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The Ketogenic Diet in a Pill: Is this Possible?

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Summary

Over the past decade, much progress has been made in understanding the mechanisms of ketogenic diet (KD) action. From the complex systemic and metabolic changes induced by the KD have emerged innovative hypotheses attempting to link biochemical adaptations to its clinical effects. Despite such developments, the fundamental question of how the KD works remains as elusive as ever. At present, it is unclear which of many potential mechanisms proposed thus far are directly relevant to the clinical effects of the KD. It is unlikely that these numerous hypotheses can be unified into a single mechanism (or a final common pathway). Nevertheless, it may be instructive to consider each of these putative mechanisms in turn and ask the following question: If the mechanism or target in question is a critical determinant of the anticonvulsant efficacy of the KD, then would a similar intervention known to be based on that mechanism yield a comparable effect? Perhaps answering this question for each mechanistic speculation might help substantiate (or invalidate) that particular hypothesis. Can the KD be packaged into a pill? At present, the answer is likely "no." We have yet to discover a "magic bullet" that completely mirrors the anticonvulsant (and potential neuroprotective) effects of the KD. However, without a clearer understanding of the mechanistic elements comprising the complex metabolic puzzle posed by the KD, we would be left only with empiric observations, and to wonder curiously how a high-fat diet can exert such profound clinical effects.

Keywords

ketogenic diet; mechanism; GABA; ketone; mitochondria; reactive oxygen species; calorie restriction; glycolysis; fatty acids

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The scientific rationale for elucidating mechanisms of disease pathogenesis or of therapeutic interventions has been traditionally based upon the lofty goal of discovering novel treatments, ones that would be more efficacious than existing options and also be devoid of side-effects altogether. Moreover, in epilepsy research, disease prevention or modification has become the "holy grail", such that we are no longer complacent with symptomatic treatment and increasing attention is being given to understanding the processes of anti-epileptogenesis itself. Researchers in the field of the ketogenic diet (KD) have also embraced these tenets and recently embarked on that all-too-familiar Quixotic journey, with the ultimate aim of reducing the "difficult" KD regimen to a simple pill. If achieved, this

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result would represent an ironic recapitulation of the early history of the KD in the United States. Although the KD experienced an initial surge of interest following its introduction in the early 1920's, it was relegated to near obscurity by the emergence of a familiar drug known as phenytoin. Henceforth, until the mid 1990's, clinicians – for obvious practical reasons – found it simpler to prescribe a pill rather than an exacting diet.

Over the past decade, much progress has been made in dissecting apart the mechanisms underlying the anticonvulsant (and potentially, neuroprotective) effects of the KD (Gasior et al., 2006; Bough & Rho, 2007). The complex systemic and metabolic changes induced by a high-fat, low-carbohydrate diet – not surprisingly – provide fertile ground for very innovative and speculative hypotheses linking certain adaptations to a net anticonvulsant effect, ones that by necessity take researchers back to the earlier days of introductory biochemistry and human physiology. While many intriguing concepts and research data have been reviewed systematically in the context of the international symposium from which this supplement stems, the fundamental question of how the KD works remains as tantalizing as ever.

Historically, many anticonvulsant medications have resulted from structural modifications of lead compounds that had themselves been discovered serendipitously. The mechanistic bases for their effectiveness have typically been elucidated post-hoc. At present, it is unclear which of many potential mechanisms reviewed in this supplement are relevant to the clinical effects of the KD. It would be far too difficult to integrate these numerous possibilities into a single unifying hypothesis (or a final common pathway), or to consider them simultaneously. Nevertheless, it might be instructive to consider each of these putative mechanisms one by one and ask a simple comparative question. If the mechanism or target in question is a critical determinant of the anticonvulsant efficacy of the KD, then would a similar intervention known to be based on that mechanism yield a comparable effect? Perhaps answering this question for each mechanistic speculation might help substantiate (or perhaps invalidate) that particular hypothesis.

Concept 1: It is GABA!

Many of our existing anticonvulsant medications exert effects on inhibitory neurotransmission, and more specifically, by enhancing synaptic levels of γ-aminobutyric acid (GABA) or modulating post-synaptic $GABA_A$ receptors (Meldrum & Rogawski, 2007; White et al., 2007). Examples of such agents include tiagabine, vigabatrin, benzodiazepines, barbiturates, felbamate, and topiramate. Thus, given the wealth of information regarding GABAergic neurotransmission, one possibility is that the KD, perhaps through ketone bodies, might be responsible for elevating synaptic levels of GABA, which would then yield an inhibitory (and potentially anticonvulsant) effect.

In support of this, Yudkoff and colleagues have published widely on the impact of ketone bodies on brain glutamate and GABA metabolism (Yudkoff et al., 2007). In one study, the addition of either acetoacetate or β-hydroxybutyrate was associated with diminished consumption of glutamate via transamination to aspartate and increased formation of labeled GABA (Daikhin et al., 1998). Ketone bodies had earlier been shown by the same group to enhance synthesis of GABA in synaptosomes prepared from rodent forebrain (Erecinska et al, 1996).

So, the natural question arises, do ketone bodies affect inhibitory (or excitatory) neurotransmission? Unfortunately, the answer is (at least for now) a fairly convincing no. Thio and colleagues (2000) showed that acute application of BHB and ACA did not affect: (1) excitatory post-synaptic potentials (EPSPs) and population spikes in CA1 pyramidal neurons after Schaffer collateral stimulation; (2) spontaneous epileptiform activity in the

hippocampal-entorhinal cortex slice seizure model; and (3) whole-cell currents evoked by glutamate, kainate, and GABA in cultured hippocampal neurons.

Furthermore, if the KD increases GABA levels in the brain, then such an effect is approximated by vigabatrin, an irreversible inhibitor of the degradative enzyme GABA-transaminase, as well as by tiagabine, a GABA re-uptake blocker that interferes with presnaptic GABA transporters (White et al., 2007). Yet, the anticonvulsant profile of the KD is distinct from that of vigabatrin and tiagabine (Hartman et al., 2007). The general approach of deriving another pill that enhances brain GABA levels may not be relevant or viable, since many seizure types seem to be exacerbated by agents that contribute to enhanced tonic inhibition, and extrasynaptic GABA receptors that mediate tonic inhibition are more sensitive to elevated ambient GABA concentrations (Sazgar & Bourgeois, 2005). Indeed, increased GABAergic inhibition in the cortex appears to underlie the mechanism of synchronization and seizure generation in two mouse models of autosomal dominant nocturnal frontal lobe epilepsy (Klassen et al, 2006)

Concept 2: Acetone and Acetoacetate!

The earliest demonstration of direct *in vivo* effects of ketone bodies was made by Keith in the early 1930's, when he determined that acetoacetate, when administered intraperitoneally in rabbits, prevented seizures induced by thujone (1933), a convulsant constituent found in many essential oils and an antagonist of $GABA_A$ receptors (Höld et al., 2000). This seminal observation was later confirmed in an audiogenic seizure-susceptible mouse model (Rho et al., 2002). More intriguingly, however, Likhodii and colleagues (2003) established the broad anticonvulsant properties of acetone in four different animal models, and when injected intraperitoneally, produced plasma and cerebrospinal fluid (CSF) concentrations consistent with those used to suppress seizures. These results confirmed and extended historical observations supporting an anticonvulsant action for acetone, through as yet undetermined mechanisms (Likhodii & Burnham, 2002). And in further support of this, other investigators found that acetone was detectable (up to a concentration of 0.7 mM) in the brains of fully controlled KD-treated patients with epilepsy using proton magnetic resonance spectroscopy (Seymour et al, 1999).

Given these observations, would it be practical to package acetoacetate or acetone into a pill? While ketone bodies *in situ* are likely to influence local cellular bioenergetics, there are profound logistical constraints precluding ease of administration in humans to achieve comparable low millimolar concentrations observed in clinical practice (Hartman & Vining, 2007). Acetoacetate is highly unstable, as it has an immediate tendency to spontaneously decarboxylate, and acetone is a well known solvent that can cause significant mucosal irritation. Finally, oral ingestion of β-hydroxybutyrate formulations to achieve such concentrations may not be readily achievable (Smith et al., 2005). These considerations pose not insignificant challenges toward the design of a ketone pill.

One of the nagging unresolved questions regarding ketone bodies is whether they correlate with seizure control. Recent studies have suggested that under certain conditions and in specific models, blood levels of ketones do not in fact correlate well with anticonvulsant effects (Hartman & Vining, 2007). However, ketone levels are known to vary considerably during the circadian cycle, mostly as a consequence of feeding schedules and subsequent metabolism of foodstuffs (DeGasquet et al., 1977). Despite numerous studies highlighting ketonemia following KD treatment, we still do not know what the true brain concentrations are, especially in the microenvironment of the highly metabolically active synapse. Moreover, there are other studies suggesting that high ketone body levels are not necessary

for clinical efficacy of a high-fat diet against medically refractory epilepsies (Pfeifer & Thiele, 2005).

Concept 3: An Increase in Bioenergetics?

One potential explanation for the anticonvulsant action of the KD argues that increased ATP synthesis should produce a positive bioenergetic balance, allowing stabilization of the resting membrane potential via enhanced activity of Na^+-K^+-ATPase (Bough & Rho, 2007). Several decades ago, De Vivo and colleagues (1978) reported that the KD increased the total quantity of bioenergetic substrates (such as adenosine triphosphate, or ATP) and elevated the energy charge in rat brain. These changes were purported to stabilize the cell membrane, especially in the face of excessive excitation. Consistent with these observations, a later human study utilizing magnetic resonance spectroscopic techniques indicated that patients with epilepsy fed a KD had elevated phosphocreatine to creatine levels in the brain (Pan et al., 1999). Recently, using cDNA microarray technology, increased expression of the mitochondrial ATP synthase β,D subunit in mouse brain was reported after KD treatment (Noh et al., 2004). And in the most comprehensive study of this kind to date, the KD was found to enhance mitochondrial biogenesis and significantly increase the number of transcripts encoding energy metabolism genes in rats (Bough et al., 2006). This increase in bioenergetic capacity enabled hippocampal slices from these animals to better withstand metabolic challenge from low glucose exposure. Taken together, the prevailing notion has been that increased energy production and reserve capacity enable greater resistance to neuronal hyperexcitability and hypersynchrony.

So is the clinical effectiveness of the KD simply a matter of increasing energy stores? If this is the case, then would it not be a simpler matter to ingest creatine, a highly bioavailable and relatively safe oral supplement, and one that is increasingly demonstrated to promote health and longevity (Beal, 2003; Bender et al., 2007; Schapira, 2008)?

Concept 4: Decreasing Reactive Oxygen Species!

It is well known that an increase in the mitochondrial membrane potential ($\triangle\psi$) can promote mitochondrial reactive oxygen species (ROS) generation through increased electron shunting (Votyakova et al., 2001). Mitochondrial uncoupling proteins (UCPs) – which are activated by fatty acids – increase proton conductance and dissipate $\triangle\psi$, thereby decreasing ROS formation (Mattson & Liu, 2003). Recent studies have implicated UCPs as potential mediators of a neuroprotective effect of the KD. Up-regulation of UCP2 expression in transgenic mice reduced seizure-induced neuronal cell death, and was associated with enhanced ATP levels and decreased ROS production (Diano et al., 2003). In normal rats, a high-fat suckling diet was protective against kainate-induced neuronal death in immature rat hippocampus, effects that were attributed to fatty acid-induced increases in UCP2 expression and reduction in ROS production (Sullivan et al., 2003). And finally, KD treatment in normal juvenile mice led to enhanced hippocampal expression and activity of all three known brain-localizable isoforms of UCP (i.e., UCP2, UCP4 and UCP5), and correlated with significant decreases in ROS levels (Sullivan et al., 2004).

Thus, if fatty acids (and perhaps more specifically, polyunsaturated fatty acids or PUFAs), enhance mitochondrial uncoupling, and if this basic downstream mechanism is responsible for both anticonvulsant and neuroprotective effects (which has yet to be demonstrated), then could taking a chemical uncoupler such as 2,4-dinitrophenol (DNP) render the same effects? Of course, it is well known that DNP, a potent mitochondrial uncoupler that greatly increases the basal metabolic rate, and once used to treat obesity in the 1930's, has a major untoward side-effect profile – namely, high fever and the risk of death. Clearly, if

mitochondrial uncoupling were to represent the essential target, then less potent (and less toxic) compounds are required, and novel delivery systems need to be developed.

Concept 5: Enhancing Glutathione?

While the relationships between seizure activity, oxidative stress and neuronal injury have yet to be clarified, previous studies have indicated that defects in antioxidant systems may contribute to seizure genesis and epileptogenesis (Cock, 2002; Patel, 2004; Liang & Patel, 2006; Shin et al, 2008). Earlier, the effects of a KD on mitochondrial ROS generation were discussed. Are there other mechanisms through which oxidative stress can be attenuated in epileptic brain?

Glutathione is an endogenous tripeptide antioxidant whose function is to prevent free radical-mediated cellular injury (Schulz et al., 2000). It is found in nearly every cell in the body, and almost exclusively in its reduced form (GSH) due to the constitutive activity of glutathione reductase which converts it from the oxidized state, glutathione disulfide (GSSG). Under conditions of oxidative stress, glutathione reductase is inducible, and hence is able to increase the reducing equivalents essential to neutralize unstable molecules such as reactive oxygen species (Schulz et al., 2000).

In rats fed a KD, Ziegler et al (2003) found an increase in antioxidant activity using a luminol oxidation assay in the hippocampus, and a four-fold increase in glutathione peroxidase activity. Consistent with these findings, Jarrett et al (2008) recently reported an up-regulation of GSH biosynthesis in adolescent rats fed a KD. Furthermore, these investigators observed improved mitochondrial antioxidant status, and proposed that these changes were responsible for preventing mitochondrial DNA from oxidant-induced damage. Collectively, these studies suggest that the KD may indeed exert neuroprotective activity.

So, if the KD acts principally to enhance glutathione levels in the brain, then would taking glutathione supplements (which are commercially available) be sufficient to protect against seizure activity? The answer is negative since available glutathione formulations are largely digested before they can get into the bloodstream, let alone to the brain. The only supplement that effectively raises glutathione levels in the body is N-acetyl-L-cysteine (NAC) which has traditionally been used to treat liver toxicity induced by toxic levels of acetaminophen. Would NAC be a suitable substitute for the KD? The clinical experience to date has been mixed, with some patients with progressive myoclonic epilepsies improving on NAC supplementation (Hurd et al., 1996; Edwards et al., 2002)

Concept 6: Reducing Glycolysis and Calorie Restriction?

Glucose restriction is believed to be a key mechanism of KD action. Calorie restriction in rodents reduced seizure susceptibility and the resultant low blood glucose levels correlated with inhibition of epileptogenesis in a genetic model of stimulus-induced epilepsy (Greene et al., 2001). Along related lines, Garriga-Canut et al. (2006) demonstrated that 2-deoxyglucose, which inhibits the glycolytic enzyme phosphoglucose isomerase, prevented seizure progression in the rat kindling model of temporal lobe epilepsy, and decreased the expression of brain-derived neurotrophic factor (BDNF) and its principal receptor, TrkB. More recently, Lian and colleagues (2007) demonstrated that fructose-1,6-bisphosphate (F-1,6-BP), a metabolite that shifts the metabolism of glucose from glycolysis to the pentose phosphate pathway, exhibits potent anticonvulsant activity in several rat models of acute seizures (i.e., pilocarpine, kainic acid, and pentylenetetrazole), and efficacy in these models exceeds that of 2-DG and KD treatment. Collectively, these emerging data indicate that the overall strategy of limiting glycolytic flux may be a powerful way of preventing acute seizures and perhaps epileptogenesis as well.

One highly studied mechanism implicated in the clinical benefits of calorie restriction involves sirtuins, a large and diverse family of enzymes that regulate gene expression. The first sirtuin, silent information regulator 2 (Sir2), was described in yeast. Sir2 is a class III histone deacetylase that uses the cofactor nicotinamide adenine dinucleotide (NAD+) in a catalytic reaction that releases nicotinamide (a feedback inhibitor) and O-acetyl ADP ribose (Imai et al. 2000; Marmorstein 2004; Sauve et al. 2006). It has been reported that increased Sir2 activity lengthens life span, and that calorie restriction increases Sir2 levels and does not promote longevity in SIR2 knockouts (Kaeberlein et al. 1999; Lin et al. 2000, 2004; Tissenbaum and Guarente 2001; Rogina and Helfand 2004). In mammals, calorie restriction increases the expression of Sirt1, the Sir2 mammalian ortholog, in various tissues, including brain. Resveratrol, a natural Sirt1 activator found in red wine, lengthens the life span of mice and prevents the age-related deterioration of their motor function (Cohen et al. 2004; Baur et al. 2006). Additionally, resveratrol stimulates AMP kinase activity in neurons (Dasgupta & Milbrandt, 2007), and more importantly, protects against kainic acid-induced seizures and oxidative stress in rats (Gupta et al., 2002).

So, if resveratrol, a diet-derived nutriceutical, can simulate the effects of calorie restriction, reduce oxidative stress, and protect against seizure activity, then drinking red wine – which contains resveratrol – might be a simpler and more enjoyable approach than coordinating a customized and restricted diet in partnership with dietitians, nurses and neurologists. Of course, most patients treated with the KD are under the legal age for drinking, and moreover, alcohol consumption at an early age – even if advocated for medically refractory epilepsy – might cause apoptotic neurodegeneration (Olney et al., 2004)!

Alternatively, if simple calorie restriction is sufficient to prevent seizure activity in patients, why not decrease total caloric intake, and not bother with the high-fat KD? However, from yet another perspective, one could consider combining the KD and calorie restriction (as has been done in animal studies). In rats fed a calorie-restricted KD, Bough and colleagues (2003) demonstrated exhibited greater paired-pulse inhibition in the dentate gyrus, elevated maximal dentate activation threshold, and an absence of “spreading depression”-like events compared with ad libitum-fed controls. These results suggest that treatment with a calorie-restricted KD may produce both anticonvulsant and anti-epileptogenic effects.

Concept 7: Leaping Toward Leptin?

Leptin is an important protein hormone that critically regulates energy intake and expenditure (Harvey, 2007; Hill et al., 2008). The mechanisms through which leptin exerts its effects on metabolism are largely unknown. Although leptin is predominantly found in adipocytes, it is also found highly expressed in areas of the hypothalamus. Interestingly, leptin modulates numerous membrane-bound ion channels, and exerts differential effects on neuronal excitability (Harvey, 2007).

The relevance of leptin to seizure susceptibility was recently highlighted by Erbayat-Altay and colleagues (2008) who demonstrated a significantly decreased threshold in leptin-deficient *ob/ob* mice to pentylenetetrazol-induced seizures. Indeed, leptin itself inhibits seizures induced by 4-aminopyridine and pentyelenetrazole-induced, possibly through blockade of AMPA receptor-mediated synaptic transmission (Xu et al., 2008). If the limiting of AMPA receptor-mediated transmission is a critical factor, it should be recalled this can also be accomplished by topiramate. With respect to the KD, the leptin signaling system is believed to contribute to slow weight gain associated with chronic treatment in both rodents and humans (Thio et al., 2006). KD-fed juvenile rodents had higher serum leptin levels and lower insulin levels than control rats fed a standard diet.

While the effects of leptin on seizure susceptibility and its relationship to KD-induced weight loss are intriguing, there are as yet no direct data supporting leptin as an anticonvulsant mediator of the KD. Certainly, the clinical implications of the study by Xu et al. (2008) are intriguing, namely, that intranasal administration of leptin might be efficacious in aborting acute seizure activity. And if the clinical effects of the KD are due in part to increased leptin levels, then accelerated development and validation of leptin as a novel anticonvulsant medication would be warranted.

Concept 8: Polyunsaturated Fatty Acids?

Polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid (DHA, C22: 6ω-3), arachidonic acid (AA, C20: 4ω-3), or eicosapentaenoic acid (EPA, C20: 5ω-3) have been reported to suppress voltage-gated sodium channels and L-type calcium channels in seizure-prone structures such as the hippocampus (Vreugdenhil et al., 1996). The KD produces elevations of both AA and DHA in serum (Fraser et al., 2003; Cunnane et al., 2002) and brain (Taha et al., 2005) of patients and animals, respectively, suggesting that these substrates might exert anticonvulsant effects by inhibiting sodium and calcium channels, like many anticonvulsant drugs (Xiao et al., 1997, 1998).

Given these findings, it is not surprising that investigators have studied the effects of dietary supplementation with PUFAs alone, to determine whether these substrates can render an anticonvulsant effect. Early case reports suggested that seizures might be better controlled with this approach (Schlanger et al., 2002). However, a recent randomized trial in adult patients with epilepsy failed to demonstrate superiority of a PUFA supplement (EPA) plus DHA, 2.2 mg/day in a 3:2 ratio) over placebo (Bromfield et al., 2008). Thus, the jury is still out as to whether PUFAs alone can mirror the clinical effects of the KD.

Concept 9: It's a bit of everything!

What investigators have elucidated over the past decade or so is that a variety of molecular, genetic, cellular, and metabolic factors are likely contributory to the clinical effects of the KD. As a generalization, it is becoming widely accepted that the mechanistic underpinnings of the KD are likely multiple, parallel, and possibly synergistic (Bough & Rho, 2007).

So the question remains, can the KD be packaged into a pill? At this stage, given our state of knowledge, the likely answer is NO. Then, could we take a polypharmacy approach and develop a number of pills, each with a distinct mechanistic target? Such a strategy would not be too different than what is practiced by adults – and especially, the elderly – who are by both necessity and choice on multi-drug regimens and/or multi-nutritional supplements, again with the goal of achieving health and warding off the ravages of aging and disease. There is likely no "magic bullet" that completely mirrors the anticonvulsant (and potential neuroprotective) effects of the KD; the same could be said for the treatment of the epilepsies – a group of related conditions with widely divergent etiologies, and hence a multiplicity of underlying pathophysiological mechanisms. Nevertheless, without dissecting the component pieces of the complex metabolic puzzle posed by the KD, we would again be left with only empiric observations, and to wonder curiously how a high-fat diet can exert such profound clinical effects.

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