An Extract of *Gymnema sylvestre* Leaves and Purified Gymnemic Acid Inhibits Glucose-Stimulated Gastric Inhibitory Peptide Secretion in Rats[1]

TOHRU FUSHIKI, AYAKO KOJIMA, TOSHIAKI IMOTO,* KAZUO INOUE AND ETSURO SUGIMOTO[2]

*Department of Food Science and Technology, Faculty of Agriculture, Kyoto University, Kyoto 606, Japan and *Department of Physiology, Faculty of Medicine, Tottori University, Tottori, Japan*

ABSTRACT Gastric inhibitory peptide release into the portal vein in response to duodenal infusion of D-glucose was studied in the presence of a leaf extract of *Gymnema sylvestre*, purified gymnemic acid and inhibitors of some putative glucose sensors and carriers in the intestinal lumen. Intraduodenal infusion of D-glucose significantly increased the portal immunoreactive gastric inhibitory peptide concentration in a dose-dependent manner. The increase in the portal immunoreactive gastric inhibitory peptide induced by glucose was significantly depressed by concomitantly infused leaf extract of *Gymnema sylvestre*, purified gymnemic acid and phlorizin but not by cytochalasin B. Mannoheptulose, which inhibits glycolysis, and procaine and lidocaine, which inhibit the vagal glucoreceptor in the lumen, did not affect portal immunoreactive gastric inhibitory peptide concentrations. These results suggest that a glucose receptor, which interacts with the leaf extract of *Gymnema sylvestre*, purified gymnemic acid and phlorizin, exists for the release of immunoreactive gastric inhibitory peptide and that the glucose receptor for gastric inhibitory peptide release is not likely to be identical with a glucose transporter or a vagal glucoreceptor in the lumen. J. Nutr. 122: 2367-2373, 1992.

INDEXING KEY WORDS:

- *gastric inhibitory peptide* • *rats*
- *gymnema sylvestre* • *gymnemic acid*
- *glucose transporter*

The effect of gastrointestinal hormones on insulin secretion, originally designated as incretin (Zunz and LaBarre 1929) and later as the enteroinsular axis (Unger and Eisentraut 1969), is mainly attributable to the insulin-releasing effect of gastric inhibitory peptide (GIP) (Brown and Otte 1978). Gastric inhibitory peptide is a gastrointestinal hormone primarily located in the duodenal mucosa (Brown et al. 1969), and its release is stimulated by glucose (Cataland et al. 1974), amino acids (Schulz et al. 1982), triglycerides and fatty acids (Ross and Shaffer 1981).

Previous studies on GIP release suggested that glucose and galactose stimulate GIP release but that fructose, mannose and sucrose do not (Ganda et al. 1979). Sirinek et al. (1983) speculated that structurally similar receptors exist for both the active transport of glucose and for GIP release. However, the detailed properties of the glucose receptor remained unclear.

The recognition of a sweet taste in response to the glucose molecule on a taste cell is a typical model for the cell-glucose interaction. In this case the existence of a cell surface glucose receptor is proposed, though the receptor protein has not yet been purified. An extract of *Gymnema sylvestre* leaves has been demonstrated to selectively suppress the sweet taste sensation in humans, and the active principle, named gymnemic acid, was determined to be a glucuronide of triterpene and was recently found to inhibit Na^+-dependent active glucose transport in the small intestine (Yoshioka 1986). It is expected, therefore, that an extract of *Gymnema sylvestre* may inhibit the GIP-release.

The present study was designed to investigate the inhibitory effects of an extract of *Gymnema sylvestre* and purified gymnemic acid on GIP-release.

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[2]To whom correspondence should be addressed.

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MATERIALS AND METHODS

Animals. Male 5-wk-old Wistar rats, obtained from Shimizu (Kyoto, Japan), were housed in an air-conditioned room at 22 ± 2°C with a lighting schedule of 12 h light (0600–1800 h) and 12 h darkness until the experiment. They were fed a standard pellet diet (rat breeding diet MF, Oriental Co., Tokyo, Japan), containing (g/100 g diet) water, 8; protein, 24.6; fat, 5.6; fiber, 3.1 and carbohydrates, 52.3. Food and water were available ad libitum. Care and treatment of experimental animals conformed with Kyoto University guidelines for the ethical treatment of laboratory animals.

Experimental design. Procedures for portal vein cannulation were previously described by Schultz et al. (1982). Food was withheld overnight, with free access to water allowed, before the experiments. After anesthesia by intraperitoneal injection of sodium pentobarbital (Nembutal, Abbott Laboratories, Chicago, IL, 50 mg/kg body wt), the abdomen was opened, and the small bowel, which was emptied of its contents, was ligated close to the pylorus and 30 cm proximal to the ileocecal junction, and finally displaced to the left to allow easy access to the portal vein. An intravenous Silastic catheter (0.02 inches i.d. × 0.037 inches o.d., Dow Corning, Midland, MI) fitted with a 23-G needle was inserted into the portal vein and filled with heparin-saline (5×10^4 IU heparin/L, 9 g/L NaCl) until blood was withdrawn. Two intraduodenal catheters (SV-21CLK, Termo, Tokyo, Japan) fitted with 21-G needles were inserted into the duodenum. One catheter (0.1 inch o.d.) for drainage was inserted 30 cm proximal to the ileocecal junction. The body temperature was kept constant at 38°C by means of electric heating pad.

Intraduodenal infusion. All experiments were conducted 20 min after surgery to allow the high blood glucose concentration due to the anesthesia and surgery to recover to the basal level. After a 20-min recovery period, infusion of saline was started at the rate of 0.5 mL/(kg·min) (Infusion A) and continued until the end of the experiment. Gymnemic acid (1 g/L), *Gymnema* leaf extract, mannoheptulose (4 mmol/L), phlorizin (5 mmol/L) cytochalasin B (50 mg/L), procaine (10 g/L) and lidocaine (10 g/L) were dissolved in Infusion A and infused at 0.5 mL/(kg body wt·min) via the duodenal catheter for 30 min, using a Terfusion syringe pump (STC-521, Termo). The infusion rates of each material were as follows: gymnemic acid, 30 mg/(kg·h); mannoheptulose, 0.12 mmol/(kg·h); phlorizin, 0.15 mmol/(kg·h); cytochalasin B, 1.5 mg/(kg·h), lidocaine, 5 mg/(kg·h) and procaine, 5 mg/(kg·h).

D-Glucose, fructose, glycine, stevioside, 3-*o*-methylglucose and 2-deoxyglucose were dissolved in saline at the concentration of 556 mmol/L [infusion rate, 16.68 mmol/(kg·h)]. The glybenclamide concentration was 100 mg/L [3 mg/(kg·h)]. Ten minutes after starting Infusion A, these substances were infused at 0.5 mL/(kg·min) via the other duodenal catheter for 20 min using the same Terfusion syringe pump (Infusion B). Before starting Infusion B (0 min), and 10 and 20 min after starting Infusion B, 500-μL blood samples were taken via the portal vein catheter and plasma glucose was determined with a C-test Wako (Wako Pure Chemicals, Tokyo, Japan). Plasma (0.2 mL) was stored at −70°C for the GIP assay.

Gastric inhibitory peptide assay. Portal vein plasma GIP was determined by means of a RIA kit (RIK7154, Peninsula Laboratories, Belmont, CA). The assay kit showed 22.8 pmol/L of a 50% maximal range for human GIP and displayed no cross-reactivity to human gastrin, big gastrin, gastrin releasing peptide, bombesin and substance P.

Extraction of gymnema leaves and purification of gymnemic acid. Dried leaves (380 mg) of *Gymnema sylvestre* were ground and homogenized with a Potter type glass homogenizer in 22 mL of saline, followed by standing for 30 min at room temperature and then centrifugation at 6000 × *g* for 30 min. The supernatant, which exhibited potent ability to block sweet taste in humans, was infused into the rat duodenum at 0.5 mL/(kg·min). Gymnemic acid was purified according to the procedure described by Kurihara (1969).

Data analysis. The blood glucose and GIP concentrations after 10 min and 20 min of infusion were expressed as relative values to those before starting Infusion B (0 min) in each rat, because the cross-reactivity of the present antibody, which is for human GIP and completely crossreacts with porcine GIP, has not been examined against rat GIP. Data are expressed as means ± SEM. Least significant difference test was used to compare means after ANOVA (Snedecor and Cochran 1967); $P < 0.05$ was considered statistically significant.

RESULTS

Change in the portal immunoreactive gastric inhibitory peptide concentration on intraduodenal infusion of D-glucose. **Figure 1***A* shows that the mean portal vein plasma immunoreactive gastric inhibitory peptide (IR-GIP) concentration showed significant and dose-dependent increases at 10 and 20 min after starting infusion of glucose. The glucose doses used were 16.68 and 8.34 mmol/(kg·h), with saline being given as a control. After 10 and 20 min of infusion, the IR-GIP level in rats infused with 16.68 mmol/(kg·h) glucose was significantly higher than that in the controls. The 8.34 mmol/(kg·h) infusion did not cause a statistically significant increase in portal plasma IR-GIP until after 20 min. Portal vein plasma glucose increased similarly to IR-GIP, upon intraduodenal infusion of glucose (Fig. 1*B*).

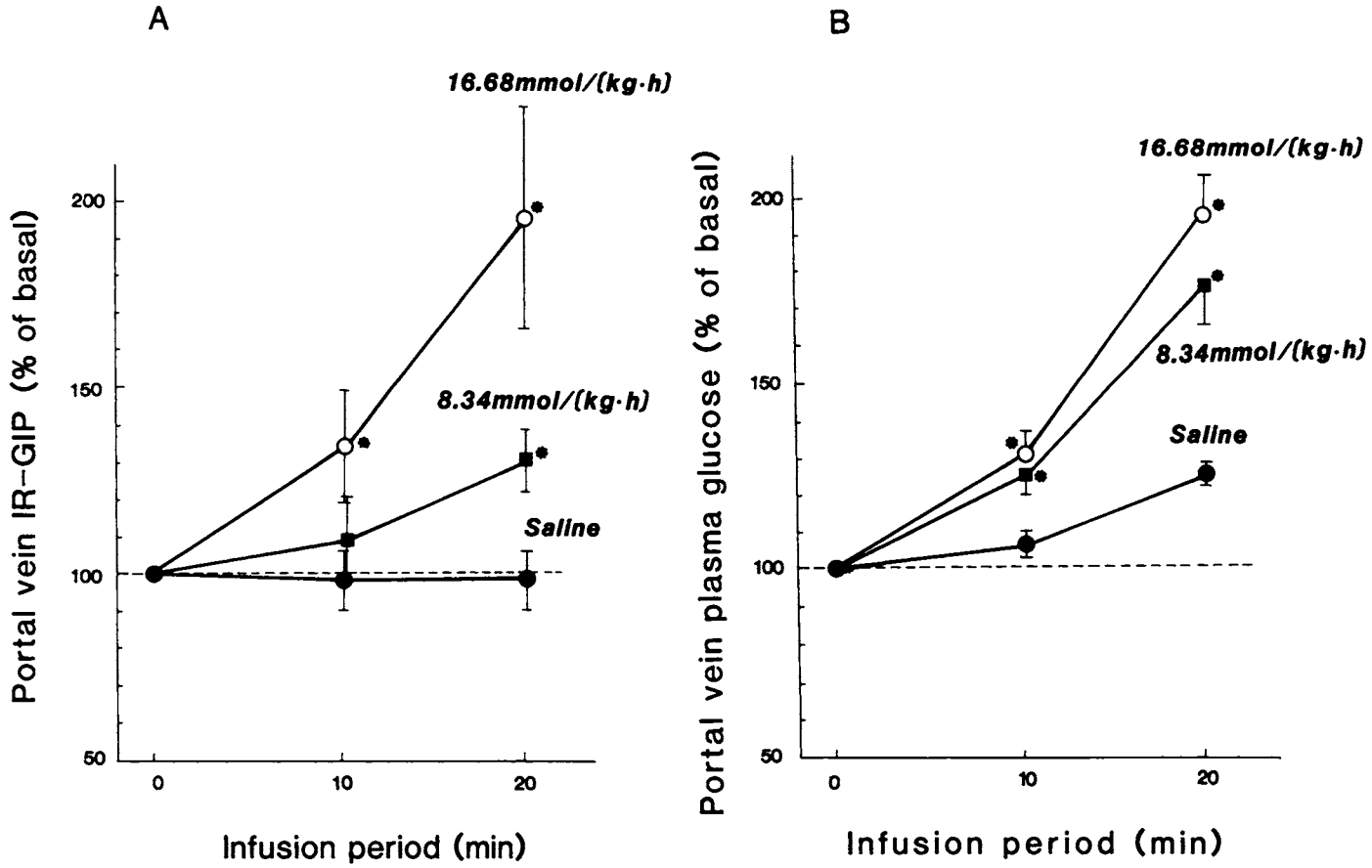

FIGURE 1 Dose-response between the glucose infusion rate and the portal immunoreactive gastric inhibitory peptide level (*A*) and glucose level (*B*) in anesthetized rats. Rats were anesthetized and then kept for 30 min, and then saline infusion was started at 0.5 ml/(kg·min) and continued throughout the experiment. Glucose in saline (556 and 278 mmol/L) was infused from 0 min until 20 min after starting the saline infusion. Portal blood was collected via the portal catheter before glucose infusion (0 min) and 10 and 20 min after starting the glucose infusion. The gastric inhibitory peptide (GIP) level was assayed by RIA and expressed as the percentage of that at 0 min. Values are means ± SEM for 7–11 rats. *Significant difference from saline infusion ($P < 0.05$). IR-GIP = immunoreactive gastric inhibitory peptide.

Effects of fructose, glycine and stevioside infusion, at the dose of 16.8 mmol/(kg·h), on the portal immunoreactive gastric inhibitory peptide concentration. Fructose, glycine and stevioside, which have a sweet taste for humans, did not cause a significant increase in portal vein plasma IR-GIP when compared with the saline control (**Fig. 2**). The portal vein IR-GIP concentrations with 20-min infusion of fructose, glycine and stevioside were significantly lower than with glucose infusion.

Effects of gymnemic acid, Gymnema leaf extract and phlorizin on portal vein immunoreactive gastric inhibitory peptide with the 16.68 mmol/(kg·h) glucose infusion. **Table 1** shows the portal vein plasma IR-GIP concentrations, which were determined after 10 and 20 min of 16.68 mmol/(kg·h) glucose infusion, in the presence of these compounds. The *Gymnema* leaf extract (380 mg of dry leaves in 22 mL of saline), gymnemic acid, at the dose of 30 mg/(kg·h), and phlorizin, at 0.15 mmol/(kg·h), all markedly suppressed the increase in portal IR-GIP, as compared with the infusion of saline. The portal vein plasma glucose concentrations are shown in **Table 2**. Only phlorizin gave significantly lower blood glucose concentrations after 20 min than infusion of glucose and saline. Gymnemic acid and *Gymnema* leaf extract infusion did not cause any significant change in the portal plasma glucose concentration.

Effect of cytochalasin B on portal immunoreactive gastric inhibitory peptide. Cytochalasin B is a potent inhibitor of glucose transporters. Glucose intake by reconstituted liposomes in fat cells was inhibited by only 9.6 mg/L cytochalasin B (Kono et al. 1981) and the glucose intake in epitrochlearis muscle was reported to be blocked by 24 mg/L of cytochalasin B (Nesher et al. 1985). Cytochalasin B (50 mg/L) at the dose of 1.5 mg/(kg·h), which would be enough for the inhibition of glucose transporters, did not significantly decrease the portal vein IR-GIP concentration (Table 1).

Effect of glybenclamide on portal immunoreactive gastric inhibitory peptide. Glybenclamide, which is a potent stimulus for insulin secretion, was infused instead of glucose at the dose of 3 mg/(kg·h). As

TABLE 1

Effects of intraduodenal infusion of gymnemic acid, phlorizin, cytochalasin B and other compounds related to glucose metabolism on immunoreactive (IR-) gastric inhibitory peptide (GIP) release into the portal vein of anesthetized rats[1]

Infusion	IR-GIP release	
	10 min	20 min
	% of 0 min	
Saline	97.3 ± 8.1[a]	97.9 ± 8.5[a]
Glucose + saline	135.4 ± 15.5[b]	194.3 ± 31.3[b]
Glucose + gymnemic acid	97.4 ± 12.2[a]	120.0 ± 10.6[a]
Glucose + *Gymnema* leaf extract	97.4 ± 23.0[a]	103.0 ± 25.9[a]
Glucose + phlorizin	110.0 ± 14.7[a,b]	108.0 ± 15.8[a]
Glucose + cytochalasin B	133.8 ± 26.1[a,b]	143.8 ± 30.3[a,b]
Glucose + mannoheptulose	145.2 ± 17.4[b]	184.0 ± 30.0[b]
Glybenclamide	98.3 ± 1.5[a]	110.6 ± 16.1[a]

[1]Values are expressed as the percentage of the GIP concentration before glucose infusion (0 min) and are means ± SEM for 5 to 11 rats. Values in a column not sharing a superscript letter are significantly different at $P < 0.05$. Infusion conditions were described in Materials and Methods.

TABLE 2

Effects of intraduodenal infusion of gymnemic acid, phlorizin, cytochalasin B and other compounds related to glucose metabolism on blood glucose concentration in the portal vein of anesthetized rats[1]

Infusion	Blood glucose	
	10 min	20 min
	% of 0 min	
Saline	107 ± 2.5[a]	126 ± 3.6[a,b]
Glucose + saline	129 ± 5.2[b,c]	195 ± 10.6[c]
Glucose + gymnemic acid	134 ± 5.8[b,c]	193 ± 6.4[c]
Glucose + *Gymnema* leaf extract	140 ± 4.5[c]	206 ± 7.0[c]
Glucose + phlorizin	117 ± 1.5[a,b]	145 ± 5.7[b]
Glucose + cytochalasin B	120 ± 5.5[a,b]	174 ± 14.7[b,c]
Glucose + mannoheptulose	129 ± 5.2[b,c]	189 ± 10.6[c]
Glybenclamide	103 ± 3.5[a]	109 ± 4.8[a]

[1]Blood glucose was expressed as the percentage of the level determined before experiment (0 min). Values are means ± SEM for 5 to 11 rats. Values within a column not sharing a superscript letter are significantly different at $P < 0.05$.

shown in Table 2, a low plasma glucose concentration, due to insulin release, was observed. However, the glybenclamide infusion did not increase portal vein plasma GIP concentration relative to the saline infusion (Table 1).

Effect of mannoheptulose on portal immunoreactive gastric inhibitory peptide. Mannoheptulose is a typical inhibitor of glucokinase (Matschinsky 1990). Mueller et al. (1982) reported that 4 mmol/L mannoheptulose completely abolished arginine-stimulated insulin release in perfused isolated pancreas. Intraduodenal infusion of 4 mmol/L mannoheptulose [0.12 mmol/(kg·h)] did not cause any significant difference in the glucose-stimulated IR-GIP release from that without infusion of mannoheptulose (Table 1). A statistically significant difference was observed between glucose + mannoheptulose infusion and saline infusion, suggesting that mannoheptulose did not inhibit IR-GIP release.

Effects of 3-o-methylglucose and 2-deoxyglucose on portal immunoreactive gastric inhibitory peptide. 3-*o*-Methylglucose can be absorbed through the active glucose transport system as well as through the passive transport system, whereas 2-deoxyglucose is absorbed via only the passive glucose transport system (Sykes et al. 1980), and both are not metabolized in intestinal cells. **Figure 3** indicates that these nonmetabolized glucose analogs did not increase the portal vein plasma IR-GIP concentration when they were infused instead of glucose at the dose of 16.68 mmol/(kg·h), regardless of their incorporation route, i.e., via active or nonactive transport. 3-*o*-Methylglucose rather decreased the IR-GIP concentration after 10 min compared with the saline control.

Intraduodenal infusion of procaine (10 g/L) and lidocaine (10 g/L) at the rate of 3 mg/(kg·h), which are blockers of neural glucose sensor in the lumen, did not affect the portal IR-GIP concentration (data not shown).

DISCUSSION

Consistent with previous studies (Schulz et al. 1982, Sirinek et al. 1983), a significant increase in portal vein plasma IR-GIP was observed in response to the duodenal infusion of D-glucose. In the present study, the infused glucose amounted to 2.78 mmol/kg for 10 min and 5.56 mmol/kg for 20 min. This is almost the same dosage as in Schulz's (1982) experimental conditions in anesthetized rats, i.e., they found that portal vein plasma GIP reached the maximal concentration within 15 min when 1.39 mmol/kg glucose was intraduodenally instilled, the maximal concentration being reached at 30 min when 2.78–5.56 mmol/kg of glucose was instilled into the duodenum. As judged from the data obtained, our standard experimental conditions [16.8 mmol/(kg·h) glucose infusion for 20 min and blood sampling at 10 and 20 min] are reasonable for detecting a physiological response of the portal vein plasma GIP concentration to glucose. Our data are also compatible with those using conscious animals (Creutzfeldt et al. 1983, Sirinek et al. 1983) and humans (Ganda et al.

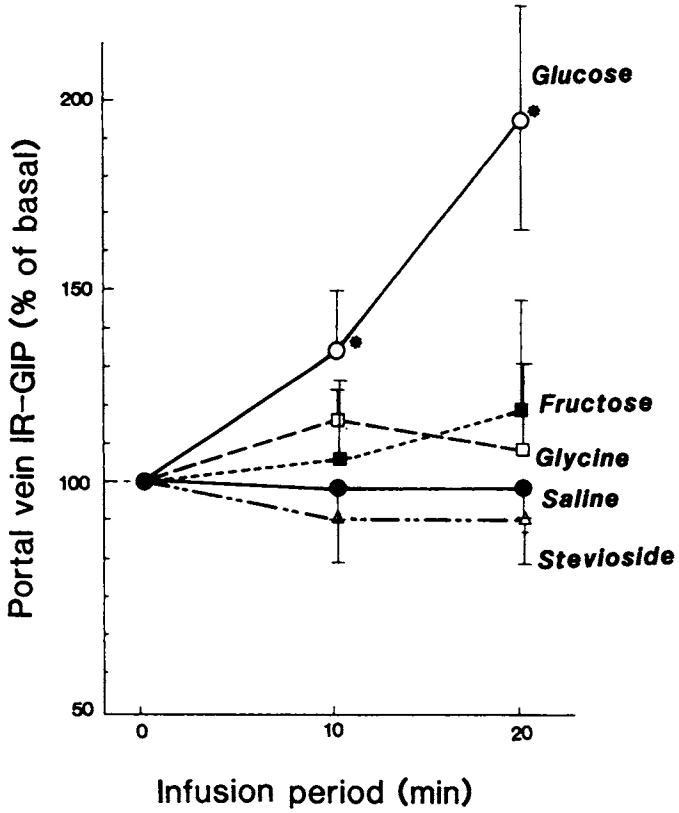

FIGURE 2 Effects of sugars and other sweet-tasting substances on the portal immunoreactive (IR-) gastric inhibitory peptide (GIP) level in anesthetized rats. 556 mmol/L glucose, fructose, glycine and stevioside were infused under the same conditions as in Figure 1. Data are expressed as the percentage of the portal GIP levels determined before infusion of the sugars and sweet-tasting substances. Values are means ± SEM for 4–11 rats. *Significant difference from saline, $P < 0.05$.

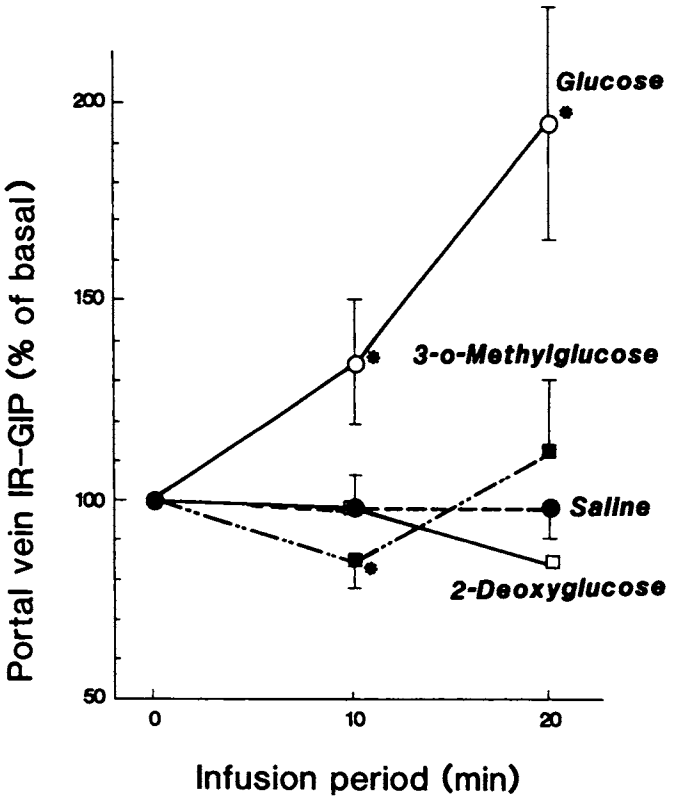

FIGURE 3 Immunoreactive gastric inhibitory peptide (IR-GIP)-release upon infusion of 3-*o*-methylglucose and 2-deoxyglucose in anesthetized rat small intestine. 556 mmol/L 3-*o*-methylglucose, 2-deoxyglucose, D-glucose and saline as a control were infused under the same conditions as in Figure 1. Data are expressed as means ± SEM for 7–11 rats. *Significant difference from saline ($P < 0.05$). Values of glucose infusion were the same as those in Figure 2. The data of 2-deoxyglucose were means of two rats and were excluded from the statistical analysis.

1979), suggesting that anesthesia, which was necessary for the present perfusion study, has a minimal influence on the GIP response. Portal vein glucose concentration increases at 20 min with saline infusion are difficult to understand. A possible explanation is that catabolic stimulations caused by stresses during the perfusion might occur via humoral and nervous systems.

Intraduodenal infusion of fructose was much less effective than glucose infusion in stimulating IR-GIP release. The present data are consistent with the results of prior studies, i.e., fructose, mannose, lactose, sorbitol and sucrose were much less effective stimulators of GIP release in normal humans and dogs (Ganda et al. 1979, Sirinek et al. 1983). Although some contradictory results for fructose and sucrose have been reported (Hallfrisch et al. 1983, Reiser et al. 1980), glucose and galactose are most effective stimulators in GIP release, with other sugars being much less effective.

In addition to the result of fructose infusion, other sweet-tasting substances, for example, glycine, stevioside and 3-*o*-methylglucose, did not induce significant increases in portal IR-GIP, suggesting that the glucose recognition system for GIP-release has a much narrower specificity than that of a sweet receptor on a taste cell. Gymnemic acid has been demonstrated to be a potent blocker of sweet taste in humans. Chewing only 1 cm square of *Gymnema* leaf in the mouth for 1–2 min can completely block a sweet taste. In the present study, a *Gymnema* leaf extract and gymnemic acid, which is one of the main bioactive components of the leaf extract, significantly decreased glucose-stimulated portal vein plasma IR-GIP. This effect does not mean that the glucose receptor for GIP release is identical with the receptor protein for sweet taste detection, because gymnemic acid does not inhibit sweet taste in rats (Kurihara 1969). Gurmarin, which is also one of the active components of *Gymnema* leaf extract, can block sweet taste in rats but did not have any effect on GIP release at a dose of 1.5 mg/(kg·h) (unpublished data). The inhibition of GIP release by gymnemic acid observed in the present study could be due to its interaction with the glucose receptor for GIP release,

which is similar in specificity to the active glucose transport system, because Yoshioka (1986) reported that an extract of *Gymnema sylvestre* leaves and gymnemic acid inhibited active transport of glucose in rats. This was supported by the finding that phlorizin markedly inhibited glucose-stimulated IR-GIP release. Phlorizin is a typical inhibitor of Na^+-dependent active transport of glucose in the small intestine (Schulz and Zalusky 1964), and a previous study with rats indicated that phlorizin decreased GIP release (Sykes et al. 1980). It is, however, not likely that the decrease in GIP release caused by gymnemic acid and the leaf extract was directly due to a reduced number of glucose molecules in the cells, because the portal glucose concentration did not necessarily coincide with the portal IR-GIP concentration. The infusion of gymnemic acid and the *Gymnema* leaf extract did not decrease the portal blood glucose concentration under the present conditions.

Sirinek et al. (1983) suggested, on the basis of their data, that the structural integrity of the glucose molecule from the C-1 to C-4 carbon atom, a free aldehyde group on the C-1 carbon atom and a cyclic structure are all necessary for both the active transport of glucose and the release of GIP. Our present data support this speculation. However, it should be noted that the binding of a glucose molecule to the carrier for the active transport of glucose does not directly cause GIP release, because 3-*o*-methylglucose, which is known to be absorbed not only through the passive transport system but also through the active transport system for glucose (Schulz and Zalusky 1964), did not stimulate IR-GIP release. The glucose sensor probably existing on the GIP-producing cells (K cells) may have the most narrow specificity for glucose molecules.

The glucose sensory system of the intestinal endocrine cells is not fully understood. Recent studies indicated that facilitative glucose transport in mammalian cells is mediated by a family of structurally related proteins, glucose transporters. Five kinds of glucose transporter have been reported and designated as Glut 1 to Glut 5, respectively. Because glucose uptake by skeletal muscle and adipose tissue is regulated by insulin, at least this increase in the rate of glucose uptake is due to an increase in the number of insulin-sensitive glucose transporters (Glut 4) in the plasma membrane (Friedman et al. 1990, James et al. 1989, Vilaro et al. 1989). Glucose transporter type 2 (Glut 2) was first found in liver (Meuckler et al. 1985), and recently found in β-cells in the pancreas and the small intestine (Orci et al. 1989, Permutt et al. 1989). Glut 2, which has a lower affinity for glucose, is proposed to be involved in the glucose sensory system in pancreas. Cytochalasin B is a potent inhibitor of all these glucose transporters. It completely inhibited the glucose uptake by muscle and adipose tissue in vitro and in vivo (Wardzala and Jeanrenaud 1983). The dose used in the present study was enough to inhibit glucose transporters, because only 50 μmol/L of cytochalasin B completely blocked glucose uptake by muscle (Nesher et al. 1985). An intraduodenal infusion of cytochalasin B [1.5 mg/(kg·h)] gave a slightly lower IR-GIP concentration; however, the difference was not statistically significant compared with results without cytochalasin B, suggesting that a glucose transporter was not directly involved in the GIP release by the small intestinal endocrine cells.

Insulin release is a typical hormone release stimulated by glucose; thus, insulin release in response to glucose may share common mechanisms with GIP release. Matschinsky (1990) advocated that glucokinase (ATP:D-hexose-6-phosphotransferase, EC 2.7.1.1) is a key enzyme for glucose recognition by β-cells as well as liver cells. This enzyme exhibits relatively low affinity for glucose and also is proposed to be a glucose sensor for insulin release in pancreatic β-cells. This enzyme is a key enzyme in glycolysis and regulates glucose metabolism. Cook and Hales (1984) proposed that glucose produces ATP and then affects the ATP-sensitive K^+channels, which regulate the secretion of insulin. Patch-clamp analysis of pancreas β-cells indicated that when the molar ratio of ATP:ADP was changed from (2.5 mmol/L)/(0.5 mmol/L) to (0.5 mmol/L)/(2.5 mmol/L), the activity of the ATP-sensitive K^+channels increased about 20-fold (Misler et al. 1986). Infusion of 4 mmol/L mannoheptulose, at which concentration it was reported to completely suppress arginine-stimulated insulin release in isolated pancreas (Mueller et al. 1982), did not affect the portal vein plasma IR-GIP concentration. This is consistent with the finding of the non-participation of the ATP-sensitive K^+channels, which was suggested by the results of infusion of glybenclamide, a potent insulin secretagogue via closure of the ATP-sensitive K^+channels (Trube et al. 1986), which must be completely blocked under the present conditions, in the effect on the portal vein IR-GIP concentration. These findings suggested that the mechanism underlying the GIP release in response to luminal glucose in the small intestine would not be the same as that underlying insulin release in response to plasma glucose in the pancreas.

The existence of a vagal glucose sensor in the duodenum has been proposed, which regulates the rate of gastric emptying, for example. Glucose transfer from the stomach to the duodenum is known to be regulated via the duodenal glucose sensor. Mei (1978) found that a glucoreceptor exists on the gastrointestinal wall. This receptor was reported to be localized to the duodenum and the proximal jejunum. Glucose and galactose preferentially stimulate the sensor, but fructose does not. This duodenal glucose sensor was blocked on 1% procaine infusion. In the present study, infusion of 10 g/L procaine and 10 g/L lidocaine in saline did not affect the glucose-induced

portal vein plasma IR-GIP concentration (data not shown), suggesting that the procain-sensitive vagal glucoreceptor would not be involved in the GIP-release.

Overall, the present data suggest that a glucose receptor with a narrow specificity for glucose may exist. This receptor interacted with phlorizin and gymnemic acid, suggesting that it is similar to the carrier for the active transport of glucose, but it does not bind to 3-*o*-methylglucose. The mechanism underlying GIP release would not involve glucokinase or the ATP-sensitive K^+channels, like insulin release in the pancreas, nor a glucose transporter family, nor the duodenal procain-sensitive vagal glucose sensor.

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