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Hypothalamic Hormones and Metabolism

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Summary

The ketogenic diet is an effective treatment for medically intractable epilepsy and may have antiepileptogenic, neuroprotective, and antitumor properties. While on a ketogenic diet, the body obtains most of its calories from fat rather than carbohydrates. This dramatic change in caloric composition results in a unique metabolic state. In turn, these changes in caloric composition and metabolism alter some of the neurohormones that participate in the complex neuronal network regulating energy homeostasis. Two observed changes are an increase in serum leptin and a decrease in serum insulin. These opposing changes in leptin and insulin are unique compared to other metabolic stimuli and may modify the activity of several cell signaling cascades including phosphoinositidyl-3 kinase (PI3K), adenosine monophosphate activated protein kinase (AMPK), and mammalian target of rapamycin (mTOR). These cell signaling pathways may mediate the anticonvulsant and other beneficial effects of the diet, though the neurohormonal changes induced by the ketogenic diet and the physiological consequences of these changes remain poorly characterized.

Keywords

ketogenic diet; leptin; insulin; anticonvulsant; antiepileptogenic; neuroprotection; antitumor

Introduction

The ketogenic diet is effective in treating medically intractable epilepsy from a variety of etiologies (Kossoff et al., 2009). Besides its anticonvulsant effects, it may have antiepileptogenic, neuroprotective, and antitumor effects (Gasior et al., 2006; Kossoff and Rho, 2009; Seyfried et al., 2009). Although the mechanisms underlying these effects are incompletely understood, mounting evidence strongly supports the concept that the beneficial effects of the ketogenic diet arise from multiple mechanisms. One potential mechanism involves changes in neurohormones. Ketogenic diet induced alterations in neurohormone levels are not surprising, and the varied effects of neurohormones on neuronal excitability and survival may contribute to the diet's beneficial effects.

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Neuronal Network Controlling Energy Homeostasis

A complex neuronal network involving multiple peripheral and central hormones regulates appetite and body weight (Berthoud and Morrison, 2008). This network helps the body to maintain an adequate supply of macronutrients and micronutrients for energy and maintenance as well as growth in children. In this manner, the network helps the body to meet its homeostatic needs, but it also makes eating a pleasurable or hedonic activity. Anatomically, multiple regions of the brain contribute to this network. The hypothalamus and nucleus accumbens have a critical role in the network, which also depends on several cortical areas including the orbitofrontal area, dorsal prefrontal area, hippocampus, and motor cortex. The network involves other subcortical structures such as the thalamus and striatum and brainstem nuclei such as the locus coeruleus.

Obviously, the areas of the brain involved in regulating macronutrient, micronutrient, and energy homeostasis must receive information regarding the body's nutritional status from the other organs of the body. Neurohormones released from these organs provide the brain with this information (Woods and D'Alessio, 2008). Vagal afferents and the hypothalamus play a key role in this process. For example, I cells in the duodenum release cholecystokinin (CCK) and L cells in the distal ileum and colon release peptide tyrosine-tyrosine (PYY) in response to the lipid and caloric content of a meal. CCK communicates with the central nervous system by acting on vagal afferents whereas PYY may act directly on the hypothalamus. Other peripherally released neurohormones involved in energy homeostasis include leptin, insulin, ghrelin, and cortisol (Havel, 2001). The first three are well-known modulators of neurons in the arcuate nucleus of the hypothalamus.

The brain responds to changes in insulin, leptin, and ghrelin because neuropeptide Y (NPY)/Agouti-related protein (AgRP) and proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons in the arcuate nucleus have receptors for these neurohormones (Barsh and Schwartz, 2002; Berthoud and Morrison, 2008) (Fig. 1). Insulin and leptin stimulate POMC/CART neurons and inhibit NPY/AgRP neurons whereas ghrelin stimulates NPY/AgRP neurons. Activation of POMC/CART neurons has an anorexigenic effect while activation of NPY/AgRP neurons has an orexigenic effect. When stimulated, POMC/CART neurons suppress food intake by releasing α -melanocyte stimulating hormone at synapses on higher order neurons in the network. In an analogous manner, activation of NPY/AgRP neurons causes the release of NPY and AgRP, which ultimately increase food intake by modulating higher order neurons in the network.

Reasons for Expecting Ketogenic Diet Induced Neurohormonal Changes

About 90% of the calories in a 4:1 ketogenic diet come from fat compared to about 30% in a regular diet (Muzykewicz et al., 2009). In principle, this change in caloric content should produce a change in some of the neurohormones involved in regulating energy homeostasis because they respond to the macronutrient content of the diet as discussed above. In addition, the ketogenic diet can change energy homeostasis because children and animals fed a ketogenic diet can grow more slowly than those fed a regular diet. Several studies show that children experience significantly slower weight gain and linear growth while on the diet (Vining et al., 2002; Williams et al., 2002; Liu et al., 2003; Peterson et al., 2005; Neal et al., 2008; Bergqvist et al., 2008; Spulber et al., 2009). Some (Uhlemann and Neims, 1972; Zhao et al., 2004; Nysten et al., 2005; Thio et al., 2006; Kennedy et al., 2007; Ribeiro et al., 2008; Samala et al., 2008; Raffo et al., 2008; Hansen et al., 2009; Thio et al., 2010) but not all (Muller-Schwarze et al., 1999; Noh et al., 2003; Thavendiranathan et al., 2003; Honors et al., 2009) studies show that rats and mice fed a ketogenic diet exhibit slower weight gain than those fed a regular diet. The inverse relationship between serum ketones

and weight in children and rodents provides indirect support for ketosis being necessary for this phenomenon (Peterson et al., 2005; Thio et al., 2006; Spulber et al., 2009). The change in weight reflects a change in energy homeostasis, a process regulated by a complex neuronal network involving several neurohormones as reviewed above. Thus, the ketogenic should alter some of the neurohormones involved in energy homeostasis based on both theoretical grounds and empiric data.

Neurohormonal Changes Induced by the Ketogenic Diet

The ketogenic diet produces multiple metabolic changes in humans and rodents, which may result in altered levels of peripherally released neurohormones (Fig. 1). Some of the expected metabolic changes in serum include increased ketones and an altered lipid profile. Though studies typically report increases in ketones ranging from 2-10 fold, not all studies report increased total cholesterol, low-density lipoprotein cholesterol, and triglycerides (Uhlemann and Neims, 1972; Schwartz et al., 1989; Bough and Eagles, 1999; Dell et al., 2001; Liu et al., 2003; Kwiterovich et al., 2003; Fraser et al., 2003; Nylen et al., 2005; Thio et al., 2006; Samala et al., 2008; Raffo et al., 2008; Spulber et al., 2009; Kinzig and Taylor, 2009; Badman et al., 2009; Hansen et al., 2009; Thio et al., 2010; Kinzig et al., 2010).

In rodents, the ketogenic diet can double fat mass as a percentage of total body mass (Thio et al., 2006; Ribeiro et al., 2008; Honors et al., 2009; Kinzig and Taylor, 2009; Kinzig et al., 2010) (Fig. 1). An expected consequence of the increase in fat mass is an increase in leptin because leptin levels are proportional to fat mass (Maffei et al., 1995). Several studies confirm this prediction by showing that the ketogenic diet may more than double serum leptin levels (Kinzig et al., 2005; Thio et al., 2006; Honors et al., 2009; Kinzig and Taylor, 2009; Kinzig et al., 2010), though some find no change (Kennedy et al., 2007).

The ketogenic diet generally (DeVivo et al., 1978; Schwartz et al., 1989; Nylen et al., 2005; Kinzig et al., 2005; Thio et al., 2006; Kennedy et al., 2007; Raffo et al., 2008; Badman et al., 2009) but not always (al Mudallal et al., 1995; Ribeiro et al., 2008; Samala et al., 2008) decreases serum glucose by 10-30% in humans and rodents (Fig. 1). This reduction in serum glucose may produce or reflect a change in insulin. Accordingly, several studies in rodents demonstrate that ketogenic diets lower serum insulin by at least 25% (Kinzig et al., 2005; Thio et al., 2006; Kennedy et al., 2007; Honors et al., 2009; Kinzig and Taylor, 2009; Badman et al., 2009). The decrease in insulin is a more consistent finding than the increase in serum leptin levels.

The ketogenic diet also affects other peripherally released hormones including ghrelin and cortisol. Serum ghrelin levels increase (Kinzig et al., 2005) or do not change in rats (Thio et al., 2006; Honors et al., 2009). In humans and rats, serum cortisol levels increase by 20% or more (Fraser et al., 2003; Thio et al., 2006).

The finding that the ketogenic diet concurrently can increase leptin and decrease insulin is unique. Generally, metabolic changes cause leptin and insulin levels to change in concert with both either increasing or decreasing. For example, conditions associated with weight loss such as fasting cause both to decrease whereas high energy states associated with weight gain, such as overeating, cause both to increase (Schwartz et al., 2003; Woods and D'Alessio, 2008). Thus, the ketogenic diet induces a unique metabolic state (Kennedy et al., 2007), and the opposing changes in leptin and insulin levels produce a unique neurohormonal state (Honors et al., 2009; Kinzig et al., 2010).

The effect of the ketogenic diet on central neurohormones involved in energy homeostasis has received less attention, but a few studies have addressed this issue. The ketogenic diet does not alter NPY gene expression in the hypothalamus and other brain regions (Tabb et

al., 2004; Kennedy et al., 2007; Kinzig and Taylor, 2009). It also does not modify AgRP gene expression in the hypothalamus (Kennedy et al., 2007). Surprisingly, the diet decreases POMC expression in the hypothalamus even though leptin should increase its expression (Kennedy et al., 2007; Kinzig and Taylor, 2009; Kinzig et al., 2010). This area deserves further study because the results likely will lead to a better understanding of the neurohormonal effects of ketogenic diet and the neuronal network involved in regulating energy homeostasis.

Potential Anticonvulsant Effects of the Neurohormonal Changes Induced by the Ketogenic Diet

The increase in serum leptin may contribute to the ketogenic diet's anticonvulsant effect because leptin has anticonvulsant properties in several *in vitro* and *in vivo* models (Table 1). Leptin diminishes neuronal bursting in cultured hippocampal neurons and epileptiform-like activity in cultured hippocampal neurons and acute hippocampal slices induced by removing extracellular Mg^{2+} (Shanley et al., 2002b; Xu et al., 2008). Although leptin does not inhibit penicillin-induced epileptiform activity *in vivo* (Ayyildiz et al., 2006; Aslan et al., 2010), it acts as an anticonvulsant against focal neocortical seizures induced by focal injections of 4-aminopyridine, a nonspecific inhibitor of voltage-gated K^+ channels (Xu et al., 2008). It also has anticonvulsant effects against generalized seizures evoked by intraperitoneal injections of pentylenetetrazole, a γ -aminobutyric acid_A receptor (GABA_AR) antagonist (Xu et al., 2008). These observations provide support for leptin having anticonvulsant effects in animal models of acute focal and generalized seizures. This anticonvulsant profile mirrors that of the ketogenic diet (Table 1). Future studies should examine whether leptin has anticonvulsant effects in an animal model of epilepsy.

These observations suggest that leptin modulates neuronal excitability. More specifically, leptin deficiency should cause enhanced excitability. If true, leptin knockout animals should be more susceptible to convulsant induced seizures. Accordingly, *ob/ob* mice, which are naturally occurring leptin knockout mice, are more susceptible to pentylenetetrazole induced seizures (Erbayat-Altay et al., 2008) (Table 1).

Several mechanisms may underlie the anticonvulsant effects of leptin (Fig. 1). It activates large conductance Ca^{2+} activated K^+ (BK) channels (Shanley et al., 2002a), and their activation appears to contribute to leptin's anticonvulsant effect against low Mg^{2+} induced epileptiform activity in hippocampal slices (Shanley et al., 2002b). In addition, leptin activates ATP sensitive K^+ (K_{ATP}) channels (Mirshamsi et al., 2004), which may mediate some of the anticonvulsant effects of the diet (Ma et al., 2007; Tanner et al., 2011). Finally, low nanomolar leptin concentrations also inhibit glutamatergic synaptic transmission mediated by α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) in hippocampal slices, but the dose response curve has a U shape with higher concentrations having no effect (Xu et al., 2008). In contrast to these presumably inhibitory effects, leptin enhances N-methyl-D-aspartate receptor (NMDAR) function (Shanley et al., 2001). Despite this apparently excitatory effect, leptin appears to have a net inhibitory effect *in vivo* based on its effect in most acute seizure models. However, the precise mechanisms responsible for its anticonvulsant effects *in vivo* remain unknown.

Like leptin, insulin can regulate neuronal excitability by modulating multiple ion channels. Insulin shares the ability to activate K_{ATP} and BK channels with leptin (O'Malley et al., 2003). It modulates glutamatergic synaptic transmission by both potentiating and inhibiting AMPAR mediated synaptic transmission (Moult and Harvey, 2008) and enhancing NMDAR mediated currents (Liu et al., 1995). These actions give insulin the potential to be a convulsant or anticonvulsant, but it may have a net dampening effect on neuronal

excitability *in vivo* (Table 1). Thus, the contribution of decreased serum insulin levels to the anticonvulsant effect of the diet requires further investigation as does the possibility of synergy between the increase in leptin and the decrease in insulin.

Potential Neuroprotective Effects of the Neurohormonal Changes Induced by the Ketogenic Diet

The increase in serum leptin may also contribute to the ketogenic diet's neuroprotective effects. Human clinical studies together with *in vivo* and *in vitro* animal experiments support the hypothesis that the diet may be of benefit in neurodegenerative conditions such as Alzheimer and Parkinson disease (Gasior et al., 2006). It may also protect neurons from damage induced by a variety of insults including seizures, ischemia, trauma, and hypoglycemia. Similarly, leptin reduces neuronal damage in experimental models of Parkinson disease, ischemia and seizures (Signore et al., 2008).

Ketogenic Diet Induced Changes in Cell Signaling

The anticonvulsant and neuroprotective effects of the ketogenic diet that involve leptin and insulin probably involve the cell signaling pathways they modulate (Fig. 1). These pathways include the Janus activated kinase (JAK)/Signal transducer and activators of transcription (STAT)/phosphatidylinositol-3 kinase (PI3K), Ras/mitogen-activated protein kinase (MAPK), and adenosine monophosphate activated protein kinase (AMPK) pathways. Leptin activates K_{ATP} and BK channels by stimulating PI3K (Shanley et al., 2002a; Mirshamsi et al., 2004), which also mediates leptin's inhibitory effect on AMPAR mediated synaptic activity (Xu et al., 2008) and its potentiation of NMDARs (Shanley et al., 2001). In contrast, insulin activates K_{ATP} and BK channel by stimulating MAPK (O'Malley et al., 2003). Leptin and insulin may modulate these ion channels because the cell signaling cascades they activate ultimately alter channel trafficking (Mirshamsi et al., 2004; O'Malley et al., 2005; O'Malley and Harvey, 2007; Moulton et al., 2010). Whether the anticonvulsant effects of the ketogenic diet and leptin *in vivo* depend on activation of these cascades is unknown.

Besides modulating ion channels, the cell signaling pathways regulated by leptin and insulin have a critical role in controlling cellular growth, proliferation, metabolism, and survival as expected from their role in energy homeostasis. The JAK/STAT/PI3K and AMPK pathways help control these processes through their effects on the tuberous sclerosis complex (TSC) composed of hamartin (TSC1) and tuberin (TSC2) (Wong, 2010; Orlova and Crino, 2010). Mutations in these proteins cause tuberous sclerosis, a disease characterized by benign tumors or hamartomas in multiple organs. A downstream effect of PI3K activation is inhibition of TSC by Akt (protein kinase B) mediated phosphorylation of tuberin. TSC inhibition activates mammalian target of rapamycin (mTOR), a serine-threonine protein kinase that promotes growth when activated. In contrast, AMPK activation stimulates TSC by phosphorylating tuberin at different sites from Akt and thereby inhibits mTOR and slows growth. The precise effect of leptin and insulin on the cell signaling cascades they modulate depends on the tissue. For example, leptin increases AMPK activity in the liver and adipose tissue but decreases it in the hypothalamus and heart (Lim et al., 2010).

The central role mTOR has in regulating growth and its sensitivity to the cell signaling pathways modulated by leptin and insulin make it a potential mediator of the effects of the ketogenic diet. The strong evidence for mTOR inhibition also having an antiepileptogenic effect only increases the appeal of this hypothesis (Wong, 2010; Orlova and Crino, 2010). The net effect of the ketogenic diet on AMPK, PI3K/Akt, and mTOR activity is difficult to predict because of the opposing changes in the serum levels of leptin and insulin and the possibility of tissue specific effects. Some recent studies have begun to address this issue. In

the hypothalamus, the ketogenic diet produces a non-significant increase in mTOR activity (Proulx et al., 2008), which could reflect the opposing changes in serum leptin and insulin levels. In the liver, the ketogenic diet increases AMPK activity but decreases Akt and mTOR activity (Kennedy et al., 2007; McDaniel et al., 2011). Interestingly, the ketogenic diet decreases Akt and mTOR activity in the hippocampus with a similar trend in the neocortex (Fig. 1), but the diet has no effect on AMPK activity in the brain (McDaniel et al., 2011).

The decrease in mTOR activity may account for some of the diet's other beneficial effects besides being an anticonvulsant (Fig. 1). Decreased mTOR activity in the brain is consistent with the diet also being antiepileptogenic. Clinical observations and animal experiments support the diet having an antiepileptogenic effect (Gasior et al., 2006; Kossoff and Rho, 2009). Clinically, the diet can produce seizure freedom that can persist long after discontinuation of the diet. The data from animal models are conflicting (Hansen et al., 2009; Linard et al., 2010), but the diet can inhibit mossy fiber sprouting after kainate induced status epilepticus (Muller-Schwarze et al., 1999) and alter the development of seizures in genetic mouse models of epilepsy (Todorova et al., 2000). Given the role of mTOR in tumor biology, inhibiting mTOR activity may contribute to the ketogenic diet's antitumor effects (Seyfried et al., 2009). At a minimum, mTOR inhibition provides a mechanistic basis for placing patients with tuberous sclerosis on the diet to treat seizures (Kossoff et al., 2005) and potentially to limit hamartoma growth (Chu-Shore and Thiele, 2010).

Conclusions

The increase in the fat content and the slower growth associated with the ketogenic diet compared to a regular diet should yield changes in some of the neurohormones involved in energy homeostasis. Accordingly, the ketogenic diet increases serum leptin and lowers serum insulin levels to produce a unique metabolic and neurohormonal state. Although evidence for the decrease in insulin having an anticonvulsant effect is lacking, experimental evidence suggests that the increase in leptin could. Furthermore, altered activity of the cell signaling pathways regulated by the neurohormones affected by the diet could play an important role in the anticonvulsant, antiepileptogenic, neuroprotective, and antitumor effects of the diet. Further studies in this area may yield new insights into the pathophysiology of epilepsy and novel therapies for epilepsy and other conditions.

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Figure 1.

Potential neurohormonal mechanisms for several ketogenic diet effects. AgRP - Agouti-related protein; AMPAR - α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; BK - large conductance Ca^{2+} activated K^{+} channels; CART - cocaine- and amphetamine-regulated transcript; JAK - Janus activated kinase; K(ATP) - ATP sensitive K^{+} channel; KGD - ketogenic diet; mTOR - mammalian target of rapamycin; NPY - neuropeptide Y; PI3K - phosphatidylinositol-3 kinase; POMC - proopiomelanocortin; CART - cocaine- and amphetamine-regulated transcript; STAT - signal transducer and activators of transcription ^aThio et al., 2006; Ribeiro et al., 2008; Honors et al., 2009; Kinzig and Taylor, 2009; Kinzig et al., 2010. ^bKinzig et al., 2005; Thio et al., 2006; Honors et al., 2009; Kinzig and Taylor, 2009; Kinzig et al., 2010 but see Kennedy et al., 2007. ^cDeVivo et al., 1978; Schwartz et al., 1989; Nylén et al., 2005; Kinzig et al., 2005; Thio et al., 2006; Kennedy et al., 2007; Raffo et al., 2008; Badman et al., 2009 but see al Mudallal et al., 1995; Ribeiro et al., 2008; Samala et al., 2008. ^dKinzig et al., 2005; Thio et al., 2006; Kennedy et al., 2007; Honors et al., 2009; Kinzig and Taylor, 2009; Badman et al., 2009. ^eShanley et al., 2002a; Shanley et al., 2002b; Xu et al., 2008. ^fMcDaniel et al. (2011) showed that the ketogenic diet reduces mTOR activity but they did not address whether this

effect results from the changes in leptin and insulin. ^gShanley et al., 2002a; Shanley et al., 2002b; Mirshamsi et al., 2004; O'Malley et al., 2005; Xu et al., 2008.

Table 1

Effect of the ketogenic diet, leptin, and insulin in several seizure models.

Agent	Seizure Model			
	<i>In Vitro</i>		<i>In Vivo</i>	
	Low Mg ²⁺	Low Mg ²⁺	4-Aminopyridine	Pentylentetrazole
Ketogenic Diet	Unknown	Anticonvulsant ^a	Anticonvulsant ^b	Anticonvulsant ^c
Leptin	Anticonvulsant ^d	Unknown	Anticonvulsant ^e	Anticonvulsant ^f
Insulin	Unknown	Unknown	Unknown	Anticonvulsant ^g
				Anticonvulsant ^h

^aMahoney et al. (1983) showed that the ketogenic diet inhibits audiogenic induced seizures in Mg²⁺ deficient rats.

^bGasior et al. (2007) showed that acetone inhibits 4-aminopyridine induced seizures.

^cBough and Eagles, 1999; Thavendiranathan et al., 2003; Nylen et al., 2005; Raffo et al., 2008; Hansen et al., 2009 but see Uhlemann and Neims, 1972; Samala et al., 2008.

^dShanley et al., 2002b; Xu et al., 2008.

^eXu et al., 2008.

^fErbayat-Altay et al., 2008; Xu et al., 2008.

^gAyyildiz et al., 2006; Aslan et al., 2010.

^hUysal et al., 1996.