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MINI REVIEW

Carbohydrate-induced secretion of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1

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ABSTRACT

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are the incretin hormones secreted from enteroendocrine K-cells and L-cells, respectively, by oral ingestion of various nutrients including glucose. K-cells, L-cells and pancreatic β-cells are glucose-responsive cells with similar glucose-sensing machinery including glucokinase and an adenosine triphosphate-sensitive K^+ channel comprising KIR6.2 and sulfonylurea receptor 1. However, the physiological role of the adenosine triphosphate-sensitive K^+ channel in GIP secretion in K-cells and GLP-1 secretion in L-cells is not elucidated. Recently, it was reported that GIP and GLP-1-producing cells are present also in pancreatic islets, and islet-derived GIP and GLP-1 contribute to glucose-induced insulin secretion from pancreatic β-cells. In this short review, we focus on GIP and GLP-1 secretion by monosaccharides, such as glucose or fructose, and the role of the adenosine triphosphate-sensitive K^+ channel in GIP and GLP-1 secretion.

INTRODUCTION

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are incretin hormones that amplify glucose-induced insulin secretion from pancreatic β-cells. Enteral ingestion of nutrition, such as carbohydrate, fat and protein, induces GIP secretion from K-cells and GLP-1 secretion from L-cells. GIP stimulates glucagon secretion from pancreatic α-cells, and promotes uptake of glucose and fat, and also accumulates triglyceride into adipose tissue. In contrast, GLP-1 suppresses glucagon secretion and inhibits gastric emptying[1,2]. These findings suggest that GLP-1 is the more suitable target for the improvement of glucose metabolism. However, L-cells are present mostly in the jejunum, ileum and colon, whereas K-cells are predominantly present in duodenum. Furthermore, GIP secretion from the duodenum plays an important role in regulating postprandial glycemic levels through its glucose-dependent potentiation of early-phase insulin secretion. GLP-1 secretion by nutrients is biphasic[3], and the transient early-phase GLP-1 secretion is considered to be mediated by the vagal nerve[4]. In the present review, we discuss recent advances in understanding the regulatory mechanisms involved in the secretion of GIP and GLP-1 stimulated by carbohydrates, including artificial sweeteners.

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GIP AND GLP-1 SECRETION INDUCED BY GLUCOSE

Plasma GIP and GLP-1 levels are elevated after oral glucose ingestion in both humans and rodents[3,5,6]. However, intravenous or intraperitoneal administration of glucose does not increase plasma GIP or GLP-1 levels[3,5,7]. In humans, plasma GIP levels peak within 5 min, whereas plasma GLP-1 levels peak at 30 min after glucose loading[3]. The mechanism and role of GIP secretion by glucose is therefore distinct from that of GLP-1 secretion.

ROLE OF TASTE RECEPTORS IN SECRETION OF GIP AND GLP-1

It has been reported that artificial sweeteners contribute to the secretion of incretins[8].

Sweeteners bind to sweet taste receptors, which consist of the heterodimers of the G-protein-coupled type 1 taste receptors (T1R2 and T1R3) to activate the signal cascade in which α-gustducin is involved. Artificial sweeteners stimulate two signal transduction pathways: a cyclic adenosine monophosphate-dependent pathway and a phospholipase C-Ins(1,4,5)P3-depen-

dent pathway. The intracellular Ca concentration is increased by these pathways' activation, which induces membrane depolarization[9]. Artificial sweeteners do not affect GIP secretion in mice, rats and humans[10–12], and glucose-induced GIP secretion is maintained in α-gustducin deficient mice[13]. Thus, the sweet receptor appears to play a minor role in the regulation of GIP secretion. Indeed, in primary murine K-cells, the expression of the sweet taste receptor is low, and the artificial sweetener sucralose does not stimulate GIP secretion from primary proximal small intestinal culture[14]. In contrast, GLP-1 secretion by glucose is severely impaired in α-gustducin-deficient mice[13], indicating that GLP-1 secretion is induced through the sweet taste signal. However, in primary murine L-cells, the expression of the sweet taste receptor is very low[15], and artificial sweetener does not induce GLP-1 secretion from either primary proximal small intestinal culture or isolated perfused rat small intestine[15,16]. Furthermore, in α-gustducin-deficient mice, glucose uptake in response to luminal carbohydrate concentrations through sodium-dependent glucose transporter (SGLT1) in enterocytes, which plays an important role in glucose-induced GIP and GLP-1 secretion, is also impaired[8]. Therefore, the contribution of α-gustducin to the regulation of secretion of GLP-1 requires further exploration.

ROLE OF FRUCTOSE TRANSPORTER IN SECRETION OF GIP AND GLP-1

Fructose is transported by a facilitative glucose transporter 5 (GLUT5) localized in the apical membrane of enterocytes and is metabolized mainly in liver. GLUT5 is highly expressed in pancreatic β-cells, K-cells and L-cells[14,15]. In mice, rats and humans, fructose does not significantly stimulate GIP secretion under normal conditions[17–19]. However, in insulin resistance *ob*/*ob* diabetic mice and streptozotocin (STZ)-induced insulin-deficient diabetic mice, fructose significantly induces GIP secretion[17,20]. In primary proximal small intestinal culture, fructose stimulates GIP secretion, although the GIP secretory response to fructose is lower than that to glucose[14]. Therefore, the mechanism of fructose-induced GIP secretion remains largely to be elucidated. In contrast, fructose significantly stimulates GLP-1 secretion in mice, rats and humans[17,18]. These results accord with an *in vitro* study using a GLUTag cell line showing that fructose significantly stimulates GLP-1 secretion[21]. It is reported that fructose directly induces insulin secretion in a glucose-dependent manner[17,22]. Whether or not fructose is metabolized in K-cells or L-cells, and the differential regulatory machinery for the secretion of GIP and GLP-1 by fructose should be investigated in further study.

SGLT1 CONTRIBUTION TO GLUCOSE-INDUCED GIP AND GLP-1 SECRETION

SGLT1, a member of the SLC5 family, localizes in the brush border or apical membrane of enterocytes, and plays an important role in the transfer of glucose or galactose from intestinal lumen into intestinal cytosol when accompanied by sodium[23]. The expression of SGLT1 is highest in the duodenum, and is reduced in the lower intestine[24]. Thus, the expression pattern of SGLT1 is similar to that of GIP secreting K-cells[25]. The mechanism of glucose-induced GLP-1 secretion has been investigated by *in vitro* study using the GLUTag cell line or primary murine L-cells[15,21,26]. It has been clarified that GLP-1 secretion is mediated by an influx of sodium through SGLT1, which induces membrane depolarization and voltage dependent-Ca^{2+} entry[15,21,26]. In contrast, the mechanism of glucose-induced GIP secretion has not been characterized, because there have been few cell lines suitable for analysis.

Recently, the contribution of SGLT1 to glucose-induced GIP and GLP-1 secretion *in vivo* has been analyzed by using SGLT1 substrate, SGLT1 inhibitor and mice deficient for SGLT1[10,27–29]. Oral administration of a SGLT1 substrate, α-methyl-D-glucopyranoside, which induces sodium influx but is not metabolized, stimulates GIP secretion[27]. Glucose-induced GIP secretion is completely blocked in mice administered glucose combined with the SGLT1 inhibitor phlorizin[10]. Furthermore, glucose-induced GIP secretion is completely abolished in SGLT1-deficient mice, and mice treated with a dual SGLT1 and SGLT2 inhibitor[28,29]. These findings show that glucose-induced GIP secretion is SGLT1-dependent.

In contrast, GLP-1 secretion is only temporally induced by α-methyl-D-glucopyranoside administration[27]. Glucose-induced GLP-1 secretion is completely blocked at 5 min after glucose load in SGLT1-deficient mice, and in dual SGLT1 and SGLT2 inhibitor treated-mice[28,29]. However, GLP-1 oversecretion is observed from 1 to 6 h after glucose administration both in SGLT1-deficient mice, and in dual SGLT1 and SGLT2 inhibitor treated-mice[29]. These findings show that glucose-induced GLP-1 secretion includes two phases; an early-phase, which is SGLT1-dependent, and a late-phase, which is SGLT1-independent. GLP-1 secretion by nutrients is well known to be biphasic[3], and the transient early-phase GLP-1 secretion is partially mediated by the vagal nerve[4]. In addition, it is considered that early-phase GLP-1 is secreted from L-cells in the proximal small intestine, and that late-phase GLP-1 is secreted from the distal intestine. Thus, differences in expression of SGLT1 along the intestinal tract and the machinery of GLP-1 secretion requires detailed examination in future study.

Interestingly, galactose, another monosaccharide transported through SGLT1, induces secretion of both GIP and GLP-1 *in vivo*[3,30,31].

ADENOSINE TRIPOSPHATE-SENSITIVE K CHANNEL CONTRIBUTION TO GLUCOSE-INDUCED GIP AND GLP-1 SECRETION

The adenosine triphosphate-sensitive K (K_{ATP}) channel consists of Kir6.2 and sulfonylurea receptor 1 (SUR1) subunits. In pancreatic β-cells, the K_{ATP} channel plays an essential role in glucose-induced insulin secretion. Glucose transported through GLUT2 is metabolized, and the resulting increase in the intracellular adenosine triphosphate/adenosine diphosphate ratio

leads to closure of the K_{ATP} channel and membrane depolarization, influx of Ca through the voltage-dependent Ca channel, and hormone secretion. It has been reported that a glucose-sensing molecule, such as GLUT2, glucokinase or K_{ATP} channels, are expressed in primary murine K- or L-cells, as in pancreatic ß-cells[14,15]. It also has been reported that tolbutamide, a sulfonylurea, directly stimulates GIP and GLP-1 secretion from primary small intestine culture or colon culture, respectively[14,15]. However, oral sulfonylurea therapy does not potentiate secretion of GIP or GLP-1 during oral glucose tolerance tests (OGTT) either in healthy subjects or type 2 diabetic patients, or in subjects with K_{ATP} channel gain-of-function mutations[32–34]. In addition, neither GIP nor GLP-1 secretion during OGTT differ between subjects with heterozygous glucokinase gene mutations and control subjects[35]. Therefore, the physiological relevance of glucose-sensing molecules expressed in K- or L-cells remains unclear.

In contrast, the contribution of the K_{ATP} channel to glucose-induced GIP secretion *in vivo* was recently reported[10]. Glucose-induced GIP secretion is enhanced in STZ-induced diabetic mice and rats[10,36]. Although the SGLT1 inhibitor phlorizin completely blocks glucose-induced GIP secretion in normoglycemic mice, in STZ-diabetic mice, phlorizin only partially blocks glucose-induced GIP secretion, but completely blocks it when combined with pretreatment with the K_{ATP} channel activator diazoxide[10]. These results suggest that under normal conditions, glucose-induced GIP secretion is SGLT1-dependent, whereas under STZ-induced hyperglycemic conditions, glucose-induced GIP secretion is dependent on both SGLT1 and the K_{ATP} channel *in vivo*. This hypothesis is summarized in Figure 1; the metabolic pathway in K-cells *in vitro* under normal and hyperglycemic condition requires investigation in future study.

The GLP-1 secretion in response to high-dose sulfonylurea has been shown in perfused rat small intestine experiments[16,37]. The authors suggest that a K_{ATP} channel-dependent pathway plays an important role in glucose-induced GLP-1 secretion when glucose passes through GLUT2 in L-cells. This accords with the fact that glucose-induced GLP-1 secretion, but not GIP secretion, is reduced in GLUT2-deficient mice[38]. Another group reported that GLP-1 is secreted in response to sulfonylurea from colon explants, but not from ileum explants in mice[39]. The differential mechanism of GLP-1 secretion between the small intestine and large intestine should also be investigated in future study.

The contribution of K_{ATP} channels to glucose-induced GIP or GLP-1 secretion has been investigated using K_{ATP} channel-deficient mice[40]. In these mice, glucose-induced GIP secretion is enhanced, although glucose-induced GLP-1 secretion is not changed compared with those in wild-type mice[10,41,42]. *Sglt1* messenger ribonucleic acid expression in duodenum and glucose uptake is increased in K_{ATP} channel-deficient mice compared with those in wild-type mice[10]. These results suggest that

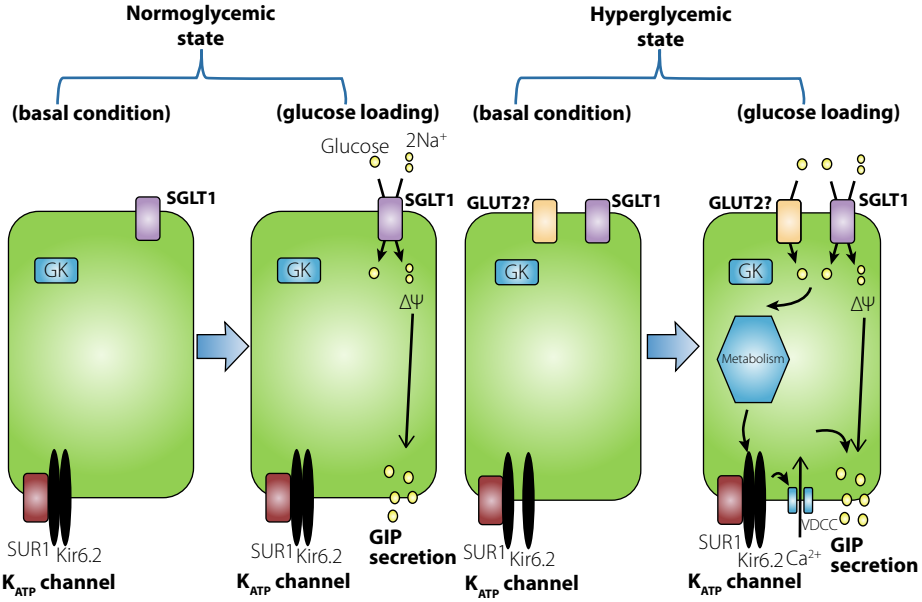

Figure 1 | Glucose-dependent insulinotropic polypeptide (GIP) secretory mechanism induced by glucose in K-cells. Under the normoglycemic state, adenosine triphosphate-sensitive K (K_{ATP}) channels in K-cells are closed in the basal condition. On glucose loading, glucose transported through sodium-dependent glucose transporter (SGLT1) induces membrane depolarization and GIP secretion from K-cells. Under the hyperglycemic condition, K_{ATP} channels in K-cells are open in basal condition. On glucose loading, incremental increase in ATP closes the K_{ATP} channel and depolarizes the membrane, generating an increase in GIP secretion in addition to the SGLT1-dependent GIP secretion. GK, glucokinase; GLUT5, glucose transporter 5.

in the absence of K_{ATP} channels, SGLT1 in the duodenum might play some role in the compensatory mechanism for glucose uptake and/or in GIP secretion *in vivo*.

The issues below require clarification regarding the contribution of K_{ATP} channels in GIP and GLP-1 secretion.

1. Localization of GLUT2: can GLUT2 localize in apical membrane in K-cells or L-cells to transport glucose from intestinal lumen? Can glucose be transported into cytosol of intestinal endocrine cells through basolateral GLUT2?
2. The interaction between intestinal absorptive epithelial cells and K-cells or L-cells regarding glucose flow.
3. The functional relationship between SGLT1 and the K_{ATP} channel in intestinal endocrine cells.

GIP AND GLP-1 SECRETION IN ISLETS

It was recently reported that GIP and GLP-1 are also expressed in pancreatic islets.

GIP is expressed in the embryonic pancreas or pancreatic α-cells in mice, pythons and humans[43,44]. Fujita *et al.*[44] reported that GIP secreted from α-cells is a shorter isoform, $GIP_{1–30}$, which is different from $GIP_{1–42}$ secreted from intestinal K-cells. They also found that $GIP_{1–30}$ is secreted from human and mice islets by arginine stimulation, and that $GIP_{1–30}$ contributes to glucose-induced insulin secretion from isolated islets *in vitro*[44]. In mice deficient in proglucagon-derived peptides[45], the insulin secretory response is enhanced during OGTT or intraperitoneal glucose tolerance test although GLP-1 is absent[7]. In these mice, immunohistochemical study shows GIP expression in pancreatic β-cells, and enhanced glucose-induced insulin secretion from isolated islets is observed. Furthermore, the insulin secretory response during OGTT or intraperitoneal glucose tolerance test and glucose-induced insulin secretion from isolated islets is remarkably reduced in mice deficient in both the GIP receptor and proglucagon-derived peptides. These results show that islet-derived GIP contributes to glucose-induced insulin secretion. Whether or not islet-derived GIP participates in glucose-induced insulin secretion under hyperglycemic condition or β-cell protection should be characterized in future study.

Glucagon and GLP-1 are produced from the same precursor, proglucagon. In pancreatic α-cells, glucagon is produced through cleavage by the enzyme prohormone convertase 1/2; in intestinal L-cells, GLP-1 and GLP-2 are produced through cleavage by enzyme prohormone convertase 1/3. It is reported that GLP-1 production in islets or the pancreas is increased in mice deficient in glucagon action, mice fed with a high-fat diet and STZ-treated rats, mainly as a result of increased prohormone convertase 1/3 expression in pancreatic α-cells[46–48]. In addition, GLP-1 secreted from isolated non-diabetic mice or human islets potentiates glucose-induced insulin secretion, showing that islet-derived GLP-1 contributes to glucose-induced insulin secretion under normal conditions[49]. Furthermore, GLP-1 secreted from islets is considered to play an important role in protection from β-cell damage.

The machinery of glucose-induced GIP or GLP-1 secretion from islets under physiological condition or in diabetic states is not well known; it has recently been reported that SGLT1 and SGLT2 are found in pancreatic α-cells in addition to K_{ATP} channels[50]. Whether or not SGLT1 or the K_{ATP} channel contributes to glucose-induced GIP or GLP-1 secretion from pancreatic α-cells should be investigated in future study.

CONCLUSIONS

There are several well-known distinct characteristics in the secretory responses to carbohydrates between GIP and GLP-1: the localization of secreting cells in the gastrointestinal tract, the response to fructose, and the contribution of SGLT1 and the K_{ATP} channel. *In vitro* analysis using primary K-cells or L-cells obtained from various parts of the gastrointestinal tract will further clarify novel physiological and pathological aspects of GIP and GLP-1.

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