Argh me Hearties of

THE KETOGENIC DIET
Overview

• What is a Ketogentic diet?
• Guided tour to Treasure Island (aka beautiful pathway map)
• The Mechanisms of the Ketogenic Diet
• Age Dependency
• Cool stuff (GABA, PUFA's Norepinephrine, energy metabolism)
• The Ketogenic Diet as a possible treatment for other disorders and diseases
What is The Ketogenic Diet?

A treatment for medically-refractory epilepsy for over 90 years. [As well as an] “alternative” therapy was originally designed to mimic the biochemical changes associated with fasting, a treatment reported anecdotally over millennia to control seizure activity.
If there is very little carbohydrate in the diet, the liver converts fat into fatty acids and ketone bodies.
Ketogenic Diet

Why is it Important to our lives?
Benefits

Popular Weight Loss Diet

Tell your brain to use ketones for fuel instead of glucose

Achieving the Optimal Fat Burning State

Sugar Burner

Fat Storing

Fat Burning

Ketosis

(Goodbye Carb Cravings)

Nutritional Ketosis

(Fat Burning Machine)

Kick the Weight with Keto

How to Lose Weight and Feel Great on a Paleo-Ketogenic Diet

Kim Knoch

Eat Fat, Lose Fat blog - http://EatFatLoseFatblog.com
Other Benefits

Kills Your Appetite

Triglycerides tend to go away
Advantages

• Lower blood pressure
• Dropping Cholesterol
• Lack of Hunger
• Better Digestion

Disadvantages

• Self Discipline
• Nausia
Mechanisms of Ketogenic Diet Action

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Abstract

Within the past two decades, interest in understanding the therapeutic mechanisms of ketogenic diet (KD) action has grown steadily. Expanded knowledge about underlying mechanisms has yielded insights into the biochemical basis of brain function, both normal and pathologic. Metabolic changes likely related to the KD’s anticonvulsant properties include – but are not limited to – ketosis, reduced glucose, elevated fatty acid levels, and enhanced bioenergetic reserves. Direct neuronal effects induced by the KD may involve ATP-sensitive potassium (KATP) channel modulation, enhanced purinergic (i.e., adenosine) and GABAergic neurotransmission, increased brain-derived neurotrophic factor (BDNF) expression consequent to glycolytic restriction, attenuation of neuroinflammation, as well as an expansion in bioenergetic reserves and stabilization of the neuronal membrane potential through improved mitochondrial function. Importantly, beyond its utility as an anticonvulsant treatment, the KD may also exert neuroprotective and anti-epileptogenic properties, heightening the clinical potential of the KD as a disease-modifying intervention. As dietary treatments are already known to evoke a wide array of complex metabolic changes, future research will undoubtedly reveal a more complex mechanistic framework for KD action, but one which should enable improved formulations offering comparable or superior efficacy with fewer side-effects, not only for epilepsy but perhaps a broader range of neurological disorders.

INTRODUCTION

The ketogenic diet (KD) is a high-fat, low-carbohydrate, adequate protein diet that has been employed as a treatment for medically-refractory epilepsy for over 90 years. This “alternative” therapy was originally designed to mimic the biochemical changes associated with fasting, a treatment reported anecdotally over millennia to control seizure activity. The hallmark features of KD treatment are the production of ketone bodies (principally β-hydroxybutyrate, acetoacetate and acetone) – products of fatty acid oxidation in the liver – and reduced blood glucose levels (Figure 1). Ketone bodies provide an alternative substrate to glucose for energy utilization, and, in the developing brain, also constitute essential building blocks for biosynthesis of cell membranes and lipids.
The Use of Animal Models

- **Acute Models**
  - Seizures induced with electrical or chemoconvulsant stimulation

- **Chronic Models**
  - Genetically induced seizures
  - Spontaneous or reflex induced seizures
Important contradictions

The anticonvulsant effects of the KD is normally seen in days to weeks however Loss of the protecting effect of the KD is seen in only hours after disruption of the diet (e.g. by intake of carbs).

Ketone bodies mediate the opening of $K_{\text{ATP}}$ channels, which leads to hyperpolarization and decreased excitability however Ketone bodies increase the levels of ATP, and ATP closes the $K_{\text{ATP}}$ channels.
Molecular Effects of the Ketogenic Diet

Ketosis (low pH) → Opening of $K_{ATP}$ channels → Reduced levels of glutamate → reduced levels of GABA → High ATP levels → more stable neuronal resting potentials → Decreased excitability → Decreased risk of seizures
Is KD Age Dependent?

• Most effective in immature animals and infants or children, younger patients than older

  “Due to greater fatty acid oxidation of breast milk which is high in fats.”

• More efficient extraction of ketone bodies from the blood and an early age-dependent surge in the expression of the monocarboxylic acid transporters, MCT1 and MCT2.

• Recent Controversy
  • γ-aminobutyric acid (GABA)-mediated responses in the early developing brain are excitatory, not inhibitory.

  - Resulted in an age-dependent hyperpolarizing shift of the GABA reversal potential in both hippocampus and neocortex

So not Age dependent???
Within The Immature Brain

• GABAergic neurotransmission might actually be inhibitory as there is a greater preponderance of energy substrates (such as ketone bodies, lactate, and pyruvate) than at later ages.

• (1) the depolarizing GABA action in neonatal hippocampal slices is not due to deficiencies in energy metabolism.

• (2) physiological plasma concentrations of BHB, lactate and pyruvate failed to affect the depolarizing actions of GABA in immature rat pups.
GABA-mediated inhibition

Facilitation of GABAergic neurotransmission has long been accepted as a critical mechanism of action for a variety of clinically effective antiepileptic drugs, and thus there is an intrinsic appeal to invoking this mechanism.

- In acute animal studies in which the KD is found to be most effective against seizures evoked by the GABAergic antagonists.

- Whereas it fails to block provoked seizures.
The Metabolic inter-relationships between brain metabolism of glutamate, Ketone Bodies and Glucose
Noradrenergic System

• Evidence
  • Increases in noradrenergic tone result in anticonvulsant activity
  • Ex: Seizures in GERP’S
• NE is required for the Anticonvulsant effect of KD
• Rise of Leptin Levels

• Increased NE release would also be predicted to promote co-release of anticonvulsant orexigenic peptides such as neuropeptide-Y (NPY) and galanin.
Leptin

- It can exert modulatory effects on neuronal excitability and suppress seizure activity

Since the KD causes a rise in leptin levels, it is possible that the KD’s mechanism, at least in part, may relate to a leptin-associated reduction in synaptic excitability.

Figure 1. Signals such as leptin and insulin are secreted in proportion to the size of the fat mass and circulate in the blood. They enter the brain and act at the level of the hypothalamus. Neuroendocrine signals from the stomach, the gastrointestinal system and the liver are sent to the hindbrain, providing information about the food that is eaten: its taste and chemical content, and how much the stomach is distended.
Polyunsaturated Fatty Acids (PUFA’s)

• A big part of the ketogenic diet

• Believed to affects cardiovascular function

• Inhibits voltage gated sodium channels and L-type calcium channels → decrease neuronal excitability

• Activates PPAR’s → decrease seizures and inhibits pro-inflammatory transcription factors
Polyunsaturated Fatty Acids (PUFA’s)

• Results have been inconclusive

• Experiment with “PUFA spread” both showed positive and negative results
Ketogenic Diet and Energy Metabolism

• KD up-regulates metabolism enzymes and mitochondrial proteins

• Rise in ATP

Why does this stop seizures?

hypothesis

Enhanced activation of Na+/K+ pump

Better maintenance of $V_{rest}$
Ketogenic Diet and Energy Metabolism

• Reduced blood glucose might be an important part of the ketogenic diet

• Blocking of glycolysis have anticonvulsant effects in animal models

• KD increase rapid refilling of Krebs cycle substrates → could oppose seizure generation

• Decreased ROS production → neuroprotective effect
Future Directions
How can a ketogenic diet be a help in other diseases?

• KD have anti-inflammatory effects
• Brain cancer – cancer cells rely on glucose
• KD improve sleep and circadian rhythm
Conclusion

• Drum Roll***

• A ketogenic diet helps preventing seizures in patients with epilepsy

• A KD could be beneficial during, and to prevent, several other disorders

• Many controversies regarding the mechanism

• More studies need to be made!
Work Cited

