K$_{ATP}$ channel as well as SGLT1 participates in GIP secretion in the diabetic state

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Abstract

Glucose-dependent insulino tropic polypeptide (GIP), a gut hormone secreted from intestinal K-cells, potentiates insulin secretion. Both K-cells and pancreatic β-cells are glucose-responsive and equipped with a similar glucose-sensing apparatus that includes glucokinase and an ATP-sensitive K$^+$ (K$_{ATP}$) channel comprising KIR6.2 and sulfonylurea receptor 1. In absorptive epithelial cells and enteroendocrine cells, sodium glucose co-transporter 1 (SGLT1) is also known to play an important role in glucose absorption and glucose-induced incretin secretion. However, the glucose-sensing mechanism in K-cells is not fully understood. In this study, we examined the involvement of SGLT1 (SLCSA1) and the K$_{ATP}$ channels in glucose sensing in GIP secretion in both normal and streptozotocin-induced diabetic mice. Glimepiride, a sulfonylurea, did not induce GIP secretion and pretreatment with diazoxide, a K$_{ATP}$ channel activator, did not affect glucose-induced GIP secretion in the normal state. In mice lacking K$_{ATP}$ channels (Kir6.2$^{-/-}$ mice), glucose-induced GIP secretion was enhanced compared with control (Kir6.2$^{+/+}$) mice, but was completely blocked by the SGLT1 inhibitor phlorizin. In Kir6.2$^{-/-}$ mice, intestinal glucose absorption through SGLT1 was enhanced compared with that in Kir6.2$^{+/+}$ mice. On the other hand, glucose-induced GIP secretion was enhanced in the diabetic state in Kir6.2$^{+/+}$ mice. This GIP secretion was partially blocked by phlorizin, but was completely blocked by pretreatment with diazoxide in addition to phlorizin administration. These results demonstrate that glucose-induced GIP secretion depends primarily on SGLT1 in the normal state, whereas the K$_{ATP}$ channel as well as SGLT1 is involved in GIP secretion in the diabetic state in vivo.

Key Words

- K$_{ATP}$ channel
- SGLT1
- GIP secretion

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Introduction

Incretins, the gut hormones such as glucose-dependent insulino tropic polypeptide (GIP) and glucagon-like peptide (GLP1), which are secreted from enteroendocrine K-cells and L-cells, respectively, following meal ingestion stimulate insulin secretion in a glucose-concentration-dependent manner to prevent postprandial hyperglycemia (Baggio & Drucker 2007, Seino et al. 2010). A recent study has shown that an alternative form of GIP lacking the C-terminus is also secreted and expressed in pancreatic α-cells (Fujita et al. 2010). The beneficial effect of incretins on insulin secretion has provided the basis for incretin-based diabetes therapies, including dipeptidyl peptidase 4 (DPP4) inhibitors and GLP1 receptor agonists, which are currently in use worldwide (Drucker & Nauck 2006). Incretins are known to be secreted through stimulation of nutrients including carbohydrates, fats, and amino acids (Diakogiannaki et al. 2012). Whereas GLP1 secretion is regulated by hormonal and neural inputs as well as by nutrients, GIP secretion is mainly due to direct stimulation of these nutrients (Brubaker 1991, Rocca & Brubaker 1999, Jang et al. 2007).

In absorptive epithelial cells in the intestine, there are two glucose transport systems: sodium-dependent glucose transport mediated by a sodium-glucose co-transporter 1 (SGLT1) present in the brush-border (Takata et al. 1992, Martín et al. 1996, Wright 1998) and facilitated glucose transport mediated by facilitative glucose transporter 2 (GLUT2) in the basolateral membrane (Kellett 2001). Glucose enters the absorptive cells by SGLT1 and exits into the blood by GLUT2. It has been reported that GLUT2 knockout mice exhibited reduced GLP1 secretion but did not show a change in GIP secretion in response to oral glucose loading (Cani et al. 2007). In contrast, studies of SGLT1-deficient mice (Gorboulev et al. 2012) and SGLT1 inhibitors (Sykes et al. 1980, Powell et al. 2013) revealed that only the early-phase GLP1 secretion at 5 min after glucose loading is significantly reduced, whereas GIP secretion is almost completely abolished. The results from these studies indicate that SGLT1 is critical in glucose-induced incretin secretion, especially GIP secretion. It has been shown that K-cells express GLUT2, glucokinase, and an ATP-sensitive K (KATP) channel consisting of Kir6.2 and sulfonylurea receptor 1 (SUR1) subunits, identical to those expressed in pancreatic β-cells (Parker et al. 2009). These findings indicate that the glucose-sensing apparatus in K-cells may be similar to that expressed in β-cells.

We previously reported that Kir6.2-deficient (Kir6.2−/−) mice entirely lack glucose-induced insulin secretion (GIIS) as assessed by perfusion of pancreatic islets (Miki et al. 1998). In contrast to GIIS, GIP secretion in response to oral glucose loading in Kir6.2−/− mice is somewhat enhanced, compared with that in Kir6.2+/+ mice (Miki et al. 2005). This indicates that the KATP channels in K-cells are activated and involved in the suppression of glucose-induced GIP secretion in the physiological state. However, the link between SGLT1 and KATP channels in GIP secretion in the normal state and diabetic state is not understood.

In this study, we demonstrate that in mice in the normal state, SGLT1 is principally responsible for glucose-induced GIP secretion; however, in the diabetic state, the KATP channel is also involved in its secretion.

Materials and methods

Materials

Standard rodent normal chow, dextrin, and high-sucrose diet were used as previously reported (Sakamoto et al. 2012, Seino et al. 2013). Dextrin hydrate, glimepiride, diazoxide, α-methyl-d-(-)-glucoside (αMG) were purchased from Wako, Osaka, Japan. Streptozotocin (STZ), phlorizin, and D-xylene were purchased from Sigma-Aldrich.

Mice

Kir6.2−/− mice were generated as described previously (Miki et al. 1998). As the Kir6.2−/− mice had been backcrossed with the C57BL/6 mouse strain for more than five generations, WT (Kir6.2+/+) C57BL/6J mice were rendered diabetic by a single injection of STZ (150 mg/kg body weight) after a 16 h fast. Control mice received injections of an equal volume of saline. Two months after STZ injection, the mice with plasma glucose concentrations higher than 11 mmol/l under the fasted state were selected and used for the experiments together with the saline-injected controls.

Induction of diabetes

Two-month-old male Kir6.2+/+ mice were rendered diabetic by i.p. injection of STZ (150 mg/kg body weight) after a 16 h fast. Control mice received injections of an equal volume of saline. Two months after STZ injection, the mice with plasma glucose concentrations higher than 11 mmol/l under the fasted state were selected and used for the experiments together with the saline-injected controls.

Plasma biochemical analyses

Blood glucose levels were measured with ANSENSE II (Bayer Medical). Plasma insulin levels were determined using an ELISA Kit (Morinaga, Tokyo, Japan). Plasma total
GIP and GLP1 levels were determined using a GIP (total) ELISA Kit (Merck Millipore, Billerica, MA, USA) and an electrochemiluminescent sandwich immunoassay (Meso Scale Discovery, Gaithersburg, MD, USA) respectively.

**Oral glucose, αMG, and saccharin administration**

Procedure-naive mice were deprived of food for 16 h and oral administration of 6 g/kg body weight D-glucose or 6.5 g/kg αMG (an equimolar amount to 6 g/kg glucose) or 0.05 g/kg sodium saccharin dehydrate by gavage was used in these experiments. After the oral administration, blood was collected at 0 and 15 min to measure blood glucose, plasma insulin, and plasma GIP levels.

**Oral phlorizin administration**

Mice were deprived of food for 16 h and then administered 6 g/kg body weight D-glucose with or without 500 mg/kg body weight phlorizin administered orally.

**Diazoxide and glucose administration**

After food deprivation for 16 h, 40 or 240 mg/kg body weight diazoxide was administered orally. Ninety minutes after diazoxide administration, 6 g/kg body weight D-glucose was administered orally.

**Voluntary feeding**

As described previously (Seino et al. 2013), both Kir6.2+/+ and Kir6.2−/− mice were trained for the experiments of voluntary feeding with standard chow or dextrin. They were deprived of food for 16 h and then given free access to standard chow or dextrin for the voluntary feeding experiments.

**Oral D-xylose administration**

Blood samples were collected 20, 60, 90, and 120 min after xylose (1 g/kg) was administered orally to determine xylose concentration. Xylose assay was carried out as previously described by Conarello et al. (2007).

**Immunohistochemistry**

The animals were killed and the duodenum from each animal was removed, fixed in 4% paraformaldehyde (PFA), and embedded in Tissue-Tek O.C.T. compound (Sakura Finetechnical, Tokyo, Japan). The tissue was frozen and stored at −80°C. The sections were cut at 10 μm thickness and incubated overnight at 4°C with primary antibodies against SGLT1 (1:200, sc-20582, Santa Cruz Biotechnology) and GIP (1:500, Y101, Yanaihara, Shizuoka, Japan), followed by 90 min incubation in Alexa Fluor-conjugated secondary antibody (1:1000, Alexa Fluor 546 or Alexa Fluor 647, Invitrogen) at room temperature. Images were taken using an HS BZ-9000 fluorescent microscope system (Keyence Corporation, Osaka, Japan).

**Isolation of tissue RNA and quantitative real-time RT-PCR**

Total RNA was extracted from the duodenum or the jejunum using RNAiso Plus (Takara Bio, Inc., Otsu, Shiga, Japan) as previously reported (Seino et al. 2008). One microgram of total RNA was reverse transcribed using the ReverTra Ace qPCR Kit (Toyobo, Osaka, Japan). After cDNA synthesis, quantitative real-time PCR was carried out in 25 μl reactions containing THUNDERBIRD qPCR Mix (Toyobo) using Mx3000 (Stratagene, La Jolla, CA, USA). The following oligonucleotide primers were used: mouse SGLT1, 5′-CATTC-CAGACGTGCACCTGTAC-3′ (sense) and 5′-TCCAGGTC-GATTGCGTCTTC-3′ (antisense). The mRNA levels were normalized with respect to those of β-actin mRNA.

**Statistical analysis**

Data are presented as mean ± S.E.M. Statistical analysis was performed by unpaired, two-tailed Student’s t-test or one-way or two-way ANOVA with Holm-Sidak multiple comparison procedure.
GIP secretion and \( K_{\text{ATP}} \) channel

Results

Metabolism of glucose in K-cells is not essential for GIP secretion

We first examined GIP secretion by oral administration of metabolizable (glucose), nonmetabolizable sugar (\( z \)-MG), or artificial sweetener (sodium saccharin dehydrate) (Fig. 1). Both glucose and \( z \)-MG stimulated GIP secretion significantly, whereas saccharin did not induce GIP secretion. Plasma GIP levels induced by glucose administration were higher than those induced by \( z \)-MG administration at 15 min. These results indicate that metabolism of glucose in K-cells is not essential for sugar-induced GIP secretion and that stimulation of the sweet taste receptor is not involved in GIP secretion.

\( K_{\text{ATP}} \) channels are not involved in glucose-induced GIP secretion in the normal state

To investigate whether \( K_{\text{ATP}} \) channels are involved in GIP secretion in vivo, we examined the effects of sulfonylurea and the \( K_{\text{ATP}} \) channel activator diazoxide on GIP secretion.

Oral administration of glimepiride (1 or 10 mg/kg), a sulfonylurea, did not change plasma GIP levels at 15 and 60 min, although plasma insulin levels were significantly elevated and blood glucose concentrations were decreased (Fig. 2a, b, and c). Blood glucose levels during oral glucose tolerance test (OGTT) were significantly elevated by pretreatment with diazoxide (Fig. 2d). GIIS was partially or completely suppressed by pretreatment with diazoxide (40 or 240 mg/kg) respectively (Fig. 2e). Glucose-induced GIP secretion was not blocked at all by pretreatment with diazoxide (Fig. 2f). However, the basal level of GIP was not decreased by pretreatment with vehicle, but was decreased significantly by pretreatment with diazoxide (Fig. 2g).

GIP secretion by carbohydrates is enhanced in \( \text{Kir6.2}^{\text{–/–}} \) mice

We then estimated the role of \( K_{\text{ATP}} \) channels in carbohydrate-induced GIP secretion. We examined GIP secretion in \( \text{Kir6.2}^{\text{+/+}} \) mice and \( \text{Kir6.2}^{\text{–/–}} \) mice deficient in the Kir6.2 component of \( K_{\text{ATP}} \) channels. Oral administration of glucose elicited significant GIP secretion in both \( \text{Kir6.2}^{\text{+/+}} \) mice and \( \text{Kir6.2}^{\text{–/–}} \) mice at 15 min. Plasma GIP levels in \( \text{Kir6.2}^{\text{–/–}} \) mice at 15 min after glucose loading were significantly higher than those in \( \text{Kir6.2}^{\text{+/+}} \) mice (Fig. 3a), and are consistent with results described in a previous report (Miki et al. 2005). Plasma GIP levels at 15 min with voluntary
feeding on dextrin were higher than those with voluntary feeding on standard chow in both Kir6.2+/+ mice and Kir6.2−/− mice, indicating that carbohydrate is a powerful GIP secretagogue. Interestingly, plasma GIP levels at 15 min in Kir6.2−/− mice with voluntary feeding on dextrin were significantly higher than those in Kir6.2+/+ mice (Fig. 3b). These results indicate that glucose-induced GIP secretion is enhanced in Kir6.2−/− mice compared with that in Kir6.2+/+ mice. Plasma GLP1 levels in Kir6.2−/− mice at 5 min after oral glucose loading did not differ from those in Kir6.2+/+ mice (Fig. 3c).

**Phlorizin completely blocks glucose-induced GIP secretion in both Kir6.2+/+ mice and Kir6.2−/− mice in the normal state**

We investigated the involvement of SGLT1 in glucose-induced GIP secretion by using phlorizin, a well-known inhibitor of SGLT1 (Alvarado & Crane 1962). Phlorizin inhibited the elevation of blood glucose levels in both Kir6.2+/+ mice and Kir6.2−/− mice (Fig. 4a). Phlorizin completely blocked glucose-induced GIP secretion at 15 min not only in Kir6.2+/+ mice but also in Kir6.2−/− mice (Fig. 4b).

**SGLT1 expression and function are enhanced in Kir6.2−/− mice**

Immunohistochemistry revealed that SGLT1 was distributed in the apical side of the duodenal absorptive epithelial cells and K-cells in both in Kir6.2+/+ mice and in Kir6.2−/− mice (Fig. 5a and b), as previously reported (Gorboulev et al. 2012). Interestingly, the expression levels of Sglt1 mRNA in the duodena of Kir6.2−/− mice were significantly higher than those in the duodena of Kir6.2+/+ mice under fasted conditions (Fig. 5c). On the other hand, the expression levels of Sglt1 mRNA in the jejuna were not different between Kir6.2+/+ mice and Kir6.2−/− mice (Fig. 5c). Since xylose is absorbed through SGLT1 in the intestine and is not metabolized, the xylose absorption test reflects the activity of SGLT1 (Fujita et al. 1998). We then measured plasma xylose concentrations. Plasma xylose concentrations after oral administration of xylose in Kir6.2−/− mice were higher than those in Kir6.2+/+ mice (Fig. 5d), indicating that xylose is absorbed through SGLT1 in Kir6.2−/− mice at a higher rate than in Kir6.2+/+ mice.

Long-term exposure to a high-sugar diet is known to increase the expression levels of Sglt1 mRNA (Miyamoto et al. 1993). To clarify whether the KATP Channel is required for the adaptive increase in Sglt1 mRNA, mice were fed with high-sucrose diet for 5 weeks. The high-sucrose diet
increased the expression levels of Sglt1 mRNA in the duodenum of both Kir6.2+/+ mice (Fig. 5e) and Kir6.2−/− mice (Fig. 5f). This result indicates that regulation of the expression of Sglt1 by intraluminal carbohydrate concentrations is K_{ATP}-channel-independent.

Both SGLT1 and K_{ATP} channels are involved in GIP secretion in the diabetic state

In STZ diabetic Kir6.2+/+ mice with severe hyperglycemia, plasma insulin levels were decreased markedly under fasted conditions (Fig. 6a and b). The expression levels of Sglt1 mRNA in the duodenum were higher in the STZ diabetic mice than those in control mice (treated with saline) (Fig. 6c).

In accordance with the increased Sglt1 mRNA expression, GIP secretion after glucose loading was significantly enhanced at 15 min in STZ-treated mice (Fig. 6d). In contrast to the normal state (Fig. 4b), plasma GIP levels were significantly elevated 15 min after concomitant administration of glucose and phlorizin in the diabetic mice (Fig. 6e). To determine whether the K_{ATP} channel is involved in glucose-induced GIP secretion in diabetic mice, they were pretreated with diazoxide (240 mg/kg) and then administered glucose and phlorizin concomitantly.

Interestingly, phlorizin completely blocked the glucose-induced GIP secretion in the diabetic mice after pretreatment with diazoxide (Fig. 6f).

Discussion

In the present study, we show that SGLT1 is critical for glucose-induced GIP secretion in the diabetic state, as well as in the normal state, while the K_{ATP} channels participate in GIP secretion only in the diabetic state.

The incretins GIP and GLP1 are essential for maintaining systemic glucose homeostasis by amplifying insulin secretion. Enhancement of incretin action in insulin secretion is a therapeutic strategy to improve glycemic control in type 2 diabetes. It has been shown that in type 2 diabetes, the insulin secretory response to GLP1 is somewhat retained whereas the response to GIP is severely impaired (Nauck et al. 1993, Seino et al. 2010). Thus, it has been thought that GLP1-induced insulin secretion is the main contributor to improvement of glycemic control by incretin therapy. However, a recent study has indicated that GIP-induced insulin secretion is also involved in the therapeutic effect in type 2 diabetes (Woele et al. 2012). In addition, GIP-overexpressing mice (Kim et al. 2012) and mice with GIP hypersecretion (Fukami et al. 2012) both exhibit good glycemic control due to excessive early-phase insulin secretion. These findings indicate that GIP-induced insulin secretion also is a contributor to improvement of glycemic control by incretin therapy.

GIP secretion is regulated by various nutrients, among which glucose is particularly important (Baggio & Drucker 2007). Glucose is transported across the apical membrane by SGLT1 (Wright 1998). SGLT1 is expressed at high levels in the upper intestine, especially the duodenum, and at moderate to low levels in the lower intestine, with an expression pattern similar to that of GIP-secreting K-cells.
It has been shown recently that entry of glucose into intestinal epithelia is required for glucose-induced GIP secretion (Moriya et al. 2009, Gorboulev et al. 2012). The results of these studies indicate that activation of SGLT1 induces GIP enhancement and/or increases glucose uptake into epithelia.

GIP-secreting K-cells and pancreatic \( \beta \)-cells are both glucose-responsive. In fact, both K-cells and \( \beta \)-cells are equipped with a similar glucose-sensing apparatus including GLUT2, glucokinase, and K\(_{\text{ATP}}\) channels comprising KIR6.2 and SUR1 (Parker et al. 2009). In pancreatic \( \beta \)-cells, glucose is transported through GLUT2 and metabolized to generate ATP. The increase in ATP concentration closes the K\(_{\text{ATP}}\) channels, depolarizing the \( \beta \)-cell membrane, inducing Ca\(^{2+}\) influx through voltage-dependent calcium channels thereby triggering insulin secretion. The closure of the K\(_{\text{ATP}}\) channels is essential for GIIS (Seino et al. 2011). It has been shown that the K\(_{\text{ATP}}\) channel inhibitor sulfonylurea directly stimulates GIP secretion in isolated K-cells (Parker et al. 2009) and that SGLT1 is required for glucose-induced GIP secretion in a study of SGLT1 knockout mice \( \text{in vivo} \) (Gorboulev et al. 2012). However, the link between SGLT1

**Figure 5**

SGLT1 expression and activity in \( \text{Kir}6.2^{+/+} \) mice and \( \text{Kir}6.2^{-/-} \) mice. Representative immunohistochemistry for SGLT1 (red), GIP (green) in the duodenum in (a) \( \text{Kir}6.2^{+/+} \) mice and (b) \( \text{Kir}6.2^{-/-} \) mice (scale bars; 100 \( \mu \)m). (c) mRNA expression of Sglt1 in the duodenum and jejunum in \( \text{Kir}6.2^{+/+} \) mice (white bars; duodenum \( n = 9 \), jejunum \( n = 5 \)) and \( \text{Kir}6.2^{-/-} \) mice (black bars; duodenum \( n = 11 \), jejunum \( n = 4 \)) under fasted conditions. (d) Plasma xylose concentrations during the oral D-xylose administration test in \( \text{Kir}6.2^{+/+} \) mice (open circles; \( n = 5 \)) and \( \text{Kir}6.2^{-/-} \) mice (filled squares; \( n = 12 \)). (e) mRNA expression of Sglt1 in the duodenum in the fed state after 5 weeks loading with standard chow (\( n = 6 \)) or a high-sucrose diet (HSD) (\( n = 6 \)) in \( \text{Kir}6.2^{+/+} \) mice. (f) mRNA expression of Sglt1 in the duodenum in the fed state after 5 weeks loading with standard chow (\( n = 12 \)) or HSD (\( n = 12 \)) in \( \text{Kir}6.2^{-/-} \) mice. (*\( P < 0.05 \), **\( P < 0.01 \), ***\( P < 0.001 \) comparing \( \text{Kir}6.2^{+/+} \) mice with \( \text{Kir}6.2^{-/-} \) mice) (\( P < 0.05 \) relative to standard chow). Data are expressed as means \( \pm \) s.e.m.
and K$_{\text{ATP}}$ channels in glucose-induced GIP secretion is not known. It has also been reported that the expression levels of SGLT1 in small intestine were increased in STZ-induced diabetic rats (Burant et al. 1994), but the relationship between SGLT1 expression and glucose-induced GIP secretion was not investigated. In this study, we clarify for the first time, to our knowledge, in vivo that glucose-induced GIP secretion in the normal state is dependent primarily on an SGLT1-dependent mechanism, while glucose-induced GIP secretion in the diabetic state involves both SGLT1- and K$_{\text{ATP}}$ channel-dependent mechanisms.

There have been a few reports showing that sulfonylureas have no effects on GIP secretion in patients with type 2 diabetes. However, the patients examined in these studies exhibited mild-to-moderate hyperglycemia (Eli-Ouaghlidi et al. 2007, Yabe et al. 2010, Stephens et al. 2011). Considering these together with the present findings, the stimulatory effect of K$_{\text{ATP}}$ channels on GIP secretion may well require a threshold level of glycemia. The mechanism of involvement of the K$_{\text{ATP}}$ channels in GIP secretion in K-cells is unknown, but deserves consideration. Given the rapid turnover of intestinal epithelia (Ferraris et al. 1992), it is possible that ATP consumption is greatly increased and causes the K$_{\text{ATP}}$ channels to remain in the closed state under normal conditions. On the other hand, in the hyperglycemic state, glucose metabolism in K-cells is impaired, reducing ATP production to levels similar to those in diabetic β-cells. Under such conditions, the K$_{\text{ATP}}$ channels are in the open state, in which inhibition of the channels is effective.

We have shown that in the normal state, the K$_{\text{ATP}}$ channels are not involved in glucose-induced GIP secretion. Kir6.2$^{-/-}$ mice are the animal model of loss-of-function mutation of the K$_{\text{ATP}}$ channel. However, we found that in Kir6.2$^{-/-}$ mice, glucose-induced GIP secretion was enhanced compared with that in Kir6.2$^{+/+}$ mice in the normal state. The K$_{\text{ATP}}$ channel participates in the basal level of GIP secretion in Kir6.2$^{+/+}$ mice (Fig. 2g). On the other hand, in Kir6.2$^{-/-}$ mice, the basal level of GIP secretion is considered to be maintained independently of the K$_{\text{ATP}}$ channel. In fact, as shown in Fig. 4b, the basal level of GIP is significantly reduced by phlorizin treatment, indicating that SGLT1 is involved in basal GIP secretion in Kir6.2$^{-/-}$ mice.

K-cells and L-cells are present predominantly in the upper and lower intestine respectively (Polak et al. 1973, Thomas et al. 1977, Damholt et al. 1999, Baggio & Drucker 2007, Egerod et al. 2012). Increased expression levels and
activity in the duodenum in \textit{Kir6.2}^{-/-} mice could thus account for the enhanced glucose-induced GIP secretion. On the other hand, glucose-induced GLP1 secretion was not altered in \textit{Kir6.2}^{-/-} mice, most probably due to the unchanged expression levels of SGLT1 in the jejunum. Results from recent studies have indicated that the nutrient-sensing mechanism differs in the duodenum and in the jejunum (Seino et al. 2008, Breen et al. 2013), and that the nutrient-sensing system in K-cells and L-cells differs in the upper and lower intestine.

Gain-of-function mutations of the K\textsubscript{ATP} channel cause neonatal diabetes and loss-of-function mutations of the K\textsubscript{ATP} channel cause persistent hyperinsulinemic hypoglycaemia of infancy (McTaggart et al. 2010). In patients carrying gain-of-function mutations of the K\textsubscript{ATP} channel, sulfonylurea stimulates insulin secretion by closing the K\textsubscript{ATP} channels of the pancreatic \beta-cells, but neither glucose-induced GIP nor GLP1 secretion is changed after sulfonylurea treatment (Pearson et al. 2006). It is of great interest to examine whether hypersecretion of GIP through SGLT1 in patients with loss-of function mutations contributes to hyperinsulinism in the disease.

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**Declaration of interest**
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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**Author contribution statement**

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