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Short Communication

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The Role of Ketone Bodies is Indispensable to Human Life

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Introduction

As to the metabolic situation at birth on animal species, there seem to be two patterns. One is the brains of neurologically precocial and mature species, and another is the brains of neurologically non-precocial and immature species including rat and human. The former can have ability of complete oxidation of glucose, which is aerobic glycolysis. However, the latter would utilize a mixed metabolism of glucose and ketone bodies in order to generate energetic and synthetic activities [1].

Mammals have the ability of converting energy stored in ketone bodies (KB) to high energy phosphates. KB can give fuel particularly to brain, heart, and skeletal muscle in several conditions, such as starvation, adherence to the neonatal period and low carbohydrate diets [2]. According to obtained biochemical data and comparison of animal species, the fetus in most animals seem to be developed by the energy gained from the ketone bodies produced [3].

There are 3 kinds of ketone bodies chemically and/or medically, including acetoacetic acid (AcAc), beta-hydroxybutyrate (β-HB) and acetone [4]. The former two has activity as ketone bodies, and the latter has no activity. Among them, β-HB is thought to be the basic engine fuel that produces necessary energy on land-living animals. β-HB has been known so far as an energy carrier from liver to peripheral tissues. Furthermore, it also plays a role of signal via extracellular receptors and acts as an endogenous inhibitor of histone deacetylases (HDACs) [5]. KB has been estimated to show beneficial efficacy for the nervous function and for neurological diseases. According to the study of acetoacetyl-CoA synthetase (AACS), KB seemed to be utilized for synthesis pathway of lipid substance, and to influence metabolic disorder in the nervous system [6].

Firstly, a ketogenic diet which contains high ratio of fat has been applicable to children with epilepsy. This treatment has been effective for long years, and continued at more than 250 medical centers in the world [7]. Thus, the potential benefits of ketogenic diet have been quite acknowledged. As one of the pediatric problem, there are many children with epilepsy who are resistant to standard anti-epileptic medicine. In such cases, ketogenic diet would be recommended as an alternative treatment. It is effective either high-fat low carbohydrate ketogenic diet or meal with high ketone bodies including AcAc, β-HB and acetone. The detail mechanism of these meals is not known yet, however, in fact KB has anticonvulsant antiepileptic effects [8].

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However, the influence of carbohydrate depleted meal on the metabolic parameters of children has not been adequately evaluated yet [9]. Based on the accumulation of cases, the development of clinical research on epilepsy would be desired in the future.

Secondly, KB would be beneficial in patients with Alzheimer's disease (AD). In patients with AD, it has been observed that glucose metabolism in the brain is specifically reduced [10]. The β-amyloid peptide Aβ interferes with their cholinergic innervation [11]. Ketone bodies are similarly used against epilepsy at rather high KB concentration, in which KB would interfere with glucose and de novo synthesis of neurotransmitter glutamate. On contrast, KB can be used for AD at lower concentration. The mechanism may be from the effect to support of energy metabolism, with possible inhibiting release of gliotransmitter glutamate [11]. Pre-symptomatic brain glucose hypo-metabolism would be contributing to the onset of AD. As the principal KB, β-HB and ACAC are the brain's main physiological alternative fuel to glucose [12].

According to some clinical trials, increasing ketone availability to the brain with moderate nutritional ketosis showed a beneficial effect on cognitive outcomes in the cases of mild-to-moderate AD [12]. As a treatment, mild to moderate ketosis can be safely obtained by a high-fat ketogenic diet and/or by supplements providing 20-70 g/day of medium-chain triglycerides. They may include the 8- and 10-carbon fatty acids octanoate and decanoate, or ketone esters. Recently developed medicine is Caprylic acid triglyceride, that is registered in the United States as a therapeutic food supplement effective for the treatment of AD [13].

Consequently, beneficial function of KB would be attributed to their ability to increase and improve mitochondrial efficiency and restore the supplement of normal reliance on glucose in the brain. Successive research concerning the therapeutic potential of KB and ketogenic diet would be expected from now, leading to the promising new area of research for Alzheimer's disease [14].

There have been various discussions about the efficacy concerning CR and LCD. In this regard, studies for animal research have been found. There are studies that insects and mice are put in an unconstrained environment associated with eating compensation freely [15]. As a result, the longest-lived result was obtained in the group of diets containing less protein and high carbohydrates [15]. It was revealed that the low total energy intake has minimal effect. These conclusions will be helpful for intervention studies of humans, insects, rodents and others.

On the other hand, many researches have revealed that nutritional intervention delays aging and age-related diseases [16]. Among them, the most widely performed intervention was calorie restriction, and restriction of protein and various amino acids (methionine, tryptophan) also showed the retardation of aging process. However, it is not yet clarified whether most influential factor may be caloric intake, protein intake, or specific amino acid [16]. For nutritional therapy, significant amount of controversy was found related to the optimal amount of dietary carbohydrate. LCD was initiated by Atkins [17]. After that, there have been lots of controversies and discussion [18,19]. At present, common understanding for LCD

would be that low-carbohydrate, high-protein diets can effectively promote weight loss associated with substantive evidence, for many ordinary individuals [20]. Standard conception and management for LCD was summarized by Feinman et al. [21]. Authors and colleagues have continued clinical research about KB and LCD for years. We investigated the elevated KB value and M value during the treatment for LCD [22]. Moreover, we also clarified the significance of KB in the axis of fetus-placenta-newborn-mother [23]. Thus, research on ketone bodies and CR/LCD would be expected to develop in future study.

Conclusion

In summary, KB has an important role for human's life. It can generate energy during fetus and newborn and necessary occasion without glucose depletion. In middle age, KB would be useful for nutritional therapy for metabolic syndrome, and for anti-aging medicine. For aged people, KB may contribute the prevention and treatment of Alzheimer dementia and other diseases. We expect KB research development for health and happiness of everyone.

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