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Rare sugar D-allulose: Potential role and therapeutic monitoring in maintaining obesity and type 2 diabetes mellitus

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ABSTRACT

Obesity and type 2 diabetes mellitus (T2DM) are the leading worldwide risk factors for mortality. The inextricably interlinked pathological progression from excessive weight gain, obesity, and hyperglycemia to T2DM, usually commencing from obesity, typically originates from overconsumption of sugar and high-fat diets. Although most patients require medications, T2DM is manageable or even preventable with consumption of low-calorie diet and maintaining body weight. Medicines like insulin, metformin, and thiazolidinediones that improve glycemic control; however, these are associated with weight gain, high blood pressure, and dyslipidemia. These situations warrant the attentive consideration of the role of balanced foods. Recently, we have discovered advantages of a rare sugar, D-allulose, a zero-calorie functional sweetener having strong anti-hyperlipidemic and anti-hyperglycemic effects. Study revealed that after oral administration in rats D-allulose readily entered the blood stream and was eliminated into urine within 24 h. Cell culture study showed that D-allulose enters into and leaves the intestinal enterocytes via glucose transporters GLUT5 and GLUT2, respectively. In addition to D-allulose's short-term effects, the characterization of long-term effects has been focused on preventing commencement and progression of T2DM in diabetic rats. Human trials showed that D-allulose attenuates postprandial glucose levels in healthy subjects and in borderline diabetic subjects. The anti-hyperlipidemic effect of D-allulose, combined with its anti-inflammatory actions on adipocytes, is beneficial for the prevention of both obesity and atherosclerosis and is accompanied by improvements in insulin resistance and impaired glucose tolerance. Therefore, this review presents brief discussions focusing on physiological functions and potential benefits of D-allulose on obesity and T2DM.

Contents

Abbreviations: T2DM, type 2 diabetes mellitus; OLETF, Otsuka Long–Evans Tokushima Fatty; LPL, lipoprotein lipase; GLUT5, glucose transporter 5; GLUT2, glucose transporter 2; GRAS, generally recognized as safe; FDA, food and drug administration; OGTT, oral glucose tolerance test; GK, glucokinase; GKRP, glucokinase regulatory protein; β-cell, beta-cell; IL-6, interleukin-6; IL-1β, interleukin-1 beta; TNFα, tumor necrosis factor-alpha; SGLT1, sodium-dependent glucose transporter 1; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin-sensitivity check index; CHE, cholinesterase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; α-SMA, alpha smooth muscle actin; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; MCP-1, monocyte chemoattractant protein 1; SR-B1, scavenger receptor class B type 1; MTP, microsomal triglyceride transfer protein; TG, triglyceride; HFCS, high fructose corn syrup; NAS, non-caloric artificial sweeteners; WHO, World Health Organization.

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1. Introduction

Currently, the incidence and prevalence of excessive weight gain followed by obesity has dramatically increased throughout the world, with the consequence that an estimated 325 million diabetes sufferers will exist during the next 25 years (Wild et al., 2004). Over consumption of sugar and high-fat diets are considered the main causative dietary factors of this situation (Giugliano & Esposito, 2008). Beyond the availability of a number of pharmacological and surgical treatments, lifestyle modifications (Asif, 2014) involving the consumption of foods with low energy density in addition to increasing physical activities are the basic therapeutic strategies to prevent the development of type 2 diabetes mellitus (T2DM).

Recently, we have been studying rare sugars that are defined as "monosaccharides and their derivatives that are rare in nature" by the International Society of Rare Sugars (https://sites.google.com/site/raresugars/). There are more than 50 kinds of rare sugar. One of them, D-allulose (previously named D-psicose), has been determined to have a low degree of energy density, exhibiting almost zero calories (Matsuo et al., 2002a) and thus has been proven to be a unique metabolic regulator of glucose and fat metabolism in a number of basic research (Hossain et al., 2011; Hossain et al., 2012; Matsuo & Izumori, 2006; Matsuo & Izumori, 2009) and clinical (Iida et al., 2013) studies. D-Allulose has demonstrated activity involving a variety of mechanisms, such as strong anti-oxidative effects, inhibitory activity toward intestinal digestive enzymes, enhanced translocation of glucokinase (GK) from the hepatic nucleus to cytoplasm, and competitive transport with glucose through the intestinal mucosa. Therefore, this review will summarize the physical properties, absorption, excretion, and physiological functions of D-allulose, as well as the potential benefits of D-allulose on obesity and T2DM with its safety and possible use as a substitute for conventional sugars.

D-Allulose is a monosaccharide with a molecular formula $C_6H_{12}O_6$. It is a C-3 epimer of D-fructose (Fig. 1), and its systematic name is D-ribo-2-hexulose. D-Allulose is also called D-psicose and the name "psicose" is derived from the antibiotic psicofuranine, from which it was isolated (Eble et al., 1959). D-Allulose is rarely encountered in nature as a component of some plants, such as *Itea* plants (Zuina) (Poonperm et al., 2007), and certain bacteria (Zhang et al., 2009), but not in higher animals. D-Allulose contains one ketone group and acts as a reducing agent. It is prepared as a white, odorless powder and is easily dissolved in water. The sweetness of D-allulose is about 70% of sucrose, melts at 90 °C, and forms caramel. As a reducing sugar, heating with amino acids, peptides, and proteins in foods induces the amino-carbonyl reaction (Maillard reaction) at a lower degree than D-glucose or D-fructose (Sun et al., 2004). These Maillard products show anti-oxidative activity and gelling properties, such as enhanced gel strength and water-holding capacity (Sun et al., 2006).

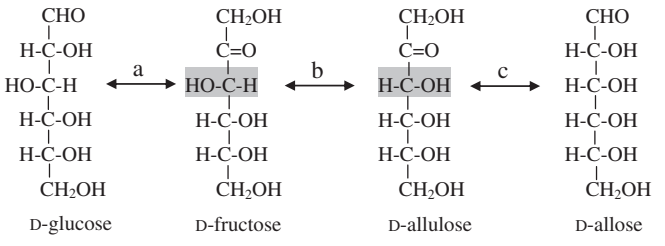

Fig. 1. Structures and enzymatic conversion of D-glucose, D-fructose, D-allulose, and D-allose. Inter-conversion between D-glucose, D-fructose, D-allulose, and D-allose is catalyzed by the following enzymes: a, xylose isomerase; b, D-tagatose 3-epimerase, c, L-rhamnose isomerase. Reactions catalyzed by D-tagatose 3-epimerase can link ketohexoses by epimerization at the C-3 position.

Although it is rarely found in nature, it has been reported that commercial mixtures of D-glucose and D-fructose obtained from the hydrolysis of sucrose or D-glucose isomerization (Cree & Perlin, 1968), as well as processed cane and beet molasses (Binkley & Wolfrom, 1953; Thacker & Toyoda, 2009), contain a small quantity of D-allulose as a result of the heating process during manufacturing. After the discovery of the key enzyme D-tagatose 3-epimerase, which converts D-fructose to D-allulose, mass production began (Izumori, 2006; Takeshita et al., 2000). Currently, D-allulose is also produced by chemical synthesis and is widely available at a much lower cost. Thus, various D-allulose-added foods have been prepared and marketed in Japan. D-Allulose was approved as generally recognized as safe (GRAS) by the US Food and Drug Administration (FDA) in June 2014 (GRAS Notice No. GRN 498) and is allowed to be used as an ingredient in a variety of foods and dietary supplements (Mu et al., 2012).

In addition to its use as a substitute sweetener, D-allulose was also reported to inhibit trichomonad growth by reinforcing the action of metronidazole (Harada et al., 2012), and to induce the up-regulation of defense-related genes in plant cultivation (Kano et al., 2011). Further research into its use as an anti-parasitic or herbicide is currently being undertaken.

2. Absorption, metabolism, and organ distribution of D-allulose

^{14}C-Labelled D-allulose was enzymatically synthesized (Morimoto et al., 2006) to study its absorption, distribution, and elimination after both intravenous and oral administration in Wister rats and the concentrations in whole blood, urine, and organs were measured. D-Allulose (100 mg/kg) was orally administered to rats that were subsequently sacrificed 10, 30, 60, and 120 min after administration. The concentrations of D-allulose in urine were 19% and 37% of the administered dose at 60 and 120 min, respectively, and almost 0% 7 days thereafter (Tsukamoto et al., 2014). Other studies detected 11–15% after 24–48 h (Matsuo et al., 2003) and 35.4% after 7 h (Whistler et al., 1974). We and others have reported that ≈70% of D-allulose was absorbed and excreted via urine (Tsukamoto et al., 2014; Whistler et al., 1974). However, a small portion of D-allulose was not absorbed in the small intestine, was conveyed to the large intestine, and ultimately found to be partly fermented in the appendix in rats (Matsuo et al., 2003), and to a lesser degree in humans (Iida et al., 2010).

Following intravenous administration, the blood concentration was decreased with a half-life of 57 min and excretion in urine was approximately 45% and 50% within 1 and 2 h, respectively (Tsukamoto et al., 2014). Autoradiography detected high levels of ^{14}C-labelled D-allulose in the liver, kidney, and urinary bladder; interestingly, however, no accumulation was observed in the brain (Tsukamoto et al., 2014).