Abstract

The incretin effect refers to the augmentation of insulin secretion after oral administration of glucose compared with intravenous glucose administration at matched glucose levels. The incretin effect is largely due to the release and action on beta-cells of the gut hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). This system has in recent years had considerable interest due to the success of incretin therapy as a glucose-lowering strategy in type 2 diabetes. In non-diabetic subjects, the incretin effect is responsible for 50–70% of insulin release during oral glucose administration. In type 2 diabetes patients, the incretin effect is impaired and contributes to only 20–35% of the insulin response to oral glucose. The reason for the defective incretin effect in type 2 diabetes has been the subject of many studies. Although the reports in the literature are mixed, most studies of GIP and GLP-1 secretary responses to oral glucose or a mixed meal have shown fairly normal results in type 2 diabetes. In contrast, the insulinotropic effects of both GIP and GLP-1 are impaired in type 2 diabetes with greater suppression of insulin secretion augmentation with GIP than with GLP-1. The suggested causes of these defects are a defective beta-cell receptor expression or post-receptor defects secondary to the diabetes milieu, defective beta-cell function in general resulting in defective incretin effect and genetic factors initiating incretin hormone resistance. Identifying the mechanisms in greater detail would be important for understanding the strengths, weaknesses and efficacy of incretin therapy in individual patients to more specifically target this glucose-lowering therapy.

Keywords: Incretin; GIP; GLP-1; Type 2 diabetes; Insulin

Résumé

L’effet incrétine dans le diabète de type 2.

L’effet incrétine correspond à l’augmentation de la sécrétion de l’insuline après une administration orale de glucose, comparée à une administration intraveineuse, pour des niveaux équivalents de glucose. L’effet incrétine est dû en grande partie à la libération et à l’action des cellules β des hormones glucose-dépendantes de l’intestin insulinotropiques polypeptide (GIP) et des peptide-1 glucagon-like (GLP-1). Ce système a bénéficié d’un fort intérêt ces dernières années dans le diabète de type 2. Chez des sujets normaux, l’effet incrétine est responsable de 50 à 70 % de la libération de l’insuline lors d’une administration orale de glucose. Dans un diabète de type 2, l’effet des incrétines est réduit et contribue seulement de 20 à 35 % de la réponse en insuline lors d’une prise orale de glucose. La raison de cet effet réduit des incrétines dans le diabète de type 2 a fait l’objet de nombreuses études. Bien que quelques divergences existent dans la littérature, la plupart des études sur les réponses sécrétoires des GIP et GLP-1 à une administration orale de glucose ou lors d’un repas ont montré des réponses relativement normales dans le diabète de type 2. En revanche, les effets insulinosécrétagogues du GIP et du GLP-1 sont réduits dans le diabète de type 2, avec une réduction plus marquée de l’effet du GIP sur l’augmentation de la sécrétion d’insuline par rapport au GLP-1. Les causes de la diminution de l’effet incrétine impliquent une diminution de l’expression des récepteurs au niveau des cellules β, des altérations de la transduction post-récepteur liées à l’hyperglycémie ou une résistance aux incrétines. La compréhension approfondie de ces mécanismes sera importante pour mieux cibler l’efficacité des thérapeutiques basées sur les incrétines.

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Mots clés : Incrétine ; GIP ; GLP-1 ; Diabète de type 2 ; Insuline
1. The incretin effect

In the 1930s, Dr Jean La Barre from Belgium introduced the term “incretin” to describe a substance in the gut mucosa that produces hypoglycaemia when injected into normal animals, but not in those who had undergone pancreatectomy [1]. Dr Hans Heller from Austria made a similar suggestion a few years later, although he suggested the term “duodenin” for this tentative substance [2]. Both La Barre and Heller suggested that the tentative substance(s) could be used in the treatment of diabetes, which was rather farsighted considering that it was only demonstrated in the early 1990s that the main incretin hormone, glucagon-like peptide-1 (GLP-1), had glucose-lowering actions in type 2 diabetes [3]. Today, incretin therapy is an established glucose-lowering strategy in type 2 diabetes and uses both GLP-1 receptor agonists and dipeptidyl peptidase (DPP)-4 inhibitors [4].

In the early 1960s, it became possible to measure insulin in plasma or serum using radioimmunoassay. The technique was then applied to the now landmark test of comparing the insulin responses to oral and intravenous glucose administration. Two independent groups presented evidence that insulin levels were raised to much higher levels after oral than intravenous glucose, thereby, confirming the incretin concept [5, 6]. The incretin effect has also been documented using perfectly matched glucose levels after intravenous and oral glucose administration in both humans [7] and experimental animals [8]. The incretin effect can be quantified as the augmented insulin secretion elicited by oral compared with intravenous administration of glucose when glucose levels during the two challenges are matched. In addition, it has been demonstrated that the incretin effect is responsible for 50–70% of the insulin response after oral glucose in healthy subjects [7]. The incretin effect is dose-dependently upregulated by increasing the oral glucose load to the extent that the circulating glucose levels after oral administration of such different glucose loads as 25 g, 75 g and 125 g are virtually the same [9].

2. Incretin effect in type 2 diabetes

In 1986 it was demonstrated that the incretin effect is reduced in type 2 diabetes patients; in 14 such patients, it contributed only approximately 20% to the insulin response to oral glucose (50 g) [7]. Later studies confirmed the reduced incretin effect in type 2 diabetes and concluded that the incretin effect contributed to approximately 35% of the insulin response to oral glucose (75 g) in type 2 diabetes, as it was demonstrated in eight patients [10] and 21 patients [11]. Furthermore, by examining the incretin effect in response to three different glucose loads (25 g, 75 g and 125 g) in eight patients with type 2 diabetes, it was found that the upregulated incretin effect on increasing the glucose load was clearly suppressed compared with the controls [9]. This reinforced the idea of a defective incretin effect in people with diabetes and also showed that there is impaired dynamic incretin adaptation with increasing glucose loads in these patients [12]. It was thus clear that, although the studies were small, the incretin effect was lower in those with type 2 diabetes than in the controls.

Several studies have addressed whether the defective incretin effect in type 2 diabetes is a primary cause of the disease or merely a secondary phenomenon arising during the progression of the disease. The conclusion of most of these studies is that the reduced incretin effect in type 2 diabetes is not a primary pathophysiological entity: for example, the relatives of patients with type 2 diabetes exhibit largely the same incretin effect as the controls [13]; and in patients with chronic pancreatitis, the incretin effect is again the same as in the controls, but reduced when secondary diabetes develops [10]. One study has also shown that the incretin effect is largely preserved in subjects with impaired glucose tolerance, although subtle differences may be seen [14]. This suggests that a perturbed incretin effect is an early phenomenon during the development of type 2 diabetes and not a defect that precedes the onset of the disease.

3. Basis of the incretin effect

The incretin effect depends largely on the two main incretin hormones, glucose-dependent insulino tropic polypeptide (GIP) and GLP-1, both of which are released after oral glucose ingestion and potentiate glucose-stimulated insulin secretion [15]. There are two major components in the incretin effect: release of incretin hormones from the gut; and the effects of incretin hormones on beta-cells, leading to insulin secretion. This suggests that the impaired incretin effect in type 2 diabetes could be due to either impaired incretin hormone secretion (incretin hormone deficiency) and/or defective insulino-tropic action of the incretin hormones (incretin hormone resistance). Several studies have explored both these possibilities.

4. Incretin hormone secretion in type 2 diabetes

The incretin hormones GIP and GLP-1 are released when nutrients from meal ingestion (or simple macronutrient ingestion) reach the cells in the gut that produce these incretin hormones [15]. Incretin hormone secretion is mediated through direct stimulation of the enteroendocrine cells by nutrients and is therefore not only dependent on the type of macronutrient or macronutrient load, but also on the rate of gastric-emptying and intestinal transit time. Incretin hormone secretion is also modulated by other gut hormones and subject to diurnal regulation, with higher secretion in the morning than in the afternoon after identical stimulation [16, 17]. Several factors may potentially affect incretin hormone secretion in type 2 diabetes (see below). It is therefore possible that the reduced incretin effect in type 2 diabetes is the result of impaired incretin hormone secretion.

However, the results of the studies looking at whether GIP secretion is defective in type 2 diabetes have been conflicting, with similar, augmented or reduced GIP secretion after oral glucose or a mixed meal in patients with type 2 diabetes vs non-diabetic controls [15, 18, 19]. This suggests that, although more studies are required to examine this issue in more detail, the overall conclusion at this time is that no major defect in GIP secretion is evident in type 2 diabetes. A similar conclusion can be reached based on the results of the many studies examining GLP-1 secretion in diabetic and non-diabetic subjects.
Discrepancies in glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) responses to a mixed meal and pure macronutrients in normal-weight and obese subjects.

<table>
<thead>
<tr>
<th>Challenge</th>
<th>GIP secretion</th>
<th>GLP-1 secretion</th>
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<tbody>
<tr>
<td>Mixed meal</td>
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<td>Glucose</td>
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<td>Fat</td>
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Data are taken from Carr et al. and Lindgren et al. [24–26]; ↓: poorer secretion in obese subjects; ↑: increased secretion in obese subjects; ↔: no difference between lean and obese subjects.

Table 1

In addition, discrepancies between studies of incretin hormone secretion in controls vs diabetic subjects may also be related to factors that, through physiological or pathophysiological actions, affect incretin hormone secretion. Examples of such factors are obesity, insulin resistance, glucose intolerance, gastric-emptying and glucose-lowering medication. All these factors have been shown to perturb GIP and/or GLP-1 responses to mixed meals or oral glucose; this suggests that, when analyzing the differences in incretin hormone responses between the controls and diabetics, all these factors may be involved if the groups are not well matched. Table 2 summarizes some of this information [14,21,28–34]. Other potential factors have not been studied in details, and further studies are required, for example, on the potential dependency of glycaemic control (HbA1c) and the duration of diabetes on the incretin hormone response to a mixed meal or oral glucose. Another important aspect, mentioned in Table 2, not to be overlooked when designing studies is the duration of the washout period for concurrent glucose-lowering medication. If patients are treated with metformin, for example, which increases GLP-1 secretion, a too short washout period (<7 days) might result in a carry-over stimulatory effect of metformin, which would mask a potential reduction in incretin hormone secretion and therefore, confound interpretation of the data [18]. Another factor that may be of relevance is the diabetes milieu, especially in the light of recent findings that lipotoxicity impairs GLP-1 secretion from isolated enteroendocrine cells [35], although whether this may also be seen in patients with diabetes not yet known. In any case, it appears that many factors can potentially affect incretin hormone secretion and so, influence the result of different studies comparing these responses in different population groups. It is therefore necessary to exercise caution when interpreting these studies and generalizing their findings to the entire patient population with type 2 diabetes.

Nevertheless, despite all these confounding factors in the interpretation of data acquired so far, some generalized conclusions may be drawn: (1) some, but not all, patients with type 2 diabetes have defective incretin hormone secretion and this appears to be more related to meal ingestion than oral glucose; but (2) impairment of the incretin effect in type 2 diabetes is, at
least in most cases, not explained by reduced incretin hormone secretion.

5. Incretin hormone-induced insulin secretion

When GIP and GLP-1 are infused intravenously, they both potently potentiate and augment glucose-stimulated insulin secretion. However, this insulinotrophic action of GIP has convincingly and repeatedly been demonstrated to be reduced in type 2 diabetes [15,18,19,36,37]. The effect appears to be associated with the diabetic condition, as it was not found in the relatives of patients with type 2 diabetes [19,38] or in women with previous gestational diabetes mellitus [39], whereas it was seen in diabetes secondary to chronic pancreatitis [40]. A reduced insulinotrophic effect of GIP was also seen in otherwise healthy subjects with experimental insulin resistance induced by a combination of a high-fat diet, sedentary lifestyle and steroid therapy [41]. If this model of insulin resistance is mimicking the insulin resistance in those with diabetes, it may be concluded that the consequence of insulin resistance is to reduce the insulinotrophic effect of GIP, which may therefore be a very early phenomenon in the development of type 2 diabetes.

Potential mechanisms contributing to defective GIP-induced insulin secretion in type 2 diabetes have been discussed. Suggested mechanisms include downregulation of the GIP receptors with poor beta-cell recognition of GIP and defective post-receptor signaling, resulting in poor GIP-induced insulin secretion [15,18,19]. However, impaired GIP-induced insulin secretion may also reflect a more generalized beta-cell dysfunction, resulting in an impaired secretory response to several challenges, one of which is GIP [19]. Another important contribution to our knowledge is that near-normalization of glycaemia in patients with type 2 diabetes has been shown to improve the insulin response to GIP [42]. This suggests that, whatever the islet mechanism to explain the impaired GIP-induced insulin secretion, hyperglycaemia may be a contributing factor and, thus, by reducing hyperglycaemia, the insulinotrophic action of GIP may return.

In contrast to the marked reduction in GIP-induced insulin secretion, the insulin response to GLP-1 is more preserved in type 2 diabetes patients [15,18,19]. This is the basis of the success of incretin therapy for the disease [4]. However, careful analysis has demonstrated that, compared with controls, the effect of GLP-1 to stimulate insulin secretion is also reduced in type 2 diabetes. Thus, Nauck et al. showed in 1993 that the insulin secretory response to GLP-1 was reduced by approximately 30% in diabetics vs controls [36]; a similar reduction in beta-cell effect of GLP-1 in type 2 diabetics was demonstrated 10 years later by Kjems et al. [43]. It has also been shown that the insulinotrophic action of GLP-1 is reduced in subjects with impaired glucose tolerance compared to those with normal glucose tolerance [44] as well as in first-degree relatives of people with type 2 diabetes [45]. This suggests that the disease is associated with impaired GLP-1 augmentation of insulin secretion and that the defect is an early phenomenon in the development of the condition. In fact, defective GLP-1-induced insulin secretion has been observed in otherwise healthy subjects with experimental insulin resistance induced by a sedentary lifestyle, high-fat diet and steroid administration [41], suggesting that insulin resistance per se can cause impaired beta-cell function of GLP-1. Whether this model of insulin resistance reflects natural insulin resistance is not yet known; if so, then impaired GLP-1-induced insulin secretion could be a very early feature in the development of diabetes. In addition, it should be emphasized that important species differences may be involved, as other results have been achieved in experimental animals. For example, insulin resistance induced by a high-fat diet in mice was associated with an upregulated beta-cell response to GLP-1 as a potentially adaptive mechanism [46].

As with impaired GIP-induced insulin secretion in type 2 diabetes, the mechanism behind the impaired insulin secretion in response to GLP-1 in the disease has yet to be established, although three different explanations have been discussed. One is that the impairment of insulin secretion in response to GLP-1 is a reflection and consequence of a generalized beta-cell dysfunction in type 2 diabetes [19]. This means that if beta-cells do not respond normally to glucose, then the potentiation of glucose-stimulated insulin secretion, the main effect of GLP-1, would also be defective. The second explanation could be that the diabetes milieu impairs the action of GLP-1, including such factors as hyperglycaemia, hyperlipidaemia and insulin resistance, as well as other factors that are associated with type 2 diabetes and which may impair beta-cell function. The finding that, as in the case of GIP, near-normalization of glycaemia also improves the insulin secretory response to GLP-1 would support such a mechanism [40]. Furthermore, it was recently observed in experimental diabetes mouse models that lipotoxicity impairs the beta-cell effect of GLP-1 and, consequently, the treatment of hyperlipidaemia also improves GLP-1-induced insulin secretion [47]. A third possibility is that some patients with type 2 diabetes may have true ‘GLP-1 resistance’ due to a genetic defect impairing the beta-cell signaling function of GLP-1. If such patients are included in studies, their defective responses will lead to a lower overall response when all the results are analyzed together. The notion of GLP-1 resistance has been proposed in a series of studies, suggesting that some genetic factors are of importance [47–50]. In fact, two gene loci (TCF7L2 and WFS1) associated with a risk of a reduced GLP-1 effect have been identified in people with type 2 diabetes, and carriers of both these risk alleles have a 15% reduction in insulin secretion during oral glucose tolerance tests [47–49]. However, more information is needed as regards these intriguing findings. The only conclusion valid at this time is that at least some patients have a reduced beta-cell response to GLP-1, although the response in most patients is sufficient to explain the good glycaemic outcome of treatment with incretin-based therapy.

Thus, it is clear that there is an impaired insulinotrophic action of GIP in type 2 diabetes and that, at least in some patients, the insulinotrophic action of GLP-1 is also reduced. In addition, the impaired overall incretin effect in most subjects is most likely a phenomenon of diabetes itself and not a primary pathological entity, and a defective insulin response to GLP-1 may arise before the onset of diabetes in some patients with genetically determined GLP-1 resistance.
6. Clinical consequences

The impaired incretin effect in type 2 diabetes is a therapeutic target as there are now tools that can both stimulate GLP-1 receptors (using GLP-1 receptor agonists) and increase circulating levels of active incretin hormones (using DPP-4 inhibitors) [4,51,52]. Incretin-based therapy may be regarded as a therapy to restore an early defect in type 2 diabetes that, in turn, targets the main islet dysfunction of the disease. Islet dysfunction in type 2 diabetes involves both alpha- and beta-cells with inappropriately high glucagon levels and, in response to requirements, with reduced insulin levels as a consequence [53,54]. The combined inhibition of glucagon secretion and stimulation of insulin secretion (by glucose-dependent mechanisms) is of particular value in incretin therapy. Indeed, the combined action on both islet cell types opens up a potential for particularly good durability of clinical effects with incretin therapy in the glucose-lowering management of type 2 diabetes. Although the disease is progressive because of the progressive beta-cell deterioration [55], the persistent capacity of incretin therapy to inhibit glucagon secretion might even preserve good glucose-lowering effects in cases of advanced beta-cell failure. Experience with long-term incretin-based therapy is therefore of great interest. Recently, a 4-year follow-up of treatment with exenatide twice daily was published and showed sustained effects [56].

Given the identified risk factors for impaired incretin effects [mainly a high body mass index (BMI) or genetic GLP-1 resistance], it may be speculated that incretin therapy would be particularly effective or particularly poor in patients with these phenotypes. However, clinical trials do not support the idea that incretin therapy is more or less efficient in obese patients. Therefore, studies of the impact of the incretin system on islet function and glucose homoeostasis and its defects in type 2 diabetes have not yet generated enough data to support the possibility of targeting incretin therapy to patients with specific characteristics. Nevertheless, the studies reporting that the insulino- tropic effect of GLP-1 is impaired and not completely normal in type 2 diabetes suggest that some patients will not respond to treatment with GLP-1 receptor agonists. In theory, these would be the patients with genetically determined GLP-1 resistance. It would now be of interest to study whether people with such GLP-1 resistance (as detected by gene sequence analysis) respond poorly to incretin therapy. Furthermore, it would be of interest to examine whether subjects with isolated GLP-1 resistance still retain any GIP action and, if so, whether it is sufficient to stimulate insulin secretion, given the known impaired insulino- tropic action of GIP in type 2 diabetes. If this is indeed the case, then DPP-4 inhibition, which results in increased levels of not only GLP-1 but also of GIP, would have a glucose-lowering action in patients with GLP-1 resistance. This would, in turn, raise the possibility of identifying those patients who would be more or less suitable for glucose-lowering therapy with GLP-1 receptor agonists or DPP-4 inhibitors from a physiological point of view.

7. Future research

Although a considerable body of knowledge has been amassed since the initial discovery of incretins some 80 years ago and the success of incretin therapy in patients with type 2 diabetes has become evident over the past several years, there is much that remains to be studied. It is important that future studies include more detailed evaluations of the variability of incretin hormone secretion and effects in well-defined subpopulations of type 2 diabetes patients, and look at whether the results of such studies have implications for a poor or good response to incretin therapy. Table 3 lists the specific topics of importance that should be examined in future clinical studies in this area.

Disclosure of interest

The author has received honoraria for lectures and been a member of advisory boards for AstraZeneca, Bristol-Myers Squibb, GSK, Eli Lilly, Novartis, Novo Nordisk, Merck and Sanofi-Aventis, which are all companies producing GLP-1 receptor agonists or DPP-4 inhibitors.

References


