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Short Report

A new way to produce hyperketonemia: Use of ketone ester in a case of Alzheimer's disease

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Abstract

Background: Providing ketone bodies to the brain can bypass metabolic blocks to glucose utilization and improve function in energy-starved neurons. For this, plasma ketones must be elevated well above the ≤0.2 mM default concentrations normally prevalent. Limitations of dietary methods currently used to produce therapeutic hyperketonemia have stimulated the search for better approaches.
Method: Described herein is a new way to produce therapeutic hyperketonemia, entailing prolonged oral administration of a potent ketogenic agent—ketone monoester (KME)—to a patient with Alzheimer's disease dementia and a pretreatment Mini-Mental State Examination score of 12.
Results: The patient improved markedly in mood, affect, self-care, and cognitive and daily activity performance. The KME was well tolerated throughout the 20-month treatment period. Cognitive performance tracked plasma β-hydroxybutyrate concentrations, with noticeable improvements in conversation and interaction at the higher levels, compared with predose levels.
Conclusion: KME-induced hyperketonemia is robust, convenient, and safe, and the ester can be taken as an oral supplement without changing the habitual diet.
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Keywords: Ketone bodies; β-Hydroxybutyrate; Pyruvate dehydrogenase; Brain insulin resistance; Fasting; Ketogenic diet; Medium-chain triglyceride; Ketone monoester

1. Background

Impairment of the brain's glucose utilization is an early feature of Alzheimer's disease (AD) and may contribute to its causation and progression [1,2]. In patients with preclinical AD, fluorodeoxyglucose positron emission tomography discloses a consistent pattern of reduction in the cerebral metabolic rate of glucose (CMRglu) in the posterior cingulate, parietal, temporal, and prefrontal locations [3]. Clinical AD symptoms almost never occur without such CMRglu decreases [3], which may be associated with local brain insulin resistance [4].

To the extent impairment of glucose utilization contributes to AD's pathogenesis, providing the AD brain with sufficient ketone bodies (KBs)—the brain's principal alternative fuel during prolonged fasting [5,6]—would likely mitigate the energy deficit, as shown in Fig. 1.

However, to deliver enough KB-derived energy to glucose-deprived parts of the AD brain, it is necessary to raise plasma KB levels significantly above the ≤0.2 mM default concentrations customary in metabolically normal individuals [6,7]. As shown in Fig. 1, KB-derived acetyl CoA enters the pathway to the Krebs (tricarboxylic acid) cycle distal to the rate-limiting mitochondrial enzyme, pyruvate dehydrogenase (PDH), thus bypassing blocks in glucose utilization such as that caused by the inhibiting effect of insulin resistance on PDH activity [8,9].

Dr. Newport, Dr. VanItallie, and M.T. King have no financial interests in ketone monoester. Dr. VanItallie is a minority shareholder in a company that produces a food product containing medium-chain fatty acids. Dr. Veech has patent right from invention determined by NIH and DHHS standards.

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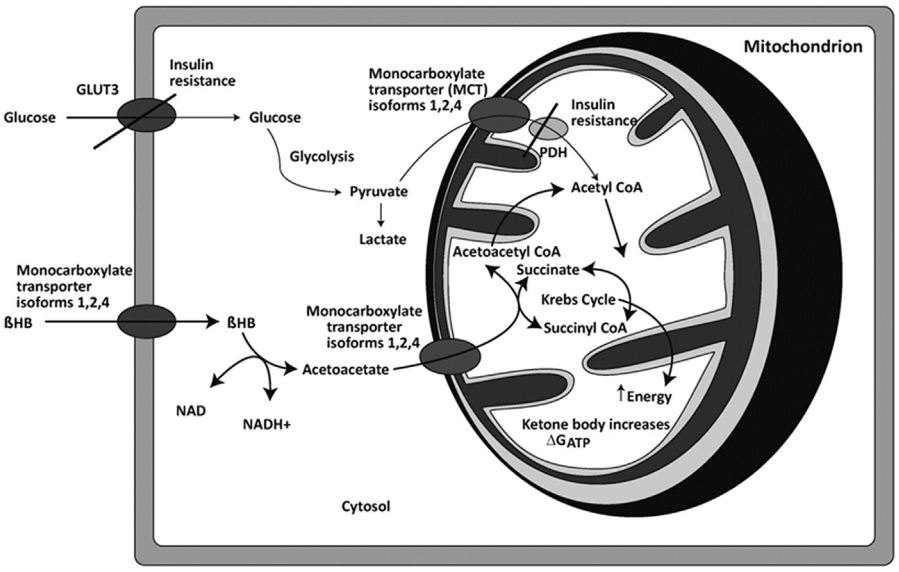

Fig. 1. Glucose and the ketone bodies, β-hydroxybutyrate (βHB) and acetoacetate (AcAc), enter neurons via different plasma membrane transporters, namely, glucose transporter 3 (GLUT3) and (ordinarily) monocarboxylate transporter 2 (MCT2), respectively. After cytosolic glycolysis, glucose-derived pyruvate enters mitochondria, undergoing oxidative decarboxylation by pyruvate dehydrogenase (PDH). The resulting acetyl CoA is then metabolized via the Krebs cycle. Inhibition of PDH activity (i.e., as caused by local insulin resistance) can reduce availability to mitochondria of energy-generating substrate, which may compromise neuronal function. In contrast, AcAc (derived in part from circulating βHB) is converted to acetyl CoA distal to the pyruvate → acetyl CoA step, thereby circumventing possible blocks to glucose metabolism at, or proximal to, that step.

Plasma ketone levels most expedient for rescue of still viable, energy-starved parts of the AD brain are unknown; however, during hyperketonemia, the rate-limiting step for KB utilization is their transport into brain, with the utilization rate increasing nearly proportionally with plasma KB concentration [10]. In eight healthy young adults, daily administration of 20 g of medium-chain triglyceride (MCTG) for 1 week, followed by 30 g/d for 3 weeks, raised plasma KB levels to a mean value throughout the study day of 0.29 mM, with a peak level of 0.48 mM. This degree of hyperketonemia was estimated to contribute up to 9% of brain energy metabolism [7].

2. Established methods for inducing therapeutic hyperketonemia

Established methods for inducing therapeutic hyperketonemia have entailed adherence to a ketogenic diet (KD) [11] and/or repetitive ingestion of MCTG [12]. Successful adherence to the very high-fat, very low-carbohydrate classical KD requires strong motivation in patients and caregivers. Liberalized versions may provide clinical benefit at lower plasma ketone levels [11].

Prolonged KD consumption may increase levels of atherogenic lipids and produce other adverse effects [6,11]. After 8 weeks on a very low-carbohydrate diet (5%–10% of calories), a group of elderly individuals with mild cognitive impairment (MCI) exhibited improved verbal memory performance ($P = .01$) [13].

MCTG users can elevate plasma ketone levels while continuing their usual diet. In a cohort of patients with MCI and AD given 20 g of MCTG/d, β-hydroxybutyrate (βHB) concentrations rose from ∼0.09 mM (before dose) to 0.3 to 0.4 mM (2 hours after dose). During hyperketonemia, cognitive performance significantly improved—but only among subjects who were apolipoprotein E (*APOE*) ε4 allele negative [12]. The highest KB levels appeared to confer most benefit. About 12.5% of the subjects discontinued participation because of minor gastrointestinal side effects.

3. A novel direct approach to the production of therapeutic hyperketonemia

Herein, we report the first use, in a patient with younger onset sporadic AD, of a potent ketogenic agent, (R)-3-hydroxybutyl (R)-3-hydroxybutyrate (referred to herein as ketone monoester [KME]) [14]. KME has undergone extensive animal [15] and human toxicity tests [14] and meets Food and Drug Administration generally recognized as safe standards. KME improves cognitive performance and reduces amyloid-β and tau deposition in cognition-relevant areas in a mouse AD model [16].

After ingestion, KME is fully hydrolyzed in the small intestine, yielding (1) βHB, carried to the systemic circulation, and (2) 1,3-butanediol, metabolized in liver to acetoacetate and βHB [15].

Study of KME's kinetics, safety, and tolerability in 27 men and 27 women found that compared with the inconvenience of preparing and consuming a KD, KME ingestion is a safe and simple method for temporarily elevating the