization and neuronal excitability. The function of BAD in the cell is modulated by its state of phosphorylation; when BAD is phosphorylated, mitochondria are stimulated to produce ATP via glucose, and when BAD is dephosphorylated or dysfunctional (e.g., BAD knockout or phosphorylation mutation), mitochondria switch to ketone bodies as their preferred fuel (36). As explained by Nika Danial, in mice with knockout of the gene encoding BAD or in mice with BAD deficiency caused by serine 155 phosphorylation mutations, neurons switch from glucose to ketones as their primary energy source, analogous to the ketogenic diet (37). When the convulsant kainic acid is administered to BAD knockout mice, less severe acute status epilepticus ensues compared to control mice, suggesting that fuel choice alters neuronal excitability and, thus, seizure sensitivity. The molecular explanation for this BAD-induced alteration in neuronal excitability may be related to the activity of plasmalemmal ATP-sensitive potassium (K_{ATP}) channels, which are opened when the intracellular level of ATP is low. Activation of K_{ATP} channels reduces cellular excitability, and ketone bodies such as β -hydroxybutyrate increase the probability of K_{ATP} channel opening. In dentate gyrus neurons of BAD knockout mice, there is increased activity of single K_{ATP} channels. Therefore, membrane excitability is directly altered by ketone-modulated effects on K_{ATP} channels. It was previously shown that ketones increased K_{ATP} function in neurons of the hippocampus and substantia nigra (38, 39). In cultured neurons from BAD knockout mice, the increased probability of K_{ATP} channel opening is reversed by pharmacologic blockade of K_{ATP} channels with tolbutamide. These results solidify the emerging concept that neuronal excitability is directly modulated by metabolic pathways, and these data raise the possibility that K_{ATP} or other cellular proteins could be a target for novel therapeutics (40).

The involvement of the mammalian target of rapamycin (mTOR) pathway in epilepsy was explored by Adam Hartman in the context of the ketogenic diet. The mTOR-containing TORC1 complex is a nutrient-sensing mechanism, responding to changes in the levels of glucose and amino acids. mTOR is regulated via 5' adenosine monophosphate-activated protein kinase (AMPK), which inhibits mTOR function; AMPK itself is regulated by hypoglycemia, fasting, and energy supply. Glucose depletion suppresses mTOR serine-threonine kinase activity, leading to reduced protein translation and induction of autophagy. Inhibitors of mTOR have been shown to reduce spontaneous seizures in several animal models in which mTOR pathway mutations are not operative, leading to the hypothesis that mTOR inhibition regulates neuronal excitability in a more general sense (41). However, the specific antiseizure effects of mTOR have not been identified. mTOR inhibition probably exerts its effects over a long-term basis rather than acutely. Evidence is accumulating that long-term dietary treatments—such as the KD or intermittent fasting—have anticonvulsant profiles dissimilar to that of the mTOR inhibitor, rapamycin (42). Rapamycin may exert its effects via changes in dendritic spine morphogenesis, modulation of ion channels

such as calcium-dependent potassium channels, or alteration of local synaptic protein translation.

Overall, scientific advances regarding ketogenic diet focus on energy needs of neurons, shared mechanisms of neuroprotection, and the emerging realization that the flux of metabolites through energy-requiring systems is a more relevant concept than simply levels of substrate. Much work needs to be done regarding different dietary effects and ketone effects in the variety of models now emerging. With the increasing number of diseases beyond epilepsy possibly modulated by dietary treatments, the remaining mechanistic questions and opportunities for new applications remain almost limitless.

Conclusion

In summary, this symposium generated considerable excitement about dietary therapies, as judged by the number of attendees and their enthusiasm, the breadth and depth of platform and poster presentations, and the influx of new researchers and centers becoming involved in this field. Plans are already underway for the 4th International Symposium to be held in Liverpool, UK, in 2014.

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