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Therapeutic Effects of Ketone Diet in Epilepsy

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Abstarct:

Ketogenic diet (KD) is a very low-carb diet, which forces the body to burn fat instead of carbs making the body produce ketones as a fuel, this is an alternative fuel used in conditions where glucose levels are low or for the treartment of seizures. KD has been proven to be effective as a medical therapy for epilepsy allowing patients to take less or no anti-epileptic drugs (AEDs), also providing a new line of therapy for those unresponsive to AEDs. Despite its successful results, the exact mechanisms by which KD works remains unclear. This is a collective review on the potential machanisms by which KD exert its anti-seizures properties.

1. Introduction:

Epilepsy is a common brain disorder characterized by recurrent seizures. Approximately 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally[1]. A wide range of antiepileptic drugs has been developed, however about 30% of patients with epilepsy fail to respond. A high-fat, low-carbohydrate diet known as a ketogenic diet was developed to assist such patients, its beneficial effects has been confirmed by a variety of clinical trials, one of them have showed 75% decrease in seizures in children on a ketogenic diet for three months. Even with these amazig results the excact mechanism through which a ketogenic diet excert its anticonvulsant effects is unclear [2].

Ketogenic diet involves significantly reducing carbohydrate consumption, and replacing it with fat. The decrease in carbs sets the body into a metabolic state called ketosis. The diet forces the body to burn fats rather than carbohydrates. Normally carbohydrates found in food get converted to glucose, which circulates around the body , also glucose is an essential source of energy for brain and is necessary for normal brain function, however if only a small amount carbohydrates are consumed in the diet, the liver converts fat into free fatty acids and ketone bodies, as for the ketone bodies, they replace glucose to become the alternative source of fuel in the brain, the two primary ketone bodies produced are acetoacetate and B-hydroxybutyrate.[3]. The infant's brain has a high ability to adapt to ketone utilization due to the presence of high levels of ketone metabolizing enzymes and monocarboxylic acid transporters, aduls also have this ability however it's demonstrated during stress events, even astrocytes can produce ketone bodies in glucose deprivation conditions._So with having in mind brain's capacity to adapt to ketone utilization, the elevated levels of ketone bodies in patients on a ketogenic diet, and the strong anticonvulsant effects detected in these patients, knowing the excact mechanism by which ketone bodies prevent seizures will allow the expension of its clinical use as well as revealing new targets for future therapy [2].

2. Discussion:

2.1 Ketone Bodies: Anticonvulsant Properties:

A study used acetoacetate on rabbits were its administration have found to be protecting against thujone-induced seizures suggesting the anticonvulsant properties of acetoacetate. Concurring with this early report, another study found that intraperitoneally administered acetoacetate and acetone, but not β-hydroxybutyrate, protected against seizures[2,3]. Acutely administered acetone, but not its metabolites, protected juvenile mice from seizures induced by pentylenetetrazol and 4-aminopyridine. All these findinds are stong evidences that acutely administered acetone and acetoacetate have intrinsic anticonvulsant properties in many standardized animal models of epilepsy [2].

2.2 Ketone Bodies: Possible Mechanisms of Action:

A number of theories have developed to explain the declined seizure threshold in the previously discussed models. One hypothesis suggest the effect of ketone bodies on Glutamate and γ-aminobutyric acid (GABA), which are the major excitatory and inhibitory neurotransmitters in the brain. Also new theories are emerging in regard to the effects of ketone bodies on neuronal membrane potential, neuronal excitability, and reactive oxygen species. Here is an overview assessing these hypotheses:

2.2.1 GABA:

Rodent models of epilepsy induced by GABA antagonists have a strong response to a ketogenic diet, making GABA signalling an important target of investigation. Several studies have demonstrated an increase of GABA levels in the cerebrospinal fluid patients on a ketogenic diet. GABA is synthesized from glutamate, which is converted to GABA by glutamate decarboxylase. Aspartate is an inhibitor of glutamate decarboxylase. Thus, by lowering the levels of aspartate it could hypothetically promote the synthesis of GABA. In support to this, A decrease in aspartate levels in cultured astrocytes was found to be associated with a one-hour exposure to acetoacetate or β-hydroxybutyrate. Another study has shown similar results were a decrease in aspartate levels was detected in the forebrain and cerebellum of mice fed a ketogenic diet [2].

2.2.2 Vesicular glutamate transporters (VGLUTs):

VGLUTs are responsible for filling pre-synaptic vesicles with glutamate under the influence of cl-. Cl^- acts as an allosteric activator of VGLUT and triggers glutamate uptake upon binding.[2] Because glutamatergic neurotransmission begins with vesicular release , compounds that play a part in the blocking of glutamate uptake into vesicles may reduce excitotoxic events , ketone bodies compete for putative cl- binding sites thus lowering VGLUT activity, causing a reduction in glutamatergic neurotransmission in vivo.[4] To further support this, acetoacetate succeeded to suppress in vivo glutamate release and seizures in rat brains exposed to 4-aminopyridine. [2]

2.2.3 Other neurotransmitters and receptors:

Using Xenopus oocytes expressing human GABAA receptors, a study have showed that a 5-minute incubation with 10mM β-hydroxybutyrate or 50 mM acetone significantly increased GABAA receptor activity [2].

Other neurotransmitters appear to be necessary in order for the ketogenic diet to achieve anticonvulsant effects. This was shown when ketogenic diet did not protect mice with adenosine A1 receptor mutations against recurrent seizures. Also the diet had seem to decrease adenosine kinase (the adenosine metabolizing enzyme) [2].

2.2.4 Ketone Bodies Prevent mitochondrial permeability transition (mPT):

A study have used kcnal-null mutant mouse which summerize the essential features of human temporal lobe epilepsy and tested the effect of KD on The mPT – an event that causes the release of reactive oxygen species (ROS) and apoptotic and necrotic cell death due to brain insult – the results where promising as KD was found to inhibit mPT by elevating its threshold. To test this further, KD was tested on mice lacking cyclophilin D (CypD) subunit of the mPT complex - an essencial binding site for the inhibition of mTP- the effect of KD on raising the mPT threshold was fully prevented in CypD-deficient animals, indicating that the anti-seizure activity of KB requires this specific subunit of the mPT complex [4].

3. Conclusion:

For anti-epileptic drugs AEDs resistant patients, ketogenic diet (KD) is considered as one treatment option. The diet was found to reduce the number and severity of seizures. The mechanisms by which the KD may work remained unclear. The potenial mechanisms discussed in this report include its effects on the major excitatory and inhibitory neurotransmitters in the brain; glutamate and GABA respectively, as well as on the mitochondrial permeability transition. KD was found to increase GABA levels by inhibiting aspartate, reduce glutamate levels by inhibiting its release, and prevent mitochondrial permeability transition.

4. References:

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