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Ketogenic diet and ketosis as therapeutic approach for a wide range of diseases

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Metabolic-based therapies such as nutritional ketosis have been proven effective for seizure disorders and various acute and chronic neurological disorders. In a healthy brain, glucose is the primary metabolic fuel for cells. However, neurodegenerative disorders are associated with impaired glucose transport and metabolism and with mitochondrial dysfunction leading to energy deficit. These features are all pathological hallmarks of Alzheimer's disease, Parkinson's disease, seizure disorders, and traumatic brain injury. Ketone bodies and TCA cycle intermediates function as alternative fuels for the brain and can potentially bypass the rate-limiting steps associated with impaired neuronal glucose metabolism. Therefore, therapeutic ketosis (elevated blood ketone levels) or a metabolic strategy that is anaplerotic can be considered as a form of metabolic therapy by providing alternative energy substrates, which may have potent cellular protective properties independent of their bioenergetic function. The brain derives over 60% of its energy from ketones when glucose availability is limited. After prolonged periods of fasting or ketogenic diet (KD), the body utilizes energy obtained from free fatty acids (FFAs) released from adipose tissue. Because the brain is unable to derive significant energy from FFAs, hepatic ketogenesis converts FFAs into ketone bodies—hydroxybutyrate and acetoacetate (AcAc)—while a percentage of AcAc spontaneously decarboxylates to acetone. By this mechanism, large quantities of ketone bodies accumulate in the blood (up to 5 mM), and this state of normal physiological ketosis can be therapeutic. Ketone bodies are transported across the blood–brain barrier by monocarboxylic acid transporters to fuel brain function. Starvation ketosis or nutritional ketosis is an essential survival mechanism that ensures metabolic flexibility during prolonged fasting, starvation, or lack of carbohydrate ingestion. Therapeutic ketosis leads to metabolic adaptations that improve brain metabolism, restore mitochondrial ATP production, decrease reactive oxygen species (ROS) production, reduce inflammation, and increase the activity of neurotrophic factors. The synaptic activity between neurons is also stabilized through mechanisms such as increased Szent-Györgyi-Krebs cycle intermediates, antioxidant effects, increased GABA-to-glutamate ratio, and activation of ATP-sensitive potassium (KATP) channels. Therapeutic ketosis can be achieved by fasting, which changes brain metabolism and can induce sustained ketone level elevation in the blood, but serious complications can result from prolonged fasting leading to starvation. Alternatively, ketosis can be achieved by a carbohydrate-restricted KD, which supplies most of the macronutrient energy in the form of fat (75– 90%). The KD mimics the effects of fasting and the lack of glucose/insulin signaling, which promotes a metabolic shift toward fatty acid utilization. KD can only induce a modest blood ketone level elevation and requires extreme dietary carbohydrate restriction for maintaining sustained (therapeutic) levels of ketosis.

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