Elevated Plasma Glucose–Dependent Insulinotropic Polypeptide Associates With Hyperinsulinemia in Impaired Glucose Tolerance

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OBJECTIVE — The role of gut-derived incretin, glucose-dependent insulinotropic polypeptide (also known as gastric inhibitory peptide [GIP]), in compensatory β-cell hypersecretion during insulin-resistant states and in transition to β-cell failure in type 2 diabetes is unknown.

RESEARCH DESIGN AND METHODS — We carried out oral glucose tolerance testing followed by blood sampling 10 times for 2 h on 68 age- and BMI-matched participants of the Baltimore Longitudinal Study on Aging (BLSA) with normal glucose tolerance (34 subjects), impaired glucose tolerance (IGT) (18 subjects with both impaired fasting and 2-h plasma glucose levels), and type 2 diabetes (16 subjects with both diabetic fasting and 2-h plasma glucose levels). We assayed plasma glucose, insulin, C-peptide, glucagon, and intact and total GIP levels and quantitated glucose and hormone responses to the oral glucose tolerance test. We also compared GIP and insulin release and sensitivity indexes between groups.

RESULTS — After glucose ingestion, subjects with IGT had both hyperinsulinemia and hyperemia, while subjects with type 2 diabetes had both β- and GIP-cell deficiency. In the former group, there was also a significant positive correlation between the augmented plasma intact and total GIP levels and both fasting and post–oral glucose load plasma insulin levels.

CONCLUSIONS — Elevated plasma GIP levels are correlated with hyperinsulinemia in the impaired glucose-tolerant state, whereas type 2 diabetes is associated with a failure to secrete adequate amounts of both GIP and insulin, indicating a common pathway of resistance to and eventually failure of glucose responsiveness in β- and GIP-cells.

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In patients with type 2 diabetes, β-cells within the islets of Langerhans in the pancreas fail to meet the increased need for insulin created by the insulin-resistant state (1). Before β-cell failure occurs, however, subjects compensate for insulin resistance for many years by increasing their secretory capacity, resulting in hyperinsulinemia (2). The failure of β-cells to continue to hypersecrete insulin underlies the conversion to clinical diabetes. The term enteroinsular axis (3) encompasses the neuro-humoral interactions long thought to exist between the endocrine pancreas and gut cell populations. In fact, the enteroendocrine system constitutes the largest system of endocrine cells in humans, both in terms of number of cells and variety of hormones produced (4). Islets of Langerhans also lie in this system, as well as the incretin-producing cells of the gut, which synthesize and release vital mediators of food-stimulated, glucose-dependent insulin secretion, which account for up to 60% of the insulin secretory response following an oral glucose load (5). The two main, if not the only physiologically relevant, incretins are glucose-dependent insulinotropic polypeptide (also known as gastric inhibitory peptide [GIP]) and glucagon-like peptide-1 (GLP-1) (6,7). The proGIP gene is expressed in gut K-cells, the majority of which are located in duodenum and upper jejunum (8). The proglucagon gene is expressed in islet α-cells, L-cells throughout the gut [most are thought to reside in lower jejunum, terminal ileum, and ascending colon (9,10)] and specialized neurons (11); both circulating incretin peptides are rapidly inactivated as insulinotropic factors by tissue and plasma dipeptidyl peptidase IV (DPP IV) by proteolytic cleavage of their first two NH_2-terminal amino acids (12). They both exert their insulinotropic effects by binding to highly specific guanosine 5′-triphosphate–binding protein–coupled receptors on the β-cell (13,14).

The possible dysregulation of incretin release or action in the pathogenesis of type 2 diabetes has not been firmly established. In contrast to GLP-1, which retains its potency as an insulinotropic factor, GIP action is clearly diminished in type 2 diabetes (15,16). The aim of the present study was to investigate whether circulating GIP is associated with the hyperinsulinemia before onset of β-cell failure and whether any dysregulation of its secretion could be linked to impaired glucose tolerance (IGT) during the insulin-resistant state or transition to type 2 diabetes. Insulin secretory defects can arise secondarily because of hyperglycemia, per se. Therefore, studying GIP secretion before onset of type 2 diabetes might help elucidate the pathophysiology of β-cell failure.

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Abbreviations: AUC, area under the curve; BLSA, Baltimore Longitudinal Study on Aging; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Subject characteristics*

	Normal glucose tolerance	IGT	Type 2 diabetes
n	34	18	16
Age (years)	69.6 ± 2.3	72.3 ± 2.3	72.1 ± 2.3
Range			
Race (%)	39–91	48–86	59–87
Caucasian (*n*)	76	83	62
African American (*n*)	21	11	25
Other (Hispanic, Chinese, etc.)	3	6	13
Sex (*n*)			
Female	15	5	3
Male	19	13	13
HbA_{1c} (%)*	5.28 ± 0.51	5.71 ± 0.54†	6.95 ± 0.88†‡
BMI (kg/m^2)	27.5 ± 0.8	28.9 ± 0.6	29.3 ± 0.9
Range	19–39	25–34	23–37
Fasting plasma glucose (mmol/l)	5.04 ± 0.08	6.37 ± 0.05†	8.19 ± 0.24†‡
Fasting plasma insulin (pmol/l)	37 ± 4	57 ± 6	61 ± 7†
Fasting plasma C-peptide (nmol/l)	0.62 ± 0.07	0.77 ± 0.08	0.89 ± 0.11
Fasting plasma glucagon (ng/l)	60 ± 10	77 ± 5	101 ± 11†
Intact fasing plasma (GIP (NH_2-terminal, pmol/l)	30 ± 3	47 ± 4†	30 ± 3‡
Total fasting plasma GIP (pmol/l)	33 ± 4	50 ± 4†	44 ± 3†
HOMA-IR	1.39 ± 0.16	2.69 ± 0.29	3.71 ± 0.45†‡
Insulinogenic index	0.88 ± 0.09	0.53 ± 0.10	0.36 ± 0.12†
Total cholesterol (mmol/l)	4.90 ± 0.18	4.78 ± 0.16	4.65 ± 0.23
HDL cholesterol (mmol/l)	1.55 ± 0.07	1.22 ± 0.05†	1.11 ± 0.06†
LDL cholesterol (mmol/l)	2.92 ± 0.16	2.99 ± 0.13	2.64 ± 0.18
Triglycerides (mmol/l)	0.91 ± 0.07	1.45 ± 0.16	1.92 ± 0.23†

Data are means ± SE, unless otherwise indicated. *Values are means ± SD. †Statistically significant difference compared with subjects with normal glucose tolerance; ‡statistically significant difference compared with subjects with IGT.

RESEARCH DESIGN AND METHODS

— We screened Baltimore Longitudinal Study on Aging (BLSA) participants not taking prescribed glucose-lowering medications who had oral glucose tolerance tests (OGTTs) during their most recent visit. Of these, we recruited 18 subjects with both impaired fasting and 2-h plasma glucose levels (6.1–6.9 and 7.8–11.0 mmol/l, respectively), 16 with newly diagnosed type 2 diabetes (by both fasting plasma glucose ≥7.0 and 2-h plasma glucose ≥11.1 mmol/l), and 34 age- and BMI-matched subjects classified with normal fasting and 2-h glucose levels to undergo a modified OGTT. Characteristics of our study population are shown in Table 1. The Committee on Human Investigation of our institution approved the study. All volunteers were informed about the nature of the study and provided written informed consent, in accordance with the Declaration of Helsinki II.

Modified OGTT in BLSA subjects

In the morning, after an overnight fast, blood was first obtained for lipid levels and HbA_{1c} determinations. Sampling of fasting plasma was also collected at baseline (time 0), after which participants drank 75 g glucose in 300 ml solution (SunDex; Fisherbrand, Pittsburgh, PA), and nine more blood samples were subsequently drawn at 5, 10, 15, 20, 40, 60, 80, 100, and 120 min after oral glucose for measurements of plasma glucose, insulin, C-peptide, glucagon, and intact and total GIP levels. To assess early-phase insulin secretion, we used the insulinogenic index (17), calculated as the ratio of the increment in the plasma insulin level (in microunits per milliliter) to that in the plasma glucose level (in milligrams per deciliter) during the first 20 min after ingestion of glucose—the lower the index, the worse the insulin secretion. To estimate an insulin resistance index, we used the homeostasis model assessment for insulin resistance (HOMA-IR) (18), calculated as the product of fasting insulin (in microunits per milliliter) and fasting glucose (in millimoles per liter) divided by 22.5. Lower indexes indicate better insulin sensitivity. We estimated the incremental changes for plasma insulin, C-peptide, and intact and total GIP levels between 0–20 and 20–120 min postchallenge and calculated the area under the curve (AUC) for the same plasma hormone concentrations versus time by the trapezoidal rule. The bodyweight and height of subjects were measured manually by a medical scale (SECA, Hanover, MD), and BMI was calculated as body weight in kilograms divided by the square of the height in meters.

Plasma hormone and biochemical assays

We assayed plasma samples for insulin and C-peptide by enzyme-linked immunosorbent assay (ELISA) (ALPCO Diagnostics, Windham, NH) with a detection limit of 1 μU/ml and 20 pmol, respec-

tively. Cross-reactivity of the insulin antibody for C-peptide and vice versa was <0.1%. We measured plasma glucagon by radioimmunoassay (Linco Research, St. Charles, MO), with a detection limit of 2 pg (100 μl plasma). We used an NH_2-terminally directed ELISA for plasma intact GIP determinations (Peninsula Laboratories, San Carlos, CA), since reports (19) suggest that such an approach yields optimal accuracy, with a detection level of 0.1 pmol (50 μl plasma), as well as a radioimmunoassay for total plasma GIP determinations (Phoenix Laboratories, Belmont, CA) with a detection level of 4 pmol (100 μl plasma). The intra-assay variation coefficients for intact GIP, total GIP, insulin, C-peptide, and glucagon were 5, 23, 3.6, 3.6, and 4.8%, respectively, and the interassay variation coefficients were 14, 0, 2.5, 3.3, and 12%, respectively. Blood used for all GIP determinations was collected in EDTA-coated tubes (1.5 μg/ml blood) containing aprotinin (40 μl/ml blood; Trasylol, Serological Proteins, Kankakee, IL) and an inhibitor of dipeptidyl peptidase IV (#DDP4, 10 μl/ml blood; Linco Research). We processed all samples from each subject for intact GIP immediately without freezing and performed all assays in duplicate. Total GIP levels were all assayed at the same time in aliquots that had been frozen just once; hence there was no interassay variation. We measured plasma glucose levels with a glucose analyzer (Beckman Instruments, Brea, CA) and HbA_{1c} with an automated DiaSTAT analyzer (Bio-Rad Laboratories, Hercules, CA). Plasma lipid levels were determined by the Clinical Core Laboratory Unit (Research Resources Branch, NIA/NIH) using an AutoAnalyzer (Synchron CX-5; Beckman Instruments).

Statistical analysis

All data were analyzed using SAS 8.2 software (SAS Institute, Cary, NC). All values are expressed as means ± SE (values for HbA_{1c} are displayed as means ± SD). Standard methods were used to compute means and SE. Repeated-measures ANOVA and Bonferroni's multiple comparison post hoc test were used to compare mean values of glucose and hormone levels, whereas one-way ANOVA with the same post hoc test was used to compare means of HOMA-IR, insulinogenic index, age, BMI, HbA_{1c}, lipids, incremental changes, and AUC in plasma hormone levels among the three groups. All data were normally distributed (Kolmogorov and Smirnov test). Simple Pearson correlation was performed between plasma insulin and plasma intact and total GIP levels (both nontransformed and log-transformed values were used because of significant variability exhibited by the relatively small population of subjects with IGT) at various time points followed by linear regression analysis. All significance tests for the comparisons were two sided, and P values <0.05 were regarded as indicating statistical significance.

RESULTS — Subjects with type 2 diabetes had a metabolic profile typical for this syndrome (Table 1): significantly higher insulin resistance indexes, HbA_{1c}, and triglyceride levels, coupled with lower HDL cholesterol levels compared with subjects with normal glucose tolerance. Subjects with IGT also had significantly elevated HbA_{1c} and lower HDL cholesterol levels.

Fasting glucose, insulin, C-peptide, and glucagon levels and their responses to oral glucose

In the impaired state, fasting plasma insulin levels were similar to normal, but hyperinsulinemia was evident after 40 min, with a later increase in C-peptide values (Table 1, Fig. 1). Type 2 diabetic subjects had increased fasting plasma insulin levels and a significantly reduced insulinogenic index from 0 to 20 min after oral glucose compared with subjects with normal glucose tolerance (Table 1, Fig. 1). Subjects with IGT also had reduced insulinogenic index, but it was not significantly different compared with diabetic individuals. As previously demonstrated (20), fasting glucagon levels were significantly higher in subjects with type 2 diabetes (Table 1), and at 120 min levels still remained almost twofold higher compared with the normal glucose-tolerant state (Fig. 1). Subjects with IGT had similar fasting glucagon levels as subjects with normal glucose tolerance, which were suppressed by the subsequent glucose load, again similar to normal glucose-tolerant subjects.

For the entire duration of the OGTT, plasma concentrations, the AUCs, and the incremental changes for glucose were significantly higher in subjects with impaired or diabetic glucose tolerance compared with subjects with normal glucose tolerance (Fig. *1*). Plasma concentrations, AUC estimates, and incremental change values for insulin during the first 20 min were significantly elevated in subjects with normal glucose tolerance compared with the other two groups (Fig. 1, Table 2). Notably, however, subjects with diabetes had lower incremental insulin and C-peptide estimates compared with the other two groups. Hyperinsulinemia in the glucose-impaired subjects, compared with the other two groups, is also reflected at the significantly higher insulin AUC estimates between 20 and 120 min postchallenge and by the significantly higher insulin and C-peptide incremental changes during the same time period in subjects with IGT compared with subjects in the other two groups. (Fig. 1, Table 2).

Fasting GIP levels and GIP response to oral glucose

Subjects with impaired and diabetic glucose tolerance had significantly higher GIP plasma levels (50 ± 4 and 44 ± 3 pmol/l, respectively) compared with subjects with normal glucose tolerance (33 ± 4 pmol/l) (Table 1, Fig. 1). After oral glucose, peak total GIP secretion was clearly much greater in subjects with IGT than in the other two groups, which were not statistically different from one other (Fig. 1). The AUC for total GIP from 0 to 20 min in subjects with IGT was significantly greater compared with the other two groups (Table 2). Moreover, from 20 to 120 min, total GIP plasma levels were significantly higher in subjects with IGT compared with subjects with normal glucose tolerance.

Subjects with IGT also exhibited significantly higher incremental total GIP changes than subjects with normal glucose tolerance during the first 20 min postglucose (Table 2).

Fasting plasma intact GIP levels were significantly higher in subjects with IGT (47 ± 4 pmol/l) compared with subjects with type 2 diabetes (30 ± 3 pmol/l) and normal glucose tolerance (30 ± 3 pmol/l) (Table 1, Fig. 1). After oral glucose, intact GIP secretion in subjects with IGT paralleled the secretion pattern of total GIP and was far greater than that in the other two groups, which were not statistically different from one other (Table 2). The AUC for intact GIP from 0 to 20 min in subjects with IGT was almost twice that of the other two groups (Table 2). Moreover,

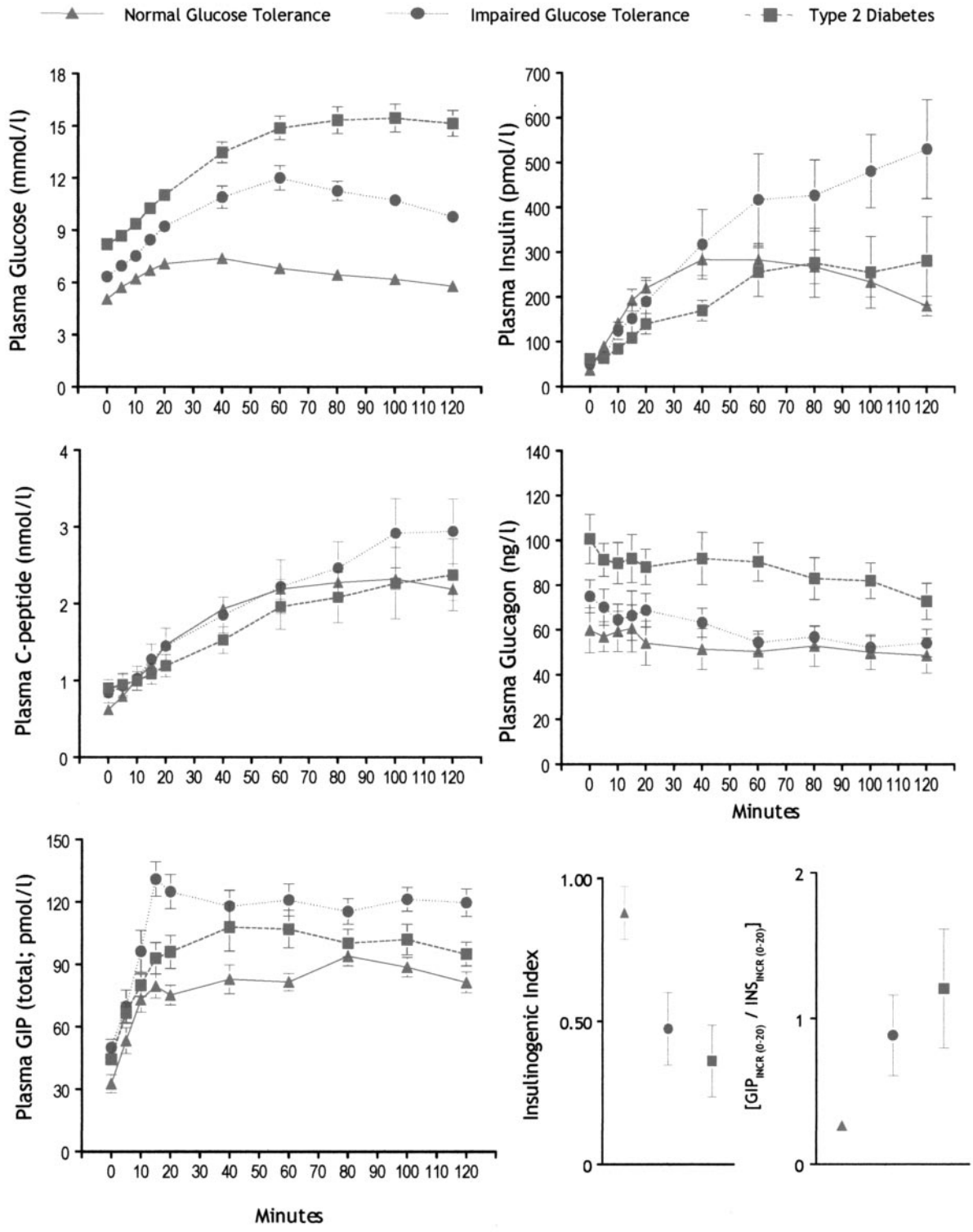

Figure 1—*Mean ± SE plasma glucose, insulin, C-peptide, glucagon, total GIP responses, the insulinogenic index (from 0 to 20 min), and the ratio of plasma insulin to total plasma GIP increment (from 0 to 20 min) during the OGTT in our study population. Glucose (75 g) was administered at time 0.*

from 20 to 120 min, the AUC in subjects with IGT increased by 60 and 94% compared with subjects with normal glucose tolerance and type 2 diabetes, respectively. Subjects with IGT exhibited significantly higher incremental intact GIP changes than subjects with normal glucose tolerance both during the first 20 min postglucose and up to the 2-h time point (Table 2).

As a composite measure of the early GIP and insulin secretory response fol-

Table 2 —*AUC measurements and incremental changes during the oral glucose tolerance test in our study population.*

	Insulin (pmol · l^{-1} · min^{-1})	C-peptide (nmol · l^{-1} · min^{-1})	Intact GIP (pmol · l^{-1} · min^{-1})	Total GIP (pmol · l^{-1} · min^{-1})
AUC 0–20 min				
Normal glucose tolerance	2,757 ± 301	21.0 ± 1.4	1,358 ± 103	1,526 ± 132
IGT	2,401 ± 356	24.0 ± 5.1	2,193 ± 274*	2694 ± 326*
Type 2 diabetes	1,780 ± 238*	20.0 ± 2.6	1,125 ± 127†	1629 ± 96†
AUC 20–120 min				
Normal glucose tolerance	25,329 ± 2990	211 ± 11	7,486 ± 618	9,948 ± 438
IGT	37,386 ± 8,312*	247 ± 34	10,138 ± 995*	13,281 ± 223*
Type 2 diabetes	23,327 ± 5,728†	192 ± 30	5,894 ± 672†	11,006 ± 184
AUC increment Δ0–20 min				
Normal glucose tolerance	183 ± 21	0.80 ± 0.07	35 ± 4	43 ± 6
IGT	143 ± 37	0.60 ± 0.35	65 ± 16*	78 ± 5*
Type 2 diabetes	78 ± 20*	0.30 ± 0.06*	36 ± 5†	61 ± 6
AUC increment Δ20–120 min				
Normal glucose tolerance	−40 ± 22	0.70 ± 0.14	−12 ± 4	6 ± 7
IGT	353 ± 78*	1.4 ± 0.5*	−31 ± 14*	9 ± 6
Type 2 diabetes	141 ± 80*	1.18 ± 0.37*	−20 ± 6	−11 ± 10

Data are means ± SE. *Statistically significant difference compared with subjects with normal glucose tolerance; †statistically significant difference compared with subjects with IGT. Minus symbol denotes decreasing values (towards baseline).

lowing the oral glucose load, the calculated ratio of the increment in plasma total GIP over the increment in plasma insulin levels during the first 20 min (Δ_{0-20}) postchallenge ($iGIR_{0-20}$ [GIR, glucose infusion rate]) (Fig. 1) was significantly higher in subjects with IGT (0.85 ± 0.40, $P < 0.05$) or type 2 diabetes (1.26 ± 0.70, $P < 0.05$) compared with subjects with normal glucose tolerance (0.31 ± 0.03), suggesting both early hypersecretion of GIP compared with insulin in IGT and inadequate GIP secretory response in type 2 diabetes, which tends to match the ineffective early-phase insulin secretion, a result of the absolute insulin-deficient state that type 2 diabetes represents.

The relationship between plasma insulin and total GIP values at various time points was also investigated. There was a positive correlation between postchallenge plasma total GIP levels with fasting and postchallenge plasma insulin levels in subjects with IGT (Pearson's correlation coefficient $r = 0.46$, between 2-h plasma levels of insulin and total GIP). Furthermore, in this group the association becomes significant between postchallenge total GIP plasma levels and fasting and 2-h plasma hyperinsulinemic responses ($r = 0.64$, between 2-h plasma levels of insulin and total GIP; values log transformed for analysis). In a similar fashion, there was also a positive correlation between fasting and postchallenge plasma insulin and postchallenge plasma intact GIP values.

CONCLUSIONS — The evolution of type 2 diabetes is related to developing insulin resistance and progressive β-cell dysfunction. Factors stimulating β-cell hypersecretion in insulin-resistant states are unknown, but our study indicates that GIP elaboration is an associated factor. Earlier reports (21) suggested, as does ours, that GIP secretion is similar in type 2 diabetes and normal glucose-tolerant states. K-cell function in the subjects with impaired fasting and 2-h postglucose challenge plasma levels has not previously been studied. Upon the transition to diabetes, β-cells no longer hypersecrete insulin and early β-cell response to glucose is diminished, concomitant with decreased GIP secretion, along with lower effectiveness of GIP as an insulinotropic factor in type 2 diabetes. Therefore, type 2 diabetes is a result of both β- and K-cell hyporesponsiveness to glucose. The importance of GIP to early insulin secretion and high-insulin-demand states is demonstrated in GIP-receptor knockout mice (22)—early insulin secretion is diminished in response to an oral glucose load, and when fed a high-fat diet, mice fail to show a compensatory increase in insulin secretion. Loss of early-phase insulin secretion has severe consequences for glucose homeostasis in that insulin-sensitive tissues are not adequately primed to transport glucose (23), and glucagon secretion (Fig. 1), free fatty acid secretion, and hepatic glucose output are not suppressed (24), resulting in continued delivery of glucose to the circulation, thus aggravating postprandial glycemia. The nutrient-elicited chemosensory and signaling mechanisms from the appearance of breakdown products of food in the duodenum (where the bulk of K-cells reside), triggering incretin release from entero-endocrine cells are unknown.

In subjects with IGT but not diabetes, not only are fasting plasma levels of GIP elevated, but there is also augmented GIP secretory response to the oral glucose load. Relative insensitivity of gut K-cells to intestinal glucose, coupled with desensitization of the GIP receptor (25), following prolonged exposure to increased GIP plasma levels in the impaired state are the likely causes of the dysregulation of GIP secretion shown here and action (15,16) seen in type 2 diabetes. Overall, in the presence of glucose intolerance there is a weaker insulin response to endogenous GIP released after an OGTT, as also demonstrated by the incremental plasma level change ratio, indicating inappropriate and ineffective GIP hypersecretion due to β-cell resistance to GIP.

GIP receptors are widely distributed outside of β-cells and may have effects on

multiple other tissues such as adipocytes (26), adrenal glands (27), endothelium (28), and brain (29). Originally described as a "gastric inhibitory peptide" due to its potent inhibition of gastric acid secretion, GIP has other diverse effects. In fat tissue, for example, receptor activation leads to increased uptake of substrates (7), and GIP also helps clear triglycerides from plasma (30). If such action was also defective, it could contribute to the hypetriglyceridemia of impaired glucose-tolerant states. GIP also has anabolic effects on bone-derived cells and GIP administration–prevented bone loss associated with ovariectomy in rodents (31,32). Thus, GIP may play an integrative role in peripheral tissues by helping coordinate targeted nutrient absorption and distribution, a homeostatic control mechanism in which disruption could be associated with hallmarks of glucose intolerance and characteristic features of the metabolic syndrome. In addition, studies have demonstrated an obligatory role for GIP signaling in the development of obesity (33), in accordance with earlier evidence indicating that obese subjects exhibit greater postchallenge GIP excursions compared with appropriately matched control subjects (34), thus further supporting its potential implication in the pathogenesis of insulin resistance preceding the onset of type 2 diabetes.

Insulin receptor signaling in β-cells plays an important role in maintaining β-cell function and mass, and it also plays a role in regulating adequate levels of the glucose-sensing genes glucokinase and GLUT2, as has been demonstrated in β-cell insulin-receptor knockout mice (35). It is possible that in humans, long-term insulin receptor resistance leads to defective signaling of the glucose-sensing genes, not only in β-cells, but also in K-cells of the duodenum, leading in turn to deficient secretion of both insulin and GIP in response to increasing glucose levels in plasma and gut, respectively.

We understand that an inherent limitation of our studies lies in the lack of definitive mechanistic conclusions regarding glucose dependence of GIP and insulin secretion in humans. However, based on those findings, we are currently investigating potential mechanisms in vitro.

One approach to treatment of type 2 diabetes is directed toward sensitizing β-cells to postprandial glucose and restoring endogenous insulin secretion before irreversible β-cell failure occurs. Pharmacological concentrations of exogenous GLP-1 have been shown to normalize blood glucose levels and to restore early-phase insulin secretion in type 2 diabetes (36) and, in the process, restoring "glucose competence" to β-cells. In contrast, this has not been shown with GIP infusions (15,16), implying that the pathology of diabetes causes K-cell malfunction (as shown from the present data) and a breakdown specifically of GIP receptor signaling. Pharmacological agents that could restore "GIP competence" might be valuable as therapeutic modalities.

In summary, this study suggests that GIP hypersecretion significantly modulates insulin secretion in insulin-resistant states and that β-cell failure in type 2 diabetes is associated with K-cell failure. Therefore, type 2 diabetes might be rightly described as being due to both β-cell failure and GIP dysregulation.

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