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Ketone Bodies have Significant Effects for Long Years Associated with Human Evolution

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Human beings have showed evolution for long years associated with the changes in metabolic programs [1]. In favorable environmental situation, growth and reproduction programs had been continued, which were anabolic metabolism. Under unfavorable environmental conditions, maintenance programs were engaged, which include dormancy and defense. Dormancy is induced by nutrient shortage relying on energy preserving catabolic metabolism. Defense is induced by infections and other aggressive factors associated with supporting anabolic metabolism [1].

From nutritional point of view, there is the comparative perspective for human evolution between i) fasting and ii) overeating. The former had been observed in human being for approximately 4 million to 7 million years [2]. Food deprivation has brought elevated ketone bodies and intensified cognition, leading to synaptic plasticity, neurogenesis and neuroprotection. This mechanism shows optimal cognitive function and resistance to injury and disease.

On the other hand, the latter has been recently observed such as non-communicable diseases (NCDs) worldwide. Food abundance has brought elevated insulin resistance and cognitive complacency, leading to synaptic dysfunction, impaired neurogenesis and neuronal degeneration. This mechanism shows suboptimal cognition and vulnerability to injury and disease [2].

Primitive men had changed into present human race. They had struggled with hunger for million years. What did they usually live on? They sometimes got hunting animals and ate muscle, visceral organ and bone marrow. These foods consist of protein and fat without carbohydrate. Their blood glucose was always subnormal, and health problem was rather hypoglycemia. That is why human body has only insulin that decreases blood glucose.

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A large change was observed about ten thousand years ago. It was agriculture that changed our lifestyle. They could start making crops such as rice, wheat, corn which content is carbohydrate. As the result, the population increased explosively in the continents, and several civilizations were born where people can work hard. There was industrial revolution during 18th century that changed our lifestyle. People tend to have less manual labors and postprandial hyperglycemia because of refined white crops. At present, we have now in other industrial revolution from immobilization and computerized society.

In contemporary society, people have continued taking too much refined cereals and carbohydrates, then insulin has been compelled to secrete for long. Consequently, non-communicable diseases (NCDs) such as obesity, diabetes, hyperlipidemia, arteriosclerosis were increasing and become medical and social problem worldwide [3].

The management of diabetes has been crucial problem. According to International Diabetes Federation (IDF), diabetic prevalence has been explosively increasing [4]. It will become from 8.8% in 2015 to 10.4% in 2040. Consequently, preventing strategy of NCD and metabolic syndrome would be necessary. The important point would be the restriction of taking carbohydrate. In European and North American countries, low carbohydrate diet (LCD) was introduced by Atkins and Bernstein [5,6]. After that, LCD has been gradually accepted for many people and patients [7].

In Japan, authors and colleagues have initiated LCD and continued clinical research of LCD, ketone bodies, Morbus (M) value, comparison of LCD and calorie restriction (CD) and so on [8,9]. For practical application, three type of diet have been proposed, such as super, standard and petite [10]. We are also developing educational workshop about LCD and anti-aging medicine through Japan LCD promotion association (JLCDPA) [11]. Furthermore, we have clarified extremely elevated ketone bodies in the axis of fetus, placenta, newborn and mother blood, indicating that ketone bodies would have crucial important role of generating energy [12].

Formerly, it was believed that brain can use energy from only glucose. After that, however, it is now known that ketone bodies (KB) can generate energy at brain and muscles, and that KB has important roles for regulating human metabolism.

There was the research of fasting therapy with metabolic changes of hormones and free fatty acid (FFA) about 100 years ago. It showed several beneficial effects for various diseases, which was probably due to elevated blood KB [13]. In case of starvation, beta-hydroxybutyrate (βHB, 3-hydroxybutyric acid, 3-OHBA) would replace glucose as a source of energy with various metabolic changes [14]. It means that a switch concerning cell fuel was changed from glucose to fatty acids [14,15]. KB inhibit amino acid metabolism and protein turnover in skeletal muscles. This would be one of the survival mechanism during adaptation to the states of catabolic condition including fasting [14,15].

From related biochemical data of the comparison among animal species, the fetus in most animals seem to be brought up by the energy produced from KB [16,17]. KB consist of 3 factors chemically and medically, which are βHB, acetoacetic acid (AcAc) and acetone [16,17]. The former two have activity as KB, and the latter has no activity. Among them, βHB is thought to be the fundamental main engine producing energy on land-living animals. βHB has been recognized for an energy carrier from liver to peripheral tissues. Furthermore, it is also an important signal via extracellular receptors and acts as an endogenous inhibitor of histone deacetylases (HDACs) [16,17].

KB has been known to have several beneficial efficacies for the nervous function and for neurological diseases. According

to the investigation of acetoacetyl-CoA synthetase (AACS), KB seemed to be utilized through the synthesis pathway of lipid substance, and to influence metabolic disorders for the nervous system [18].

Regarding pediatric medical problem, there are lots of children with epilepsy who are resistant to standard anti-epileptic medicine so far. In such cases, ketogenic diet would be worthwhile to try as a treatment. Ketogenic diet has been effective, whether it is either high-fat low carbohydrate ketogenic diet or meal with high ketone bodies including AcAc, βHB and acetone. The detail mechanisms of these meals are not clarified yet, but KB has actually anticonvulsant antiepileptic effects to satisfactory degree [19].

For children, the influence of meal with little carbohydrate on the metabolic parameters has not been clarified in detail yet [20]. The treatment has been estimated to be effective and related practice and research has been continued at more than 250 medical centers worldwide [21]. Clinical research on epilepsy would be expected to be developed in the future by the accumulation of the epileptic cases.

Regarding medical problem for the elderly, KB would be beneficial for Alzheimer's disease (AD). Glucose metabolism in the brain has been observed to be specifically reduced in AD [22]. The β-amyloid peptide Aβ will interfere with the cholinergic innervation [23]. KB is similarly used against epilepsy at rather high KB concentration, in which KB would interfere with glucose and de novo synthesis of neurotransmitter glutamate. On the other hand, KB can be used for AD at lower concentration. The mechanism seems to be the support of energy metabolism, with inhibiting release of gliotransmitter glutamate [23].

From medical and biological points of view, current topics were described concerning the correlation among human metabolism and evolution, fat and ketone bodies, carbohydrate and LCD. This article would be expected to be some reference to various research.

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