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TITLE

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 (an 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.

Key words: GLP-1, GIP, Allulose

Abbreviations:

GLP-1, glucagon-like peptide-1; GIP, Glucose-dependent insulinotropic poypeptide; Allulose, D-Allulose*; GLUT5, glucose transporter 5; SGLT, sodium–dependent glucose cotransporter;*

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S. K. is an MN, TI, and YK are employees of Matsutani Chemical Industry.

MH, TH, and HH, have nothing to declare.

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 allulose-induced GLP-1 secretion.

Materials and Methods

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.

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 AM to 8:00 PM). 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 decribed 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).

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.

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].

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.

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 (14mg/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.

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.

Results

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 (Figure 1A), being significantly higher than those in the control group (Figure 1A and 1B). In addition, allulose (0.5, 1.0, and 2.0 g/kg) induced GLP-1 secretion in a dose-dependent manner (Figure 1C and 1D). 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] (Figure 1A, 1B, 1E, and 1F). In contrast, no difference was found between the control and dextrin groups (Figure 1A and 1B). These results demonstrate that oral administration of allulose markedly increases GLP-1 secretion in rats.

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 (Figure 2A). Active GLP-1 levels 60 min after allulose administration were also significantly higher than in control rats (Figure 2B). No difference was found in plasma GIP levels between untreated and allulose-treated rats (Figure 2C). In contrast, oral glucose increased GIP levels 60 min after administration without an increase in plasma GLP-1 levels. These results show that allulose does not induce GIP secretion.

To investigate the rate of allulose absorption in the digestive tract, the luminal allulose content was determined in allulose-treated rats. The remaining allulose content 60 min after administration was highest in the stomach (25 %) and lower in the jejunum, ileum, and

cecum (~10 %). After 150 min, allulose migrated to the lower intestine, as the remaining content was highest in the cecum (Figure 2D). In contrast, only 3.6 % of glucose was detected in the stomach 60 min after oral administration (Figure 2E), indicating rapid and efficient absorption of this sugar in the small intestine. These results suggest that allulose is absorbed much slower than glucose in the digestive tract of rats.

GLP-1 secretion was induced by luminal allulose but by intraperitoneal allulose

To examine whether allulose stimulates GLP-1 secretion from the apical or basolateral side of the intestine, we administered allulose in the peritoneum. In contrast to oral administration (Figure 1A, 1B, and 1C), intraperitoneal allulose did not cause any increment in plasma GLP-1 levels in awake rats (Figure 3A). On the other hand, duodenal administration of allulose at 0.5 g/kg and 1.0 g/kg increased portal GLP-1 levels significantly after 30 min, and at 30 and 60 min, respectively in anesthetized rats (Figure 3B). Both allulose and glucose similarly increased plasma GLP-1 levels 30 and 60 min after administration into the ileum, where GLP-1-producing L cells are abundantly present [17] (Figure 3C). These results suggest that allulose needs to be present in the intestinal lumen to induce GLP-1 secretion.

Possible involvements of sweet taste receptor or monosaccharide transporters in allulose-induced GLP-1 secretion

To investigate the underlying mechanisms by which luminal allulose simulates GLP-1 secretion, we examined the involvement of molecules that mediate glucose- or fructose-induced GLP-1 secretion, such as the sweet taste receptor [18] and monosaccharide transporters [14, 16,19]. Consistent with the results described above (Figure 3B), luminal allulose (0.5 g/kg) sustainably increased portal GLP-1 levels (Figure 4A).

However, GLP-1 levels increased only slightly in the group treated with allulose + xanthohumol (14 mg/kg, 0.5 g/kg) (Figure 4B). The administration of xanthohumol did not affect GLP-1 secretion (Figure 4B). We also investigated the effects of the SGLT1 inhibitor phloridzin [14] and of the sweet taste receptor antagonist lactisole [15] on GLP-1 secretion. Figure 4C shows that these inhibitors did not lower allulose-induced GLP-1 secretion.

Discussion

In the present study, we found that plasma GLP-1 levels were sustainably elevated by oral administration of allulose without affecting GIP levels, in contrast to oral glucose. In addition, luminal allulose-induced GLP-1 secretion was abolished in the presence of xanthohumol. Although the cellular mechanisms are remained unclear, these results reveal a potent and lasting effect of orally administered allulose on GLP-1 secretion in vivo.

The stimulatory effect of allulose on GLP-1 secretion was unexpectedly higher than that of glucose, fructose, and RMD. This effect could be attributed to a relatively slow intestinal absorption rate of allulose [20], unlike glucose and fructose [21]. The low absorption rate may help luminal allulose to reach the lower part of the small intestine where GLP-1-producing L-cells are abundantly present. In fact, allulose remained in the intestinal lumen up to 150 min after administration, in contrast to glucose (Figure 2D). Contrary to our expectations, no increase in plasma GLP-1 levels by dextrin was observed, which may be due to the rapid absorption of liberated glucose in the proximal small intestine [22, 23]. Consistent with this interpretation, administration of dextrin rapidly raised blood glucose levels (data not shown).

In the present study, oral glucose failed to stimulate GLP-1 secretion, while intra-ileal administration of glucose stimulated GLP-1 secretion with a potency similar to that of allulose, suggesting that a higher dose is required for oral glucose to reach the ileum and

thereby induce GLP-1 secretion. In contrast, secretion of GIP was increased by glucose but not by allulose, which could be due to the preferential distribution of K cells in the upper small intestine [24, 25]. The selective effects of allulose and fructose on GLP-1 secretion but not on GIP secretion [16], and the similar GLP-1 secretory responses to both sugars, suggest that these epimers may trigger GLP-1 secretion through a common mechanism.

The potent effect of allulose on GLP-1 secretion when injected in the intestinal lumen but not in the peritoneum indicates that the sugar exerts its effect in the lumen of small intestine. Because allulose was administered into the intestinal lumen at a nearly isotonic condition (0.5 g/10 mL = 278 mmol/L), an osmotic effect seems not be responsible for the allulose-induced GLP-1 secretion as well as fructose-induced GLP-1 secretion [14].

The SGLT1 inhibitor phloridzin failed to reduce allulose-induced GLP-1 secretion, which suggests that allulose stimulates GLP-1 secretion by a mechanism distinct from that of glucose. Although it is generally believed that the sweet taste receptor is not sensitive to lactisole in rodents, a recent study demonstrated that lactisole inhibited the glucose-sensing T1R3 receptor in mouse pancreatic β-cells [15]. Therefore, we tentatively conclude that the sweet taste receptor is not involved in allulose-induced GLP-1 secretion. Induction of GLP-1 secretion by luminal allulose was inhibited by xanthohumol but not by phloridzin. The hop-drived polyphenol has been reported to inhibit glucose/fructose transport [12, 13]. These results suggest that allulose stimulates GLP-1 secretion via GLUT5 or another monosaccharide transporter. Involvement of GLUT5 has also been proposed in fructose-induced GLP-1 secretion [16]. Fructose is metabolized to produce ATP, causing membrane depolarization that results in GLP-1 release. Although a previous study suggested that allulose is absorbed through GLUT5 in intestinal Caco2 cells [21], this sugar is not metabolized as an energy source [10]. Allulose likely stimulates GLP-1 secretion thorough a cellular mechanism only partially similar to that of fructose. On the other hand,

allulose promotes intracytoplasmic translocation of glucokinase in hepatocytes [26]. It is possible that glucokinase is activated by intracellular allulose, triggering the glycolytic pathway by utilizing glucose transported from the basolateral membrane [27]. The process increases ATP production and leads to depolarization, which induces GLP-1 secretion [14, 28]. Interestingly, GIP secretion was not induced by allulose, although K cells also express GLUT5 [27]. We investigated the effects of allulose on the GLP-1-producing, model cell line GLUTag [29]. However, no increase in GLP-1 secretion was observed in this cell line (data not shown). Although the GLUTag cells reportedly express GLUT5, the cell line may lack some factors responsible for sensing allulose, or the appropriate experimental conditions to observe an allulose-induced GLP-1 secretion have not been found. It is further possible that unknown indirect pathway to stimulate L cells might be involved in the intestinal tissue. Further studies are needed to elucidate the cellular mechanisms involved in allulose-induced GLP-1 secretion.

In summary, the present study demonstrates that oral allulose has a potent and lasting effect on GLP-1 secretion without affecting GIP secretion. Luminal rather than plasma allulose stimulates GLP-1 secretion, possibly thorough an indirect action to L cells via epithelial monosaccharide transporter that is sensitive to xanthofumol. Although the molecular mechanisms remain unclear, our study has showed that it is possible to selectively stimulate GLP-1 secretion without enhancing GIP secretion using a non-metabolizable food factor. There is strong demand for such a specific GLP-1 releaser [30], and allulose may be the first orally available GLP-1 releaser for translational research in humans to provide the various beneficial effects of increasing endogenous GLP-1 levels [31].

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Legends

Figure 1.

Changes (A, C, and E) in plasma GLP-1 levels after oral administration of water (control), allulose, resistant dextrin (RMD), dextrin, and fructose in conscious rats. The area under the curve (AUC) (B and D) and incremental AUC (iAUC) (F) were calculated by the trapezoidal rule. Blood samples were collected before (0 min) and after (30–240 min) oral administration of test solutions (10 mL/kg). (A) white circles, Control (water) (n=12); black circles, 2.0 g/kg allulose (n=12); black triangles, 2.0 g/kg RMD (n=12); black squares, 2.0 g/kg dextrin (n=12). (C) white circles, Control (water) (n=8); light gray circles, 0.5 g/kg allulose (n=8); dark gray

circles, 1.0 g/kg allulose (n=8); black circles, 2.0 g/kg allulose (n=8). (E) black circles, 2.0 g/kg allulose (n=7); white rhombus, 2.0 g/kg fructose (n=6). Values are shown as mean ± SEM. Two-way ANOVA *P* values were all <0.05 in (A), <0.05, <0.05, and 0.17 in (C), <0.05, <0.05, and 0.42 in (E), for treatment, time, and treatment x time, respectively. Asterisks (*) indicate significant differences compared to the control treatment at the same time point (Dunnett's test, $P<0.05$). Plus signs (+) indicate significant differences compared to the value at 0 min within each treatment (Dunnett's test, $P<0.05$). Hash signs (#) indicate significant differences compared to the control treatment (B), compared to 0 g/kg (D) (Dunnett's test, $P<0.05$), and between treatments (F) (Student's t-test, $P<0.05$).

Figure 2.

Plasma total GLP-1 (A), active GLP-1 (B), and total GIP (C) levels in portal vein blood, and the luminal recovery rate 60 min and 150 min after oral administration (10 mL/kg) of water (control), allulose (2 g/kg) (D), and glucose (2 g/kg) (E). White bar, untreated (0 min) (n=8); gray bar, allulose after 60 min; black bar, allulose after 150 min (n=4, each time point); light diagonal bar, glucose after 60 min; diagonal bar, glucose after 150 min (n=4, each time point). Values are shown as mean ± SEM. Hash signs (#) indicate significant differences compared to the untreated group (Dunnett's test, $P<0.05$).

Figure 3.

GLP-1 secretion in response to intraperitoneal or intraluminal administration of allulose. (A) Blood samples were collected before (0 min) and after (30–240 min) intraperitoneal administration of test solutions (4 mL/kg). White circles, Control (water) (n=6); light gray circles, 0.5 g/kg allulose (n=5); dark gray circles, 1.0 g/kg allulose (n=5). Values are shown as mean ± SEM. Two-way ANOVA *P* values for intraperitoneal administration are all >0.05

for treatment, time, and treatment x time.

Changes in plasma GLP-1 levels in portal plasma after administration of saline (control) and allulose into the duodenum (B), and after administration of saline (control), allulose, and glucose into a ligated ileal loop (C) in anesthetized rats. Blood samples were collected before (0 min) and after (15, 30, and 60 min) administration of test solutions (10 mL/kg) into the duodenum or the ileal loop. (B) white circles, Control (saline) (n=6); light gray circles, 0.5 g/kg allulose (n=8); dark gray circles, 1.0 g/kg allulose (n=6). (C) white circles, Control (saline) (n=6); light gray circles, 0.5 g/kg allulose (n=8); dark gray triangles, 0.5 g/kg glucose (n=6). Values are shown as mean ± SEM. Two-way ANOVA *P* values were <0.05, <0.05, and 0.74 in (B), <0.05, <0.05, and 0.84 in (C) for treatment, time, and treatment x time, respectively. Asterisks (*) indicate significant differences compared to control treatment at the same time point (Dunnett's test, $P<0.05$). Plus signs (+) indicate significant differences from the value at 0 min within each treatment (Dunnett's test, $P<0.05$).

Figure 4.

Changes (A) and area under the curve (B) in plasma GLP-1 levels in portal plasma after duodenal administration of saline (control), allulose, xanthohumol, and allulose + xanthohumol in anesthetized rats. Blood samples were collected before (0 min) and after (30 and 60 min) administration of test solutions (10 mL/kg) into the duodenum. (A) white circles, Control (saline) (n=7); white triangles, 14 mg/kg xanthohumol (n=6); black circles, 0.5 g/kg allulose (n=8); black squares, 0.5 g/kg allulose + 14 mg/kg xanthohumol (n=7). Variation (C) in plasma GLP-1 levels after oral administration of allulose (1 g/kg), allulose + phloridzin (300 mg/kg), allulose + low lactisole (2.25 mg/kg), and allulose + high lactisole (4.5 mg/kg) in conscious rats. Blood samples were collected before (0 min) and after (30–180 min) administration of test solutions (10 mL/kg). Values are shown as mean ± SEM. Two-way

ANOVA *P* values are all <0.05 (A), <0.05, <0.05, and 0.84 (C) for treatment, time, and treatment x time, respectively. Asterisks (*) indicate significant differences compared to control treatment at the same time point (Dunnett's test, *P*<0.05). Plus signs (+) indicate significant differences from the value at 0 min within each treatment (Dunnett's test, *P*<0.05). Hash signs (#) indicate significant differences compared to the control treatment (Dunnett's test, *P*<0.05).

Graphical abstract

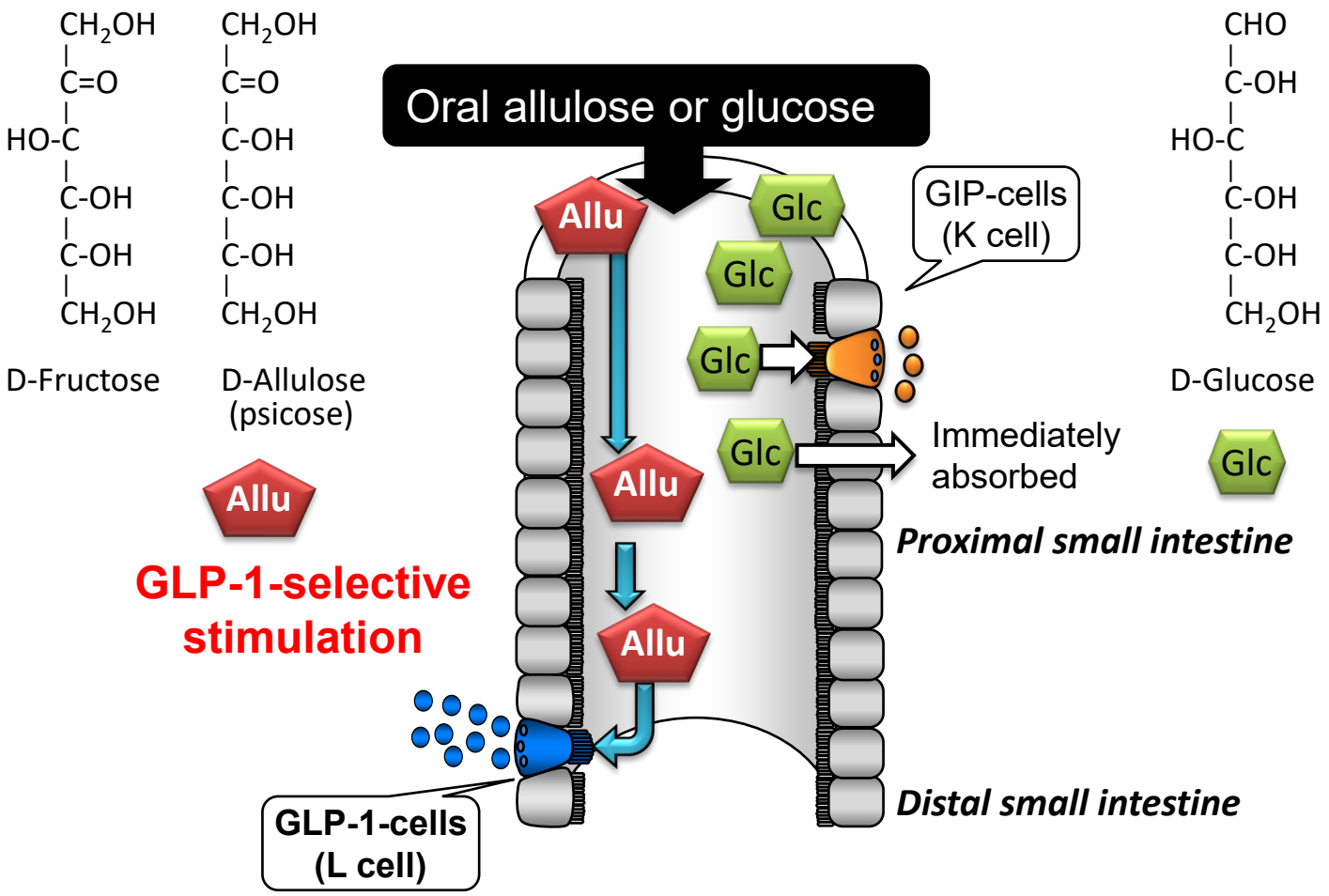


Figure 1

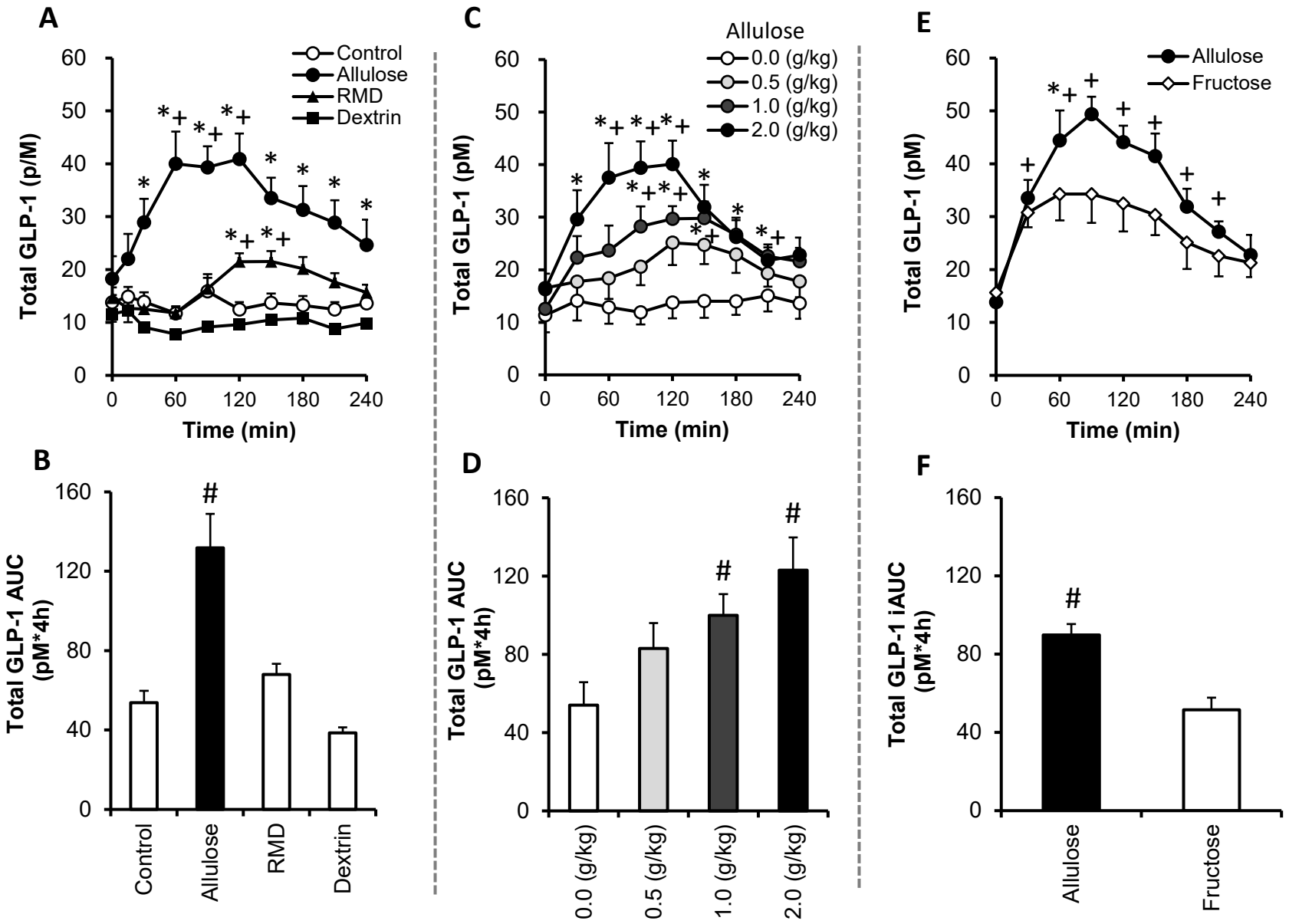

A
Control
Allulose
RMD
Dextrin
Total GLP-1 (p/M)
Time (min)
C
Allulose
0.0 (g/kg)
0.5 (g/kg)
1.0 (g/kg)
2.0 (g/kg)
Total GLP-1 (pM)
Time (min)
E
Allulose
Fructose
Total GLP-1 (pM)
Time (min)
B
Total GLP-1 AUC (pM*4h)
Control
Allulose
RMD
Dextrin
D
Total GLP-1 AUC (pM*4h)
0.0 (g/kg)
0.5 (g/kg)
1.0 (g/kg)
2.0 (g/kg)
F
Total GLP-1 iAUC (pM*4h)
Allulose
Fructose

Figure 2

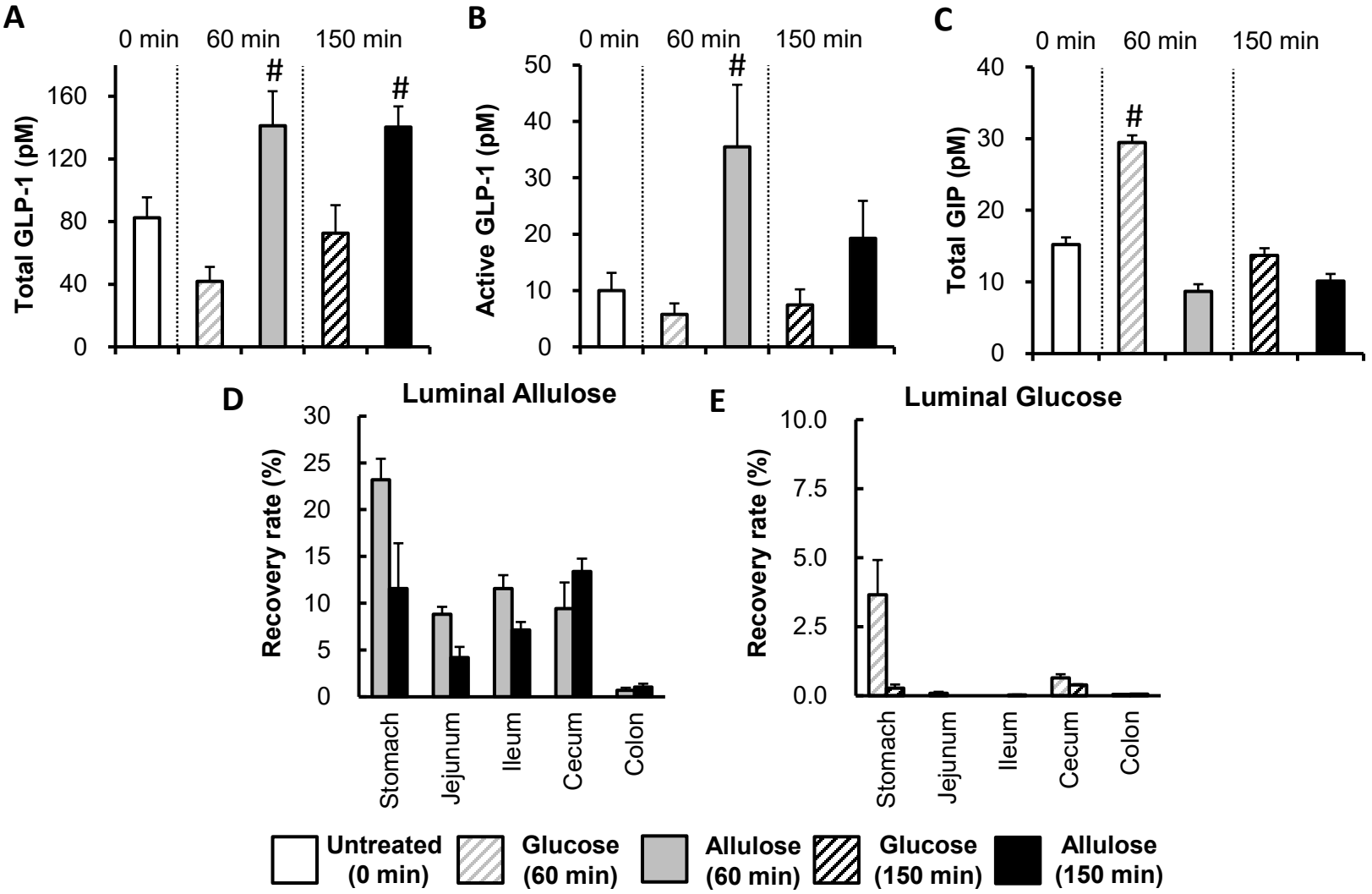

A
0 min
60 min
150 min
Total GLP-1 (pM)
0
40
80
120
160
#
#
B
0 min
60 min
150 min
Active GLP-1 (pM)
0
10
20
30
40
50
#
C
0 min
60 min
150 min
Total GIP (pM)
0
10
20
30
40
#
D
Luminal Allulose
Recovery rate (%)
0
5
10
15
20
25
30
Stomach
Jejunum
Ileum
Cecum
Colon
E
Luminal Glucose
Recovery rate (%)
0.0
2.5
5.0
7.5
10.0
Stomach
Jejunum
Ileum
Cecum
Colon
Untreated (0 min)
Glucose (60 min)
Allulose (60 min)
Glucose (150 min)
Allulose (150 min)

Figure 3

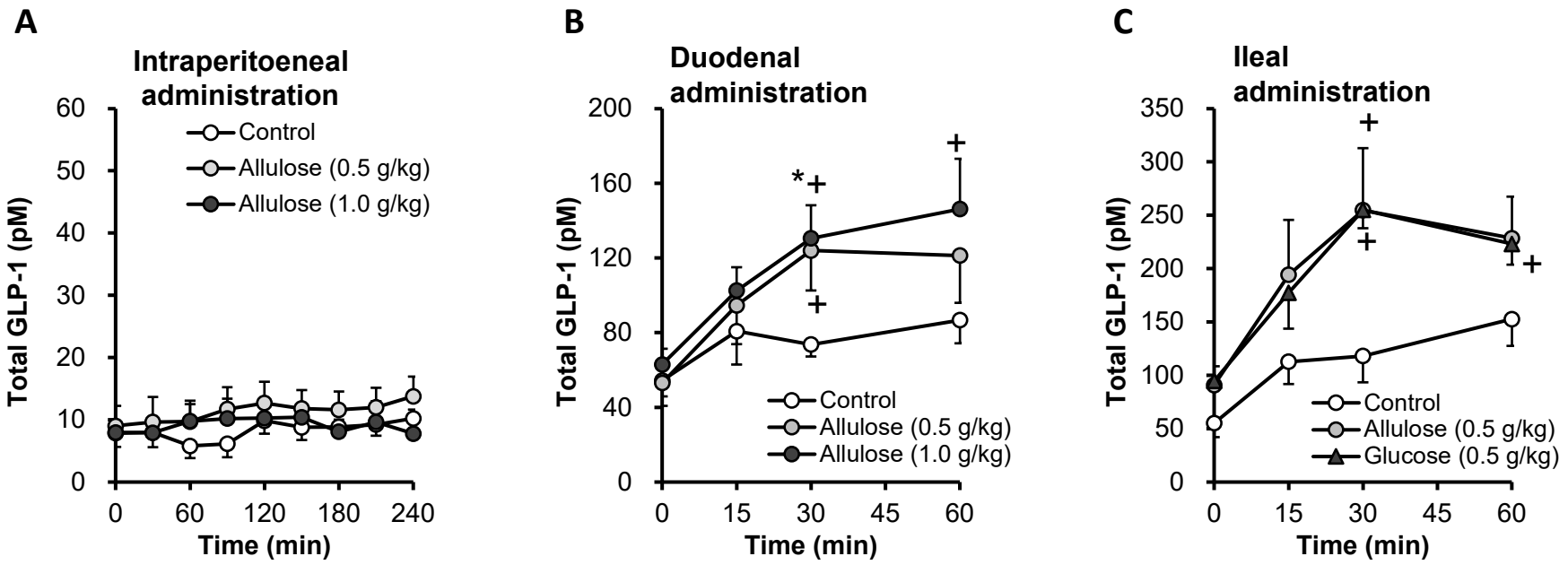
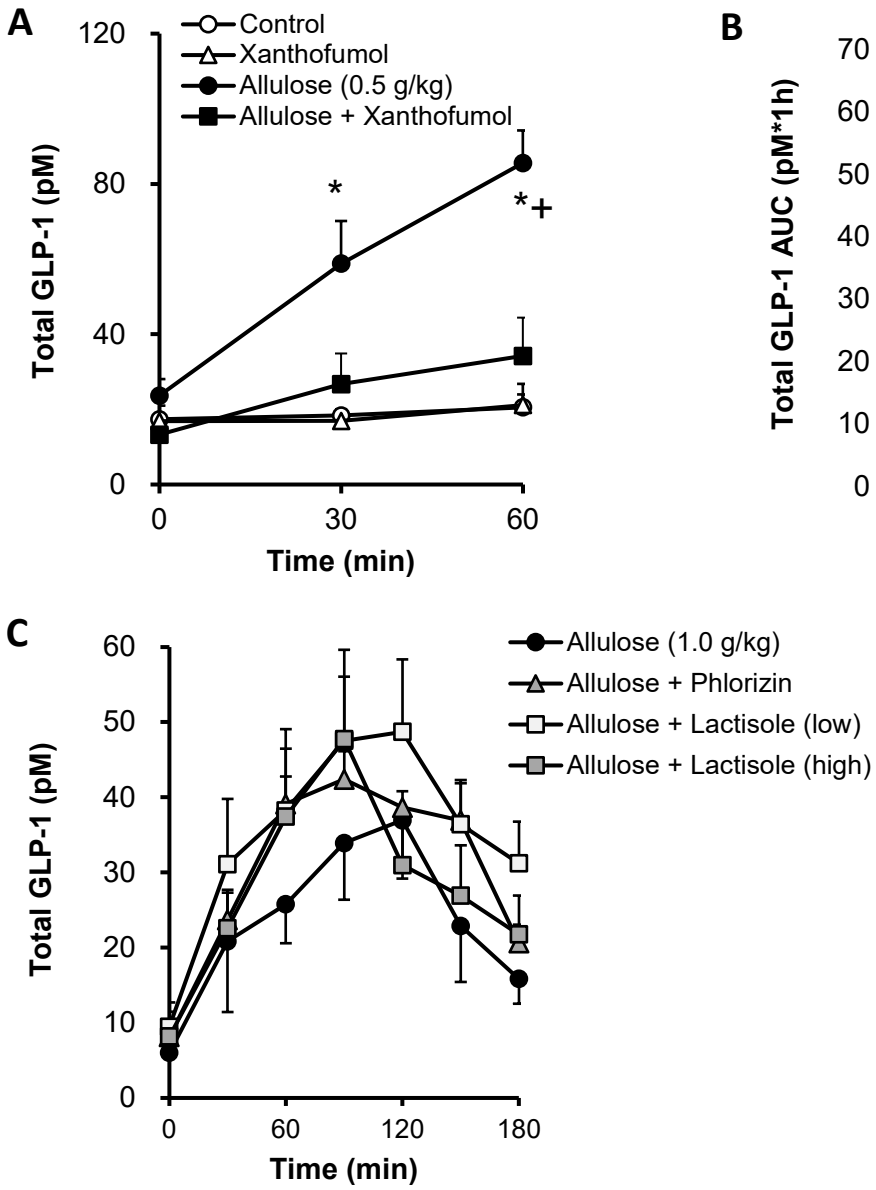

A
Intraperitoeneal administration
Total GLP-1 (pM)
Time (min)
Control
Allulose (0.5 g/kg)
Allulose (1.0 g/kg)
B
Duodenal administration
Total GLP-1 (pM)
Time (min)
Control
Allulose (0.5 g/kg)
Allulose (1.0 g/kg)
C
Ileal administration
Total GLP-1 (pM)
Time (min)
Control
Allulose (0.5 g/kg)
Glucose (0.5 g/kg)

Figure 4


A
Control
Xanthofumol
Allulose (0.5 g/kg)
Allulose + Xanthofumol
Total GLP-1 (pM)
120
80
40
0
0
30
60
Time (min)
*
*+
B
Total GLP-1 AUC (pM*1h)
70
60
50
40
30
20
10
0
#
Control
Xanthofumol
Allulose
Allulose+Xanthofumol
C
Allulose (1.0 g/kg)
Allulose + Phlorizin
Allulose + Lactisole (low)
Allulose + Lactisole (high)
Total GLP-1 (pM)
60
50
40
30
20
10
0
0
60
120
180
Time (min)