The nervous system and metabolic dysregulation: emerging evidence converges on ketogenic diet therapy

David N. Ruskin  
*Trinity College*, david.ruskin@trincoll.edu

Susan A. Masino  
*Trinity College*, susan.masino@trincoll.edu

Follow this and additional works at: [https://digitalrepository.trincoll.edu/facpub](https://digitalrepository.trincoll.edu/facpub)

Part of the [Medicine and Health Sciences Commons](https://digitalrepository.trincoll.edu/facpub)
A link between metabolism and brain function is clear. Since ancient times, epileptic seizures were noted as treatable with fasting, and historical observations of the therapeutic benefits of fasting on epilepsy were confirmed nearly 100 years ago. Shortly thereafter a high fat, low-carbohydrate ketogenic diet (KD) debuted as a therapy to reduce seizures. This strict regimen could mimic the metabolic effects of fasting while allowing adequate caloric intake for ongoing energy demands. Today, KD therapy, which forces predominantly ketone-based rather than glucose-based metabolism, is now well-established as highly successful in reducing seizures. Cellular metabolic dysfunction in the nervous system has been recognized as existing side-by-side with nervous system disorders – although often with much less obvious cause-and-effect as the relationship between fasting and seizures. Rekindled interest in metabolic and dietary therapies for brain disorders complements new insight into their mechanisms and broader implications. Here we describe the emerging relationship between a KD and adenosine as a way to reset brain metabolism and neuronal activity and disrupt a cycle of dysfunction. We also provide an overview of the effects of a KD on cognition and recent data on the effects of a KD on pain, and explore the relative time course quantified among hallmark metabolic changes, altered neuron function and altered animal behavior assessed after diet administration. We predict continued applications of metabolic therapies in treating dysfunction including and beyond the nervous system.

**Keywords:** adenosine, epilepsy, glucose, inflammation, long-term potentiation, metabolism, pain, seizure
ATP, phosphocreatine) and increased capacity for energy generation, rightward, elevate the threshold for maximal electrical activity, and to block spreading depression-style events in the hippocampus in vivo (Bough et al., 2003). There have been surprisingly few detailed studies on detailed synaptic effects, likely because of the difficulty in performing such studies in vivo, coupled with the typical glucose-based incubation protocol for in vitro slices; to date, a “KD” incubation protocol has not been standardized, although recent work sampling cerebrospinal fluid in KD-fed animals might provide a starting point (Samala et al., 2011). Currently, the major proposed mechanisms for such increased inhibition and/or decreased excitation include increased levels of adenosine, a major inhibitory neuromodulator (Masino and Geiger, 2008); increased levels of γ-aminobutyric acid (GABA), a major inhibitory neurotransmitter (Yudkoff et al., 2007; Omote et al., 2011); decreased glutamate, a major excitatory neurotransmitter (Lund et al., 2009; Juge et al., 2010) and direct effects of elevated ketone bodies on ion channels (Ma et al., 2007).

Inhibition increased or decreased excitability, if sufficiently strong, might not only suppress seizures but also influence normal brain function. Many types of normal brain function, as well as recovery from injury, are thought to depend on synaptic plasticity, i.e., the malleability, either temporary or long-lasting, of the strength of neuronal communication (Davis et al., 1992; Goosens and Maren, 2002). Long-term potentiation (LTP) is a sustained increase in synaptic efficacy which can be observed in a number of brain regions including its original discovery site, the hippocampus (Bliss and Lømo, 1973; Bramham and Srebro, 1989; Clugnet and LeDoux, 1990; Bonci and Malenka, 1999; Mahon et al., 2004). Studies have linked metabolism and LTP (Potter et al., 2010); we and our collaborators characterized the effects of a KD on hippocampal LTP with the hypothesis that KD-related inhibition or reduced excitation might affect brain plasticity (Koranda et al., 2011). We recorded hippocampal signals through chronically implanted electrodes in freely moving rats. After 3 weeks on a 7:1 KD, baseline synaptic measurements were taken in the perforant path-dentate gyrus pathway and LTP was induced with tetanic stimulation and the response measured over the next 2 days. The KD had no significant effects on measures of short-term plasticity (paired-pulse depression, paired-pulse facilitation), and did not prevent LTP induction, whereas the magnitude of the potentiation was significantly smaller in KD-fed rats. The LTP magnitude remained lower in these rats out to the longest tested time point (48 h). As discussed below, cognitive effects of the diet are mixed in animals and overall positive in humans. In addition, it is important to note that 7:1 is a stronger diet ratio than that used clinically, animals used had never had seizures, and another paper looking at the KD on LTP in vivo in anesthetized animals did not find any differences (Thio et al., 2010).

To test the role of adenosine in the KD’s ability to reduce seizures, we and our collaborators recently tested the effectiveness of a KD in a transgenic mouse with spontaneous hippocampal electrographic seizures due to adenosine deficiency. These mice overexpress the adenosine-metabolizing enzyme adenosine kinase (ADK) in brain (Fedele et al., 2005), and tonic levels of the endogenous inhibitor adenosine are therefore lower than normal. At baseline, seizures recorded with chronically implanted electrodes occur five times per hour, on average (Masino et al., 2011). After being fed on a 7:1 KD for 3 weeks, seizure frequency dropped almost

**FIGURE 1** | Ketogenic diets can produce prompt and sustained ketosis and mild hypoglycemia in experimental rodents. Here, young male Sprague-Dawley rats were fed with one of two ketogenic diets for 19 days, or remained fed with normal rodent chow. Both KDs, with strengths of 3:1 and 7:1 (BioServ 5140 and 3666, respectively), produced similar and significantly increased blood ketones and reduced blood glucose within 2 days and lasting until the last test day. Number of subjects was 12–14.

*<p><0.05, **p < 0.01, ***p < 0.001, comparisons to control diet. Authors' unpublished data.

### METABOLISM, PLASTICITY, AND SYNAPTIC ACTIVITY

The KD might alleviate seizures and other pathological states partially by providing elevated levels of high-energy molecules (e.g., ATP, phosphocreatine) and increased capacity for energy generation (increased mitochondrial number; Seyfried and Mukherjee, 2005; Bough and Rho, 2007; Masino and Geiger, 2008). Yet, numerous other changes due to the KD have been hypothesized to underlie increased inhibition and/or decreased excitation in brain, and thus to an anticonvulsant/neuroprotective state. In normal humans fed a KD, electroencephalography and transcranial magnetic stimulation demonstrated increased inhibition in the cerebral cortex, with a magnitude similar to that seen after benzodiazepine administration (Cantello et al., 2007). With the more extensive investigation possible in experimental animals, a KD was shown to enhance paired-pulse depression, shift the input/output relationship rightward, elevate the threshold for maximal electrical
90%. This antiseizure effect depended on low glucose (seizures were restored by a peripheral injection of glucose), and activation of the adenosine A1 receptor subtype (A1R; seizure activity was restored by injection of a selective A1R antagonist). Together, this evidence suggests that the KD exerts antiseizure effects by restoring adenosine levels and A1R activation via mechanisms related to low glucose.

Further support for this idea is provided by transgenic mice lacking A1Rs. These mice also have spontaneous electrographic seizures in the hippocampus, but the KD has no effect on seizure frequency in A1R knockout mice, and is partially effective in mice heterozygous for the A1R (Masino et al., 2011). Although these models all involve seizures induced by a lack of adenosinergic modulation, the results are likely generalizable: adenosine has been found to be anticonvulsive/antiseizure in virtually every seizure model in which it has been tested (excepting A1R knockout mice – providing further evidence for the primary anticonvulsant role of A1Rs). Adenosine in particular, and a KD in general, might offer providing further evidence for the primary anticonvulsant role of A1Rs (Masino et al., 2011). Although these models all involve seizures induced by a lack of adenosinergic modulation, the results are likely generalizable: adenosine has been found to be anticonvulsive/antiseizure in virtually every seizure model in which it has been tested (excepting A1R knockout mice – providing further evidence for the primary anticonvulsant role of A1Rs). Adenosine in particular, and a KD in general, might offer providing further evidence for the primary anticonvulsant role of A1Rs (Masino et al., 2011).

Several lines of evidence suggest that reduced glucose is critical for antiseizure effects.

We modeled key aspects of the KD in vitro by maintaining or increasing intracellular ATP while decreasing extracellular glucose in individual CA3 pyramidal neurons in acute hippocampal slices. We varied ATP (0.5–5.0 mM; 2 mM is standard) in the patch pipet and changed glucose concentration of the bathing solution from 11 mM (standard) to either 7 or 3 mM (Kawamura et al., 2010). Note that 3 mM glucose is still a physiological level; in vivo brain concentrations are near 3 mM (Hu and Wilson, 1997; Shram et al., 1997). Moderately lowered extracellular glucose has been reported to attenuate epileptiform activity in brain slices (Kirchner et al., 2006), whereas experimental studies of pathological hypoglycemia often remove glucose completely from the bathing medium (aglycemia; Tromba et al., 1992; Zhu and KRMjevic, 1993).

We found that when intracellular ATP levels were adequate or high (1.0–5.0 mM), reducing extracellular glucose provoked an outward (inhibitory) current, with a larger current found with a reduction to 3 mM versus to 7 mM (Figure 2). This outward current was fully reversible on return to 11 mM glucose and had a reversal potential near the equilibrium potential for K+, and was blocked by the non-selective K+ channel antagonist Ba2+ (Kawamura et al., 2010). If intracellular ATP levels were low (0.5 mM), reducing glucose produced a transient inward (excitatory) current instead (Figure 2). Therefore, moderately low extracellular glucose can inhibit hippocampal neurons that have sufficient or abundant energy stores. Furthermore, this inhibition was completely blocked by application of an A1R antagonist and was not present in neurons from A1R knockout mice (Figure 2; similar to observations in vivo; Masino et al., 2011) implying increased adenosine levels produced the inhibition (conversely, diabetic hyperglycemia seems to be related to reduced signaling through A1Rs (Duarte et al.,

**KETOGENIC DIET FOR A BRAIN SLICE: RELAXING IN REDUCED GLUCOSE?**

Compared to in vivo, in vitro paradigms can provide tighter control over experimental variables, allowing for a more thorough characterization of mechanisms. Effects of KD feeding on baseline excitability are inconsistent in vitro, however (Stafstrom et al.,

![Figure 2](https://example.com/figure2.png)
Altered cognition and affect in children with seizure disorders has channels and ATP release remains to be demonstrated directly. under these conditions, to KATP channels (Kawamura et al., 2010). Together, this study and Masino et al. (2011) suggest that a KD can limit seizures (at least those involving the hippocampus) through a mechanism dependent on low glucose and abundant high-energy molecules and involving augmentation of adenosine levels.

In our in vitro study, we manipulated ATP only in the patched neuron, suggesting an autocrine mechanism to increase adenosine. How might this autoinhibition occur? ATP might be metabolized intracellularly to adenosine, which would then be released. Loading pyramidal neurons with adenosine + ATP versus ATP alone, however, suggested that the current was not mediated by direct adenosine release (Kawamura et al., 2010). Alternatively, ATP might be released and then metabolized to adenosine. Cells can release ATP by several mechanisms (Dubayak, 2009), and extracellular ATP is metabolized rapidly to adenosine (Dunwiddie et al., 1997). One prominent non-exocytotic ATP release mechanism in neurons and glia is ATP passage through channels composed of connexins or pannexins (Stout et al., 2002; Schock et al., 2008; Iwabuchi and Kawahara, 2011). Through a series of physiological and pharmacological experiments, we determined that pannexin channels were the source of extracellular ATP. Taken together, our data are consistent with a process by which lowered extracellular glucose promotes release of ATP via pannexins. ATP is then converted extracellularly to adenosine, which activates A1R coupled, under these conditions, to KATP channels (Kawamura et al., 2010). This pathway is likely to underlie the A1R-mediated anticonvulsant effect produced by the KD in vivo. Certainly, mild hypoglycemia and enhanced adenosine tone can underlie its anticonvulsant effect (Masino et al., 2011), whereas the in vivo involvement of pannexin channels and ATP release remains to be demonstrated directly.

**KETOGENIC DIET’S EFFECT ON COGNITION AND MOOD: NEGATIVE, THEN POSITIVE?**

Altered cognition and affect in children with seizure disorders has always been a concern. Regarding pharmacological therapies, several authors have shown that children with epilepsy – even those whose seizures were well-controlled with antiepileptic drugs – had decreased cognitive function compared to their peers (Devinsky, 1995; Thompson et al., 2000; Drane and Meadow, 2002). The exact mechanism of cognitive decline is unknown: traditional antiepileptic drugs decrease membrane excitability, increase postsynaptic inhibition, or reduce network synchronization to decrease excessive excitability associated with seizure development (Loring, 2005). These neurophysiological mechanisms, if sufficiently strong, will not only suppress seizures but also impair normal brain function. The incidence of cognitive side effects is increased at higher dosing and with polypharmacy which might be necessary for significant seizure control (Loring and Kimford, 2001). Thus, the cognitive and affective state of a medicated epileptic patient results from a balance of forces including the negative effects of the disease state (seizures, abnormal interictal brain activity, abnormal sleep), the positive effects of the anticonvulsive medication (seizure control), and the negative side effects of the anticonvulsive mediation (which can include sedation and/or abnormal sleep).

The KD might offer fewer chronic negative side effects than medication, and given that it has been in use for over 90 years, serious or systematic negative consequences would likely have surfaced by now. In research studies, KDs (albeit at a much stronger ratio than used clinically) reduced brain mass in juvenile rodents (Cheng et al., 2004; Zhao et al., 2004) and KDs can affect body growth in children (who are typically on the diet temporarily; Liu et al., 2003; Peterson et al., 2005; Neal et al., 2008b) but to our knowledge negative KD effects on human brain development and growth have not been quantified. Notably, recurrent clinical hypoglycemia can lead to a cumulative cognitive impairment (Langan et al., 1991; Deary et al., 1993) – although this effect might not be directly applicable because the hypoglycemia in these studies was episodic and much more severe than the chronic reduced (but not abnormal) glucose levels associated with the KD. Overall, positive and negative short- and long-term effects of this strict diet on cognition and mood remain under-examined clinically, particularly in pediatric patients.

It is worthwhile to consider that any assessment of cognitive or affective state associated with a KD should occur at multiple time points, as effects of the KD (including anticonvulsive effects) clearly evolve. There are limitations to combining data from different laboratories due to differing methodologies, different KDs, etc. Yet in surveying the research literature, it seems fairly clear that there is a biphasic effect on locomotor behavior: reduced activity characterizes KD onset, whereas increased activity predominate after a few weeks. Effects of a KD on locomotion in rodents (compiled informally from the literature) are shown in Figure 3. Notably, a biphasic pattern over time after diet initiation
is found in clinical literature relating to cognition, mood, and vitality. Soon after beginning a KD, subjects often complain of lethargy (Vining et al., 1998; Lefevre and Aronson, 2000); in children, intolerable drowsiness is a reported side-effect that sometimes leads to cessation of KD treatment (Neal et al., 2008a). Yet, after weeks on the diet, subjects report heightened vitality, physical functioning, and alertness (Hallböök et al., 2007; Mosek et al., 2009; Yancy et al., 2009). In some cases these positive effects may be at least partially due to reduced seizure frequency, but similar positive effects are also described in non-epileptic subjects. This delay in beneficial effects is reminiscent of the delay often observed in anticonvulsant effects (Kossoff et al., 2008a).

Studies of the KD in epileptic patients rarely characterize mood, which might understandably be poor during the initial lethargic/drowsy stage. Several weight-loss studies, however, included affective measures and found positive effects of KD on mood in overweight subjects as early as 2 weeks into diet treatment, and lasting many weeks (Halyburton et al., 2007; McClernon et al., 2007; Brinkworth et al., 2009; Yancy et al., 2009). Two of these studies provide some evidence against this result simply being a psychological effect of weight loss (Brinkworth et al., 2009; Yancy et al., 2009). Thus, beneficial effects on mood (as well as weight loss) await those who conquer the early stage after KD initiation. Studies of patients with epilepsy on the KD, including children, have either reported improved cognition anecdotally (Sirven et al., 2011) or a direct action on cognition/attention. Investigations in non-epileptic adult subjects (thus without confounding antiepileptic medications) have more specifically addressed cognition and the KD. One study found a transient, moderate impairment in one cognitive task (but not two other tasks) at 1 week of diet treatment but found no impairments at later time points (Wing et al., 1995); two studies examining chronic KD treatments reported improved processing speed and working memory lasting up to 1 year (Halyburton et al., 2007; Brinkworth et al., 2009). This pattern seems to parallel the biphasic effect on activity and vitality noted above.

A minority of animal studies have reported impairments in learning and memory, specifically in a task of spatial reference memory (Su et al., 2000; Zhao et al., 2004). Other studies, however, have failed to find any detrimental effect of the KD on learning and memory in rodents in various mazes or in fear conditioning (Hori et al., 1997; Todorova et al., 2000; Silva et al., 2005; Appelberg et al., 2009; Thio et al., 2010). We tested normal mice of both sexes in a simple working memory task after feeding on a 7:1 KD at a number of time points, up to 10 weeks, and found no effect of the KD (though hyperactivity did appear beginning at 2 weeks (Ruskin et al., 2011a). It is worth noting that a KD not only does not impair but in fact reverses age-related deficits in learning and other cognitive measures in aged, but otherwise healthy, dogs and rodents (Pan et al., 2010; Xu et al., 2010). Taken together, these results largely support the beneficial nature of KD feeding on mood and cognition in patients.
studies have found exclusively positive outcomes: after KD treatment, patients with type I or II diabetes had improved control of blood glucose, and many could have their medications reduced or eliminated (Gumbiner et al., 1996; Yancy et al., 2005; Westman et al., 2008; Dressler et al., 2010). In addition, type I diabetic patients (and, based on one report, children with epilepsy) prefer foods that are high in fat and low in carbohydrates (Amari et al., 2007; Snell-Bergeon et al., 2009), which might be attempted self-medication. The mixed animal results might result from the use of very strict KDs (Garbow et al., 2011; Park et al., 2011), or from the diabetic propensity of many laboratory rodent strains. Thus, the KD might benefit diabetic patients both by alleviating neuropathic pain and treating the underlying glycemic control dysfunction.

Finally, the KD would be predicted to be effective against inflammatory pain. Chronic inflammation is typically accompanied by pain due to the release of prostaglandins and the consequent sensitization of sensory neurons (Mense, 1983). Some of the most common sources of inflammatory pain are rheumatoid arthritis, chronic inflammatory bowel disease, pancreatitis, back pain, and some cancers. We found that a KD reduced experimental inflammation-induced swelling and plasma extravasation (Ruskin et al., 2009), and clinical studies describe positive effects of a KD on liver inflammation in non-alcoholic fatty liver disease (Tendler et al., 2007; Pérez-Guisado and Muñoz-Serrano, 2011). Regarding mechanisms linking metabolism to inflammatory pain, reactive oxygen species are a major component of inflammation, and limiting reactive oxygen species should contribute to limiting inflammation. Accordingly, ketogenic metabolism should produce fewer free radicals and reactive oxygen species through affecting the mitochondrial co-enzyme Q couple and the cytoplasmic glutathione couple (Veech, 2004). Indeed, as expected, treatment with ketones reduces the level of reactive oxygen species (Noh et al., 2006a; Kim et al., 2007, 2010; Maalouf et al., 2007; Haces et al., 2008; Maalouf and Rho, 2008), as does KD feeding (Sullivan et al., 2004).

Regarding inflammatory pain, by virtue of their high-fat content KDS should also activate peroxisome proliferator-activated receptors (PPARs). These nuclear receptors bind long-chain polyunsaturated fatty acids, and consequently induce transcriptional changes that culminate in enhanced lipid metabolism (Moya-Camarena et al., 1999; Diradourian et al., 2005; Michalik et al., 2006). Genetic knockout of a major PPAR (the α subtype) augments inflammatory reactions (Cuzzocrea et al., 2006), whereas synthetic PPAR agonists reduce experimentally induced inflammation (Cuzzocrea et al., 2003; LoVerne et al., 2005). This latter effect appears to involve reduced transcription of pro-inflammatory genes (Blanquart et al., 2003) and seems to be invoked by the KD (Jeong et al., 2011). Synthetic PPAR agonists are analgesic against inflammatory pain (LoVerne et al., 2006). In addition to these effects, PPAR activation augments neuroprotective against ischemic damage (Tai et al., 2008, 2009), hypoglycemic damage (Yamada et al., 2005), and traumatic brain and spinal injury (Prins et al., 2005; Appelberg et al., 2009; Hu et al., 2009a,b; Prins and Hovda, 2009; Schwartzkroin et al., 2010; Streijger et al., 2011), and improves injury-related deficits in cognition and movement after traumatic brain and spinal injury, respectively (Appelberg et al., 2009; Streijger et al., 2011). Ketosis is apparently crucial to these effects as direct application of ketones to in vitro tissue is also protective against hypoglycemia and ischemia (Samoilova et al., 2010), oxidative stress (Kim et al., 2007), and excitotoxicity (Massieu et al., 2003; Noh et al., 2006b; Maalouf et al., 2007; Samoilova et al., 2010). The mechanisms are likely to involve reduced reactive oxygen species, reduced tissue excitability, and enhanced production of high-energy molecules.

Based on evidence for neuroprotection against acute insults, and recognition that metabolic dysfunction accompanies chronic neurological disease, researchers are expanding into animal models of more slowly-acting neurodegenerative diseases. Positive effects of KD feeding have been found in models of amyotrophic lateral sclerosis (Zhao et al., 2006), Parkinson’s disease (Cheng et al., 2009; Yang and Cheng, 2010), and Alzheimer’s disease (Van der Auwera et al., 2005; Mohamed et al., 2010). In addition, KD feeding reverses aging-related impairments in brain biochemistry in animals (Studzinski et al., 2008; Bajetti et al., 2010). Direct application of ketones is also beneficial in models of Parkinson’s disease (Kashiwaya et al., 2000; Tieu et al., 2003) and Alzheimer’s disease (Kashiwaya et al., 2000).

Huntington’s disease, which involves the death of neurons in the caudate and putamen, is thought to involve excitotoxicity and mitochondrial dysfunction (Strada-Sanchez et al., 2008;
Damiano et al., 2010). Based on findings reviewed above, we characterized the effects of a strict (7:1) KD in a rapidly progressing Huntington's disease model, the R6/2 mouse (lifespan less than 16 weeks). KD feeding began at 6 weeks of age, when motor impairments are still minor (Ruskin et al., 2011a). The KD did not increase lifespan or alleviate motor impairments, but, importantly, it did not negatively affect either. However, the KD did delay significantly the onset of progressive weight loss, which is a major problem in patients (Sanberg et al., 1981; Lanska et al., 1988). In addition, the KD reversed a modest working memory impairment in female mice, and working memory is known to be affected in patients with Huntington's disease (Lange et al., 1995; Lawrence et al., 1996) as well as other neurological disorders and aging.

The lack of effect on lifespan or locomotor activity may signal that beneficial effects of a KD might not be similar across neurodegenerative disorders, might depend on the severity or rate of progression, or might differ in different animal models of a disorder; alternatively, the KD might need to be optimized for strength and composition for different conditions. Although it seems paradoxical that the KD, normally associated with weight loss, might maintain, or increase body weight under particular conditions, our data suggest that KD feeding could alleviate Huntington's disease-associated cachexia, and, as noted above, in patients a higher body mass is associated with slower disease progression (Myers et al., 1991). Based on this finding, the KD might also deserve consideration for treatment of other cachexias; for instance, that associated with cancer (Colomer et al., 2007). Indeed, the KD is beginning to be used as an anti-tumorigenic treatment (Klement and Kamberer, 2011; Seyfried et al., 2012) and so could provide dual benefits. If the anti-neurodegenerative effects found in animal models of Parkinson's disease, Alzheimer's disease, and aging are successfully extended to humans, the KD could also have dual benefits, delaying the primary degenerative condition and alleviating the working memory problems common to these conditions (Halyburton et al., 2007; Brinkworth et al., 2009; Ruskin et al., 2011a).

LOOKING AHEAD

A KD offers known benefits for epilepsy, and it is apparent that the relationship between metabolism and brain function offers primary therapeutic opportunities. Basic and clinical research is acutely aware that metabolic dysfunction and comorbidities propagate lifelong impacts on nervous system function. Particularly promising unrealized opportunities for intervention and restoration of metabolic homeostasis occur during development, after injury, and during disease progression – all windows with high levels of plasticity and remodeling. New insight into mechanisms could accelerate development of treatments.

ACKNOWLEDGMENTS

Supported by the National Institutes of Health (P20RR017699, R15NS065446, R15NS066392, R01NS065957), the National Science Foundation (IOS0843585), the CHDI Foundation, and Trinity College.

REFERENCES

Al-Khalifa, A., Mathew, T. C., Al-Zaid, N. S., Mathew, E., and Dashki, H. (2011). Low carbohydrate ketogenic diet prevents the induction of diabetes using streptozotocin in rats. Exp. Toxicol. Pathol. 63, 663–669.

Al-Khalifa, A., Mathew, T. C., Al-Zaid, N. S., Mathew, E., and Dashki, H. M. (2009). Therapeutic role of low-carbohydrate ketogenic diet in diabetes. Nutrition 25, 1177–1185.

Amari, A., Dahlquist, L., Kosoff, E. H., Vining, E. P. G., Trescher, W. H., and Slifer, K. J. (2007). Children with seizures exhibit preferences for foods compatible with the ketogenic diet. Epilepsy Behav. 11, 98–104.

Aoki, T. T. (1981). Metabolic adaptations to starvation, semistarvation, and carbohydrate restriction. Prog. Clin. Biol. Res. 67, 161–177.

Appelberg, K. S., Hovda, D. A., and Prins, M. L. (2009). The effects of a ketogenic diet on behavioral outcome after controlled cortical impact injury in the juvenile and adult rat. J. Neurotrauma 26, 497–506.

Balietti, M., Giorgetti, B., Di Stefano, G., Casoli, T., Platano, D., Solazzi, M., Bertoni-Freddari, C., Ascardi, G., Lattanzio, E., and Fattoretti, P. (2010). A ketogenic diet increases succinic dehydrogenase (SDH) activity and recovers age-related decrease in numeric density of SDH-positive mitochondria in cerebellar Purkinje cells of late-adult rats. Microon 41, 143–148.

Belfrage, M., Sollevi, A., Segerdahl, M., Jolund, K. F., and Hansson, P. (1995). Systemic adenosine infusion alleviates spontaneous and stimulus-evoked pain in patients with peripheral neuropathy. Pain Anal. 81, 713–717.

Blanquat, C., Barbier, O., Fruchard, J. C., Staels, B., and Glineur, D. (2011). Homeostatic bioenergetic network regulation: a novel concept to avoid pharmacoresistance in epilepsy. Expert Opin. Drug Discov. 6, 713–724.

Bonci, A., and Malenka, R. C. (1999). Properties and plasticity of excitatory synapses on dopaminergic and GABAergic cells in the ventral tegmental area. J. Neurosci. 19, 3723–3730.

Bough, K. J., and Rho, J. M. (2007). Anticonvulsant mechanisms of the ketogenic diet. Epilepsia 48, 43–58.

Bough, K. J., Schwartzkroin, P. A., and Rho, J. M. (2003). Caloric restriction and ketogenic diet diminish neuronal excitability in rat dentate gyrus in vivo. Epilepsia 44, 752–760.

Bough, K. J., Wetherington, J., Hassel, B., Pare, J. E., Gavrilyuk, J. W., Greene, J. G., Shaw, R., Smith, Y., Geiger, J. D., and Dingledine, R. J. (2006). Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. Ann. Neurol. 60, 223–235.

Bramham, C. R., and Srebro, B. (1989). Synaptic plasticity in the hippocampus is modulated by behavioral state. Brain Res. 493, 74–86.

Brinkworth, G. D., Buckley, J. D., Noakes, M., Clifton, P. M., and Wilson, C. I. (2009). Long-term effects of a very low-carbohydrate diet and a low-fat diet on mood and cognitive function. Arch. Intern. Med. 169, 1873–1880.

Cantello, R., Varrasi, C., Tarletti, R., Cecchin, M., D’Andrea, F., Veggio, P., Bellomo, G., and Monaco, P. (2007). Ketogenic diet: electrophysiological effects on the normal human cortex. Epilepsia 48, 1756–1763.

Cheng, B., Yang, X., An, L., Gao, B., Liu, X., and Liu, S. (2009). Ketogenic diet protects dopaminergic neurons against 6-OHDA neurotoxicity via up-regulating glutathione in a rat model of Parkinson’s disease. Brain Res. 1286, 25–31.

Cheng, C. M., Hicks, K., Wang, J., Eagles, D. A., and Bondy, C. A. (2004). Caloric restriction augments brain glutamic acid decarboxylase-65 and -67 expression. J. Neurosci. Res. 77, 270–276.

Clugnet, M.-C., and LeDoux, J. E. (1990). Synaptic plasticity in fear conditioning circuits: induction of LTD in the lateral nucleus of the amygdala by stimulation of the medial geniculate body. J. Neurosci. 10, 2818–2824.
Colomer, R., Moreno-Nogueira, J. M., Garcia-Luna, P. F., Garcia-Peris, P., Garcia-De Lorenzo, A., Zarazaga, A., Quevedo, L., Del Llano, J., Usain, L., and Castimiro, C. (2007). N-3 fatty acids, cancer and cachexia: a systematic review of the literature. Br. J. Nutr. 97, 823–831.

Costenla, A. R., De Mendonca, A., and Ribeiro, J. A. (1999). Adenosine modulates synaptic plasticity in hippocampal slices from aged rats. Brain Res. 851, 228–234.

Cullingford, T. E., Dolphin, C. T., and Sato, H. (2002). The peroxisome proliferator-activated receptor α-selective activator ciprofibrate upregulates expression of genes encoding fatty acid oxidation and ketogenesis enzymes in rat brain. Neuropharmacology 42, 724–730.

Cuzzocrea, S., Mazzon, E., Dugo, L., Davis, S., Butcher, S. P., and Mor-Avi, J. (1999). Severe hypoglycemia and intelligence in adult patients with insulin-treated diabetes. Diabetes 42, 341–344.

Dell, C. A., Likhodi, S. S., Musa, K., Ryan, M. A., Burnham, W. C., and Cunnane, S. C. (2001). Lipid and fatty acid profiles in rats consuming different high-fat ketogenic diets. Lipids 36, 373–378.

DeVinsky, O. (1995). Cognitive and behavioral effects of antiepileptic drugs. Epilepsia 36, S46–S65.

DuVico, D. C., Leckie, M. P., Ferrenberg, J. S., and McDougal, D. B. Jr. (1978). Chronic ketosis and cerebral metabolism. Ann. Neurol. 3, 999–1010.

Ding, S., and Lund, P. K. (2011). Role of intestinal inflammation as an early event in obesity and insulin resistance. Curr. Opin. Clin. Nutr. Metab. Care 14, 328–333.

Dirdaroudian, C., Giraud, J., and Pegorier, J.-P. (2005). Phosphorylation of PPARs from molecular characterization to physiological relevance. Biochimie 87, 33–38.

Dong, L., Luo, R., Tong, Y., Cai, X., Mao, M., and Yu, D. (2011). Lack of association between ABCB1 gene polymorphisms and pharmacoresistant epilepsy: an analysis in a western Chinese pediatric population. Brain Res. 1391, 114–124.

Drane, D. L., and Meadow, K. J. (2002). Cognitive and behavioral effects of antiepileptic drugs. Epilepsy Behav. 3, 549–553.

Dressler, A., Reithofer, E., Schneemann, M., and Feuerbach, L. (2010). Mito- and mitochondrial brain injury in juvenile rats. J. Leukoc. Biol. 87, 199–207.

Estrada-Sanchez, A. M., Mejia-Tober, J., and Massieu, L. (2008). Excitotoxic neuronal death and the pathogenesis of Huntington’s disease. Arch. Med. Res. 39, 265–276.

Fede, D. E., Gouder, N., Guttinger, M., Garb, G., and Wilson, C. J., Noakes, M., Buckley, J. D., Keogh, J. B., and Clifton, P. M. (2007). Low- and high-carbohydrate weight-loss diets have similar effects on mood but not cognitive performance. Am. J. Clin. Nutr. 86, 580–587.

Farah, K., Tandon, P., Holmes, G. L., and Stafstrom, C. E. (1997). Ketogenic diet: effects on expression of kindled seizures and behavior in adult rats. Epilepsia 38, 750–758.

Fujii, S., Kuroda, Y., Ito, K.-I., Itoh, S., Yamazaki, Y., Sasaki, H., and Kuroda, Y. (2000a). Effects of A1 and A2 adenosine receptor antagonists on the induction and reversal of long-term potentiation in guinea pig hippocampal slices of CA1 neurons. Cell. Mol. Neurobiol. 20, 331–343.

Gwak, Y. S., Tan, H. Y., Nam, T. M., Paik, K. S., Hulsebosch, C. E., and Leem, J. W. (2006). Activation of spinal GABA receptors attenuates chronic central neuropathic pain after spinal cord injury. J. Neurotrauma 23, 1111–1124.

Haces, M. L., Hernandez-Fonseca, K., Medina-Campos, O. N., Montiel, T., Pedraza-Chávarri, J., and Massieu, L. (2000). Cerebrospinal fluid lactate contributes to protection of ketone bodies against oxidative damage induced during hypoglycemic conditions. Exp. Neurol. 211, 85–96.

Hu, Y., and Wilson, G. S. (1997). Rapid changes in extracellular rat brain glucose observed with an in vivo glucose sensor. J. Neurochem. 68, 1745–1752.

Hu, Z.-G., Wang, H.-D., Jin, W., and Yin, H.-X. (2009a). The protective effect of the ketogenic diet on traumatic brain injury-induced cell death in juvenile rats. Brain Inj. 23, 439–465.

Hu, Z. G., Wang, H.-D., Jin, W., and Yin, H. X. (2009b). Ketogenic diet reduces cytochrome c release and cellular apoptosis following traumatic brain injury in juvenile rats. Ann. Clin. Lab. Sci. 39, 76–83.

Kingston, R. F., and Masino, K. A. (2000a). Long-term potentiation observed upon blockade of adenosine A1 receptors in rat hippocampus is N-methyl-D-aspartate receptor-dependent. Neurosci. Lett. 291, 81–84.

Ruskin and Masino Ketogenic diet and nervous system Frontiers in Neuroscience | Neuropharmacology March 2012 | Volume 6 | Article 33 | 8
Kinsman, S. L., Vining, E. P., Quaskey, S. A., Mellits, D., and Freeman, J. M. (1992). Efficacy of the ketogenic diet for intractable seizure disorders: review of 58 cases. Epilepsia 33, 1132–1136.

Kirchner, A., Velisova, J., and Velisek, L. (2006). Differential effects of low glucose concentrations on seizures and epileptiform activity in vivo and in vitro. Eur. J. Neurosci. 23, 1512–1522.

Klement, R. J., and Kammerer, U. (2011). Is there a role for carbohydrate restriction in the treatment and prevention of cancer? Nutr. Metab. 8, 75.

Koranda, J. L., Ruskin, D. N., Marino, S. A., and Blaise, J. H. (2011). A ketogenic diet reduces long-term potentiation in the dentate gyrus of fear-irrelevant behaving rats. J. Neurophysiol. 106, 662–666.

Kossoff, E. H., Laux, L. C., Blackford, R., Morrison, P. F., Pzik, P. L., Hamdy, R. M., Turner, Z., and Nordli, D. R. Jr. (2008a). When do seizures usually improve with the ketogenic diet? Epilepsy 49, 329–333.

Kossoff, E. H., Rowley, H., Sinha, S. R., and Vining, E. P. G. (2008b). A prospective study of the modified Atkins diet for intractable epilepsy. Epilepsia 49, 316–319.

Langan, S. J., Deary, I. J., Hepburn, D. A., and Frier, B. M. (1991). Cumulative cognitive impairment following recurrent severe hypoglycaemia in adult patients with insulin-treated diabetes mellitus. Diabetologia 34, 337–344.

Lange, K. W., Sahakian, B. J., Quinn, N. P., Marsden, C. D., and Robbins, T. W. (1995). Comparison of executive and visuospatial memory function in Huntington’s disease and dementia of Alzheimer type matched for degree of dementia. J. Neurol. Neurosurg. Psychiat. 58, 598–606.

Lanska, D. J., Lanska, M. J., Lavine, L., and Schoenberg, B. S. (1988). Conditions associated with Huntington’s disease at death: a case-control study. Arch. Neurol. 45, 878–880.

Laugerette, E., Vors, C., Peretti, N., and Michalski, M.-C. (2011). Complex links between dietary lipids, endogenous endotoxins and metabolic inflammation. Biochimie 93, 39–45.

Lawrence, A. D., Sahakian, B. J., Hodges, J. R., Rosser, A. E., Lange, K. W., and Robbins, T. W. (1996). Executive and mnemonic functions in early Huntington’s disease. Brain 119, 1633–1645.

Lefevre, F., and Aronson, N. (2000). Ketogenic diet for the treatment of refractory epilepsy in children: a systematic review of efficacy. Pediatrics 105, 466.

Linard, B., Ferrandon, A., Koning, E., Nehlig, A., and Raffo, E. (2010). Ketogenic diet exhibits neuroprotective effects in hippocampus but fails to prevent epileptogenesis in the lithium-pilocarpine model of mesial temporal lobe epilepsy in adult rats. Epilepsia 51, 1829–1836.

Liu, Y.-M. C., Williams, S., Basaldula-Hammond, C., Stephens, D., and Curtis, R. (2003). A prospective study: growth and nutritional status of children treated with the ketogenic diet. J. Am. Diet. Assoc. 103, 707–712.

Loring, D. W. (2005). Cognitive side effects of anti-epileptic drugs in children. Curr. Opin. Neuropathol. 12, 24–32.

LoVerme, J., Fu, J., Astarita, G., La Rana, G., Russo, R., Calignano, A., and Piomelli, D. (2005). The nuclear receptor PPAR-γagonist rosiglitazone mediates the anti-inflammatory actions of palmitoylethanolamide. Mol. Pharmacol. 67, 15–19.

LoVerme, J., Russo, R., La Rana, G., Fu, J., Farthing, J., Mattace-Raso, G., Meli, R., Hohmann, A., Calignano, A., and Piomelli, D. (2006). Rapid broad-spectrum analgesia through activation of peroxisome proliferator-activated receptor-α. J. Pharmacol. Exp. Ther. 319, 1051–1061.

Lund, T. M., Risa, Ø., Sonnewald, U., Schousboe, A., and Waagepetersen, H. S. (2009). Availability of neuronal transmitter glutamate is diminished when β-hydroxybutyrate replaces glucose in cultured neurons. J. Neurochem. 110, 80–91.

Ma, W., Berg, J., and Yellen, G. (2007). Ketogenic diet metabolites reduce firing in central neurons by opening KATP channels. J. Neurosci. 27, 3618–3625.

Maalouf, M., and Rho, J. M. (2008). Oxidative impairment of hippocampal long-term potentiation involves activation of protein phosphatase 2A and is prevented by ketone bodies. J. Neurosci. Res. 86, 3322–3330.

Maalouf, M., Sullivan, P. G., Davis, L., Kim, D. Y., and Rho, J. M. (2007). Ketones inhibit mitochondrial production of reactive oxygen species following glucose deprivation in rat hypothalamic slices. Redox Rep. 12, 131–138.

Mahlon, S., Deniau, J.-M., and Charpier, S. (2004). Corticostratal plasticity: life after the depression. Trends Neurosci. 27, 460–467.

Malan, T. P. Jr., Mata, H. P., and Porreca, F. (2002). Spinal GABAA and GABAB receptor pharmacology in a rat model of neuropathic pain. Anesthesiology 96, 1161–1167.

Malmberg, A. B., and Yaksh, T. L. (1993). Pharmacology of the spinal action of ketorolac, morphine, ST-91, U50488H, and L-PIA on the formalin test and an isobolographic analysis of the NSAID interaction. Anesthesiology 79, 270–281.

Mantis, J. G., Fritz, C. L., Marsh, J., Heinrichs, S. C., and Seyfried, T. N. (2009). Improvement in motor and exploratory behaviour in Rett syndrome mice with restricted ketogenic and standard diets. Epilepsy Behav. 15, 133–141.

Masino, S. A., and Geiger, J. D. (2008). Are purines mediators of the anticonvulsant/neuroprotective effects of ketogenic diets? Trends Neurosci. 31, 273–278.

Masino, S. A., Gockel, I. A., Wasser, C. D., Pomery, L. T., Wagener, I. F., Gavriluk, J. W., and Geiger, J. D. (2007). The relationship among ATP, adenosine and a ketogenic diet. Soc. Neurosci. Abstr. 595, 512.

Masino, S. A., Li, T., Theofilas, P., Ruskin, D. N., Fredholm, B. B., Geiger, J. D., Aronica, E., and Beison, D. (2011). A ketogenic diet suppresses seizures in mice through adenosine A1 receptors. J. Clin. Invest. 121, 2679–2689.

Massieu, L., Haces, M. L., Montiel, T., and Hernández-Fonseca, K. (2003). Acetocacete protects hippocampal neurons against glutamate-mediated neuronal damage during glycolysis inhibition. Neuroscience 120, 365–378.

McClenincer, F. I., Yancy, W. S. Jr., Eberlein, J. A., Atkins, R. C., and Westman, E. C. (2007). The effects of a low-carbohydrate ketogenic diet and a low-fat diet on mood, hunger, and other self-reported symptoms. Obesity (Silver Spring) 15, 182–187.

Mense, S. (1983). Basic neurobiological mechanisms of pain. Am. J. Med. Sci. 3, 4–14.

Michaikl, L., Auerwey, J., Berger, J. P., Chatterjee, V. K., Glass, C. K., Gonzalez, F. J., Grimaldi, P. A., Kadowaki, T., Lazar, M. A., O’Rahilly, S., Palmer, C. N. A., Platukis, J., Reddy, J. K., Spiegelman, B. M., Staels, B., and Wahli, W. (2006). International Union of Pharmacology. LXI. Peroxisome proliferator-activated...
Ketogenic diet and nervous system

Ruskin and Masino

Ketosis and epilepsy: 31P spectroscopic imaging at 4.1 T. Epilepsy 40, 703–707.

Pan, Y., Larrson, B., Araujo, J. A., Lai, W., De Rivera, C., Santana, R., Gore, A., and Milgram, N. W. (2010). Dietary supplementation with medium-chain TAG has long-lasting cognition-enhancing effects in aged dogs. Br. J. Nutr. 103, 1746–1754.

Park, S., Kim, D. S., Kang, S., and Daily, J. D. (2011). A ketogenic diet impairs energy and glucose homeostasis by the attenuation of hypothalamic leptin signaling and hepatic insulin signaling in a rat model of non-obese type 2 diabetes. Exp. Biol. Med. 236, 194–204.

Pascual, O., Casper, K. B., Kubera, C., Zhang, J., Revilla-Sanchez, R., Sul, J.-Y., Takano, H., Moss, S. J., McCarthy, K., and Hayden, P. G. (2005). Astrocytic purinergic signaling coordinates synaptic networks. Science 310, 113–116.

Pérez-Guisado, J., and Muñoz-Serrano, A. (2011). The effect of the Spanish Ketogenic Mediterranean Diet on nonalcoholic fatty liver disease: a pilot study. J. Med. Food 14, 677–680.

Peterson, S. I., Tangney, C., Pimentel-Zablah, E. H., Hjelmgren, B., Booth, G., and Berry-Kravis, E. (2005). Changes in growth and seizure reduction in children on the ketogenic diet as a treatment for intractable epilepsy. J. Am. Diet. Assoc. 105, 718–725.

Picot, M. C., Baldy-Moulinier, M., Dauzé, J. P., Dujols, P., and Crespel, A. (2008). The prevalence of epilepsy and pharmacoresistant epilepsy in adults: a population-based study in a Western European country. Epilepsia 49, 1230–1238.

Porpiglia, M., Mastaitis, J. W., Isoda, F., Grosjean, E., Zheng, F., and Mobbs, C. V. (2011). Reversal of diabetic nephropathy compared to a ketogenic diet. PLoS ONE 6, e18604. doi:10.1371/journal.pone.0018604

Potter, W. B., O’Riordan, K. J., Vining, E. P. G., and Freeman, J. H. (2008b). Growth of thalamic leptin signaling and hepatic hypothesis signaling in an adult mouse model of Huntington’s disease. Physiol. Behav. 103, 501–507.

Prins, M. L., Fujiyama, L. S., and Hovda, D. A. (2005). Age-dependent reduction of cortical contusion volume by ketones after traumatic brain injury. J. Neurosci. Res. 82, 413–420.

Prins, M. L., and Hovda, D. A. (2009). The effects of age and ketogenic diet on local cerebral metabolic rates of glucose after controlled cortical impact injury in rats. J. Neurotrauma 26, 1083–1093.

Pulsifer, M. B., Gordon, J. M., Brandt, J., Vining, E. P. G., and Freeman, J. M. (2001). Effects of ketogenic diet on development and behavior: preliminary report of a prospective study. Dev. Med. Child Neurol. 43, 301–306.

Rex, C. S., Kramar, E. A., Colgin, L. L., Lin, B., Gall, C. M., and Lynch, G. (2005). Long-term potentiation is impaired in middle-aged rats: regional specificity and reversal by adenosine receptor antagonists. J. Neurosci. 25, 5956–5966.

Ruskin, D. N., Kawamura, M. Jr., and Masino, S. A. (2009). Reduced pain and inflammation in juvenile and adult rats fed a ketogenic diet. PLoS ONE 4, e8349. doi:10.1371/journal.pone.0008349

Ruskin, D. N., Ross, J. L., Kawamura, M. Jr., Ruiz, T. L., Geiger, J. D., and Masino, S. A. (2011a). A ketogenic diet delays weight loss and does not impair working memory or motor function in the R6/2 J mouse model of Huntington’s disease. Physiol. Behav. 103, 501–507.

Ruskin, D. N., Suter, T. A. C. S., and Masino, S. A. (2011b). Dissociation of hypoglycaemia, ketosis, and hypoglycaemia with two ketogenic diets in the rat. Soc. Neurosci. Abstr. 383.04.

Samala, R., Klein, J., and Borges, K. (2011). The ketogenic diet changes metabolic levels in hippocampal extracellular fluid. Neurochem. Int. 58, 5–8.

Samoiola, M., Weisspapir, M., Abdelmalak, P., Velumian, A. A., and Carlén, P. L. (2010). Chronic in vitro ketosis is neuroprotective but not anticonvulsant. J. Neurochem. 113, 826–835.

Sanberg, P. R., Fischer, H. C., and Mark, R. F. (1981). Body weight and dietary factors in Huntington’s disease patients compared with matched controls. Med. J. Aust. 1, 407–409.

Schock, S. C., LeBlanc, D., Hakim, A. M., and Thompson, C. S. (2008). ATP release by way of connexin 36 hemichannels mediates ischemic tolerance in vitro. Biochem. Biophys. Res. Commun. 368, 138–144.
Ketogenic diet and nervous system

Schwartzkroin, P. A., Wenzel, H. J., Lyeth, B. G., Poons, C. C., DeLancey, A., Van, K. C., Campos, L., and Nguyen, D. V. (2010). Does ketogenic diet alter seizure sensitivity and cell loss following fluid percussion injury? Epilepsy Res. 82, 74–84.

Seyfried, T. N., Marsh, J., Shelton, L. M., Huysentruyt, L. C., and Mukherjee, P. (2012). Is the restricted ketogenic diet a viable alternative to the standard of care for managing malignant brain cancer? Epilepsy Res. PMID: 21885251. [Epub ahead of print].

Seyfried, T. N., and Mukherjee, P. (2005). Targeting energy metabolism in brain cancer: review and hypothesis. Nutr. Metab. 2, 30.

Shafer, M., Gulati, S., Kalra, V., Agarwala, A., and Kabra, M. (2009). Seizure control and biochemical profile on the ketogenic diet in young children with refractory epilepsy–Indian experience. Seizure 18, 446–449.

Shram, N. E., Netchiporouk, L. I., Martelo, C., Jaffe-Reznick-Renault, N., and Cuspuglio, R. (1997). Brain glucose: volumetric determination in normal and hyperglycaemic rats using a glucose microsensor. Neuroreport 8, 1109–1112.

Silva, M. C., Rocha, J., Pires, C. S., Ribeiro, L. C., Broele, G., Leite, M. C., Almeida, L. M. V., Tramontina, F., Ziegler, D. R., and Gonçalves, C. (2007). The effect of a low-carbohydrate, ketogenic diet a viable alternative to the standard of care for managing malignant brain cancer? Endocrinology 151, 8589–933.

Stout, C. E., Costantini, J. L., Naus, C. C., and Charles, A. C. (2002). Intercellular calcium signaling in astrocytes via ATP release through connexin hemichannels. J. Biol. Chem. 277, 10482–10488.

Streitger, E., Plunet, W. T., Lee, H. T., Liu, J., Lam, C. K., Park, S., Hilton, B. J., Fransen, B. L., Matheson, K. A., Assimac, P., Kwon, B. K., and Tetzlaff, W. (2011). Ketogenic diet improves forelimb motor function after spinal cord injury. Soc. Neurosci. Abstr. 255, 90.

Studzinski, C. M., Mackay, W. A., Beckett, T. T., Henderson, S. T., Murphy, M. P., Sullivan, P. G., and Burnham, W. N. (2008). Induction of ketosis may improve mitochondrial function and decrease steady-state and β-predursor protein (APP) levels in the aged dog. Brain Res. 1226, 209–217.

Su, S. W., Sogawa, M. R. C. Y., Silveira, D. C. H., Holmes, G. L., and Stafstrom, C. E. (2000). Timing of ketogenic diet initiation in an experimental epilepsy model. Brain Res. Dev Brain Res. 125, 131–138.

Sullivan, P. G., Rippy, N. A., Dorenbos, K., Concepcion, R. C., Agarwal, A. K., and Rho, J. M. (2004). The ketogenic diet increases mitochondrial uncoupling protein levels and activity. Ann. Neurol. 55, 576–580.

Swink, T. D., Vining, E. P., and Freeman, J. M. (1997). The ketogenic diet: Adv. Pediatr. 44, 297–329.

Tabaka, K., Matsumoto, K., Murakami, Y., and Watanabe, H. (2001). Ame- liorative effects of paeoniflorin, a major constituent of peony root, on adenosine A1 receptor-mediated impairment of passive avoidance performance and long-term poten- tiation in the hippocampus. Biol. Pharm. Bull. 24, 496–500.

Tai, K.-K., Nguyen, N., Pham, L., and Truong, D. D. (2008). Ketogenic diet prevents cardiac arrest-induced cerebral ischemic neurodegen- eration. J. Neurotransm. 115, 1011–1017.

Tai, K.-K., Pham, L., and Truong, D. D. (2009). Intracranial administration of glibenclamide or 5- hydroxydecanoate does not reverse the neuroprotective effect of ketogenic diet against ischemic brain injury-induced neurodegeneration. Brain Res. 123, 1081–1088.

Tendler, D., Lin, S., Yancy, W. S. Jr., Mavropoulos, J., Sylvestre, P., Rockey, D. C., and Westman, E. C. (2007). The effect of a low-carbohydrate, ketogenic diet on nonalcoholic fatty liver disease: a pilot study. Dig. Dis. Sci. 52, 589–593.

Theiler, J. P., and Schwartz, M. W. (2010). Minireview: inflammation and obe- sity pathogenesis: the hypothala- mus heats up. Endocrinology 151, 4109–4115.

Thio, L. L., Rensing, N., Maloney, K. S., Wozniak, D. F., Xiong, C., and Yamada, K. A. (2010). A ketogenic diet does not impair rat behavior or long-term potentiation. Epilepsia 51, 1619–1623.

Thio, L. L., Wong, M., and Yamada, K. A. (2000). Ketone bodies do not directly alter excitatory or inhibitory hippocampal synaptic transmission. Neurology 54, 325–331.

Thompson, P. J., Baxendale, S. A., Dun- can, J. S., and Sander, J. W. (2000). Mitochondria: a genetic model for idiopathic epilepsy. Epilepsia 41, 933–940.

Todorov, M. T., Tandon, P., Madore, R. A., Stafstrom, C. E., and Seyfried, T. N. (2000). The ketogenic diet inhibits epileptogenesis in EL mice: a genetic model for idiopathic epilepsy. Epilepsia 41, 844–850.

Tromba, C., Salvaggio, A., Racagni, G., and Volterra, A. (1992). Hypoglycemia-activated K+ channels in hippocampal neurons. Neurosci. Lett. 143, 185–189.

Van der Auwera, I., Wera, S., Van Leuven, F., and Henderson, S. T. (2000). Hypoglycemia-activated K+ pathways in hippocampal neurons. Neurosci. Lett. 307, 210–214.

Yang, W. S. Jr., Almiraill, D., Maciejew- ski, M. L., Kolotkin, R. L., McDuffie, J. R., and Westman, E. C. (2009). Effects of two weight-loss diets on health-related quality of life. Qual. Life Res. 18, 281–289.

Yancy, W. S. Jr., Foy, M., Chalecki, A. M., Vernon, M. C., and Westman, E. C. (2005). A low-carbohydrate, keto- genic diet to treat type 2 diabetes. Nutr. Metab. 2, 34.

Yudkoff, M., Daikhin, Y., Melson, T. M., Nissin, I., Sonnewald, U., and Nis- sim, I. (2007). The ketogenic diet and brain metabolism of amino acids: relationship to the anticon- vulsant effect. Annu. Rev. Nutr. 27, 415–430.

Zhang, D. S., Ren, L. M., and Zhang, L. (2004). Relation between adeno- sine A1 receptor and NMDA recep- tor on synaptic transmission in den- tate gyrus of hippocampus. J. Cereb. Blood Flow Metab. 24, 289–299.

Zhang, D. S., Ren, L. M., and Zhang, L. (2004). Relation between adeno- sine A1 receptor and NMDA recep- tor on synaptic transmission in den- tate gyrus of hippocampus. J. Cereb. Blood Flow Metab. 24, 289–299.
Zhao, Z., Lange, D. J., Voultian-iouk, A., MacGrogan, D., Ho, L., Suh, J., Humala, N., Thiagarajan, M., Wang, L., and Pasinetti, G. M. (2006). A ketogenic diet as a potential novel therapeutic intervention in amyotrophic lateral sclerosis. BMC Neurosci. 7, 29. doi:10.1186/1471-2202-7-29

Zhu, P. J., and Krnjevic, K. (1993). Adenosine release is a major cause of failure of synaptic transmission during hypoglycaemia in rat hippocampal slices. Neurosci. Lett. 155, 128–131.

Ziegler, D. R., Gamaro, G. D., Araújo, E., Bassani, M. G., Perry, M. L. S., Dalmaz, C., and Gonçalves, C.-A. (2005). Nociception and locomotor activity are increased in ketogenic diet fed rats. Physiol. Behav. 84, 421–427.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 23 December 2011; paper pending published: 16 January 2012; accepted: 23 February 2012; published online: 26 March 2012.

Citation: Ruskin DN and Masino SA (2012) The nervous system and metabolic dysregulation: emerging evidence converges on ketogenic diet therapy. Front. Neurosci. 6:33. doi: 10.3389/fnins.2012.00033

This article was submitted to Frontiers in Neuropharmacology, a specialty of Frontiers in Neuroscience. Copyright © 2012 Ruskin and Masino. This is an open-access article distributed under the terms of the Creative Commons Attribution Non Commercial License, which permits non-commercial use, distribution, and reproduction in other forums, provided the original authors and source are credited.