The Role of Gastric Inhibitory Polypeptide in the Augmented Insulin Response to Sucrose

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To evaluate the role of gastric inhibitory polypeptide (GIP) in the augmented insulin response to sucrose, seven normal volunteers ingested four separate meals of 100 g sucrose (S), 50 g glucose (G), 50 g fructose (F), and 50 g glucose + 50 g fructose (G + F). Serum insulin, glucose, and GIP were measured. In each of the 3 h after sugar ingestion the integrated insulin response to (S) was greater than to (G) with the 3-h total being 104% greater. The integrated glucose response to (S) was slightly greater than to (G) in the first and second hours but the differences were not significant. Integrated GIP response to (S) was greater than to (G) in hours 2 and 3. Although significant insulin and glucose responses to (F) occurred in hour 1, G + F led to insulin and glucose responses similar to G. G + F led to greater GIP levels than G in hour 3. These studies show that GIP may play a role in the augmented insulin response to S in hours 2 and 3. This may result from delayed gastric emptying and glucose absorption. The augmentation of insulin to S in the first hour may result from fructose, extra glucose equivalent of the sucrose test solution, or from endocrine mechanisms other than those subserved by GIP. DIABETES CARE 5: 379–385, JULY–AUGUST 1982.

In 1976 Crapo, Reaven, and Olefsky reported that the insulin secretion following oral sucrose was greater than that produced by an equimolar amount of oral glucose.[1] They postulated that the effect may be due to the fructose component of sucrose either acting directly as a potentiator of insulin secretion or by its conversion to glucose. However, in Crapo et al.'s study, the blood glucose responses with oral sucrose and oral glucose were nearly identical. Thus it is unclear whether the hyperinsulin response seen with sucrose is due to one of the two mechanisms involving fructose.[2–5]

Gastric inhibitory polypeptide (GIP) has been demonstrated to be insulinotropic in man.[6] In the presence of elevated blood glucose levels, this hormone augments insulin secretion, an effect not seen when glucose levels are normal.[7–10] Therefore, differences in insulin responses found with similar blood glucose levels, as in the sucrose-glucose studies, may be attributed to differences in GIP levels. We recently demonstrated that GIP secretion occurs with sucrose ingestion and that the serum insulin levels achieved were related to the GIP levels.[11] The objective of this study was to determine the role of GIP in the augmented insulin response to sucrose.

MATERIALS AND METHODS

Subjects and protocol. The protocol was approved by the Human Studies Committee at The Ohio State University. Seven normal subjects, four men and three women, aged 21–37 yr were studied on the Clinical Research Center. All were within 10% of their ideal body weight and were instructed to ingest at least 300 g carbohydrate daily for the 3 days before each test meal. None of the volunteers had a family history of diabetes mellitus and none were taking medications.

Four different carbohydrate meals: 100 g sucrose (S), 50 g glucose (G), 50 g fructose (F), and 50 g glucose plus 50 g fructose (glucose + fructose; G + F) were given to each volunteer in random order with each test meal given at least 1 wk apart. The studies were performed following an overnight 12-h fast with the carbohydrates ingested in a 3-min period as a solution of 300 ml. Venous blood was sampled through a heparinized indwelling needle at 0, 15, 30, 45, 60, 120, and 180 min. The blood was immediately centrifuged at room temperature and the serum stored at −20°C.

Radioimmunoassay and chemical analysis. Serum glucose concentrations were determined using the glucose-oxidase

method (Beckman glucose analyzer, Beckman Instruments Inc., Fullerton, California). Duplicate values agreed within 5 mg/dl and the mean was used for analysis. Serum insulin was assayed by radioimmunoassay with guinea pig antiporcine insulin antiserum (Research Products International Corp., Elk Grove Village, Illinois) and purified porcine insulin as standard (Eli Lilly Co., Indianapolis, Indiana). Polyethylene glycol was used to separate bound and free peptide.[12] This assay was sensitive to 0.25 μU/ml serum with the interassay and intraassay coefficients of variation being 8% and 3%, respectively. Serum gastric inhibitory polypeptide (GIP) was measured using a modification of the radioimmunoassay method of Kuzio et al.[13] Rabbit antiporcine GIP antisera (a gift from Dr. Vincent Marks RK/34/IIIc) was used, and it did not cross-react with porcine secretin, porcine glucagon, synthetic human gastrin, highly purified CCK, vasoactive intestinal polypeptide, and pancreatic polypeptide. Purified porcine GIP was used for assay standards. Polyethylene glycol was employed to separate bound and free peptide. The sensitivity of the GIP assay was 50 pg/assay tube or 250 pg/ml serum. Interassay and intraassay coefficients of variation were 15% and 5%, respectively.

Statistical analysis. The incremental responses of insulin, glucose, and GIP were calculated for each of the four meals. The integrated responses for the entire 180-min time period of the study and for the 0–60-min, 60–120-min, and 120–180-min time periods were calculated using the trapezoidal rule.[14] Data were assessed with a standard computer program analysis of variance (ANOVA).[15] A three-way analysis was used for the time-dependent incremental curves and two-way analysis was used for the integrated data. F values and P values are presented with each graph. The least significant difference (LSD) was calculated for each analysis of variance to compare responses at individual time points or time periods.[16] Two responses that differ by a value greater than or equal to the LSD are significantly different at the $P \leq 0.05$ level. LSD values are given with each graph. Asterisks are used in each graph to indicate responses that are significantly ($P \leq 0.05$) greater (*) or less (**) than the responses to the glucose meal.

RESULTS

Mean glucose, insulin, and GIP responses to test meals (Table 1). Depicted in Table 1 are the mean GIP, insulin and glucose responses to each sugar ingestion. Glucose responses were no different with both the oral sucrose ingestion and glucose plus fructose ingestion compared with glucose alone. However, the glucose response to fructose ingestion was significantly lower compared with the glucose ingestion at 15,

TABLE 1
Mean GIP, insulin, and glucose responses after glucose, fructose, sucrose, or fructose plus glucose

		Time in min					
N = 7	Fasting	15	30	45	60	120	180
				Glucose ingestion			
Glucose (mg/dl)	89 ± 4	117 ± 8	142 ± 20	122 ± 8	106 ± 7	88 ± 4	86 ± 4
Insulin (μU/ml)	8 ± 1	33 ± 6	47 ± 8	35 ± 7	26 ± 8	13 ± 2	7 ± 1
GIP (pg/ml)	335 ± 50	700 ± 80	760 ± 65‡	800 ± 85‡	755 ± 70	505 ± 55	340 ± 45
				Fructose ingestion			
Glucose (mg/dl)	86 ± 3	91 ± 4†	100 ± 9†	96 ± 8†	92 ± 8	86 ± 5	86 ± 3
Insulin (μU/ml)	7 ± 1	15 ± 2†	20 ± 4†	19 ± 3†	16 ± 2	9 ± 2	7 ± 1
GIP (pg/ml)	300 ± 42	280 ± 40†	260 ± 45†	245 ± 40†	255 ± 40†	295 ± 40†	280 ± 40
				Sucrose ingestion			
Glucose (mg/dl)	89 ± 3	120 ± 9	142 ± 20	136 ± 18	120 ± 8	94 ± 5	81 ± 3
Insulin (μU/ml)	7 ± 1	35 ± 6	53 ± 8	65 ± 9*	48 ± 8*	18 ± 3	13 ± 3
GIP (pg/ml)	250 ± 42	620 ± 60	650 ± 45	645 ± 50	720 ± 75	660 ± 60*	380 ± 45
				Fructose + glucose ingestion			
Glucose (mg/dl)	89 ± 3	120 ± 9	152 ± 23	128 ± 19	98 ± 10	96 ± 10	76 ± 8
Insulin (μU/ml)	7 ± 1	35 ± 7	42 ± 7	34 ± 6	24 ± 6	17 ± 2	11 ± 3
GIP (pg/ml)	245 ± 41	600 ± 70	595 ± 55	580 ± 50	640 ± 70	525 ± 50	280 ± 40

Results are $\bar{x}$ ± SE.
* Responses that are significantly ($P < 0.05$) greater than the responses to the glucose meal.
† Responses that are significantly ($P < 0.05$) less than the responses to the glucose meal.
‡ = significantly greater than sucrose ($P < 0.05$).

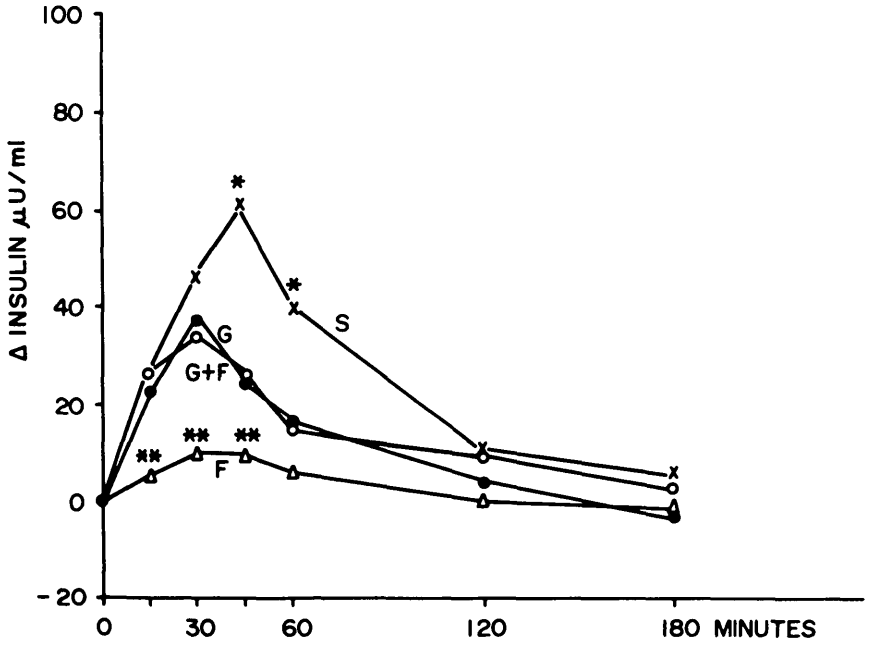

FIG. 1. Incremental insulin response to test meals; x, Sucrose (S); ●, Glucose (G); O, Glucose + Fructose (G + F); △, Fructose (F); F = 4.03, P = 0.025, LSD = 14.5 μU/ml.

30, and 45 min. Sucrose elicited a significantly greater insulin response at 45 and 60 min compared with glucose. In contrast, fructose produced a significantly lower insulin response at 15, 30, and 45 min compared with glucose. Ingestion of glucose led to a significantly greater rise of GIP at 30 and 45 min compared with sucrose. Sucrose ingestion produced a significantly greater response of GIP than glucose at 120 min.

Incremental (Δ) insulin responses to test meal (Figure 1). Ingestion of sucrose led to a significantly greater insulin response at 45 and 60 min than did ingestion of glucose (58.4 vs. 25.2 μU/ml and 40.4 vs. 16.5 μU/ml; $P < 0.05$ for both). Ingestion of fructose led to a significant rise of insulin (paired t test $P < 0.01$) but this response was less than for glucose at 15, 30, and 45 min. There was no significant difference of the insulin response with the glucose + fructose test meal from that with glucose alone. The sucrose-induced insulin response was therefore also greater than the response to glucose + fructose.

Incremental glucose responses to test meals (Figure 2). The glucose response to sucrose was greater than to glucose at 45 and 60 min but these differences were not significant at the $P \leq 0.05$ level. The response to glucose + fructose was similar to glucose alone but was significantly less than to sucrose at the 60-min time. Fructose ingestion led to a significant rise in serum glucose (paired t test $P < 0.01$) but this was less than with glucose at 15, 30, and 45 min.

Incremental GIP responses to test meals (Figure 3). Ingestion

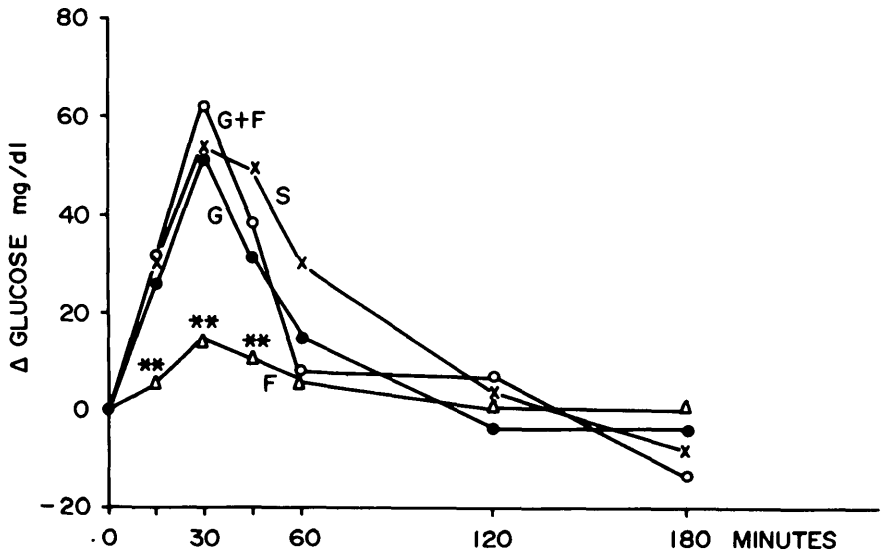

FIG. 2. Incremental glucose response to test meals; x, Sucrose (S); ●, Glucose (G); O, Glucose + Fructose (G + F); △, Fructose (F); F = 3.32, P = 0.05, LSD = 17.2 mg/dl.

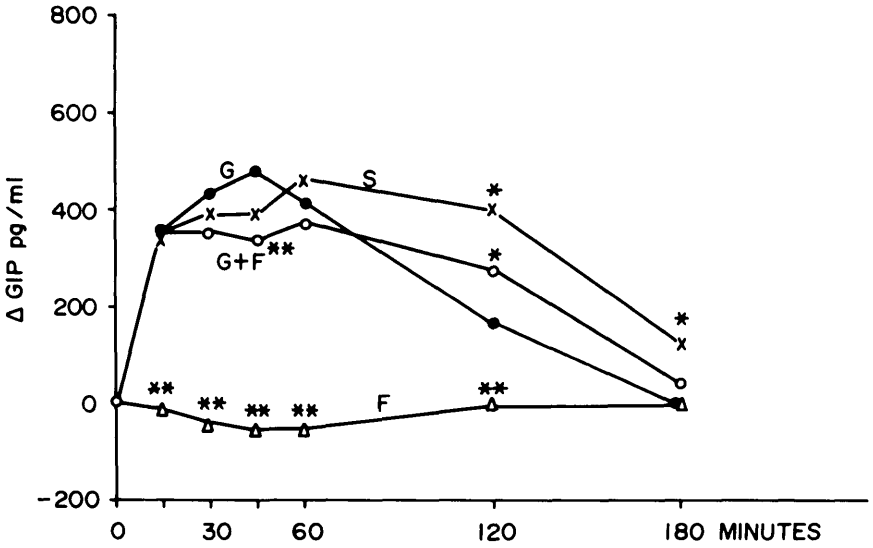

FIG. 3. *Incremental GIP response to test meals; x, Sucrose (S); ●, Glucose (G); O, Glucose + Fructose (G + F); Δ, Fructose (F); F = 31.97, P = 0.0001, LSD = 98 pg/ml.*

of sucrose led to a significantly greater GIP response at 120 and 180 min than did glucose. The GIP levels following fructose did not change significantly and consequently were less than for glucose at the 15 through 60-min times. The GIP response to the glucose + fructose test meal was less than to glucose ($P < 0.05$) at 45 min but was greater than glucose at 120 min.

Integrated insulin responses 0–180 min (Figure 4). The integrated insulin response over the entire 180 min of the study was greatest for sucrose, 4290 μU-min/ml, and least for fructose, 508 μU-min/ml. Both of these were significantly different than the insulin response to glucose, 2097 μU-min/ml. The glucose + fructose test meal led to an integrated insulin response (2551 μU-min/ml) slightly greater than to glucose alone but the difference when calculated for the 180-min period was not statistically significant. The insulin response to sucrose was thus greater than the responses either to glucose alone or to glucose + fructose.

Integrated responses 0–60 min (Figure 5). In the 0–60-min period of the study the integrated serum insulin response (upper panel) to sucrose was significantly greater than to glucose, or to glucose + fructose. Fructose led to the least response of the four meals. There was no difference in the responses between glucose + fructose and that of glucose alone. The serum glucose response (middle panel) to sucrose, glucose + fructose, and glucose alone were not significantly different although sucrose provided a greater response than glucose. The response to fructose was significantly less than to the other three meals. The serum GIP response

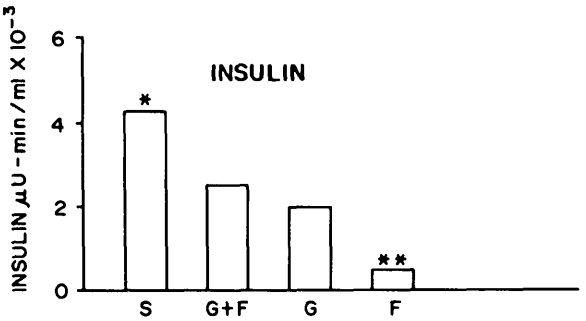

FIG. 4. *Integrated insulin response to test meals 0–180 min. Sucrose (S); Glucose (G); Glucose + Fructose (G + F); Fructose (F); F = 7.91, P = 0.0004, LSD = 1436 μU-min/ml.*

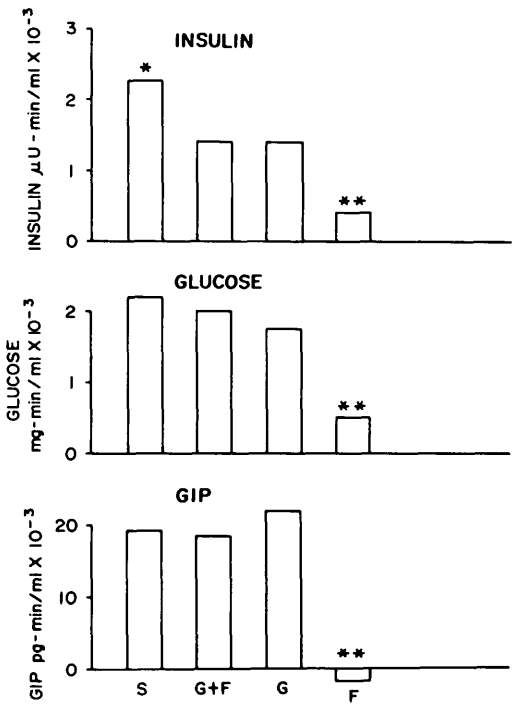

FIG. 5. *Integrated responses to test meals 0–60 min. Sucrose (S); Glucose (G); Glucose + Fructose (G + F); Fructose (F); Insulin: F = 9.38, P = 0.0001, LSD = 670 μU-min/ml. Glucose: F = 5.42, P = 0.0034, LSD = 943 mg-min/dl. GIP: F = 36.8, P = 0.0001, LSD = 4862 pg-min/ml.*

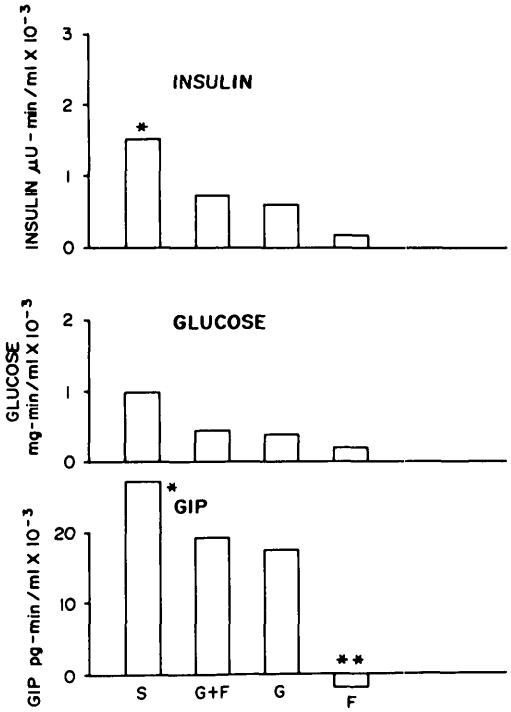

FIG. 6. *Integrated responses to test meals 60–120 min. Sucrose (S); Glucose (G); Glucose + Fructose (G + F); Fructose (F); Insulin: F = 4.15, P = 0.01, LSD = 715 μU-min/ml. Glucose: F = 0.74, P = 0.57, LSD = 1060 mg-min/dl. GIP: F = 29.25, P = 0.0001, LSD = 5816 pg-min/ml.*

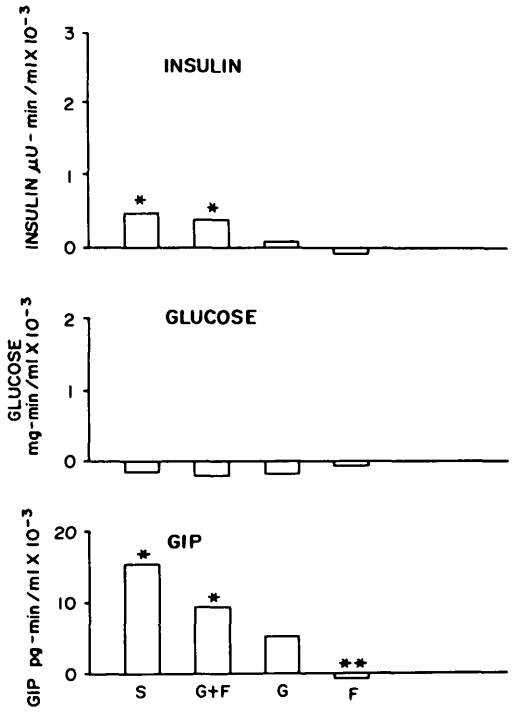

FIG. 7. *Integrated responses to test meals 120–180 min. Sucrose (S); Glucose (G); Glucose + Fructose (G + F); Fructose (F); Insulin: F = 6.97, P = 0.0009, LSD = 268 μU-min/ml. Glucose: F = 0.13, P = 0.97, LSD = 677 mg-min/dl. GIP: F = 23.85, P = 0.0001, LSD = 3892 pg-min/ml.*

(lower panel) was similar with sucrose, glucose + fructose, and glucose. There was not a significant GIP response to fructose.

Integrated responses 60–120 min (*Figure* 6). In the second hour of the study the insulin response (upper panel) to sucrose was again significantly greater than to glucose + fructose or to glucose alone. The responses to glucose + fructose, glucose, and fructose were not statistically different in this period. The glucose response to sucrose (middle panel) was greater than following the other three meals but the differences between the meals were not statistically significant. In this period the GIP response to sucrose (lower panel) was greater than to glucose or glucose + fructose.

Integrated responses 120–180 min (*Figure 7*). In this period the sucrose and glucose + fructose test meals led to significantly greater insulin responses (upper panel) and GIP responses (lower panel) than did glucose. The GIP response to sucrose was significantly greater than with glucose + fructose.

DISCUSSION

These results confirm the findings of Crapo et al.[1] that the insulin response to 100 g of oral sucrose is greater than that to 50 g of oral glucose even though the glucose content of the two preparations is similar. At all time points evaluated, the incremental insulin levels following sucrose were greater than for glucose so that during each of the 3 h of the study the integrated insulin response was significantly greater for sucrose. The purpose of the 100-g sucrose, 50-g glucose study design is to match the glucose content of sucrose to that of the glucose drink so that an augmented insulin response to sucrose could be attributed to factors other than its glucose content. However, 1.0 g of sucrose is the molar equivalent of 0.526 g of anhydrous glucose or 0.573 g of glucose monohydrate.[2] In this study glucose monohydrate was used and the glucose equivalent of the sucrose test solution was 14.6% greater than the glucose solution. It is possible that the increased insulin response could be attributed to this "extra" glucose in the sucrose since mean glucose levels were 14 mg/dl higher at 45 and 60 min after sucrose. However, the peak insulin response to sucrose was 69% greater than that following glucose and the integrated response to sucrose was 104% greater than that to glucose.

When fructose alone is ingested, most of the derived glucose is converted to liver glycogen but a significant rise of venous blood glucose does occur as demonstrated by the present and other studies.[5,17–20] Simultaneous with the glucose rise there is a significant increase in peripheral insulin levels. When the insulin response to 50 g of fructose was arithmetically added to the response to glucose alone, the combined insulin response curve was similar to that of sucrose only in the 0–60-min period.[21] The insulin levels achieved with oral

glucose are proportional to the glucose load, with larger doses of glucose yielding higher insulin levels.[22–25] Thus, the augmented insulin response to sucrose primarily in the first hour could be due to an increased glucose load[22–25] either as "extra" glucose and/or as the fructose moiety is metabolized to glucose[26,27] without a substantial increase in the glucose response levels.

Serum levels of gastric inhibitory polypeptide increased with glucose, sucrose, and glucose + fructose test meals but not with fructose (Figure 3). The largest stimulus to GIP secretion was provided by sucrose. Analysis of the integrated GIP responses showed that enhanced GIP secretion with sucrose occurred in the second and third hours (Figures 5–7). It is unlikely that osmolality played any role in the GIP response since mannitol or hypertonic saline does not elicit a GIP response in the intestine.[28] GIP's role in the enteroinsular axis is to augment insulin secretion at a time when it would normally occur.[8] Accordingly, although GIP is secreted with ingestion of glucose, fat, and amino acids, it is only with glucose and amino acids that it augments insulin secretion.[29,30] Glucose clamp studies in man have shown that the arterial level of serum glucose must rise 20 mg/dl for GIP to significantly augment insulin levels.[10] In the second hour of our sucrose study, the average venous glucose level was 17 mg/dl above basal so it is likely that GIP significantly affected insulin secretion during this period. Since the venous glucose levels in the third hour averaged slightly less than baseline and since arterial levels would be only 5–10 mg/dl greater,[31] the effect of GIP on insulin secretion during this time is not as clear. However, it is possible arterial venous differences in the concentration of glucose may have been substantial but this seems unlikely to have affected insulin secretion in view of the present findings. The integrated levels of both insulin and GIP were significant during this period (Figure 7). GIP secretion with oral glucose is dependent on the size of the glucose load and the effectiveness of intestinal transport.[24,32] By inhibiting glucose transport with phloridzin both GIP and insulin secretion are reduced.[32] Thus, it must be concluded that despite low venous glucose levels a significant quantity of glucose was absorbed during the third hour of the sucrose study leading to insulin and GIP secretion.

In the third postcibal hour, the glucose + fructose test meal led to integrated insulin and GIP responses that were similar to sucrose and significantly greater than with glucose (Figure 7). These findings with glucose + fructose and sucrose may be fructose mediated since this moiety is common to both solutions. It has been shown that fructose augments glucose-stimulated insulin secretion by adding to the substrate metabolized in the islets.[33] Following fructose ingestion, the venous levels of this sugar rise 3–10 mg/dl.[2,3] Since islet metabolism of fructose is about 1/10 the rate of glucose, it is unlikely that the 0.5 mM (9 mg/dl) fructose could contribute greatly to the substrate pool when the peripheral glucose level is 5 mM (90 mg/dl) or greater.[33] As shown in this study, and also in that of Ganda et al., oral fructose does not stimulate GIP secretion.[34] Therefore, the findings with sucrose or glucose + fructose cannot be attributed to a direct effect of fructose on GIP or insulin secretion.

The GIP curves following glucose + fructose and sucrose both showed prolonged responses with peak levels at 60–120 min postcibal (Figure 3). These were distinct from the curve with oral glucose where peak levels occurred at 30–60 min. Since GIP secretion seems to be coupled to glucose transport,[26,32] the delayed GIP secretion may be related to a delay in transport. There are separate intestinal transport pathways for fructose and glucose, so it is unlikely that fructose interfered directly with glucose transport.[18] The delay with sucrose could be attributed to the required hydrolysis by sucrose, however, this step is more rapid than glucose transport and therefore is not rate limiting.[27] Furthermore, the delay also occurred with the monosaccharide mixture. We conclude then that the prolonged GIP response to sucrose and glucose + fructose may represent a delay in gastric emptying and subsequent delay in intestinal glucose absorption. In this regard, Elias et al. demonstrated that fructose given alone as a test meal will inhibit gastric emptying.[35] Furthermore, glucose and fructose appear to be additive in this effect equaling the inhibition produced by an equal osmolar quantity of sucrose.[35]

To summarize our data, oral intake of 100 g of sucrose caused a significantly greater insulin response than 50 g of glucose in each of the 3 h following ingestion. The GIP response was greater with sucrose than glucose in the second and third postcibal hours. The increased GIP levels in the second hour probably augmented the sucrose-induced insulin levels and may have contributed to the increased insulin seen in the third hour. The prolonged response of GIP to the sucrose and glucose + fructose test meals may have reflected delayed gastric emptying and subsequent delayed glucose absorption. The increased insulin response in the first hour following sucrose could be attributed to the fructose moiety of sucrose, extra glucose equivalent of the sucrose test solution, or from endocrine mechanisms other than those subserved by GIP.

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REFERENCES

[1] Crapo, P. A., Reaven, G., and Olefsky, J.: Plasma glucose and insulin responses to orally administered simple and complex carbohydrates. Diabetes *25*: 741–47, 1976.

[2] Macdonald, I., and Turner, L. J.: Serum-fructose levels after sucrose or its constituent monosaccharides. Lancet *1*: 841–43, 1968.

[3] Macdonald, I., Keyser, A., and Pacy, D.: Some effects, in man, of varying the load of glucose, sucrose, fructose, or sorbitol on various metabolites in blood. Am. J. Clin. Nutr. *31*: 1305–11, 1978.

[4] Curry, D. L., Curry, K. P., and Gomez, M.: Fructose potentiation of insulin secretion. Endocrinology *91*: 1493–98, 1972.

[5] Bohannon, N. V., Karam, J. H., and Forsham, P. H.: Endocrine responses to sugar ingestion in man. J. Am. Diet. Assoc. *76*: 555–60, 1980.

[6] Brown, J. C., and Otte, S.: Clinical studies with gastric inhibitory polypeptide. World J. Surg. *3*: 553–58, 1979.

[7] Dupre, J., Ross, S. A., Watson, D., and Brown, J. C.: Stimulation of insulin secretion by gastric inhibitory polypeptide in man. J. Clin. Endocrinol. Metab. *37*: 826–28, 1973.

[8] Creutzfeldt, W.: The incretin concept today. Diabetologia *16*: 75–85, 1979.

[9] Pederson, R. A., and Brown, J. C.: The insulinotropic action of gastric inhibitory polypeptide in the perfused isolated rat pancreas. Endocrinology *99*: 780–85, 1976.

[10] Anderson, D. K., Elahi, D., Brown, J. C., Tobin, J. D., and Andres, R.: Oral glucose augmentation of insulin secretion. J. Clin. Invest. *62*: 152–61, 1978.

[11] Reiser, S., Michaelis, O. E., IV, Cataland, S., and O'Dorisio, T. M.: Effect of isocaloric exchange of dietary starch and sucrose in humans on the gastric inhibitory polypeptide response to a sucrose load. Am. J. Clin. Nutr. *33*: 1907–11, 1980.

[12] Desbuquois, B., and Aurbach, G. D.: Use of polyethylene glycol to separate free and antibody-bound peptide hormones in radioimmunoassay. J. Clin. Endocrinol. Metab. *33*: 732–38, 1971.

[13] Kuzio, M., Dryburgh, J. R., Malloy, K. M., and Brown, J. C.: Radioimmunoassay for gastric inhibitory polypeptide. Gastroenterology 66: 357–64, 1974.

[14] Johnson, R. E., and Kiokemeister, F. L.: Calculus with Analytical Geometry. Boston, Allyn and Bacon, Inc., 1960, p. 258.

[15] S. A. S. Version 79.3A. Statistical Analysis System Institute, Inc., P.O. Box 10066, Raleigh, North Carolina.

[16] Steel, R. G. D., and Torrie, J. H.: Principles and Procedures of Statistics. New York, McGraw-Hill Book Co., Inc., 1960, p. 106.

[17] Swan, D. C., Davidson, P., and Albrink, M. J.: Effect of simple and complex carbohydrates on plasma non-esterified fatty acids, plasma-sugar, and plasma-insulin during oral carbohydrate tolerance tests. Lancet *1*: 60–63, 1966.

[18] Gray, G. M.: Carbohydrate digestion and absorption. N. Engl. J. Med. *292*: 1225–30, 1975.

[19] Cook, G. C.: Absorption products of D(-) fructose in man. Clin. Sci. Mol. Med. *37*: 675–87, 1969.

[20] Crapo, P. A., Kolterman, O. G., and Olefsky, J. M.: Effects of oral fructose in normal, diabetic, and impaired glucose tolerance subjects. Diabetes Care 3: 575–81, 1980.

[21] Reynolds, J. C., Falko, J. M., O'Dorisio, T. M., and Cataland, S.: The role of gastric inhibitory polypeptide in the hyperinsulin response to oral sucrose. Clin. Res. *28*: 232A, 1980.

[22] Sisk, C. W., Brunham, C. E., Stewart, J., and McDonald, G. W.: Comparison of the 50- and 100-gram oral glucose tolerance test. Diabetes *19*: 852–62, 1970.

[23] de Nobel, E., and van't Laar, A.: The size of the loading dose as an important determinant of the results of the oral glucose tolerance test. Diabetes *27*: 42–48, 1978.

[24] Falko, J. M., Crockett, S. E., Cataland, S., O'Dorisio, T. M., Kramer, W., and Mazzaferri, E. L.: The effect of increasing doses of ingested glucose on insulin and gastric inhibitory polypeptide (GIP) concentrations in man. Clin. Endocrinol. *13*: 587–93, 1980.

[25] Forster, H., Haslbeck, M., and Mehnert, H.: Metabolic studies following the oral ingestion of different doses of glucose. Diabetes *21*: 1102–1108, 1972.

[26] Sykes, S., Morgan, L. M., English, J., and Marks, V.: Evidence for preferential stimulation of gastric inhibitory polypeptide secretion in the rat by actively transported carbohydrates and their analogues. J. Endocrinol. *85*: 201–207, 1980.

[27] Gray, G. M., and Ingelfinger, F. J.: Intestinal absorption of sucrose in man: interrelation of hydrolysis and monosaccharide product absorption. J. Clin. Invest. *45*: 388–98, 1966.

[28] O'Dorisio, T. M., Spaeth, J. T., Martin, E. W., Sirenek, K. R., Thomford, N. R., Mazzaferri, E. L., and Cataland, S.: Mannitol and glucose: effects on gastric acid secretion and endogenous gastric inhibitory polypeptide (GIP). Am. J. Dig. *23*: 1079–83, 1978.

[29] Crockett, S. E., Cataland, S., Falko, J. M., and Mazzaferri, E. L.: The insulinotropic effect of endogenous gastric inhibitory polypeptide in normal subjects. J. Clin. Endocrinol. Metab. *42*: 1098–103, 1976.

[30] Thomas, E. B., Mazzaferri, E. L., Crockett, S. E., Mekhjian, H. S., Gruemer, H. D., and Cataland, S.: Stimulation of secretion of gastric inhibitory polypeptide and insulin by intraduodenal amino acid perfusion. Gastroenterology *70*: 523–27, 1976.

[31] Whichelow, M. J., Wigglesworth, A., Cox, W. J., Butterfield, J. H., and Abrams, M. E.: Critical analysis of blood sugar measurements in diabetes detection and diagnosis. Diabetes *16*: 219–26, 1967.

[32] Ebert, R., and Creutzfeldt, W.: Decreased GIP secretion through impairment of absorption. Front Hormone Res. *7*: 192–201, 1980.

[33] Zawalich, W. S., Rognstad, R., Pagliara, A. S., and Matschinsky, F. M.: A comparison of the utilization rates and hormone-releasing actions of glucose, mannose, and fructose in isolated pancreatic islets. J. Biol. Chem. *252*: 8519–23, 1977.

[34] Ganda, O. P., Soeldner, J. S., Gleason, R. E., Cleator, I. G. M., and Reynolds, C.: Metabolic effects of glucose, monnose, galactose, and fructose in man. J. Clin. Endocrinol. Metab. *49*: 616–22, 1979.

[35] Elias, E., Gisbon, G. J., Greenwood, L. F., Hunt, J. N., and Tripp, J. H.: The slowing of gastric emptying by monosaccharides and disaccharides in test meals. J. Physiol. *194*: 317–26, 1968.