Nutrient regulation of pancreatic β-cell function in diabetes: problems and potential solutions

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Abstract
Increasing prevalence of obesity combined with longevity will produce an epidemic of Type 2 (non-insulin-dependent) diabetes in the next 20 years. This disease is associated with defects in insulin secretion, specifically abnormalities of insulin secretory kinetics and pancreatic β-cell glucose responsiveness. Mechanisms underlying β-cell dysfunction include glucose toxicity, lipotoxicity and β-cell hyperactivity. Defects at various sites in β-cell signal transduction pathways contribute, but no single lesion can account for the common form of Type 2 diabetes. Recent studies highlight diverse β-cell actions of GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide). These intestinal hormones target the β-cell to stimulate glucose-dependent insulin secretion through activation of protein kinase A and associated pathways. Both increase gene expression and proinsulin biosynthesis, protect against apoptosis and stimulate replication/neogenesis of β-cells. Incretin hormones therefore represent an exciting future multi-action solution to correct β-cell defect in Type 2 diabetes.

Introduction
The physiological role of pancreatic β-cells is to sense an increase in the circulating concentration of glucose (and other nutrients) after feeding and to secrete an appropriate amount of insulin into the blood to ensure prompt and efficient metabolic disposal [1]. Regulation of this process is further aided by the actions of incretin hormones and neural pathways that make up the enteroinsular axis [2]. Defects in nutrient regulation of insulin secretion and resistance to the cellular actions of insulin are both key to the development of Type 2 (non-insulin-dependent) diabetes. The purpose of the present article is to briefly discuss the nature of the β-cell defect in Type 2 diabetes, to consider short-comings of current drug treatments and to review possible future solutions offered by a new antidiabetic drug class, namely stable incretin hormone analogues [3].

Diabetes
There are two types of diabetes which together affect up to 3–7% of the population in Western societies. Type 1 (insulin-dependent) diabetes, caused by autoimmune destruction of pancreatic β-cells, usually develops before adulthood and requires insulin injection [4]. Type 2 diabetes more often manifests in later life and accounts for approx. 95% of all cases. It is commonly treated through diet and prescription of drugs to increase the secretion and action of insulin [4]. Both forms of diabetes are becoming increasingly common and costs to annual healthcare budgets range from 10 to 14%. Worldwide, cases of diabetes are expected to reach epidemic proportions by 2025, with more than 300 million individuals being affected. This sharp increase partly reflects changes of diet and lifestyle in developing countries and the strong link of Type 2 diabetes with obesity and increasing age. Thus, in Western societies, the aged population is increasing and obesity rates have almost tripled over the past 20 years. Poor diabetes control results in many complications, including vascular disease, kidney failure, blindness, lower leg amputation, impotence and mental disease [4]. Accordingly, the search for new and improved treatments for diabetes represents an important ongoing challenge [5].

Current treatments for Type 2 diabetes
Type 2 diabetes is associated with two key defects, namely (i) impairment of pancreatic β-cell function and (ii) insulin resistance at target tissues such as muscle, liver and adipose tissue. The ideal treatment for Type 2 diabetes should preferably tackle both of these defects. Dietary management is important, as reducing adiposity will enhance insulin action and glucose disposal [6]. However, moderate or severe hyperglycaemia invariably requires drug intervention [5,7,8]. Current therapies act by enhancing insulin secretion (sulfonylureas; meglitinides) or reducing insulin resistance (biguanides; thiazolidinediones) [5,7,8]. Additional options include α-glucosidase inhibitors (acarbose; miglitol) to reduce the rate of carbohydrate digestion and absorption. Unfortunately, all of the available agents are limited in efficacy by the progressive deterioration of β-cell function that occurs throughout the natural history of Type 2 diabetes. Thus a future treatment that could boost insulin secretion and prevent or reverse this gradual β-cell decline would be highly beneficial.

Key words: diabetes, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), incretin hormone, insulin, pancreatic β-cell.

Abbreviations used: DPP4, dipeptidyl peptidase IV; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; MODY, maturity-onset diabetes of the young; PKA, protein kinase A.

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Regulation of pancreatic β-cell and diabetes

The inability of pancreatic β-cells to recognize and respond to glucose is a hallmark of Type 2 diabetes. Glucose is not only the primary regulator of β-cell function but dictates the insulinotropic potency of many other secretagogues [9]. Signals generated by these agents are normally integrated at the level of the β-cell through a complex network of second messenger and effector pathways. For glucose stimulation of insulin secretion, this primarily involves the steps of glucose transport, metabolism, ATP production, K-ATP channel closure, membrane depolarization and influx of Ca²⁺ through voltage-dependent calcium channels. Elevated Ca²⁺ then triggers exocytosis. Interestingly, the sulfonyleureas and meglitinide drugs act by binding to the sulfonyleurea receptor component of K-ATP channels to decrease K⁺ permeability and trigger Ca²⁺ entry [10,11]. However, these agents do not recapitulate the less well-understood augmentation pathways activated through β-cell glucose metabolism [9,12,13]. As a result, they do not replenish insulin stores and can lead to eventual desensitization and/or exhaustion of β-cells [14]. Elevation of intracellular Ca²⁺ also activates various enzymes such as adenylate cyclase (producing cAMP) and phospholipase C (producing diacylglycerol and inositol 1,4,5-trisphosphate). Such enzyme systems are also activated by specific receptors for hormonal and neural components of the enteroinsular axis, leading to activation of PKA (protein kinase A) and PKC that promote protein phosphorylation and sensitization of the secretory machinery to action of secretagogue action of Ca²⁺.

From the above, it follows that a lesion at any one locus in the sequence of events linking glucose recognition to discharge of insulin by exocytosis might contribute to defective insulin secretion. This has fuelled an extensive search for mutations in the key islet regulatory genes (encoding enzymes, ion channels etc.) in populations with Type 2 diabetes [15]. Such a research has unveiled a number of previously unidentified and rare forms of MODY (maturity-onset diabetes of the young) that represent 1–2% diabetes and result from inherited mutations in genes for glucokinase or different transcription factors affecting β-cells [15]. Elevation of intracellular Ca²⁺ also activates various enzymes such as adenylate cyclase (producing cAMP) and phospholipase C (producing diacylglycerol and inositol 1,4,5-trisphosphate). Such enzyme systems are also activated by specific receptors for hormonal and neural components of the enteroinsular axis, leading to activation of PKA (protein kinase A) and PKC that promote protein phosphorylation and sensitization of the secretory machinery to action of secretagogue action of Ca²⁺.

Table 1 | MODY genes and incretin hormones

<table>
<thead>
<tr>
<th>MODY gene</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODY 1</td>
<td>HNF-4α</td>
</tr>
<tr>
<td>MODY 2</td>
<td>Glucokinase</td>
</tr>
<tr>
<td>MODY 3</td>
<td>HNF-1α</td>
</tr>
<tr>
<td>MODY 4</td>
<td>IPF-1</td>
</tr>
<tr>
<td>MODY 5</td>
<td>HNF-1β</td>
</tr>
<tr>
<td>MODY 6</td>
<td>NeuroD1</td>
</tr>
</tbody>
</table>

Functional characteristic | GLP-1 | GIP |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose-dependent stimulation of insulin secretion</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Stimulate β-cell expansion</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Enhance β-cell survival</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Suppress glucagon secretion</td>
<td>✓</td>
<td>–</td>
</tr>
<tr>
<td>Inhibition of hepatic glucose production</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Inhibition of hepatic insulin extraction</td>
<td>✓</td>
<td>–</td>
</tr>
<tr>
<td>Inhibition of gastric emptying</td>
<td>✓</td>
<td>–</td>
</tr>
<tr>
<td>Extrapancreatic glucose-lowering actions</td>
<td>✓</td>
<td>–</td>
</tr>
<tr>
<td>Enhance satiety</td>
<td>✓</td>
<td>–</td>
</tr>
<tr>
<td>Reduce body weight</td>
<td>✓</td>
<td>–</td>
</tr>
<tr>
<td>Lower blood glucose</td>
<td>✓</td>
<td>–</td>
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</tbody>
</table>

The incretin hormones

The concept of the ‘enteroinsular axis’ was conceived to describe all ‘gut factors’ that contribute to enhanced insulin secretion following the ingestion of a meal [17]. It was suggested later that the axis comprised nutrient, neural and hormonal components. Creutzfeldt [2] laid down the two key criteria required for the classification of incretin hormones. First, an incretin must be released in response to nutrients, particularly carbohydrates, and secondly, it must stimulate insulin secretion at physiological concentrations. The two main incretin hormones, GLP-1 and GIP, are now well established [3]. These peptide hormones have surpassed expectations as antihyperglycaemic agents because they not only have potent insulin-releasing actions, but they also lower blood glucose by other pancreatic and extrapancreatic actions.
Incretin hormone actions in the pancreatic β-cell

Incretin hormones act in several distinct ways to lower blood glucose, the most notable being potent stimulation of insulin secretion (Figure 1). Insulin release stimulated by the incretin hormones occurs in a glucose-dependent manner. This serves to minimize the risk of hypoglycaemia [18,19], a difficulty faced by insulin-releasing sulfonylureas and meglitinides presently used for Type 2 diabetes therapy [5]. This particular characteristic has been fundamental to the recent therapeutic interest in both GLP-1 and GIP. As shown in Table 1 (part b), the incretin hormones have been shown to exhibit several other actions, including inhibition hepatic glucose production [20,21], decrease of insulin clearance [22] and promotion of glucose uptake [23,24] in peripheral tissues, which may further contribute to glucose lowering in Type 2 diabetic patients.

The antidiabetic profile of incretin hormones has been further raised by mounting evidence that suggests that both GLP-1 and GIP enhance the growth, differentiation, proliferation and survival of pancreatic β-cells [3] (Table 1, part b). Thus a large number of reports indicate that the incretin hormones are involved in modulating pancreatic β-cell mass. GLP-1 and GIP can increase the overall mass of β-cells by (i) reducing β-cell apoptosis, (ii) increasing islet cell proliferation and (iii) causing differentiation of cells to a β-cell phenotype. GLP-1 agonists have demonstrated anti-apoptotic effects on islets and β-cells in animal models of Type 1 and Type 2 diabetes [25–27]. GIP has also been shown to inhibit β-cell apoptosis [28–30]. In vitro experiments that indicated that GLP-1 stimulates islet cell proliferation [31,32] are corroborated by several in vivo studies [33–35]. The proliferative effect of GLP-1 on β-cells may partly be attributed to the stimulation of insulin gene transcription and insulin biosynthesis [36]. GIP has been shown to stimulate β-cell proliferation synergistically with glucose in the islet INS-1 cell line [28,37]. Findings in our laboratory and others indicate that GLP-1 promotes the differentiation of a pancreatic ductal cell line to an endocrine cell phenotype [38,39]. Cells differentiated using GLP-1 express islet hormones, the glucose transporter Glut-2 and are capable of insulin secretion [38,39]. Evidence also indicates that GIP may help promote differentiation of embryonic stem cells to a β-cell phenotype [40]. The effects of the incretin hormones to stimulate cellular proliferation, inhibit apoptosis and promote differentiation of insulin-producing cells indicate that their therapeutic use could slow β-cell decline and avoid the risk of β-cell exhaustion.

Development of DPPIV (dipeptidyl peptidase IV)-resistant incretin analogues with enhanced potency

One of the major obstacles encountered in the therapeutic development of GLP-1 and GIP has been their rapid degradation in the circulation, which chiefly occurs as a result of the enzyme, DPPIV (EC 3.4.14.5) [41]. DPPIV cleaves N-terminal dipeptides from both GLP-1 (His7-Ala8) and GIP (Tyr1-Ala2) (Figure 2). Truncated metabolites GLP-1-(9–36)-amide and GIP-(3–42) lack insulinotropic activity and may act at high concentrations antagonistically on their respective receptors.

DPPIV is an enzyme that prefers an alanine, proline or hydroxyproline residue in the penultimate N-terminal position. GLP-1 and GIP possess similar N-terminal regions, i.e. His7-Ala8-Glu9 and Tyr1-Ala2-Glu3 respectively (Figure 2), which explains their susceptibility to DPPIV degradation. Three different types of structural modifications have been investigated to safeguard GLP-1 and GIP against DPPIV degradation. The first involves, extension of the N-terminal His7 and Tyr1 positions of GLP-1 and GIP respectively by various chemical modifications [42,43]. The second involves amino acid substitution at Ala8 [44] and Glu9 [45,46] of GLP-1, and at Ala2 [47] and Glu1 [48,49] of GIP respectively. Finally, GLP-1 and GIP have been acylated with long- or short-chain fatty acids to promote longer biological action through albumin binding [50,51].

All three types of modification have led to the generation of GLP-1 or GIP analogues with reduced or even complete resistance to degradation by DPPIV. This attribute appears to be a relatively straightforward to attain. However, these modifications have variable effects on biological activity producing analogues with enhanced, neutral or inferior potency.
GLP-1 and GIP have peptide structures that can be modified either N-terminally to prevent DPPIV degradation or C-terminally by acylation to promote binding to albumin and counter renal filtration.

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**Figure 2** | Engineering of structural modified incretin hormones for enhancement of β-cell function and diabetes therapy

GLP-1 and GIP have peptide structures that can be modified either N-terminally to prevent DPPIV degradation or C-terminally by acylation to promote binding to albumin and counter renal filtration.

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**Conclusion**

Dysfunction and decline of pancreatic β-cells are key features of Type 2 diabetes. Mechanisms underlying β-cell defects are at present poorly understood and currently available anti-diabetic drugs targeting insulin secretion are far from ideal in their action. New research suggests that emerging incretin hormone therapies could significantly counter β-cell decline and failing insulin secretion, representing a potential solution to a more effective means of treating Type 2 diabetes.

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**References**


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