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Neuroprotection in metabolism-based therapy

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Summary Metabolism-based therapy has been used successfully in the treatment of seizures but study of its use in other neurodegenerative disorders is growing. Data demonstrating the use of different forms of metabolism-based therapy in human trials of Alzheimer disease and Parkinson disease are discussed. Animal and *in vitro* studies have shed light on metabolism-based therapy's mechanisms in these diseases, as well as ALS, aging, ischemia, trauma and mitochondrial cytopathies. Additional insights may be obtained by considering the role of metabolism-based therapy in cell disability and death (specifically apoptosis, excitotoxicity, and autophagy).

Introduction

'When I use a word,' Humpty Dumpty said, in a rather scornful tone,' it means just what I choose it to mean, neither more nor less.'

''The question is,'' said Alice, ''whether you *can* make words mean so many different things.'' (*Through the Looking-Glass—Chapter Six*)

One common theme in medicine is that treatments used for one indication eventually are used in other diseases. Metabolism-based therapy (Table 1) was historically implemented for epilepsy but its use now has been demonstrated in a variety of neurological illnesses. Metabolism-based therapy's effects in epilepsy may result from a variety of mechanisms. For example, the ketogenic diet, the most widely implemented form of metabolism-based therapy in neurology, may have either anticonvulsant or anti-epileptic mechanisms in epilepsy. However, most studies have not been designed to distinguish between these mechanisms. This distinction becomes more important when illnesses other than epilepsy are considered. To facilitate this distinction, and for the sake of clarity, definitions used here:

Anticonvulsant: prevents the occurrence of acute seizures.
Antiepileptic therapy: suppresses or prevents epilepsy (i.e., the disease process that predisposes to recurrent unprovoked seizures).
Neuroprotectant: protects neurons from injury or degeneration.

These three terms frequently commonly are used interchangeably but from a mechanistic perspective, may share only limited overlap (Fig. 1).

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Table 1 Metabolism-based therapies for epilepsy and other neurological disorders (selected list from human and animal studies).

Classical ketogenic diet
MCT ketogenic diet
Ketone body supplementation
Polyunsaturated fat supplementation
Fenofibrate (peroxisome proliferator-activated receptor-alpha agonist)
Modified Atkins diet
Low Glycemic Index Treatment
Calorie restriction (including intermittent fasting)
2-Deoxy-D-glucose
Fructose-1,6-bisphosphate
Triheptanoin oil
Rapamycin

Background

The ketogenic diet is the one of the oldest forms of metabolism-based anticonvulsant therapy (Hartman and Vining, 2007). However, forms of metabolism-based anticonvulsant therapy have expanded significantly, encompassing other dietary regimens, including calorie restriction (perhaps the oldest and most widely-implemented of all) (Greene et al., 2001), the modified Atkins Diet (Kossoff et al., 2003), and the Low Glycemic Index Treatment (Pfeifer and Thiele, 2005). Metabolism-based therapy also encompasses pharmacological treatments such as 2-deoxy-D-glucose (Stafstrom et al., 2009), fructose-1,6,-bisphosphate (Lian et al., 2007), fenofibrate (Porta et al., 2009), and triheptanoin oil (Willis et al., 2010). These forms of metabolism-based therapy have anticonvulsant mechanisms of action that are distinct from commercially available medicines. The longstanding belief that metabolism-based therapies shares anticonvulsant mechanisms with one another also has been challenged (Hartman et al., 2010). Thus, they will be discussed separately here to facilitate comparisons and contrasts (data on polyunsaturated fats have been discussed extensively in the literature, so they will not be considered in detail here). The perspective emphasized here will be on neuroprotection, rather than anticonvulsant and antiepileptic effects.

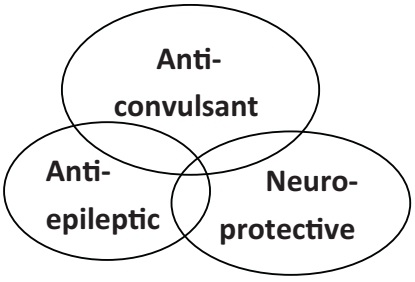

Figure 1 There is some, but not complete, overlap between neuroprotection, antiepileptic agents, and anticonvulsant therapy.

Epilepsy

Human studies: supportive data

The ketogenic diet has been used for nearly 90 years as a treatment for seizures (Bailey et al., 2005). Numerous case series demonstrated its effectiveness but its efficacy was further demonstrated in a randomized trial (Neal et al., 2008). The possibility of a more persistent beneficial effect was raised by a retrospective survey of children treated with a ketogenic diet showing that 13% of 150 children with medically intractable epilepsy (having failed to respond to an average of 6–7 medicines) were seizure free 3–6 years after initiation of the diet – and only one of the children was still consuming the diet (Hemingway et al., 2001). In this series, 29 children were not taking any anticonvulsants and an additional 28 were taking only one medicine. One interpretation is that these data support a disease-modifying or neuroprotective effect. A ketogenic diet also was successful in treating status epilepticus in two adults in status epilepticus (Wusthoff et al., 2010). A ketogenic diet stopped seizures in seven of nine patients with FIRES (fever induced refractory epileptic encephalopathy in school age children) (Nabbout et al., 2010). The diet was stopped in one of the seven patients, who then relapsed into status epilepticus and died. However, remissions have been reported after medication use as well, suggesting that a ketogenic diet simply may have been the 'right' anticonvulsant for these particular patients.

Human studies: conflicting data

Not all the data for the ketogenic diet in epilepsy have been positive. A ketogenic diet was associated with resolution of epileptiform activity in medically refractory continuous spike waves of sleep (CSWS) in only one of five children after 2 years of treatment (one additional child had a 20% improvement in spike-wave index) (Nikanorova et al., 2009). There were no changes in IQ or neuropsychological testing in this group but improved attention and behavior was noted in 2 patients. Thus, a ketogenic diet is anticonvulsant in some, but not all, cases (the same can be said for commercially available anticonvulsants, as well). In the FIRES series, the six surviving patients all eventually developed epilepsy, providing some evidence against a ketogenic diet having long-term disease-modifying effects in all cases, even when it has provided a significant anticonvulsant effect.

Animal data

Data from animal models of epilepsy have been remarkably similar to human studies. One model of a mixed genetic-environmental epilepsy, the EL mouse, stopped having seizures after administration of a ketogenic diet (Todorova et al., 2000). However, this effect was transient, lasting only 4 weeks. The mechanism for decreased seizure protection was believed to be loss of ketosis and increasing blood glucose levels. Similarly, protection against electrical kindling-induced seizures has been reported but this effect was only transient (Hori et al., 1997). A ketogenic diet's protective effects after exposure to chemoconvulsants

appears to be more consistent, including spontaneous recurrent seizures after kainic acid-induced status epilepticus (Muller-Schwarze et al., 1999) and clonic convulsions after kindling with pentylenetetrazol (Hansen et al., 2009).

Summary

The ketogenic diet's utility in patients with medically refractory epilepsy suggests its mechanism of action is distinct from medicines currently in clinical use, making it a valuable component of our armamentarium. Whether a ketogenic diet has disease-modifying properties is less clear. Data in both humans and animals suggest its anticonvulsant properties may be stronger than its ability to prevent the development of epilepsy. Other forms of metabolism-based therapy have not been studied extensively in long term studies that would shed light on anti-epileptic and disease-modifying effects in epilepsy.

Other neurological illnesses — human and animal models

Alzheimer disease (AD)

A number of metabolic derangements have been associated with AD, including β-amyloid-induced toxicity, glucose dysregulation (Sims-Robinson et al., 2010), and abnormal glycogen synthase kinase activity (Baum et al., 1996). Therefore, metabolism-based therapy may have the potential to prevent progression of the pathology associated with AD.

Ketogenic diets and ketone bodies: mixed results

A randomized, double-blind clinical placebo-controlled study of a medium chain triglyceride preparation showed a significant improvement in standardized tests of cognitive function in patients with mild to moderate AD lacking the APOε4 genotype, providing Class I evidence for the efficacy of this approach (Henderson et al., 2009). Patients with the APOε4 genotype did not benefit, however. A medium chain triglyceride diet also improved mitochondrial respiration but there was only a trend toward decreased Aβ 40 and 42 levels in aged beagles (Studzinski et al., 2008). These data provide *in vivo* support for prior *in vitro* work showing that BHB protects against Aβ 42-induced toxicity in cultured hippocampal neurons (Kashiwaya et al., 2000). Rodent trials have documented efficacy of a ketogenic diet in decreasing amounts of β-amyloid deposition, although performance in a novel object recognition test was not improved (Van Der Auwera et al., 2005).

Calorie restriction

Interestingly, calorie restriction also decreased β-amyloid deposition (Qin et al., 2006). The effect of calorie restriction may involve SIRT1, a sirtuin that appears to be responsible for extending lifespan in lower organisms (Qin et al., 2006). Exploratory behavior was better in a triple-transgenic murine model of AD after a 40% calorie restriction diet or an intermittent fasting paradigm (started at 3 months of age, continued until 10 or 17 months), compared to an ad lib control diet (Halagappa et al., 2007). Complications and adverse reactions to calorie restriction in rodent models also have been reported (reviewed in Maalouf et al., 2009), indicating the need for caution when translating these studies into human patients. Differences in behavior paradigms between a ketogenic diet and forms of calorie restriction highlight the need to consider these treatments separately and provide an opportunity for further study.

Parkinson disease (PD)

Human data

PD is characterized by loss of dopaminergic neurons in the substantia nigra pars compacta. A ketogenic diet was associated with an improvement in Unified Parkinson's Disease Rating Scales in five adults (Vanitallie et al., 2005). One potential explanation however, is that the change in diet led to changes in levodopa absorption (Jabre and Bejjani, 2006). One patient in the series required a decrease in her carbidopa/levodpa dose because of increased dyskinesias.

Animal data

Animal data for models of PD provide more direct evidence for a neuroprotective effect of ketone bodies. Treatment with β-hydroxybutyrate (BHB), one of the ketone bodies that is elevated during a ketogenic diet, was associated with decreased neuronal loss in the substantia nigra pars compacta after treatment with the mitochondrial electron transport chain complex I toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a commonly used model of PD (Tieu et al., 2003). In addition, oxygen consumption in mitochondria isolated from MPP+-treated brain tissue was increased after incubation with BHB, indicating improved mitochondrial viability. BHB protection was eliminated by treatment with 3-nitropropionic acid, a succinate dehydrogenase toxin, suggesting that BHB's effect requires intact complex II (succinate dehydrogenase is part of complex II). These data provide *in vivo* support for prior *in vitro* work showing that BHB protects against MPP+-induced toxicity in cultured mesencephalic neurons (Kashiwaya et al., 2000). Pretreatment for 6 months with a 30% calorie restriction diet also led to improved movement distance and speed in a cohort of rhesus monkeys after hemiparkinsonism induced by unilateral carotid artery injection of MPTP (Maswood et al., 2004). This improvement was associated with increased glia-derived neurotrophic factor (GDNF) in the ipsilateral striatum. No changes were noted in brain-derived neurotrophic factor (BDNF). In summary, the MPTP model of PD has demonstrated the role of BHB and calorie restriction in protecting against a complex I toxin, although the clinical relevance is still somewhat unclear.

Neurological illnesses modeled in rodents

Some neurological illnesses have been studied in rodents but not humans. In some, human trials are underway.

Amyotrophic lateral sclerosis (ALS)

A ketogenic diet preserved motor neuron counts in a transgenic mouse model of ALS (SOD1-G93A), with a significant

prolongation of time to failure in the Rotarod test (Zhao et al., 2006). Mitochondria isolated from the brains of these mice, after exposure to BHB, showed increased ATP levels and rates of ATP synthesis. They also were more resistant to a challenge with rotenone (complex I inhibitor) than malonate (a complex II inhibitor), implying that improvements in mitochondrial function require functioning complex II, similar to what was noted above (Section 'Parkinson disease (PD)'). There is a clinical trial underway to evaluate the effectiveness of a ketogenic diet in patients with ALS (Clinicaltrials.gov identifier: NCT01035710).

Aging

Ketogenic diets

In late-adult rats, medium chain triglyceride diet (10% and 20% MCT) exposure for 8 weeks was associated with an increased density of synapses and synaptic mitochondria in neurons in the outer molecular layer of the dentate gyrus (an 'anti-aging' effect), but in contrast, these parameters were decreased in neurons from the stratum molecular of the CA1 region (an 'accelerated aging' effect) (Balietti et al., 2008). After exposure to the 20% MCT diet, these rats showed an increase in numerical density of succinate dehydrogenase-positive mitochondria in Purkinje cells from the cerebellar vermis (an area that shows age-related degeneration) (Balietti et al., 2010). Conflicting findings between neurons in various regions suggest that metabolism-based therapy has different effects that may be specific for a given cell type. These data provide further support (but do not prove) the hypothesis that ketone bodies exert their effects through an effect on complex II (see Section 'Amyotrophic lateral sclerosis (ALS)'). Using a different model, a ketogenic diet was associated with improvements in an object recognition test and T-maze in aged rats, although the specific mechanism of neurodegeneration in that model is unknown (Xu et al., 2010).

Calorie restriction

A 30% calorie restriction for 20 years leads to a decrease in age-related neurodegeneration in rhesus monkeys, evidenced by increased volumes of gray matter in subcortical structures (including the putamen and cingulate gyrus), although changes were not noted in frontal and temporal cortex (the latter two areas show volume loss in aging humans) (Colman et al., 2009).

Post-ischemia models

Brain ischemia

A number of metabolic pathways are activated after prolonged ischemia (Semenza, 2007). Adolescent rats pretreated for 25 days with a ketogenic diet showed less degeneration of neurons in the CA1 field of the hippocampus, Purkinje cells in the cerebellum, and thalamic reticular nucleus after global cerebral ischemia induced by cardiac arrest after cardiac vessel occlusion (in contrast, levetiracetam did not protect these neurons in this model) (Tai et al., 2008). Protection against focal ischemia (measured by infarct volume) after middle cerebral artery occlusion in young adult rats was noted after treatment with either a ketogenic diet (pretreatment for 3 weeks) or intracerebroventricular BHB infusion (pretreatment for 4 days) (Puchowicz et al., 2008). Elevated levels of the anti-apoptosis protein Bcl-2 were noted in rats treated with either regimen, compared to controls. Acetoacetate pretreatment and BHB post-treatment (but not pretreatment) protect against post-stroke ischemia in rats (Massieu et al., 2001; Suzuki et al., 2002). In a different model, calorie restriction and intermittent fasting decreased the volume of infracted tissue, as well (Marie et al., 1990). Further study of these treatments after (rather than before) induction of strokes would increase the translational utility of this approach.

Heart ischemia

A ketogenic diet also may provide benefit in heart muscle after ischemia. Hearts from adult rats on a ketogenic diet for 19 weeks were subjected to an isolated heart perfusion model that was designed to mimic effects of global ischemia (Al-Zaid et al., 2007). Compared to a normal diet, tissue from ketogenic diet-treated rats showed an increase in reperfusion recovery in coronary flow, a persistence of functional recovery, and an increased number of mitochondria.

Mitochondrial cytopathies

Mitochondria have long been suspected to the primary organelle where ketogenic diets exert their effects, given their role in metabolism and neuroprotection (Bough and Rho, 2007). The use of ketogenic diets in patients with mitochondrial disorders has been evolving. Initial concerns about deficits in fatty acid metabolism have been replaced by the realization that some patients actually may benefit from a ketogenic diet (Kang et al., 2007). In the laboratory, mice that accumulate mitochondrial DNA mutations with age ('Deletor' mice) showed decreased numbers of ragged red fibers and decreased muscle mitochondrial structural distortion after treatment with a ketogenic diet (Ahola-Erkkila et al., 2010). These data provide *in vivo* support for a similar finding in cultured cells (Santra et al., 2004).

Traumatic brain injury

Use of a ketogenic diet in traumatic brain injury is covered elsewhere in this supplement.

Potential mechanisms of neuroprotection

Overview: cell death and disability

Ultimately, neurprotection is responsible for preservation of cell viability and function. Much of the current work on neuroprotection uses models and paradigms that focus on cell death. Cell death actually represents a spectrum of various mechanisms and morphological subtypes, including necrosis, apoptosis, and autophagy. Growing evidence has demonstrated significant mechanistic overlap between them. Processes that contribute to cell protection via

antioxidant effects (e.g., glutathione) are discussed elsewhere in this supplement.

Apoptosis

Apoptosis is a programmed form of cell death that can be triggered by a number of extracelluar and intracellular stimuli that activate a proteolytic cascade (involving caspases) (Gorman, 2008). In contrast to some forms of cell death that result from energy failure, apoptosis requires ATP to proceed. A balance of pro-death factors (e.g., Bad, Bim, Bax, and Bak) and anti-death factors (e.g., Bcl-2 and Bcl-x_L) maintains the balance of cell viability and the need for orderly tissue remodeling (which plays key roles in organ development and maturation). In terms of neurological disorders, blocking apoptosis (e.g., a Bax/Bak conditional double knockout) increases neuron survival in neurological disorders, such as a murine model of ALS (Reyes et al., 2010). A number of apoptosis proteins (including Bad, Bim, and Bax) have roles in cell death after status epilepticus (Niquet and Wasterlain, 2004). The role of these proteins in less severe forms of cellular disability (i.e., intermittent recurrent seizures, rather than status epilepticus) is unknown.

The importance of 'apoptosis proteins' in maintaining normal cell function and viability has been increasingly recognized (Cheng et al., 2006). For example, Bcl-x_L has a role in cell metabolism and is necessary for synaptic activity (Li et al., 2008), while Bad plays a role in glycolysis (Danial et al., 2003). This raises the possibility that these proteins play roles in both normal cellular activity as well as cell death (Cheng et al., 2006). Thus, studies only examining the role of these proteins in neuronal death could be extended by studying their role during normal cell function as well as periods of cellular disability (i.e., before a death stimulus).

A ketogenic diet appears to decrease morphological changes associated with apoptosis after kainic acid exposure (Noh et al., 2003). One potential neuroprotective effect of a ketogenic diet may be to prevent dissociation of the pro-apoptosis protein Bad from its binding partner 14-3-3 (Noh et al., 2006). Dissociation of Bad from 14-3-3 is one way to activate the apoptosis cascade.

Excitotoxicity

Excititoxicity results from overexposure of cells to the excitatory neurotransmitter glutamate and has mechanistic features of both necrosis and apoptosis (Ankarcrona et al., 1995). Reactive oxygen and nitrogen species play an important role in this type of cell death and are discussed elsewhere in this supplement. Ligands such as NMDA, AMPA, and kainic acid bind different types of glutamate receptors and activate similar cascades (Lau and Tymianski, 2010). Studies examining the effect of a ketogenic diet on kainic acid-induced cell death have shown different results in different strains of mice (Noh et al., 2003; Samala et al., 2008). Hippocampal slices exposed to NMDA show less cell death after incubation with BHB compared to control media but interestingly, BHB did not improve induced epileptiform-like firing in these preparations (Samoilova et al., 2010). This finding stands in some contrast to other recent data showing that another ketone body produced during a ketogenic diet, acetoacetate, alters chloride transport in vesicular glutamate transporters, which would be predicted to alter glutamate trafficking (Juge et al., 2010). The difference in specific ketone body (i.e., BHB not suppressing epileptiform activity but acetoacetate altering glutamate trafficking) is consistent with animal studies showing that acute treatment with acetoacetate, but not BHB, is anticonvulsant in mice (Rho et al., 2002). Neocortical neurons exposed to BHB and acetoacetate produced less reactive oxygen species after exposure to glutamate (Maalouf et al., 2007). Both intermittent fasting (i.e., every-other day fasting) and the glycolysis inhibitor 2-deoxy-D-glucose pretreatment protect against kainic acid-induced CA3 neuronal death in adult rats (Bruce-Keller et al., 1999; Lee et al., 1999). BDNF may play a neuroprotective role in the intermittent fasting paradigm (contrasted with the lack of BDNF changes in the MPTP model, noted in Section 'Parkinson disease (PD)') (Duan et al., 2001). Together, these data suggest a role for ketone bodies, limited caloric intake, and decreased glucose utilization in protection against excitotoxicity, although the effects of BHB and acetoacetate may differ. Growth factors, such as BDNF and GDNF may play different roles in metabolism-based therapies, depending on the paradigm studied.

Autophagy

Autophagy in neurological disorders

Autophagy ('self-eating') is an energy-requiring programmed form of protein and organelle catabolism. Autophagy provides macromolecules for use in times of stress (in part, a recycling system) and is important in cell death, survival under stress, and cell 'quality control' (Yang and Klionsky, 2010). Blocking autophagy leads to loss of cortical and cerebellar neurons and accumulation of intraneuronal inclusion bodies containing ubiquitinated proteins (Komatsu et al., 2006). Abnormalities in autophagy also have been demonstrated in neurological disorders that involve accumulation of abnormal proteins, such as AD (Jaeger and Wyss-Coray, 2010).

Lafora disease, one form of progressive myoclonus epilepsy, involves accumulation of cytoplasmic polyglucosan inclusions but it is not clear whether they are the cause or the effect of the disorder (Knecht et al., 2010). Mutations in Laforin, one of the proteins affected in this disease, are associated with decreased autophagy, raising the question of whether correcting this process would improve outcomes (Aguado et al., 2010). A trial in patients with Lafora disease showed a ketogenic diet did not halt progression of illness but four of the five patients had mutations in malin (the other protein mutated in Lafora disease) and patients were studied after the progressive nature of their illness had been established (Cardinali et al., 2006). Utility of a ketogenic diet in patients earlier in their course or in those with laforin mutations is unknown.

Autophagy and mTOR

One link between autophagy and metabolism is the mTOR (mammalian target of rapamycin) pathway (Laplante and Sabatini, 2009). mTOR is sensitive to changes in glucose

Table 2 Studies of metabolism-based therapies in neurodegenerative diseases.

Treatment	Human		Animal and/or *in vitro*					
	AD	PD	AD	PD	ALS	Aging	Post-ischemia	Mitochondrial cytopathy
'Classical' ketogenic diet		X	X		X	X	X	X
MCT	X		X					
Ketone bodies			X	X	X	X	X	
CR			X	X				

AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; CR, calorie restriction; MCT, medium chain triglyceride; PD, Parkinson disease.

and protein levels and has an effect on protein synthesis, lipid metabolism, and lipid synthesis (Laplante and Sabatini, 2009). Decreases in mTOR activity lead to increased autophagy. Laforin's activity in the autophagy pathway (noted above) is mediated via mTOR (Aguado et al., 2010). Further demonstrating the importance of mTOR in neurological disease, patients with tuberous sclerosis complex (TSC) have mutations in the mTOR pathway and treatment with the mTOR inhibitor rapamycin decreases seizure frequency in patients with TSC (Orlova and Crino, 2010; Krueger et al., 2010). Independent of its effect in TSC, rapamycin also decreases spontaneous recurrent seizures after kainic acid-induced status epilepticus, suggesting an additional role for mTOR inhibition in decreasing epileptogenesis (Zeng et al., 2009). Rapamycin improves spatial memory and decreases Aβ 42 levels in a transgenic mouse model of AD (PDAPP), with a concomitant increase in neuronal autophagy (Spilman et al., 2010). Rapamycin also decreases the extent of brain damage in a neonatal rat hypoxia-ischemia model, with a concomitant increase in autophagy (Carloni et al., 2010). Together, these findings suggest a neuroprotective role for the nutrient signal-integrating mTOR pathway.

Common themes in different neuroprotection models

In reviewing the literature, some common themes emerge regarding the neuroprotective effects of metabolism-based therapies. Because of the convergence of metabolic processes and neuroprotection, much work has focused on mitochondria. Mitochondrial oxygen consumption and increased ATP synthesis have been noted after BHB exposure and these effects appear to be mediated via a complex II-dependent mechanism in some models described here. Although this points to ketone bodies enhancing mitochondrial function in neurons, there are data showing cell-specific changes in synaptic mitochondrial density (with both increases and decreases) after medium chain triglyceride diets in aged rodents, indicating the effect of ketone bodies may be restricted to a subset of neurons. Other measures of mitochondrial parameters have shown changes after exposure to a ketogenic diet, as well. Studies of a ketogenic diet in SSADH-deficient mice showed an increase in mitochondrial area (a surrogate measure of mitochondrial biomass) in the somata of pyramidal cells from CA1 hippocampal neurons (Nylen et al., 2009). Nonepileptic rats on a ketogenic diet had increased numbers of transcripts for many mitochondrial proteins and increased mitochondrial fragmentation in dentate gyrus neurons (Bough et al., 2006). How these parameters translate into a neuroprotective effect is unclear. Increased ATP levels may make a compromised neuron more 'resistant' to an electrical insult but an alternative explanation is that adenosine (a product of ATP metabolism) may, by itself, exert neuroprotective effects (Masino et al., 2009). Neuroprotective effects of a ketogenic diet and BHB at the mitochondrial level also may be mediated by protective factors such as Bcl-2 and other apoptosis-related proteins, or by relieving oxidative stress (discussed elsewhere in this supplement).

Other potential neuroprotective mechanisms of metabolism-based therapy may include growth factors (e.g., BDNF or GDNF) or sirtuins, as discussed previously. There is a handful of preclinical studies pointing to the beneficial effects of mTOR inhibition in neurodegenerative disorders. Finally, the ketone body acetoacetate may modulate glutamate trafficking, providing a potential common link between some forms of metabolism-based therapy and many types of neurodegenerative disorders.

Conclusions

Metabolism-based therapy encompasses a number of different specific interventions (Table 1). Metabolism-based therapies have been used in epilepsy and their application is being actively investigated in a number of other neurodegenerative disorders (Table 2). As some of these interventions involve lifestyle changes and in order to optimize the population of patients that might benefit most from them, there has been a significant effort to unravel their neuroprotective mechanisms. In order to characterize specific effects of metabolism-based therapies, future studies would benefit from designs that distinguish between anticonvulsant, antiepileptic, and neuroprotective mechanisms.

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