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Secretion of GLP-1 but not GIP is potently stimulated by luminal D-Allulose (D-Psicose) in rats

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ABSTRACT

Glucagon-like peptide 1 (GLP-1), an incretin gastrointestinal hormone, is secreted when stimulated by nutrients including metabolizable sugars such as glucose and fructose. D-Allulose (allulose), also known as D-psicose, is a C-3 isomer of D-fructose and a rare sugar with anti-diabetic or anti-obese effects in animal models. In the present study, we examined whether an oral administration of allulose could stimulate GLP-1 secretion in rats, and investigated the underlying mechanisms. Oral, but not intraperitoneal, administration of allulose (0.5–2.0 g/kg body weight) elevated plasma GLP-1 levels for more than 2 h in a dose-dependent manner. The effects of allulose on GLP-1 secretion were higher than that of dextrin, fructose, or glucose. In addition, oral allulose increased total and active GLP-1, but not glucose-dependent insulinotropic polypeptide (GIP), levels in the portal vein. In anesthetized rats equipped with a portal catheter, luminal (duodenum and ileum) administration of allulose increased portal GLP-1 levels, indicating the luminal effect of allulose. Allulose-induced GLP-1 secretion was abolished in the presence of xanthohumol (a glucose/fructose transport inhibitor), but not in the presence of inhibitors of the sodium-dependent glucose cotransporter 1 or the sweet taste receptor. These results demonstrate a potent and lasting effect of orally administered allulose on GLP-1 secretion in rats, without affecting GIP secretion. The potent and selective GLP-1-releasing effect of allulose holds promise for the prevention and treatment of glucose intolerance through promoting endogenous GLP-1 secretion.

1. Introduction

Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are gastrointestinal hormones called incretins that have insulinotropic effects [1], and incretin mimetics and enhancers have been used to treat type-2 diabetes. Secretion of GLP-1 and GIP is stimulated by luminal nutrients, and the mechanisms involved have been recently unveiled. However, attempts for prevention and treatment of glucose intolerance through stimulated production and/or release of endogenous GLP-1 have not been successful.

Prevention and treatment of diabetes have also been attempted using “rare sugars”, which are defined as monosaccharides and their derivatives that are present in limited quantities in nature [2]. D-Allulose (allulose), also known as D-Psicose, a C-3 epimer of D-Fructose, is a non-caloric rare sugar with 70% of the sweetness of sucrose [3]. Administration of allulose reduced visceral fat in obese rats [4], improved insulin resistance [5], and suppressed postprandial blood glucose levels [6]. Because GLP-1 has beneficial effects beyond glucose metabolism [7], we hypothesized that allulose might increase GLP-1 secretion.

In the present study, we examined whether oral administration of allulose stimulates GLP-1 secretion in rats. Plasma GLP-1 levels were measured in peripheral and portal blood, and allulose was administered intraperitoneally or into the intestinal lumen to assess the site of action. Moreover, we investigated the involvement of sugar sensors in the gut to explore the mechanisms underlying

Abbreviations: GLP-1, glucagon-like peptide-1; GIP, Glucose-dependent insulinotropic polypeptide; Allulose, D-Allulose; GLUT5, glucose transporter 5; SGLT, sodium–dependent glucose cotransporter.

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allulose-induced GLP-1 secretion.

2. Materials and methods

2.1. Materials

D-Allulose, maltodextrin (dextrin, PINEDEX2), and resistant maltodextrin (RMD, Fibersol2) were provided by Matsutani Chemical Industry. Phloridzin dihydrate and (±)-2-(*p*-methoxyphenoxy) propionic acid (lactisole) were purchased from Sigma (St. Louis, MO, USA). Xanthohumol was purchased from Tokyo Chemical Industry (Tokyo, Japan). The remaining reagents were purchased from Wako Pure Chemical Industries (Osaka, Japan) unless otherwise specified.

2.2. Animals and measurement of plasma gut hormones

Male Sprague Dawley (SD) rats (7 weeks old, 200–220 g) were purchased from Japan SLC (Hamamatsu, Japan). Animals were housed in individual cages, had free access to water, and received a semi-purified AIN-93G diet [8] containing 25% casein. Animal experiments were performed after an acclimation period (4–7 days) at 23 ± 2 °C with a 12 h light and dark cycle (light period, 8:00 a.m. to 8:00 p.m.). Rats were fasted for 16 h before the experiments. This study was approved by the Hokkaido University Animal Committee, and the animals were maintained in accordance with the Guide for the Care and Use of Laboratory Animals of Hokkaido University.

Plasma gut hormone levels were measured in plasma samples collected from the tail vein, or the portal vein as described below [9]. Total GLP-1, active GLP-1, and total GIP levels were measured using the respective ELISA kits (EZGLP1T-36K, EGLP-35K, EZRMGIP-55K; Millipore, Billerica, MA).

2.3. Oral administration of allulose on plasma GLP-1 levels

Allulose, RMD, dextrin, fructose, or water (control) were orally administered at 0.5–2.0 g/kg in 10 mL/kg using a feeding tube (5 Fr; Atom Medical, Tokyo, Japan). Blood samples (175 μL) were collected from the tail vein before (0 min) and every 30 min until 240 min after allulose administration.

2.4. Oral administration of allulose on portal GLP-1 and GIP, analysis of luminal allulose

Allulose or glucose at 2.0 g/kg were orally administered and portal blood samples (1 mL) taken under 50 mg/kg sodium pentobarbital anesthesia (Somnopentyl injection; Kyoritsu Seiyaku, Tokyo, Japan). Contents of the digestive tract (stomach, jejunum, ileum, cecum, and colon) were collected by washing with distilled water 60 or 150 min after the oral administration, and luminal contents of allulose and glucose were measured as previously described [10].

2.5. Intraperitoneal and intraluminal administration of allulose

Allulose (0.5 or 1.0 g/kg) dissolved in sterilized water (4 mL/kg) was intraperitoneally administered (4 mL/kg). Blood samples were collected and total plasma GLP-1 levels were measured as described above.

Intraluminal administration of allulose was performed as follows. A middle abdominal incision was made in rats under sodium pentobarbital anesthesia (50 mg/kg) as previously described [11]. After a basal (0 min) blood collection from the portal catheter, saline (10 mL/kg) or allulose (0.5 or 1.0 g/kg) were directly administered into the duodenum or ligated ileal loop (30 cm length, between 5 and 35 cm from the cecum). Portal blood samples (300 μL) were collected into a syringe containing aprotinin, heparin, and a DPP-IV inhibitor 15, 30, and 60 min after allulose administration.

2.6. Effects of inhibitors for monosaccharide transporter and sweet taste receptor

A portal catheter was inserted in rats under anesthesia as described above. After collecting a basal (0 min) blood sample, allulose (0.5 g/kg), xanthohumol (14 mg/kg), allulose (0.5 g/kg), or allulose (0.5 g/kg) with xanthohumol (14 mg/kg) dissolved in 0.5% hydroxypropyl methylcellulose (HPMC) were administered into the duodenum (10 mL/kg). Xanthohumol reportedly has inhibitory effects on glucose or fructose transport [12,13]. HPMC (0.5%) solution was administered as control. Blood samples were collected through the portal catheter 30 and 60 min after administration.

In a separated experiment, The SGLT1 inhibitor phloridzin (300 mg/kg) [14] or the sweet taste receptor antagonist lactisole (2.25 or 5.0 mg/kg) [15] dissolved in 0.5% HPMC were orally administrated (10 mL/kg) with allulose (1.0 g/kg), and tail vein blood samples were collected as described above.

2.7. Statistical analysis

Results are expressed as mean ± SEM. Statistical significance was determined using one-way or two-way ANOVA to assess the main effects (treatment and time), as well as the interaction effects (treatment × time), using JMP Pro software version 12 (SAS Institute, NC, USA). Statistical significance between mean values was evaluated using Dunnett's test or Student's t-test as appropriate.

3. Results

3.1. A single oral administration of allulose increased plasma GLP-1 levels in rats

Plasma GLP-1 levels in the allulose-treated group increased during the first 60 min, remained constant for the next 60 min, and gradually returned to basal levels (Fig. 1A), being significantly higher than those in the control group (Fig. 1A and B). In addition, allulose (0.5, 1.0, and 2.0 g/kg) induced GLP-1 secretion in a dose-dependent manner (Fig. 1C and D). The comparison of allulose with dextrin (digestible), RMD (less digestible), and fructose showed that allulose induced clearly higher plasma GLP-1 levels than RMD or fructose, both of which were reported to stimulate GLP-1 secretion [9,16] (Fig. 1A, B, 1E, and 1F). In contrast, no difference was found between the control and dextrin groups (Fig. 1A and B). These results demonstrate that oral administration of allulose markedly increases GLP-1 secretion in rats.

3.2. Oral administration of allulose stimulated GLP-1 but not GIP secretion

We next determined whether allulose affected GLP-1 and GIP levels in the portal vein. Portal blood was collected after oral administration of allulose or glucose (2.0 g/kg) to detect changes in gastrointestinal hormone levels immediately after release. Total plasma GLP-1 levels in allulose-treated rats were significantly higher than in control rats both 60 and 150 min after oral administration (Fig. 2A). Active GLP-1 levels 60 min after allulose administration were also significantly higher than in control rats (Fig. 2B). No difference was found in plasma GIP levels between untreated and allulose-treated rats (Fig. 2C). In contrast, oral glucose increased GIP levels 60 min after administration without an