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Review

Gastric Inhibitory Polypeptide: the neglected incretin revisited☆

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Abstract

After the ingestion of fat- and glucose-rich meals, gut hormones are secreted into the circulation in order to stimulate insulin secretion. This so-called ''incretin effect'' is primarily conferred by Glucagon-like peptide 1 (GLP-1) and Gastric Inhibitory Polypeptide (GIP). In contrast to GLP-1, GIP has lost most of its insulinotropic effect in type 2 diabetic patients. In addition to its main physiological role in the regulation of endocrine pancreatic secretion, GIP exerts various peripheral effects on adipose tissue and lipid metabolism, thereby leading to increased lipid deposition in the postprandial state. In some animal models, an influence on gastrointestinal functions has been described. However, such effects do not seem to play an important role in humans. During the last years, the major line of research has focussed on GLP-1, due to its promising potential for the treatment of type 2 diabetes mellitus. However, the physiological importance of GIP in the regulation of insulin secretion has been shown to even exceed that of GLP-1. Furthermore, work from various groups has provided evidence that GIP contributes to the pathogenesis of type 2 diabetes to a considerable degree. Recent data with modified GIP analogues further suggested a possibility of therapeutic use in the treatment of type 2 diabetes. Thus, it seems worthwhile to refocus on this important and—sometimes—neglected incretin hormone. The present work aims to review the physiological functions of GIP, to characterize its role in the pathogenesis of type 2 diabetes, and to discuss possible clinical applications and future perspectives in the light of new findings.

Keywords: Incretin effect; Insulin secretion; Treatment of type 2 diabetes; Glucagon-like peptide 1; Pathogenesis of type 2 diabetes

1. Introduction

Almost 100 years ago, Moore et al. [1] first reported on the antidiabetogenic effect of an extract of duodenal mucous membranes. The authors proposed a stimulation of pancreatic secretion to be mediated by this extract. However, it took another 60 years until the establishment of an immunoassay for insulin allowed Dupré and Beck [2] to show an insulinotropic effect of intestinal mucous extracts in normal human subjects. In contrast, no stimulation of insulin release could be observed in juvenile-onset diabetic subjects [2].

Before this insulinotropic effect of a duodenal mucous extract had been observed, an inhibitory influence on gastric acid secretion was demonstrated. Therefore, in 1930, Kosaka and Lim [3] proposed the term ''enterogastrone'', based on their observations, that gastric acid secretion and gastric emptying could be inhibited by intravenously infused extracts of intestinal mucosa.

Further purification of such extracts that were devoid of cholezystokinin-pancreozymine (CCK-PZ) activity confirmed the presence of other intestinal hormones with inhibitory effect on gastric acid secretion [4,5]. Based on these effects, the name ''Gastric Inhibitory Peptide'' was proposed by Brown et al. in 1971. Brown and Dryburgh [6] were the first to report the complete amino acid sequence of the newly discovered peptide in 1971. The inhibitory effects on H^+ secretion were further observed in innervated canine Bickel-type pouches [7], but could later not be confirmed in humans [8].

The assumption that intestinal peptides must be involved in the regulation of postprandial insulin secretion has been based on the classical experiments by Elrick et al. [9] and McIntyre et al. [10]. They found that the insulin responses to oral glucose exceeded those measured after intravenous administration of equivalent amounts of glucose. Their

☆ This review article is dedicated to Professor Dr. Werner Creutzfeldt, the father of the incretin concept on the occasion of his birthday.

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Table 1
Comparison of the effects of Gastric Inhibitory Polypeptide (GIP) and Glucagon-like peptide (GLP-1)

	GIP	GLP-1	Reference
Insulin secretion in normal subjects	Stimulation	Stimulation	[14,133]
Insulin secretion in type 2 diabetic patients	Reduced stimulation	Preserved stimulation	[27]
Insulin extraction	Reduction	No effect	[112]
Glucagon secretion	No effect	Suppression	[27,163]
B-cell proliferation	Stimulation	Stimulation	[106,107]
Gastric emptying	Acceleration (?)	Deceleration	[93,95]
Gastric acid secretion	No effect	Slight suppression	[92,164]
Lipogenesis	Stimulation	Stimulation	[77,79]
Satiety	Not examined	Enhancement	[135]
Body weight	Not examined	Reduction	[165]

findings led to the conclusion that gut-derived factors, so-called *incretins*, influence postprandial insulin release [2,9]. Accordingly, the stimulation of insulin secretion by GIP was shown in dogs [11], isolated perfused rat pancreas [12,13], and, later, also in humans [14–18]. Therefore, the alternative term "Glucose-Dependent Insulinotropic Polypeptide" may be even more suitable for GIP, as proposed by Brown and Pederson [19].

Since a hypersecretion of GIP following oral glucose was observed in type 2 diabetic patients, it was hypothesized that a diminished responsiveness of insulin secretion towards GIP might take part in the development of type 2 diabetes [20,21]. Along this hypothesis, a reduced insulinotropic effect of GIP was described after the intravenous administration of the peptide in type 2 diabetic patients [22–28]. Interestingly, the other incretin hormone, Glucagon-like peptide 1 (GLP-1) was shown to stimulate insulin secretion in different stages of type 2 diabetes effectively [27] (Table 1), although both peptides share similar signal transduction pathways after binding to different, non-cross-reacting receptors [29,30]. Therefore, due to its promising potential in the treatment of type 2 diabetes, the major interest of research has recently focused on GLP-1, whereas only minor effort has been undertaken to the further examine GIP and its actions.

However, a considerable number of recent findings make it worthwhile to further eludicate the role of GIP in the pathogenesis of type 2 diabetes and to discuss a possible role of the peptide in the future treatment of this widespread chronic disease.

2. Secretion and degradation of Gastric Inhibitory Polypeptide

Polak et al. [31] first localized Gastric Inhibitory Peptide-secreting cells in the duodenum and jejunum. They anticipated D_1 cells to be the origin of the peptide. However, based on their studies in pigs and dogs, Buffa et al. identified so-called K-cells to be responsible for the secretion of GIP [32–34]. Whereas these K-cells were found predominantly in the proximal gut [32], the distal gut was believed to mainly contain the GLP-1-secreting L-cells [35,36] (Fig. 1). Recent observations, however, indicate that GLP-1 and GIP are in principle co-localized throughout the gastrointestinal tract [37,38].

The ingestion of carbohydrate- and lipid-rich meals has been shown to be the main stimulant for the secretion of GIP [11,21,39,40]. However, the mediation of GIP secretion following meal ingestion has not been totally understood yet. GIP secretion reaches peak concentrations already 15–30 min after the intake of oral glucose or lipids, long before the substrates ingested are present in the gut [11,21,39,40]. Therefore, an involvement of the vagus nerve in the stimulation of GIP secretion, as also discussed for the secretion of GLP-1 [41], seems likely.

On the other hand, the identification of glucokinase expression in the K-cells indicates a glucose-sensing mechanism, similar to that operating in pancreatic B-cells, to be involved in the secretion of GIP [42]. In addition, the secretion of GIP is closely correlated to the secretion of GLP-1 [43], although the mechanism underlying this co-secretion is still unclear. One possible explanation is a paracrine interaction between both incretin hormones, as indicated by recent data in dogs [44,45].

Rapidly after its secretion into the circulation, intact GIP [1–42 amide] is cleaved at the NH_2-terminus yielding the fragment GIP [3–42 amide] [46–49] (Fig. 2). The enzyme dipeptidyl-peptidase IV (DPP IV), that also cleaves GLP-1 and many other peptides of the glucagon/secretin family, has been shown to be responsible for the degradation of GIP [1–42] amide [47,50,51]. The truncated GIP [3–42 amide] has lost its biological activity regarding the stimulation of insulin secretion and may even act as an antagonist of GIP at its receptor [46,52,53]. Using different radioimmunoassays with various antibodies raised against either the C-terminus or the N-terminus of the peptide, the biological half life of intact GIP was shown to be approximately 7 min, whereas it was more than 17 min for the amount detected with C-terminal directed antibodies [49]. Therefore, it is evident that the biological half life of GIP is much shorter than estimated in earlier studies using assays that do not distinguish between intact GIP and its metabolites [54,55].

The importance of DPP IV in the inactivation of peptide hormones involved in the regulation of insulin secretion was further shown in animal studies using DPP IV inhibitors. Administration of DPP IV inhibitors led to a significant improvement of glucose homeostasis [50,56,57]. Furthermore, the generation of a mouse model with a targeted disruption of the CD26 gene (synonymous for DPP IV) showed the importance of DPP IV in the inactivation of incretin hormones [58]. One must consider that DPP IV activity is much greater in some animals than in man

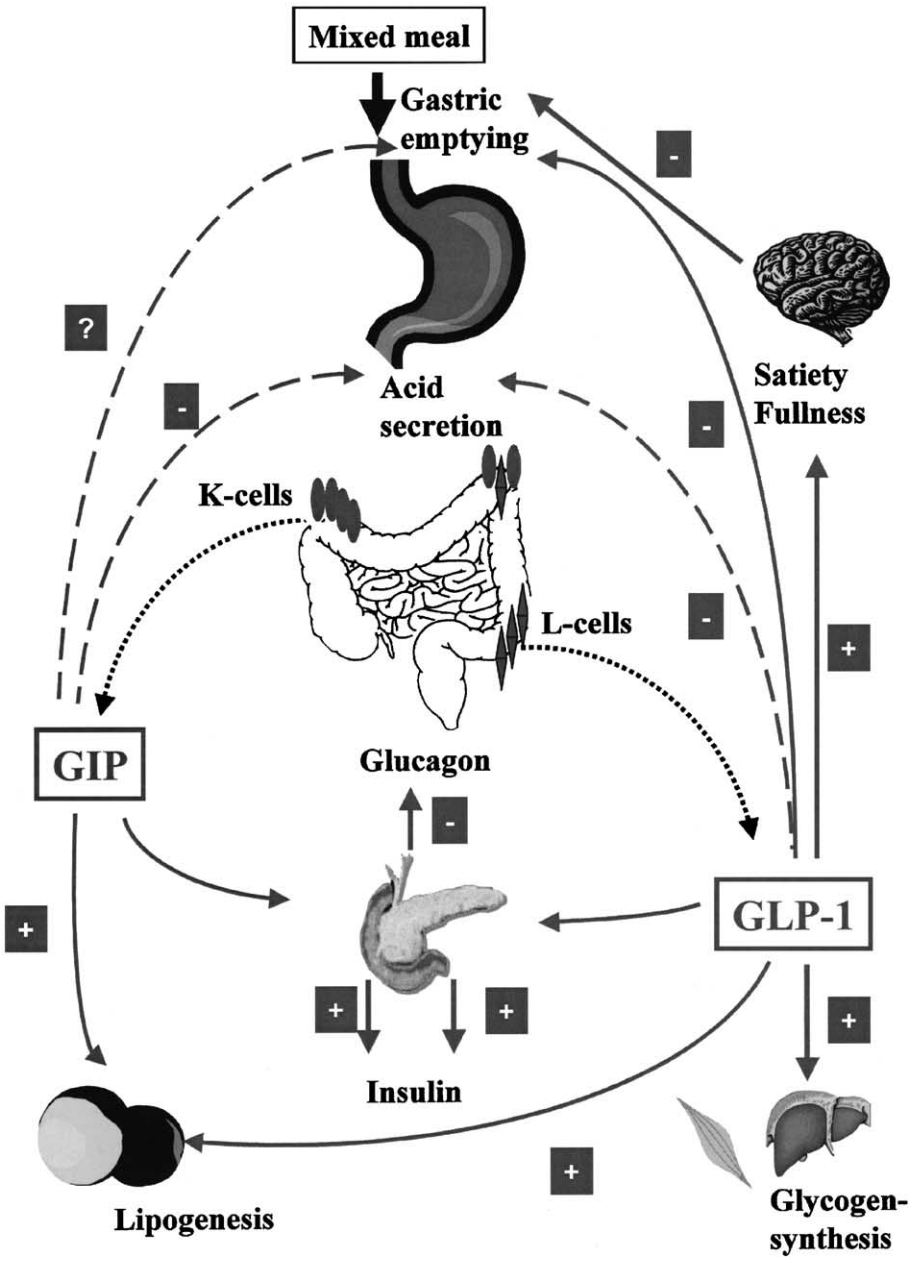

Fig. 1. Interactions of Glucagon-like peptide 1 (GLP-1) and Gastric Inhibitory Polypeptide (GIP) with peripheral tissues and organs. After meal ingestion, the incretin hormones GIP and GLP-1 are secreted from the K-cells and from the L-cells throughout the gut. GIP stimulates insulin secretion from the endocrine pancreas, increases lipogenesis, and suppresses gastric acid output, whereas the effects on gastric emptying have not been finally clarified yet. GLP-1 stimulates insulin secretion, suppresses glucagon secretion, increases glycogen synthesis, increases satiety and fullness, and inhibits gastric emptying and acid secretion. Dotted lines indicate putative actions that are not proven in humans.

[47,50]. In humans, however, clinical evidence for a glucose-lowering potential of DPP IV inhibition is still lacking.

A central role of the kidneys in the clearance of GIP has been anticipated from elevated concentrations of GIP in patients with renal failure and uremia [49,59–61]. Moreover, renal brush border membranes contain high amounts of DPP IV [47]. Renal arterio-venous differences of the GIP concentrations supported these observations [62]. Despite earlier studies reporting no hepatic extraction of GIP in rats and dogs [63,64], recent data by Deacon et al. [57] in pigs further suggested an involvement not only of the kidneys, but also of the liver and the peripheral skeletal muscles in the removal of intact GIP.

3. The role of Gastric Inhibitory Polypeptide in the physiology of lipid metabolism and adipose tissue

An anabolic function of GIP was expected from the observation of elevated plasma concentrations of immunor-

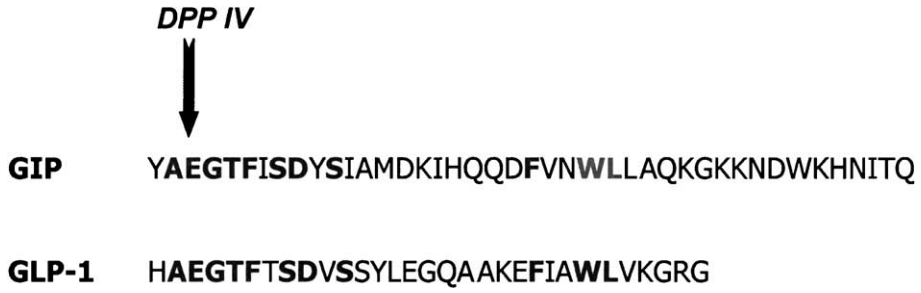

Fig. 2. Amino acid sequence of human Gastric Inhibitory Peptide and Glucagon-like peptide 1. Sequence homologies are indicated in bold letters. The arrow points to the cleaving site of dipeptidyl-peptidase IV [47].

eactive GIP in obese and in type 2 diabetic patients [65–68], as well as in *ob/ob* mice [69]. However, these data could not be confirmed in all studies [22,70–72]. These conflicting results have been attributed to different study conditions, including the composition of the test meals applied to stimulate GIP secretion, preceding daily caloric intake, and the influence of different insulin clearance rates leading to various degrees of hyperinsulinemia [73]. In addition, it is important that these studies were based on C-terminally directed radioimmunoassays that do not allow to distinguish between the biologically intact GIP [1–42 amide] and the N-terminally degraded, biologically inactive, GIP [3–42 amide]. Recent data using a novel assay for the intact peptide [49] did not reveal significant differences in the fasting and postprandial GIP concentrations between type 2 diabetic patients and matched healthy subjects [74]. A biological function for GIP in lipid metabolism is further indicated by the stimulation of GIP release in the presence of fat [21,40] (Fig. 1).

In cultured preadipocytes, incubation with GIP dose-dependently stimulates lipoprotein lipase activity [75]. This effect is unique to GIP and not mimicked by the other incretin hormone, GLP-1, that, despite similar actions on insulin secretion [27], has no effect on lipoprotein–lipase activity [76]. In addition, GIP has been shown to induce fatty acid incorporation into adipose tissue in epididymal fat pads [77] and obese Zucker rats [78], and to stimulate fatty acid synthesis in omental adipose tissue [79]. The lipolytic glucagon effect on adipocytes can potently be inhibited by simultaneous incubation with GIP [80,81]. Consistent with a biologically important function of GIP on lipid metabolism, GIP receptor mRNA has been detected in adipose tissue [82]. More convincingly, studies in rat adipocytes provided evidence that these receptors stimulate intracellular cAMP production after ligand binding [83]. Such direct effects on adipocytes are supported by recent data showing increased lipid accumulation in adipocytes incubated with GIP [84].

In dogs, infusion of porcine GIP significantly lowered the rise in plasma triglycerides after infusion of chylomicrons, suggesting a role for GIP in the disposition of ingested fat [85], but these findings could not be confirmed in other systems [86]. After intraduodenal infusion of a lipid test meal in rats, plasma triglyceride increments were attenuated under the simultaneously infusion of GIP. In addition, immunoneutralisation of endogenous GIP by injection of GIP antiserum increased the triglyceride rise following a fat load [87]. However, the drop of triglyceride concentrations may secondarily be explained by a rise in insulin concentrations [88]. Therefore, it is difficult to distinguish between direct GIP effects on fat deposition and an indirect effect based on the insulinotropic GIP effect. Recent data obtained in mice with a GIP receptor knock-out further suggested an important role for GIP in the regulation of adipose tissue mass, as a high-fat diet did not lead to obesity in these animals [89]. Therefore, it is possible that GIP represents an "insulin-sensitizer" in adipose tissue.

In humans, however, there is no clear evidence for an effect of GIP on lipid metabolism [90]. It seems worthwhile to study the effects of GIP on triglyceride and free fatty acid levels in more detail.

4. The biological role of Gastric Inhibitory Polypeptide in stomach physiology

Before the physiological importance of GIP as an incretin was realized, the peptide was believed to act predominantly on the stomach. This assumption has been based on early studies with impure, cholezystokinin (CCK)-containing, peptide-preparations, revealing inhibitory actions on motor activity and acid secretion in the canine stomach [5]. In denervated pouches of the stomach, a dose-dependent inhibition of pentagastrin-stimulated gastric acid secretion was shown using a highly purified preparation of GIP [6,7]. This seemed to duplicate the original observations showing inhibitory effects on gastric acid secretion due to impurities in available CCK preparations. Therefore, GIP was thought to act as an inhibitor of gastric functions. Based on these observations, the newly discovered intestinal peptide was named Gastric Inhibitory Polypeptide [6]. Later, with the infusion of porcine GIP in intact dogs, only infusion rates leading to concentrations exceeding the physiological range were shown to inhibit gastric acid secretion [91]. In

humans, a significant inhibition of gastric acid output was also observed after the infusion of pharmacological doses of porcine GIP [8] (Fig. 1). However, all these studies were performed using porcine GIP that, as mentioned above, does not completely cross-react with antibodies raised against human GIP, thereby leading to an underestimation of circulating concentrations [46]. Therefore, Nauck et al. [92] studied the effects of physiological doses of synthetic human GIP alone, and in co-infusion with human GLP-1 in humans. In this study, neither GIP nor GLP-1 inhibited gastric acid secretion under physiological conditions (Table 1). However, in the combination of GIP and GLP-1, a slight, but significant decrement in chloride output as well as a reduction of total acid output was observed [92]. Therefore, it seems that under physiological conditions, the effect of GIP on gastric acid secretion in humans is negligibly low. While GLP-1 is known to be a potent inhibitor of gastric emptying [93,94], GIP seems to act in an opposite way, leading to accelerated emptying of the stomach [95] (Fig. 1).

In conclusion, although the impact of GIP on the regulation of gastrointestinal function appears to be the negligible compared to the effects on endocrine pancreatic secretion, some effects seem to exist. In humans, however, these effects have not yet been studies in detail.

5. Effect of Gastric Inhibitory Polypeptide on endocrine pancreatic secretion

Already before the complete amino acid sequence of GIP was described [6], Dupré and Beck [2] reported a stimulation of insulin release after intravenous administration of an extract of intestinal mucosa, although the composition of this extract was still unknown. An insulinotropic action of endogenous GIP was further expected from the observation of similar increases of plasma insulin and GIP levels following ingestion of glucose, fat, amino acids, or test meals [19]. Indeed, a stimulation of insulin secretion by GIP was found in isolated perfused rat pancreas [13,96], in dogs [11], and also in humans [14,24,97] (Fig. 1). A significant insulinotropic effect, however, was only observed in presence of elevated glucose concentrations [11,13,98]. The glucose dependency of the insulinotropic GIP effects was confirmed by stepwise hypo-, eu-, and hyperglycemic clamp studies with the infusion of GIP [16,99,100], whereas concomitant hyperinsulinemia had no effect on GIP-stimulated insulin secretion [15].

Since increased glucose-induced insulin secretion was attributed to the rise of postprandial GIP secretion also in type 2 diabetic patients, antidiabetic properties of GIP were discussed already in the 1970s [22]. Accordingly, porcine GIP was infused into type 1 and type 2 diabetic patients. However, insulin secretion following GIP infusion was significantly lower in diabetic patients compared to normal subjects [23,101].

The amino acid sequence of porcine GIP was shown to differ from human GIP in two amino acid positions [52]. Therefore, it seemed probable that the circulating GIP concentrations in humans had been underestimated based on radioimmunoassays using porcine GIP standards. Furthermore, using porcine GIP in humans requires a proof of equipotent properties of human and porcine GIP. As a result, infusions with the aim of reaching plasma concentrations that resemble those after oral meal ingestion had chosen suboptimal doses. In addition, commercially available preparations of GIP were shown to contain the biologically inactive fragment GIP [3–42 amide] (32%), cholezystokinin [CCK-33] (2%), CCK-39 (2%), and possible other undefined peptides. Thus, the effects observed are indistinguishable from the effects of the additional peptides in the solutions infused [46]. Therefore, it was meaningful to study the insulinotropic properties of synthetic human GIP in more detail. In normal subjects, GIP was shown to act as a potent stimulus of insulin secretion under hyperglycemic conditions [55,100].

It was concluded that the effect of endogenously released GIP is an important mechanism of postprandial insulin secretion, whereas the physiological role of GIP in the fasting state seems to be less important. In normal subjects, GIP is responsible for approximately 60% of the incretin effect [98]. Likewise, administration of GIP antagonists or GIP antisera markedly reduces the postprandial insulin release in rats [102–104]. This is further supported by studies in GIP receptor knock-out mice. These animals display normal fasting glucose levels, but elevated glucose levels after oral glucose, highlighting the importance of GIP in the postprandial state [105] (Fig. 3).

In contrast to other insulin secretagogues, GIP not only releases insulin from B-cells, potentially leading to a B-cell exhaust, but also stimulates cellular proliferation of insulin producing cells [106]. Similar proliferative effects on the endocrine pancreas have also been described for GLP-1 [107,108], making a role for the incretin hormones in the maintenance of B-cell mass probable (Table 1).

Whereas GLP-1 still stimulates insulin secretion effectively in type 2 diabetic patients, the insulinotropic effect of GIP is markedly reduced in type 2 diabetic patients [27], thereby leading to a reduced incretin effect in these patients [109].

Furthermore, glucagon secretion from the isolated perfused rat pancreas has been shown to be stimulated by GIP [13]. This glucagonotropic effect was inhibited in the presence of glucose [13]. In human studies with the infusion of synthetic human GIP, no influence on glucagon secretion was seen [27,28], whereas GLP-1 is known to strongly suppress glucagon secretion [27,110] (Table 1; Fig. 1). The only exception seem to be patients with liver cirrhosis [111].

Recently, it has been proposed that GIP may also exert some effects on insulin extraction [112]. An involvement of the incretin effect in the clearance of insulin has been suggested from the discrepancy between plasma C-peptide and insulin responses to oral glucose compared to an intra-

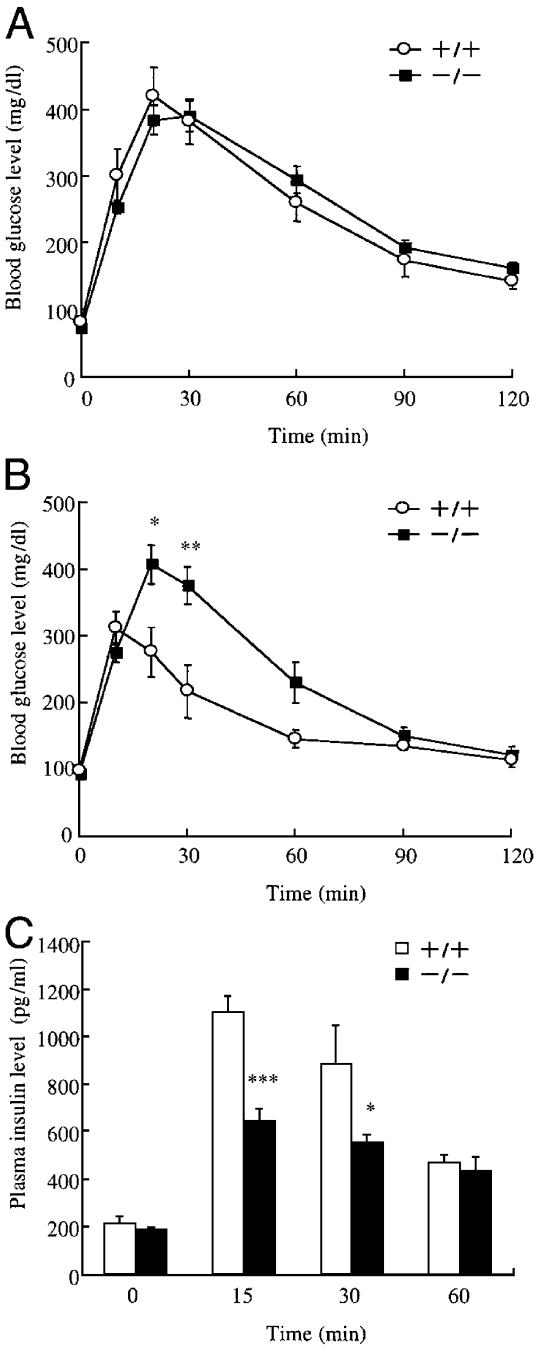

Fig. 3. Glucose tolerance test in mice with a targeted disruption of the GIP receptor (GIPR−/−) and wild type mice (GIPR+/+). (A) Intraperitoneal glucose tolerance test in age-matched GIPR+/+ (n=4) and GIPR−/− (n=6). (B) Oral glucose tolerance test in the same groups of mice. (C) Corresponding plasma insulin levels after oral glucose loading. Statistical significance was assessed by using unpaired t-test. Values are indicated as mean±S.E. *p<0.05; **p<0.001 for GIPR−/− mice vs. GIPR+/+. From Ref. [105], with kind permission.

venous glucose load [98,113]. More evidence for an effect of GIP on insulin extraction came from the observation of higher increments of insulin concentrations compared to the rise of C-peptide levels under the infusion of GIP [112] (Table 1).

6. Contribution of Gastric Inhibitory Polypeptide to the pathogenesis of type 2 diabetes

The reduced response of insulin secretion to the administration of exogenous GIP comprises a characteristic defect of the type 2 diabetic phenotype.

Therefore, the question arises whether the loss of the GIP effect represents a specific phenomenon that might be involved in the pathogenesis of type 2 diabetes or whether it is the result of an impaired B-cell function in more general terms. In addition, the molecular defect underlying the loss of the GIP effect in type 2 diabetes remains unclear. One potential explanation is that the reduced insulinotropic effect of GIP develops due to chronic desensitisation of the GIP receptor [114]. Such a desensitisation has been postulated due to the loss of insulinotropic activity of intravenous GIP after continuous infusion into rats [114] and from elevated GIP levels found in some studies in type 2 diabetic patients [22,115]. However, a recent study did not confirm higher plasma concentrations of either total or intact GIP in type 2 diabetic patients in the fasting and in the postprandial state [74]. A central role of G proteins in the GIP receptor desensitisation has been concluded from studies with cells transfected with the GIP receptor and proteins involved in the regulation of G protein signalling [116]. Mutation analyses indicated that cysteine residues in the C-terminus of the GIP receptor play an important role in mediating the desensitisation and down-regulation of the receptor [117,118].

Considering the preserved insulinotropic activity of the other incretin hormone, GLP-1, that shares most of its signalling pathways with GIP, it is conceivable that the reduced insulinotropic effect of GIP is due to a specific defect [27]. Interestingly, recent data suggest that different abnormalities of the incretin effect are typical for the diabetic phenotype: on the one hand, the secretion of GLP-1 has been shown to be impaired in type 2 diabetic patients [74], whereas the effect is nearly totally sustained, thereby opening a great potential for the treatment of type 2 diabetes with GLP-1 [119–121] (Table 1). The secretion of GIP, on the other hand, is normal in type 2 diabetic patients [74], but its effect is lost [27,28]. In total, these findings point to a specific defect in the responsiveness of pancreatic B-cells towards GIP. The basis of this defect, however, is yet unclear. It has been speculated already in 1997 that an abnormal GIP receptor might be involved in this defect [122]. Indeed, a diabetic phenotype develops in mice with a targeted GIP receptor knock-out [105] (Fig. 3). In humans, however, no mutation of the GIP receptor could be linked to type 2 diabetes in different populations [123,124]. On the other hand, a reduced GIP effect could be caused by reduced expression of GIP receptors on pancreatic B-cells [122]. This hypothesis is supported by recent data from Lynn et al. [125] showing reduced expression of GIP receptors on islet cells of diabetic Zucker fatty rats. In humans, no data exist regarding the number of GIP receptors on B-cells and their

contribution to the pathogenesis of type 2 diabetes. Moreover, the molecular basis of this defect is yet unclear and needs further study.

If one assumes a specific impairment of GIP signalling to be a constitutive element of the type 2 diabetic phenotype, it is reasonable to postulate this aspect to be present also in a subgroup of their first-degree relatives as well. According to epidemiological studies, these persons carry an individual life-time risk of approximately 40–50% to develop type 2 diabetes themselves [126]. Along this hypothesis, we have recently described a reduced insulinotropic effect of GIP in at least a subgroup of 50% of normal or (in one case) impaired oral glucose tolerant first-degree relatives of type 2 diabetic patients, pointing to a primary, possibly genetically determined defect [28] (Fig. 4). However, to finally confirm our hypothesis that a reduced insulinotropic effect of GIP precedes the development of type 2 diabetes, it will be necessary to follow-up the participants of this study prospectively during the following years. As the contribution of GIP to the incretin effect is approximately 60% in healthy subjects [100], one might expect a quantitative reduction of the incretin effect, as typical for the type 2 diabetic state [109], in those persons as well. This hypothesis, however, could not be confirmed by recent data from our group, showing normal incretin effects in first-degree relatives of type 2 diabetic patients despite a reduced insulinotropic effect of GIP [43]. This may on the one hand lead to the assumption that the physiological importance of GIP for the postprandial glucose homeostasis is less than previously expected or that other, yet unknown, incretin-like mechanisms may compensate for the reduced GIP effects. However, for the other known incretin, GLP-1, no compensatory hypersecretion can be observed in type 2 diabetic patients or in their first-degree relatives [43,74]. In contrast, it is conceivable that the impairment of the stimulatory effect of GIP on diabetic B-cells reflects an insulin secretory defect in more general terms. Accordingly, it is well known that also the insulinotropic response to intravenous glucose is already diminished in patients at high risk for type 2 diabetes during their prediabetic state [127–130].

The observation that GIP only stimulates insulin secretion in the presence of elevated glucose concentrations [14,100], whereas it has nearly no effect under normoglycemic conditions [112], make synergistic actions of glucose and GIP within the B-cells likely. According to this hypothesis, we did not find any differences in the insulinotropic

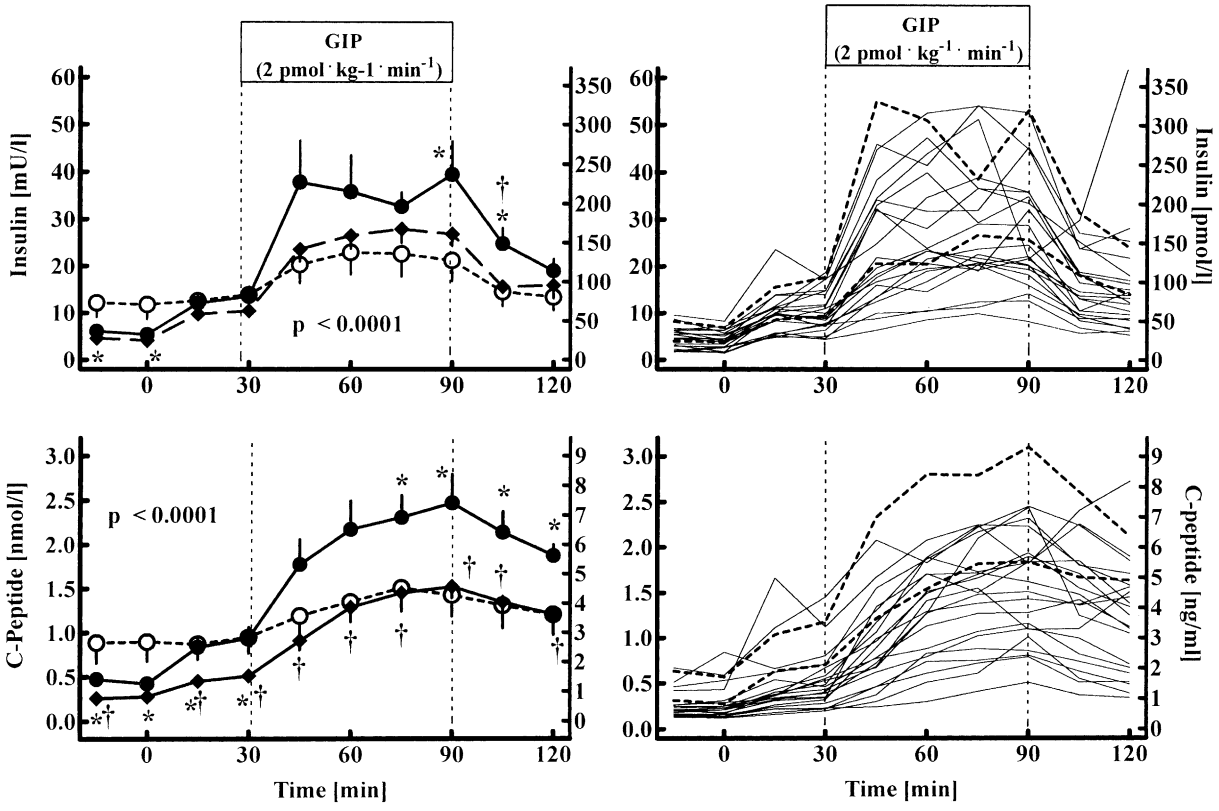

Fig. 4. Left panels: Plasma concentrations of insulin (upper panel) and C-peptide (lower panel) in 21 first-degree relatives of type 2 diabetic patients (filled diamonds), 10 type 2 diabetic patients (open circles), and 10 healthy control subjects (filled circles) participating in hyperglycemic clamp experiments with intravenous infusions of GIP (2 pmol kg^{-1} min^{-1}). Mean±S.E.M. *P* values: repeated-measures ANOVA (A: between subject/patient groups; B: with time; AB: interaction of group and time). *: Significant difference ($p<0.05$) to type 2 diabetic patients; †: significant difference ($p<0.05$) to normal subjects (Student's *t*-test). Right panels: Individual plasma concentrations (thin lines) of insulin (upper panel) and C-peptide (lower panel) in 21 first-degree relatives shown in relation to the upper and lower 95% CI for normal subjects (thick dashed lines). Modified according to Ref. [28].

response to a bolus injection of GIP in the fasting state between first-degree relatives of type 2 diabetic patients and control subjects without a family history of type 2 diabetes (unpublished observations). A synergistic effect of GIP and glucose on insulin secretion is further supported by data from Holz et al. [131]. In this study, B-cells were incubated with either glucose, GLP-1, or with both secretagogues. Changes of the membrane potential were recorded as a marker of stimulation using the patch-clamp technique. When treated with either glucose or GLP-1, a number of cells were found to be insensitive to each secretagogue. However, pretreatment with GLP-1 increased the number of cells responding to glucose and, in turn, pretreatment with glucose increased the number of GLP-1-responsive cells. The authors named this phenomenon induction of "glucose competence" [131]. Accordingly, mice with a targeted disruption of the GLP-1 receptor comprise abnormalities of the glucose homeostasis even in the fasting state [132]. Considering the similar intracellular pathways of GIP and GLP-1 signalling in pancreatic B-cells, a similar induction of "glucose competence" might be possible for GIP. For the proliferative effects of GIP on B-cells, synergistic actions of glucose and GIP have recently been described [106]. In the light of this hypothesis, a diminished insulin secretory capacity of B-cells in response to either glucose or GIP might reflect the metabolic consequences of the same B-cell defect.

7. Possible clinical applications of Gastric Inhibitory Polypeptide

Despite its physiological importance for the maintenance of postprandial glucose homeostasis, during the last years, only minor emphasis has been put on the search for clinical applications of GIP, whereas the major line of research has focussed on the application of GLP-1 in the treatment of type 2 diabetes. Indeed, it seems probable that due to its beneficial effects on insulin and glucagon secretion [27,95,100, 133,134], on satiety and body weight [135–137], and its proliferative effects on pancreatic B-cells [107,108], GLP-1 or its analogues will find its way into the therapy of type 2 diabetes soon [119,121,138].

However, since the insulinotropic effect of GIP is lost in type 2 diabetic patients [27], the application of the peptide in the treatment of type 2 diabetes does not seem to display any advantage compared to the use of GLP-1. On the contrary, whereas GLP-1 has been shown to reduce appetite and body weight in various animal models [139–144] as well as in humans [135–137], GIP increases fat deposition [77–79,85,89], thereby possibly increasing body weight and worsening insulin sensitivity. On the other hand, inhibition of GIP degradation leading to increased plasma concentrations of intact GIP is one important mode of action of the inhibitors of the enzyme dipeptidyl-peptidase IV [48, 56,57,145]. Based on their effects on insulin secretion and glucose homeostasis, these agents are being discussed as potential oral antihyperglycemic agents [57,145–150].

A more promising potential for the treatment of type 2 diabetes may come from developed formulations of GIP with an NH_2-terminal modifications [151–155]. Such modified peptides have been shown to be resistant to DPP IV degradation resulting in a prolonged biological half life [152] and to have enhanced antihyperglycemic activity [151]. Accordingly, intraperitoneal administration increased insulin response to glucose and lowered plasma glucose concentrations in obese diabetic *ob/ob* mice [153]. An introduction of modified GIP analogues into the treatment of type 2 diabetes may be possible, as, similar to GLP-1, due to the glucose dependency, the insulinotropic effect of GIP does not lead to hypoglycemia.

The observation that at least 50% of normal glucose tolerant first-degree relatives of type 2 diabetic patients already show a reduced insulinotropic response to exogenous GIP under hyperglycemic clamp conditions, similarly to type 2 diabetic patients, led to the hypothesis that a loss of GIP effect might precede the development of type 2 diabetes [28]. This hypothesis, however, will have to be confirmed by follow-up examinations. It might be worthwhile to evaluate the insulinotropic response to GIP in patients at high risk for type 2 diabetes to obtain information about the individual risk for the disease.

Given the observation that the expression of GIP receptors is reduced in diabetic Zucker fatty rats [125], one might further suspect a specific, possibly genetically determined, defect. In case that such defect can be localized, a genetic screening examination of patients at high risk for type 2 diabetes could become possible.

A role for GIP in the future treatment of type 2 diabetes has furthermore been proposed based on its strongly glucose-dependent release from K-cells similarly to the rise of insulin following a glucose load [156–158]. The glucose dependency of GIP secretion has been referred to the presence of glucokinase in these cells [42]. This feature made the K-cells an interesting target for genetic modifications. As yet, glucose normalisation by genetically engineered insulin secreting cells was limited by the absence of a regulatory element leading to uncontrolled insulin secretion and, accordingly, to hypoglycemia [159–162]. Thus, transfection of a GIP tumor cell line with the human preproinsulin gene led to the transcription of human preproinsulin mRNA. Injection of this GIP/ins fragment into pronuclei of mouse embryos resulted in the production of human insulin in the duodenum and stomach of those transgenic mice and caused complete normalisation of blood glucose levels in streptozotocin-treated transgenic mice [42]. These data highlighted the importance of the K-cells for the possible future treatment of diabetes mellitus.

In conclusion, GIP plays an important role in the physiologic control of postprandial glucose and lipid homeostasis, whereas its effects on gastrointestinal functions in humans appear negligible. Deterioration of the insulino-

tropic effect of GIP, possibly synergistically with glucose, is suspected to represent one major element contributing to the pathogenesis of type 2 diabetes. N-terminally modified GIP analogues should be further investigated for their potential role in the treatment of type 2 diabetes. Moreover, due to its glucose-dependent secretion, GIP-secreting cells may become a target for future gene therapy of diabetes. Thus, 30 years after the isolation and structural characterisation of GIP, it seems worthwhile to refocus on the examination of its physiological actions and the signalling pathways. The eludication of the molecular basis of its diminished effect in type 2 diabetes may substantially increase our knowledge of the pathogenesis of this disease.

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