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Ketohexokinase (KHK) Physiology and Treatments in Obesity and Fructose Metabolism

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Description

Obesity is defined as a disproportionate body weight for height with excessive accumulation of subcutaneous and visceral adipose tissue. Over the past decades, number of obesity patient multiplied. Obesity has turned into a medical issue worldwide. According to a survey from WHO in 2016, more than 1.9 billion adults were overweight or obese [1]. By 2030, there will be 3.3 billion people who have a BMI greater than 25 kg/m2 [2]. Obesity is associated with the development of type 2 diabetes mellitus, cardiovascular infection, systemic inflammation and particular kinds of cancer [3]. Some of these obesity-associated diseases belong to metabolic syndrome [4]. In recent years, several factors leading to obesity have been disclosed. Among these, excessive intake of fructose may contribute heavily to the epidemic of obesity, type 2 diabetes mellitus, Non-Alcoholic Fatty Liver Disease (NAFLD) and other metabolic disease [5-7]. Herein, we review the biochemistry, physiology of fructose metabolism and generalize the current treatment progress.

As a simple ketohexose, fructose is derived mostly from fruits, honey, and vegetables. It is the sweetest natural sugar. Sucrose composed of 50% fructose and 50% glucose, and High-Fructose Corn Syrup (HFCS) are commonly used as sweeteners in many processed foods and carbonated beverages. Worryingly, in recent decades, the fructose consumption has increased dramatically. Upon oral ingestion, fructose is absorbed in the small intestine and transported into enterocytes and hepatocytes *via* Glucose transporter5 (Glut5). Upon entering the cells, fructose is initially metabolized to Fructose-1-Phosphate (F1P) by Ketohexokinase (KHK) with Adenosine Triphosphate (ATP) depletion [8]. The consuming of ATP leads to the production of Reactive Oxygen Species (ROS) and Uric Acid (UA) which is a major etiologic factor in gout. F1P could be converted by aldolase B to GA and DHAP. GA is phosphorylated by Triose kinase (Triok) to GA3P which could be resynthesized into glucose *via* gluconeogenesis. Both GA3P and DHAP could be metabolized into lactate and pyruvate which are used for lipogenesis. Unlike the glucose metabolism pathway, there is no negative feedback regulation of fructokinase to prevent it from metabolizing fructose [9-11]. Compared to glucose, fructose significantly elevates *de novo* Lipid (DNL) synthesis [12]. According to our knowledge, there are several potential mechanisms for leading to obesity or other metabolic syndrome associated with fructose: (1) High doses of fructose can induce both hepatic and peripheral insulin resistance [13]; (2) Excessive consuming fructose lead to hyper energy intake; (3) Dietary fructose improves the survival of intestinal cells and increases intestinal villus length resulting to the promotion of the nutrient absorption [5] (Figure 1).

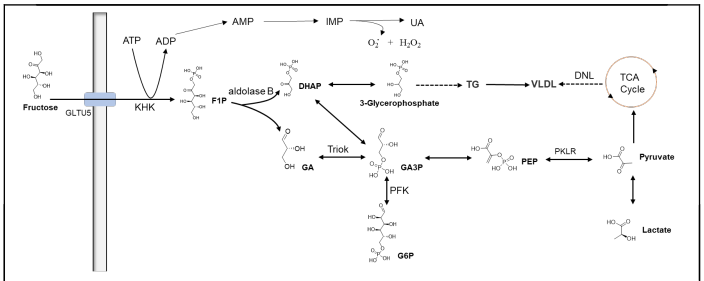

Figure 1: Fructose metabolism. Note: KHK: ketohexokinase; ATP: Adenosine triphosphate; AMP: adenosine monophosphate; IMP: inosine monophosphate; GA: glyceraldehyde; DHAP: dihydroxyacetone phosphate; GA3P: glyceraldehyde 3-phosphate; PFK: phosphofructokinase; PKLR: pyruvate kinase, liver and red blood cell; PEP: phosphoenolpyruvate; DNL: *de novo* lipogenesis.

KHK is the significant fructose metabolic enzyme that initiates the phosphorylation of fructose on position C1 utilizing ATP as a cofactor [14-16]. KHK is expressed as two distinct isoforms (KHK-A and KHK-C) from a single gene [17]. Although the affinity of KHK-A for fructose is more potent than KHK-C, KHK-C is the primary isoform because of that KHK-C is expressed at high levels in key metabolic tissues including liver and small intestine while KHK-A is expressed on low levels. Additionally, KHK knockout mice were fully protected from fructose-induced increases in body weight, serum lipid and serum insulin [18]. In especial, liver-specific knockout or knockdown of KHK can protect against fructose-induced metabolic disease including obesity [19]. These results support that fructose is metabolized by KHK especially in the liver.

Based on the above evidence, KHK inhibitors or KHK expression downregulation appeared to be potential therapeutic strategy for fructose metabolic diseases. Pharmaceuticals have paid considerable attention to discover novel KHK inhibitors. In 2011, Johnson & Johnson Pharmaceutical reported a KHK inhibitor with high potency but in low exposure due to a high metabolic clearance [20]. PF-06835919, discovered by Pfizer in 2015, is currently in two Phase 2a studies (NCT06089265, NCT05463575). Preclinical studies showed dose-dependent (p.o., 75 mg/kg and 300 mg/kg) downregulation of HOMA-IR, Hs-CRP, triglyceridemia, uric acid, and upregulation of adiponectin level under a high-fructose diet after PF-06835919 was administrated for six weeks [21]. The results indicated that KHK inhibition may be helpful for treatment of fructose-induced metabolic diseases. Compared to PF-06835919, Eli Lilly and Company reported a novel KHK inhibitor with high potency on enzyme and cell in 2020

[22]. Shandong Xuanzhu Pharma, TuoJie Biotech (Shanghai), and LG Chem etc. also disclosed KHK inhibitors, respectively [23-25].

Except for KHK inhibitors, KHK expression downregulation *via* siRNA technology has been developed in recent years. Compared to wild type group, KHK knockout mice on 8 weeks assay revealed lower TG level, liver weight, insulin resistance with normal glucose level [26]. These results inspired the development of KHK siRNA technology. Alnylam Pharmaceuticals reported their siRNA candidates (AD-1613400 and AD-1613243) in 2022 [27]. Results showed that single dose administration (s.c., 3 mg/kg) to cynomolgus monkeys led to durable and potent inhibition of KHK mRNA expression and KHK protein. In the same year, Boehringer Ingelheim reported a siRNA product (KHK-1334) for reducing the expression of KHK. Administration of KHK-1334 (s.c., 6 mg/kg) to cynomolgus monkeys resulted in significant knockdown of KHK mRNA and KHK protein expression in the liver [28].

Conclusion

Over the past decades, number of obesity patient multiplied. Obesity has turned into a medical issue worldwide. Obesity is associated with the development of type 2 diabetes mellitus, cardiovascular infection, systemic inflammation and particular kinds of cancer. Excessive intake of fructose may contribute heavily to the epidemic of obesity, type 2 diabetes mellitus, NAFLD and other metabolic disease. Some promising KHK inhibitors or KHK siRNA silencers have been developed with attractive results.

Acknowledgement

None

Conflict of Interest

None

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