Is the Diminished Incretin Effect in Type 2 Diabetes Just an Epi-Phenomenon of Impaired β-Cell Function?

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Type 2 diabetes is characterized by a deficit in β-cell mass, impaired insulin secretion in response to various stimuli (1–3), as well as a variable extent of insulin resistance (4). More specifically, regarding β-cell function, a significant reduction of the incretin effect, i.e., the postprandial augmentation of insulin secretion by gut hormones, has been described in patients with type 2 diabetes (5). Thus, while the two incretin hormones gastric inhibitory polypeptide (glucose-dependent insulinotopic polypeptide [GIP]) and glucagon-like peptide 1 (GLP-1) are held responsible for ~50–70% of the postprandial insulin responses in healthy individuals (6), their contribution to the overall insulin responses after oral glucose ingestion may amount to <20% in patients with type 2 diabetes (5,7). The reasons underlying the loss of incretin activity in type 2 diabetes are still incompletely understood. The present article reviews the available evidence regarding disturbances in the enteroinsular axis in patients with type 2 diabetes and provides possible explanations for their etiologies, focusing on the personal experience of the authors.

Secretion of incretin hormones in patients with type 2 diabetes. Because the incretin effect has been related to the secretion and insulinotropic action of GIP and GLP-1 (8,9), it was obvious to compare these parameters between patients with type 2 diabetes and healthy control subjects: Regarding the secretion of GIP, elevated, normal, and reduced plasma levels have been described in patients with type 2 diabetes (10–15). However, taking together all the evidence available, the secretion of GIP appears to be relatively unchanged in type 2 diabetic patients. For GLP-1 release, the case is even more complex. Several studies have reported significant reductions in GLP-1 levels after mixed meal ingestion in patients with type 2 diabetes (10,16,17). In addition, one study has found minor impairments in GLP-1 levels in individuals with impaired glucose tolerance (IGT) (16). However, upon more careful evaluation, the defects in GLP-1 secretion in these patients with type 2 diabetes were only found ~2–3 h after meal ingestion, whereas GLP-1 levels were rather unaltered in the immediate postprandial period. Thus, the observed impairments in GLP-1 release do not seem to coincide with the alterations in insulin secretion typically found in patients with type 2 diabetes. Furthermore, these reports are contrasted by a number of other studies showing normal GLP-1 responses in type 2 diabetic patients compared with healthy individuals (11,18–20). Overall, GLP-1 concentrations appear to be highly variable between individuals, both with and without type 2 diabetes, mean values being relatively normal in most groups with type 2 diabetes (18), suggesting that impaired GLP-1 release is not a typical prerequisite for the development of the disease (21). Figure 1 depicts the integrated GLP-1 levels after oral glucose ingestion in relation to the respective glucose concentrations in the fasting state and 120 min after oral glucose ingestion in 48 individuals with different degrees of oral glucose tolerance (11).

Insulinotropic effect of incretin hormones in type 2 diabetes. The relatively normal secretion of GIP and GLP-1 is contrasted by their diminished activity in patients with type 2 diabetes. In the case of GLP-1, the insulinotropic activity is usually referred to as being largely preserved in patients with type 2 diabetes, which has led to the broad utilization of its glucose-lowering potential in the pharmacotherapy of type 2 diabetes (22). However, upon careful examination, the amount of insulin released in response to a supra-physiological GLP-1 infusion during hyperglycemic clamp conditions has also been found to be reduced by ~29% compared with healthy control subjects (23). Furthermore, studies applying a graded glucose infusion protocol have demonstrated a significant impairment in the β-cell responsiveness to the combined administration of GLP-1 and glucose (24). However, the extent to which the insulinotropic activity of GLP-1 is reduced in patients with type 2 diabetes appears to be less pronounced than the defects found in response to intravenous glucose (25) and can almost be fully compensated for by raising GLP-1 plasma concentrations to higher levels (24). By these means, the hyperglycemia in patients with type 2 diabetes can readily be normalized by the intravenous administration of GLP-1 (26), even at relatively low doses (27). Taken together the available evidence, there does not seem to be a severe impairment in GLP-1 action in patients with type 2 diabetes. The modest impairments in insulin release found during GLP-1 administration are most likely a consequence of the general impairment in β-cell function in patients with type 2 diabetes (2).

For GIP, a marked impairment in the insulinotropic activity has uniformly been described in all studies administering the hormone to patients with type 2 diabetes (23,28–31). Thus, during hyperglycemic clamp conditions, an intravenous infusion of GIP in patients with type 2 diabetes elicited only 46% of the insulin responses found in healthy control subjects (23). Unlike with GLP-1, this lack of insulinotropic efficacy cannot be offset by raising GIP doses even to highly supra-physiological concentrations (30). Interestingly, the loss of GIP activity seems to be more pronounced during its continuous infusion than after an intravenous

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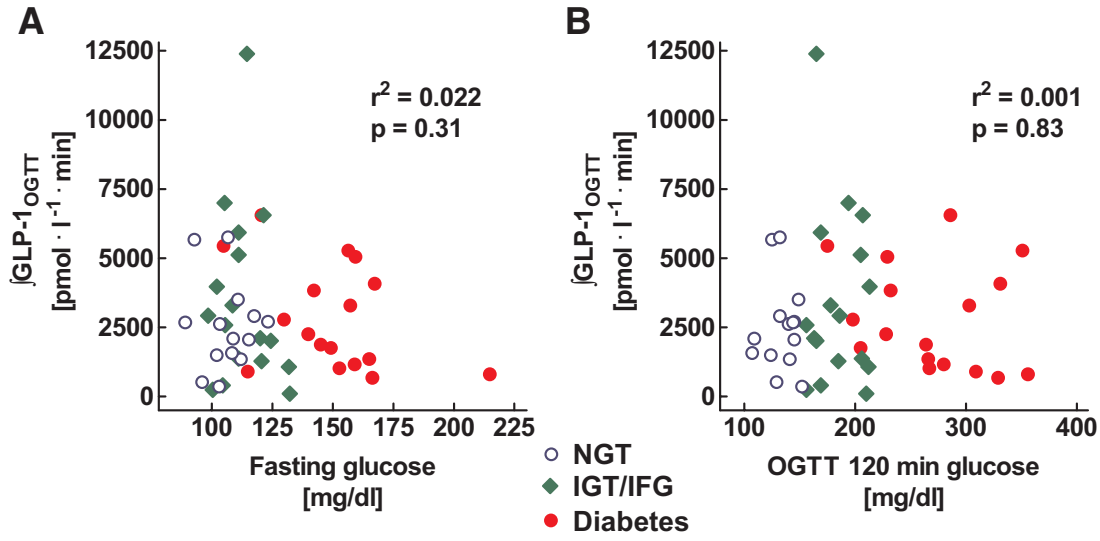

FIG. 1. Relationship between the glucose concentrations at fasting (*A*) and 120 min after the ingestion of 75 g oral glucose (*B*) and the respective integrated GLP-1 levels measured over 240 min after oral glucose ingestion in 14 nondiabetic individuals (blue), 17 people with impaired glucose tolerance or impaired fasting glucose (green), and 17 patients with type 2 diabetes (red). Individual data were taken from ref. 11. r^2 and *P* values were calculated by linear regression analyses. NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

bolus administration of the peptide (30–32). Consistent with the reduction of its insulinotropic activity, infusing GIP to hyperglycemic patients with type 2 diabetes has no significant glucose-lowering effect (33). The lack of glucose-lowering activity of GIP in type 2 diabetes may also partly be related to its stimulation of glucagon release (34), which counteracts its residual glucose-lowering actions.

Does the reduction of the incretin effect predispose the development of type 2 diabetes? To address whether the diminished incretin effect is a primary, possibly genetically determined, defect predisposing the development of type 2 diabetes, we have undertaken a series of studies in nondiabetic individuals at high risk for the disease: In initial experiments, first-degree relatives of patients with type 2 diabetes, patients with overt type 2 diabetes, and healthy control subjects were examined with the intravenous infusion of GIP during a hyperglycemic clamp experiment (29). Under these conditions, the amount of insulin released in response to GIP was markedly impaired in the type 2 diabetic patients and intermediate in the first-degree relatives, suggesting an early impairment in GIP action in ~50% of these individuals. However, upon further analysis it became obvious that these first-degree relatives also exhibited a similar impairment in insulin secretion after intravenous glucose administration, thereby suggesting that the reduced insulin levels found during GIP and glucose co-administration were secondary to a more general impairment in insulin secretion rather than a specific defect in GIP action. Interestingly, when we tested the effects of GIP administered as an intravenous bolus at normal fasting glucose levels in a larger cohort of first-degree relatives, we were unable to detect any impairment in the insulinotropic activity of GIP (32). Consistent with these findings, the relative size of the incretin effect, as well as the secretion of GIP and GLP-1 after oral glucose ingestion, were completely normal in first-degree relatives (35); furthermore, the same cohort studied previously did not develop disturbances of oral glucose tolerance during 4 years of follow-up, as expected for a high-risk population, and insulin sensitivity in those with a lesser insulinotropic response to GIP was higher, making the lower insulin secretory response still adequate for the prevailing degree of insulin resistance (36). Taken together, these studies did not reveal any evidence for the existence of a specific defect in GIP action in first-degree relatives of patients with type 2 diabetes.

Women with a history of gestational diabetes are another group at high risk for developing type 2 diabetes. Because the typical metabolic abnormalities in these women may be different from those in the first-degree relatives, we decided to examine the potential disturbances in the incretin system in these women as well. Thus, the group of women included in this study was predominantly characterized by insulin resistance rather than by β-cell dysfunction (37). Interestingly, there were no differences in insulin secretion in response to GIP administered by continuous infusion during a hyperglycemic clamp or as an intravenous bolus in the fasting state between the women with previous gestational diabetes and control subjects. Likewise, GLP-1 and GIP levels after oral glucose ingestion were normal in the women with previous gestational diabetes (37). Taken together, the findings in the first-degree relatives of patients with type 2 diabetes and the women with a history of gestational diabetes seemed to refute the hypothesis that the loss of GIP activity and the impaired incretin effect in patients with type 2 diabetes are due to a primary defect predisposing the development of the disease (21,38). Rather, the loss of incretin activity seems to go along with the other metabolic abnormalities in type 2 diabetes.

In support of this concept, Vilsbøll et al. (39) were able to demonstrate that a reduced insuliotropic effect of GIP is not only present in patients with "typical" type 2 diabetes, but that it can also be found in patients with other types of diabetes, such as maturity-onset diabetes of the young or diabetes secondary to pancreatitis. Subsequent studies determining the percentage contribution of the incretin effect in such patients were able to confirm these initial findings (40).

Potential factors responsible for the reduced incretin effect in type 2 diabetes. The importance of the diminished incretin effect for the dysregulation of postprandial glucose control in type 2 diabetes becomes

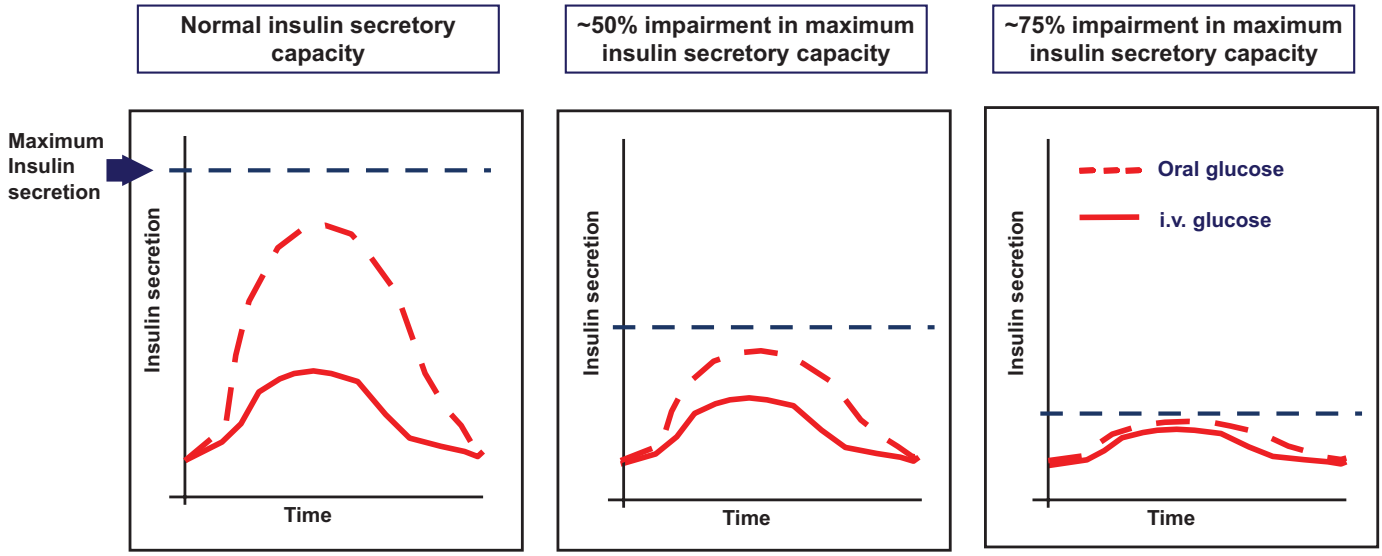

FIG. 2. Hypothetical impact of a general impairment in β-cell function on the incretin effect: In individuals with a normal insulin secretory capacity, an oral glucose load elicits a much greater insulin secretory response than an intravenous (i.v.) glucose load. With a decreasing β-cell secretory capacity, the insulin response to the oral glucose load is relatively more diminished than the insulin response to intravenous glucose infusion. By these means, the incretin effect, i.e., the difference in the insulin responses to oral and intravenous glucose, diminishes with declining β-cell function. For details, see text.

evident from experiments in animals with a genetic knockout of the GIP or GLP-1 receptor as well as from earlier experiments with GIP immune-neutralization (41–43).

The reasons underlying this phenomenon are less well established, and three possible factors appear possible:

Diminished maximum insulin secretory capacity. The incretin effect is defined by the differences in the insulin secretory responses elicited by oral glucose administration and intravenous glucose infusion (6,8). Of course, in terms of β-cell stimulation the oral glucose load represents a much more potent stimulus, because it combines the insulinotropic effects of circulating glucose, the incretin hormones GIP and GLP-1 (and potentially other ones), as well as some minor effects of afferent vagal nerves (8). In contrast, the insulinotropic effect of the intravenous glucose infusion is restricted to the direct stimulatory effects of circulating glucose. By these means, comparing the insulinotropic activity of oral and intravenous glucose does not only examine the efficacy of the incretin hormones GIP and GLP-1, but it also compares the effects of a relatively modest activator of insulin release (i.e., hyperglycemia) with a relatively potent stimulus of insulin release (i.e., oral glucose). Given the limited maximum secretory capacity of the β-cells in patients with type 2 diabetes (44), it is obvious that the insulinotropic response to a larger stimulus would be relatively more impaired that that of a less potent secretagogue. In other words, the difference between the insulin responses elicited by a potent secretagogue and a weaker secretagogue would be expected to shrink down with diminishing β-cell function (and perhaps mass). Furthermore, the total amount of glucose administered via the oral route (~50 g) typically exceeds the amount of glucose infused intravenously (~20 g) during isoglycemic clamp experiments. Because the insulin response to glucose is usually markedly impaired in patients with type 2 diabetes, this might further contribute to the diminished incretin effect in such patients. On that basis, the diminished incretin effect in patients with type 2 diabetes may simply reflect the reduced maximum secretory capacity of the β-cells in such patients rather than a specific problem in incretin secretion or action. The hypothetical consequences of a reduction in β-cell mass and/or function for the incretin effect are demonstrated in Fig. 2. Consistent with this view, we observed a linear inverse relationship between fasting glucose concentrations and the "size" of the incretin effect (percentage difference in the insulin responses between oral and intravenous glucose stimulation) in 48 individuals with and without diabetes (Fig. 3). This interpretation is further supported by the finding that a diminished incretin effect can also readily be observed in patients with other types of diabetes (45), and by the fact that it can be restored through pancreas transplantation in patients with type 1 diabetes (46). However, further studies will be required to substantiate this hypothesis.

Reduced GLP-1 secretion. One popular explanation for the diminished incretin effect in type 2 diabetes has been a reduction of GLP-1 secretion (47). This hypothesis has been based on studies demonstrating reductions in meal-

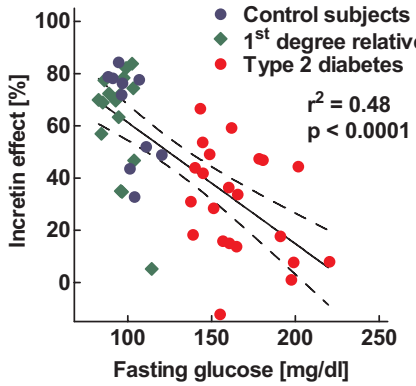

FIG. 3. Relationship between the relative percentage contribution of the incretin effect on the overall insulin responses after oral glucose ingestion and to the respective fasting glucose concentrations in 48 individuals with and without diabetes. Individual data were taken from refs. 35 and 7. The solid line denotes the regression line calculated by regression analyses in relation to the upper and lower 95% CIs.

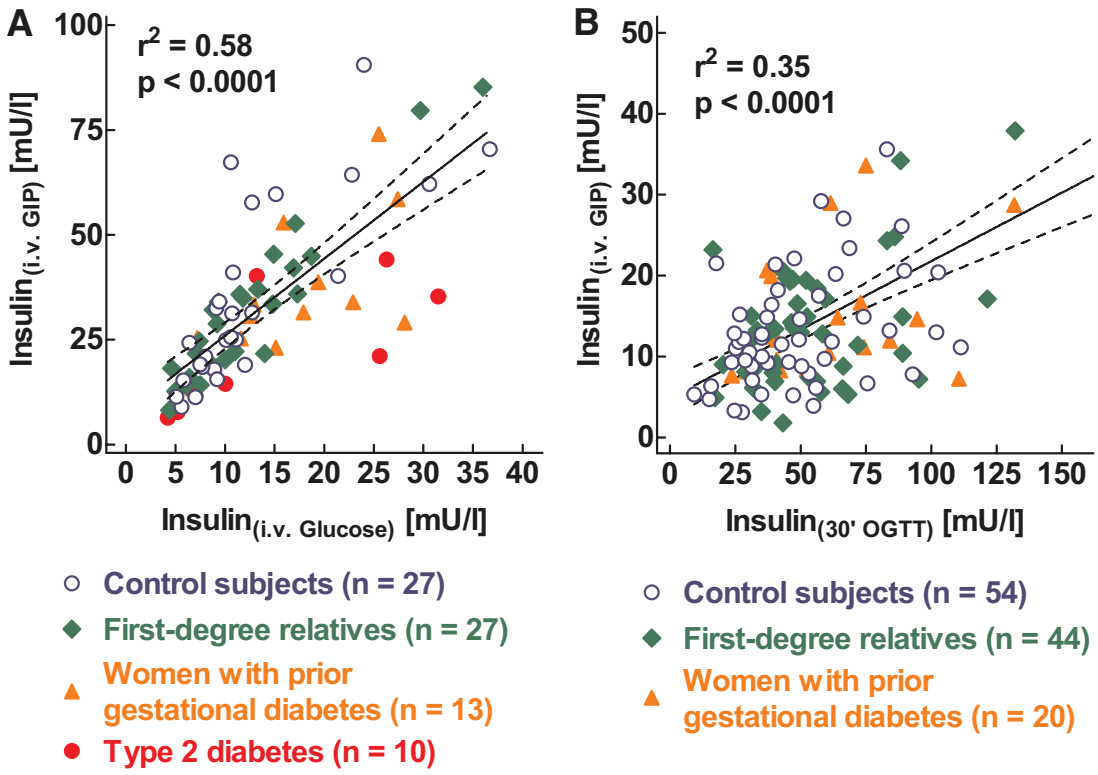

FIG. 4. ***A*: Relationship between the plasma insulin levels during the intravenous (i.v.) administration of glucose alone and the insulin levels during the combined administration of i.v. glucose and GIP in 27 healthy control subjects, 27 first-degree relatives of patients with type 2 diabetes, 13 women with previous gestational diabetes, and 10 patients with type 2 diabetes. Individual data were taken from refs. 29, 35, and 37. *B*: Relationship between the plasma insulin levels during the intravenous administration of GIP and glucose and the insulin levels measured 30 min after oral ingestion of 75 g glucose in 54 healthy control subjects, 44 first-degree relatives of patients with type 2 diabetes, and 20 women with previous gestational diabetes. Individual data were taken from refs. 32 and 37. The solid line denotes the regression line calculated by regression analyses in relation to the upper and lower 95% CIs.**

induced GLP-1 concentrations in patients with long-standing type 2 diabetes and subjects with impaired glucose tolerance (10,16,17). However, because the timing of the impairments in GLP-1 concentrations (~2–4 h after meal ingestion) does not coincide with the typical defects in meal-induced insulin release (~30–60 min after meal ingestion), such impairment in GLP-1 release cannot plausibly explain the loss of incretin activity in patients with type 2 diabetes. Furthermore, the majority of studies in patients with type 2 diabetes have failed to show similar impairments in GLP-1 concentrations (18), suggesting that in the vast majority of diabetic patients defects in GLP-1 release do not explain the diminished incretin effect. It is, however, possible that changes in the level of glycemia have an impact on the individual GIP and GLP-1 responses after meal ingestion. Along these lines, the postprandial concentrations of GIP and GLP-1 were found significantly lower during hyperglycemic clamp conditions compared with euglycemia, probably driven by a glucose-induced delay in gastric emptying (48). It is therefore conceivable that acute elevations in circulating glucose levels may partly blunt postprandial incretin responses. By this reasoning, the increased GLP-1 levels that have been reported after the administration of metformin may simply be due to the glucose-lowering effect of the drug (49). However, even though hyperglycemia appears to acutely lower GLP-1 secretion, it is completely unclear whether chronic hyperglycemia has a negative impact on GLP-1 levels as well. Correlation analyses did not reveal a significant association between fasting or postchallenge glucose concentrations and GLP-1 release (Fig. 1). Taken together, changes in GLP-1 secretion may occur under different conditions, but a general reduction in GLP-1 release fails to explain the reduced incretin effect in type 2 diabetes.

Specific loss of GIP activity. A number of studies have compared the insulinotropic effect of GIP in patients with type 2 diabetes and healthy control subjects. Uniformly, a relative reduction of GIP activity has been described in these studies (23,28–31). However, while this may certainly suggest a defect in GIP signaling, one should not forget that the efficacy of other secretagogues, especially glucose, is also severely impaired in these patients (3,44,50). Thus, in a direct comparison between patients with type 2 diabetes and healthy control subjects, the insulinotropic effect of an intravenous glucose bolus was found to be reduced by ~85% in the diabetic patients (51), and other studies have clearly shown a reduction in first-phase insulin release in response to glucose with increasing fasting glucose levels (52). The magnitude of the impairment in glucose-induced insulin secretion therefore seems to be comparable to the respective defect in GIP-induced insulin secretion described in other studies (23,30). To address this point, we have correlated the insulin secretory responses to GIP administration with the respective responses to intravenous glucose administration in a large group of individuals (n = 77), including patients with type 2 diabetes, first-degree relatives of patients with type 2 diabetes, women with a history of gestational diabetes, and healthy subjects (Fig. 4). Indeed, there was a tight correlation between the insulin responses to GIP and to glucose administration in these studies, consistent with the idea that the impairment in

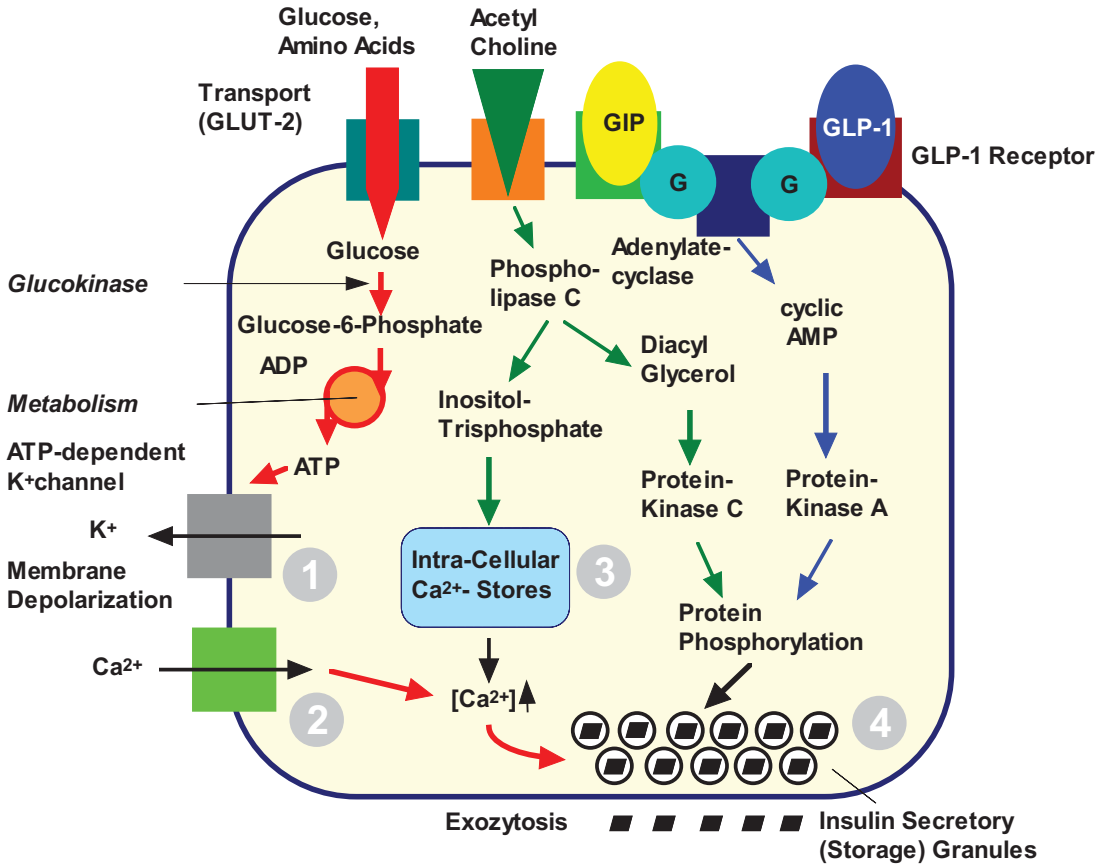

FIG. 5. Intracellular actions of GIP and GLP-1 on the β-cell. Several cellular functions are affected: closing of the ATP-dependent potassium channel (*1*); calcium influx in response to action potentials (*2*); release of calcium from intracellular stores (*3*); and the readiness with which insulin storage granules are released (*4*), probably depending on protein phosphorylation. These effects are tightly linked to the glucose-dependent generation of ATP, meaning that GLP-1 and GIP augment insulin release only in the presence of hyperglycemia. For details, see ref. 74.

GIP-induced insulin secretion goes along with a defect in glucose-induced insulin secretion. A less close relationship was observed between the insulin release elicited by the intravenous bolus administration of GIP at normal fasting glucose levels and the insulin concentrations 30 min after oral glucose ingestion (Fig. 4). Given that GIP acts in concert with glucose to enhance insulin secretion (Fig. 5), it is possible that the inability of GIP to augment insulin secretion during hyperglycemia is primarily due to the lack of glucose-potentiation of insulin release in patients with diabetes. However, while such an argument may seem to plausibly explain the loss of GIP action in patients with type 2 diabetes, one striking phenomenon still remains unexplained: Why does GLP-1 still potently stimulate insulin release during hyperglycemia in patients with type 2 diabetes? Possibly, the unequal insulinotropic efficacy of GIP and GLP-1 in patients with type 2 diabetes is due to an additional (and yet unexplored) mechanism of action rather than due to a specific defect in GIP signaling. In fact, both GIP and GLP-1 have been shown to exert their actions through binding to G-protein–coupled receptors on the β-cells, activation of adenylate cyclase, and subsequent cAMP generation (53). In addition, PI 3-kinase activation has been reported for both GIP and GLP-1. However, while these downstream signaling mechanisms are rather similar for both incretin hormones, recent studies have suggested a preferential upregulation of insulin receptor substrate 2 (IRS-2) through epidermal growth factor receptor activation by GLP-1 (54). This and other yet unexplored mechanisms may therefore contribute to the unequal efficacy of GIP and GLP-1 in patients with type 2 diabetes.

Working models for the loss of GIP activity in type 2 diabetes. Assuming that a specific problem in GIP signaling in patients with type 2 diabetes does indeed exist, the obvious question arising is: What are the reasons underlying such defect? In fact, the loss of insulinotropic GIP effects in type 2 diabetes despite the relatively well preserved activity of GLP-1 is quite surprising because both incretins are structurally similar, are released under almost identical conditions, and share similar signaling pathways inside the β-cell (53,55). Thus, both hormones bind to similar but distinct seven–membrane spanning G-protein–coupled surface receptors leading to intracellular cAMP generation and intracellular calcium release (53,55). However, this does not exclude alterations in the function or quantitative expression of the GIP receptor in patients with type 2 diabetes (56).

Considering the loss of GIP efficacy in type 2 diabetes in light of the available evidence from clinical studies as well as from animal and tissue culture based experiments, two different working models seem to arise:

Genetic defects in GIP signaling. The lack of GIP effect in type 2 diabetes has given rise to try and link polymorphisms in the GIP receptor with the type 2 diabetic phenotype. Two earlier studies from Europe and Japan have failed to establish an association between type 2 diabetes and GIP receptor polymorphisms (57,58). A more

recent study found a slightly impaired action of GLP-1, but not GIP in carriers of the T allele of rs7903146 TCF7L2 (59). Likewise, Schäfer and colleagues found a reduced insulinotropic effect of GLP-1 in carriers of the rs10010131 polymorphism of the WFS1 gene (60) as well as in carriers of TCF7L2 polymorphisms (61). These studies therefore suggest that genetic alterations in GLP-1 action may play a role in type 2 diabetes (62), which is surprising, given the relatively well preserved efficacy of GLP-1 in such patients (23). However, a genetic defect in GIP action predisposing to type 2 diabetes has not yet been established. Clearly, further studies in this area will be required.

Down-regulation/desensitization of the GIP receptor in response to hyperglycemia. The idea of a reduced expression of GIP receptors in patients with type 2 diabetes has already been expounded in 1997 (56), but until now no data regarding GIP receptor expression on islets from humans with and without type 2 diabetes have become available, owing to the limited accessibility of human pancreatic tissue. However, a couple of experimental studies have lent support to this concept: Lynn et al. (63) found reduced GIP receptor mRNA and protein levels in islets from Vancouver diabetic fatty rats, suggesting an impaired receptor expression in response to hyperglycemia. Subsequent experiments from the same group found a down-regulation of the GIP receptor in a transfected β-cell line (INS-cells) (64). More recently, Xu et al. (65) found reduced GIP mRNA levels in hyperglycemic rats after a 90% partial pancreatectomy. Interestingly, these effects could be reversed by glucose-normalization using phlorizin treatment. However, in the same study the expression of the GLP-1 receptor was regulated by hyperglycemia in a similar manner (65), which is rather inconsistent with the clinical findings on GIP and GLP-1 efficacy in patients with type 2 diabetes (23). In addition to this downregulation of the GIP receptor in response to hyperglycemia, a desensitization of the GIP receptor in response to chronically elevated GIP concentrations has also been described in GIP receptor–transfected cell lines (66). However, since elevations in GIP plasma concentrations are not a typical finding in most patients with type 2 diabetes (67), this mechanism is less likely to contribute to the impairment of GIP efficacy in type 2 diabetes.

To examine the impact of chronic hyperglycemia on GIP-induced insulin release, we have compared the relative stimulation of insulin secretion during the intravenous administration of GIP at hyperglycemic clamp conditions in a total of 93 individuals with the respective fasting glucose concentrations at the day of the experiment (Fig. 6). The insulin responses to GIP were found relatively normal in the individuals presenting with fasting glucose concentrations of less than ~100 mg/dl. However, as glucose concentrations exceeded this level, there was a progressive decline in GIP activity on insulin secretion, with an almost complete loss of efficacy in patients with overt hyperglycemia of 150–250 mg/dl. Thus, even though the association between the insulinotropic effect of GIP and the respective fasting glucose levels cannot serve to prove any causality, these analyses are very consistent with the concept of a GIP receptor downregulation in response to high glucose concentrations. The potential factors contributing to the diminished incretin effect in type 2 diabetes have been summarized as a working model in Fig. 7.

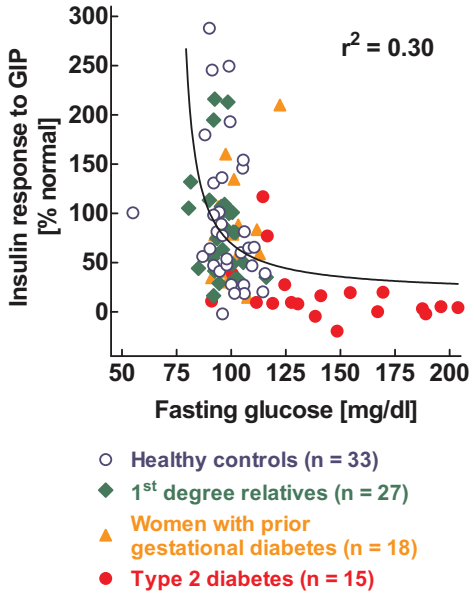

FIG. 6. Relationship between the relative increase in insulin secretion during the intravenous administration of GIP at hyperglycemic clamp conditions and the respective fasting glucose concentrations in 93 individuals with and without diabetes. The relative increments in insulin secretion were expressed in relation to the mean values obtained in the individuals with normal glucose concentrations (fasting glucose levels <100 mg/dl). Individual data were taken from refs. 29, 30, and 35. The solid line denotes the regression line calculated by nonlinear regression analyses using an exponential decay function.

Can the incretin effect be restored by normalizing hyperglycemia? Assuming that the relative impairment of the incretin effect and the loss of GIP activity in patients with type 2 diabetes are secondary to the chronic hyperglycemia, the clinical implication would be that normalizing the hyperglycemia in these patients should also restore the insulinotropic effect of GIP. Højberg and colleagues (68–70) set out to address this point by subjecting eight patients with type 2 diabetes in poor glycemic control (A1C levels 8.6 ± 1.3%) to a 4-week intensive insulin treatment with the aim of completely normalizing glycemia in these patients. The insulin responses to GIP and GLP-1 were determined before and after the intervention during a hyperglycemic clamp experiment. There was indeed a significant improvement in insulin secretion in response to both GIP and GLP-1 after glucose lowering (68), whereas no effects were found with regards to the secretion of both hormones after meal ingestion (69). However, a complete regain of GIP activity to the levels found in healthy subjects was not accomplished in this study (68). Furthermore, the observed improvements in insulin secretion were not specific to the actions of GIP but also affected the insulinotropic effect of GLP-1 as well as the overall β-cell responses to meal ingestion (69). It is therefore difficult to fully ascribe these phenomena to the reversal of a specific defect in incretin signaling. In fact, a number of previous studies have demonstrated that lowering hyperglycemia in patients with type 2 diabetes can also lead to marked improvements of insulin secretion in response to intravenous glucose and other secretagogues, probably mediated by the mechanism of β-cell rest (71–73). In addition, although glucose control was significantly improved by the insulin treatment in this study, complete normoglycaemia was not achieved in these patients at the end of the study (mean glucose concentrations 7.4 mmol/l [133 mg/dl]) (68). Based on the analyses of our studies

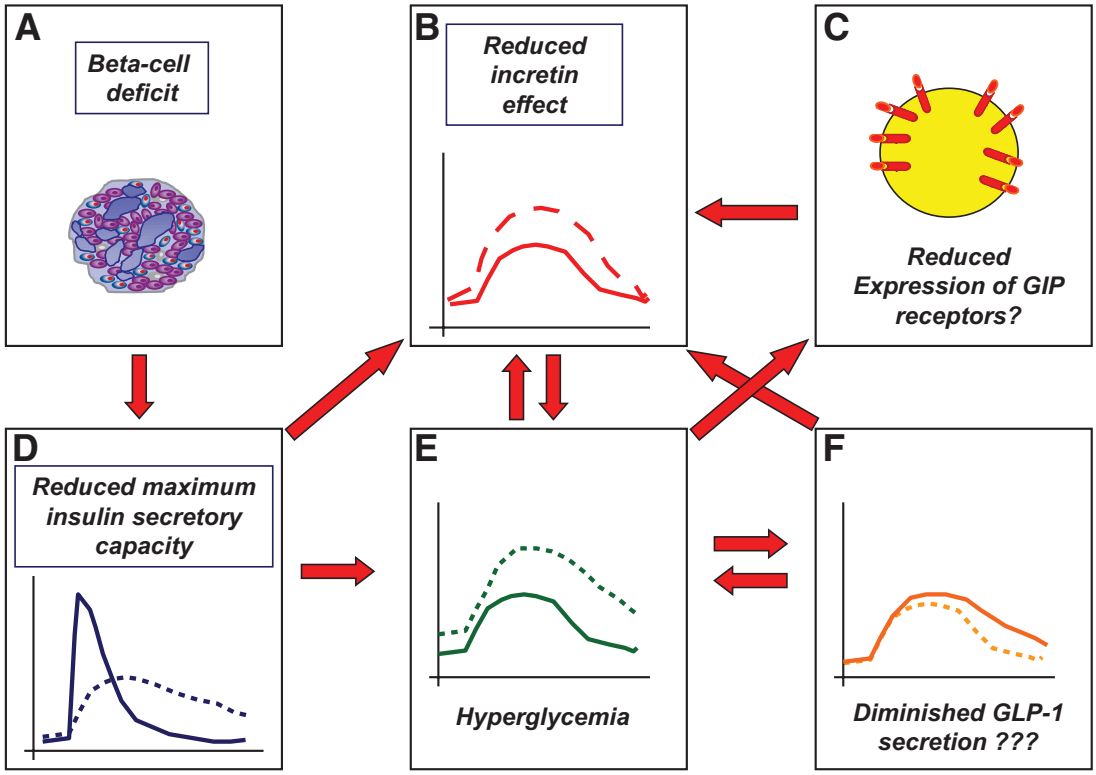

FIG. 7. Working model for the diminished incretin effect in type 2 diabetes: The reduction in β-cell mass (*A*) leads to a significant impairment in the maximum insulin secretory capacity of the β-cells (*D*). The reduced secretory capacity leads to a preferential impairment of the relative insulin response to oral glucose, whereas a relatively normal insulin response to intravenous glucose (a comparably weaker β-cell stimulus) can still be maintained. The defects in β-cell function and the impaired incretin effect (*B*) lead to chronic hyperglycemia (*E*), which may diminish GLP-1 secretion (*F*) and impair GIP action through GIP-receptor downregulation (*C*), thereby further diminishing the incretin effect. Genetic factors may independently modify β-cell mass and function as well as GLP-1 secretion. Dashed lines in *D*, *E*, and *F* indicate the respective patterns typical of patients with type 2 diabetes, solid lines show the respective normal patterns. The dashed line in *B* illustrates the insulin levels after oral glucose ingestion; the solid line shows the respective patterns after isoglycemic intravenous glucose administration.

presented herein, both the incretin effect and the relative activity of GIP were still severely impaired in individuals with similar fasting glucose concentrations. Nevertheless, the studies by Madsbad and Højberg clearly demonstrate that reducing the hyperglycemia in patients with type 2 diabetes can also elicit significant improvements in the incretin effect.

Conclusions and outlook. The diminished incretin effect in patients with type 2 diabetes was described more than 20 years ago (5), but even now the underlying causes remain elusive. Although a couple of studies have described alterations in the postprandial concentrations of GIP and GLP-1, there is little evidence to suggest that impairments in incretin secretion play a major role in the pathogenesis of type 2 diabetes (21). The insulinotropic action of the incretin hormones is clearly impaired in patients with type 2 diabetes, with GLP-1 retaining significantly more efficacy than GIP (23). However, the magnitude of the reduction in GIP efficacy in patients with type 2 diabetes appears to be comparable to the impairment in glucose-induced insulin secretion in such patients, suggesting that the impaired GIP-induced insulin secretion may largely be secondary to of a general impairment in β-cell function. In addition, there is evidence from preclinical and clinical studies that hyperglycemia further reduces the insulinotropic effect of GIP, possibly through downregulation of the GIP receptor (63). Ultimately, the diminished incretin effect in patients with type 2 diabetes may be a consequence of the inability of the β-cells to provide an appropriate secretory response to a large stimulus (i.e., oral glucose), whereas a smaller stimulus (i.e., intravenous glucose) may still elicit a relatively normal insulin response (Fig. 2). On the basis of such reasoning, the reduction of the incretin effect in patients with diabetes may simply be an epi-phenomenon of chronic hyperglycemia, independent of any primary defect in GIP or GLP-1 action. Reducing hyperglycemia and enhancing β-cell function in general terms may therefore also improve the incretin effect, independent of specific interventions related to circulating levels of GIP or GLP-1.

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