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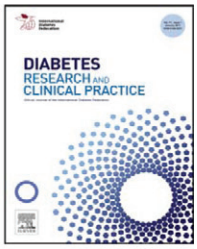

Incretin effect: GLP-1, GIP, DPP4

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ABSTRACT

The term incretin effect was used to describe the fact that oral glucose load produces a greater insulin response than that of an isoglycemic intravenous glucose infusion. This difference has been attributed to gastrointestinal peptides GLP-1 and GIP. Since incretin effect is reduced in subjects with type 2 diabetes, despite GLP-1 activity preservation, two forms of incretin-based treatment have emerged: GLP-1R agonists, administered subcutaneously and DPP-4 inhibitors, administered orally. There is a great interest whether incretin-based treatment will be associated with sustained long-term control and improvement in β-cell function. The observation that GLP-1R agonists improve myocardial function and survival of cardiomyocytes highlights the need for further studies. Incretin-based therapies offer a new option and show great promise for the treatment of type 2 diabetes.

1. Introduction

Enteral nutrition provokes the secretion of the gut hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), involved in the disposal of absorbed glucose, through the stimulation of insulin secretion. Up to two-thirds of the insulin normally secreted in relation to meal, though, is due to the insulinotropic actions of GLP-1 and GIP. The term incretin effect was originally used to describe the fact that oral glucose load produces a greater insulin response than that of an isoglycemic intravenous glucose infusion [1]. This difference between the two ways of glucose administration has been attributed to incretin hormones GLP-1 and GIP. GIP is a 42 aminoacid peptide synthesized in enteroendocrine K cells in the proximal small bowel [2]. GLP-1 is derived from proglucagon through post-translational processing. GLP-1 is synthesized in enteroendocrine L cells in the distal ileum and colon and it exists in two molecular forms GLP-1 (7-37) and GLP-1 (7-36) amide [3]. Normal plasma levels of GLP-1 in the fasted state are 5–10 pmol/L and 15–50 pmol/L after eating.

The actions of GIP and GLP-1 are transdused by the engagement of G-protein-coupled receptors expressed on pancreatic α- and β-cells and in peripheral tissues, including the central nervous system, gastrointestinal tract, heart and lungs. Activation of incretin receptors increases c-AMP levels and insulin secretion in a glucose dependent manner [4]. More sustained incretin binding to receptors increases insulin biosynthesis through protein kinase A activation. It also triggers proliferative pathways and protects from apoptotic β-cell death, which leads to expansion of the β-cell mass in both rodent and human islets [5,6]. GLP-1 also suppresses glucagon secretion from α-cells, which reduces hepatic glucose production, in a glucose-dependent manner. However glucagon release is fully preserved in cases of hypoglycemia, even in the presence of pharmacological concentrations of GLP-1 [7].

Extrapancreatic actions of GLP-1 include its actions on gastrointestinal tract and central nervous system. GLP-1 delays transit of nutrients from the stomach to the duodenum [8]. Intracerebroventicular administration of GLP-1 inhibits food intake in rodent studies [9]. GLP-1 action in the brain may also be neuroprotective, via activation of anti-apoptotic signaling pathways in specific neurons [10]. GLP-1 can reduce the amyloid beta peptide levels in the brain in vivo and pro-

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tect cultured hippocampal neurons against death induced by amyloid beta peptide [11]. GLP-1 receptor deficiency in mice exhibits a learning and memory deficit phenotype, which is restored after hippocampal GLP-1 receptor gene transfer [12]. GLP-1 administered IV increased heart rate and blood pressure in rats [13]. Similar effects in human studies have not been reported. GLP-1 receptor signaling modulates the function and survival of cardiomyocytes via a p70S6 kinase activation, in normal and postischemic isolated rat hearts [14].

In a pilot study, in 10 human patients with left ventricular dysfunction and acute MI following angioplasty, GLP-1 was administered as a 72-hour infusion. GLP-1 significantly improved left verticular function, global wall and regional wall motion score indices ($p < 0.01$) [15]. GLP-1 agonist liraglutide significantly reduced the infarct size and improved the survival in normoglycemic and diabetic mice after acute coronary artery ligation [16]. Several gut peptides, including GIP, GLP-1, GLP-2 and PYY, regulate bone resorption and bone formation. The effects of short term administration of GLP-1 in male Wistar rats produced modest increases of osteocalcin levels and small increases in bone mineral density [17].

GIP receptors are expressed on adipocytes. GIP receptor knockout mouse is resistant to the development of diet induced obesity. Furthermore, GIP receptor deficient ob/ob mice exhibited a 41% reduction in body weight and lower levels of plasma cholesterol, triglycerides and FFA [18]. The structure of GIP and GLP-1 reveals an alanine at position 2, rendering these peptides ideal putative substrates for the aminopeptidase DPP-4. Very rapid degradation of GIP and GLP-1 by DPP-4 was first reported by Mentlein and colleagues in 1993 [19].

2. Incretin effect and type 2 diabetes

In 1986, Nauck and colleagues, demonstrated that the incretin effect was diminished in subjects with type 2 diabetes [20]. This reduced incretin effect has been attributed to defective GIP action and reduced GLP-1 secretion [21].

The preserved action of GLP-1 and the diminished GIP responsitivity in experimental and clinical models of type 2 diabetes is an important issue. The ineffectiveness of GIP may be a result of chronic desensitization of the GIP receptor and the inappropriate expression of the GIP receptor in the islets. Increased levels of peptides are seen as a potential explanation for desensitization of receptors. There is a controversy as to whether GIP levels are elevated, normal, or lowered in type 2 diabetes.

One possible explanation for this diversity may be that plasma GIP levels are a matter of the duration of diabetes. It is possible, however, that hyperglycemia per se or its metabolic consequences, and not elevated GIP levels, could lead to the unresponsitivity of β-cells to GIP. High glucose levels in the diabetic range increase the degree of ubiquitination of GIP receptor. This is a new concept to downregulation of receptors on β-cells. The metabolic state results in GIP receptors ubiquitination in a ligand independent manner. The synthesis of GIP receptor is not likely to be altered by hyperglycemia. Another explanation for the ineffectiveness of GIP is an increase in DPP-4 activity, which could inactivate GIP prior to its action on β-cell. The levels of circulating DPP-4 in diabetic animals are similar to normal, so this explanation can be ruled out. A study performed in first-degree relatives of patients with type 2 diabetes showed a reduced insulinotropic activity of GIP, suggesting a possible inherited condition for the blunted response to GIP [22]. The available data suggest that a component of the defective GIP response in diabetic patients may be due to hyperglycemia, and as such it may be partially reversible following treatment of diabetes. A study of 8 diabetic subjects demonstrated that intensive insulin treatment for 4 weeks significantly improved β-cell responsiveness to GIP and GLP-1 by a factor of three to four fold [23].

Similarly, diabetic patients treated with a sulfonylurea 1 hour prior to GIP infusion showed that the sulfonylurea increased the insulin response to GIP infusion [24]. These data suggested that the diminished response to GIP in diabetic patients may not be permanent and may be reversible following treatment of hyperglycemia.

However, the fact is that incretin activity of GLP-1 in type 2 diabetes is preserved. Continuous subcutaneous administration of native GLP-1 to type 2 patients lowers fasting and postprandial glucose levels, HbA_{1C} and also results in weight loss [25]. The continuous administration is necessary because of the rapid inactivation of native GLP-1 peptide by the DPP-4. However, this is inconvenient and alternative therapeutic approaches are required. Two forms of incretin-based treatment have emerged: GLP-1R agonists, administered subcutaneously, and DPP-4 inhibitors, administered orally.

3. GLP-1R agonists

Exendin-3 and exendin-4 are naturally occurring peptides. The saliva of the lizard *Heloderma suspectum* contains these peptides, which were named exendins in that they were isolated from an exocrine gland and were subsequently shown to have endocrine actions [26]. Exendin-4 exhibits 52% aminoacid identity with human GLP-1 and displays similar functional properties to GLP-1. Exendin-4 has a glycine at position 2, hence it is not a substrate for the DPP-4 and has a longer half life in vivo. Exenatide is a synthetic form of exendin-4 and is the first GLP-1R agonist that has been approved by the FDA in April 2005, for the treatment of type 2 diabetes.

The 3 AMIGO studies compared the effects of adding exenatide to previous therapy with sulfonylurea, metformin, or metformin plus a sulfonylurea [27–29]. Exenatide at doses 5 or 10 μg twice daily significantly reduced fasting glucose and HbA_{1C} (0.86%, 0.78% and 0.8% with exenatide plus sulfonylurea, exenatide plus metformin and exenatide plus metformin and sulfonylurea respectively). Body weight loss was progressive with a mean 1.6 kg, 2.8 kg and 1.6 kg weight loss respectively, after 30 weeks of treatment with 10 μg exenatide twice daily. The results of 3 AMIGO studies led to the approval of exenatide by the FDA.

Exenatide has been studied as initial monotherapy for type 2 diabetes. Exenatide 10 μg twice daily resulted in a reduction in H HbA_{1C} of 0.9% with about 60% of patients

achieving a target of HbA_{1C} less than 7%. Exenatide was approved for use as initial monotherapy in patients with type 2 diabetes on October 30 2009. Exenatide has been studied in combination with either pioglitazone or rosiglitazone in subjects with type 2 diabetes [30]. A mean HbA_{1C} reduction of 0.89% was observed in the exenatide treated group. Twice daily exenatide was compared versus once daily insulin glargine or biphasic insulin aspart 70/30 in patients with type 2 diabetes inadequately controlled with oral agents. Exenatide and insulin glargine produced comparable reductions in HbA_{1C} of about 1.1% [31]. Glycemic control achieved with insulin aspart was markedly superior to that achieved with exenatide and significantly more insulin treated patients achieved target HbA_{1C} goals of less than 7% or 6.5% [32]. However the patients on insulin gained weight, whereas patients on exenatide lost weight. Baseline HbA_{1C} values were approximately 10.2% and the duration of diabetes was 9 years. In a previous study comparing exenatide versus biphasic insulin aspart, the HbA_{1C} reduction was similar in the two groups (exenatide –1.04% versus biphasic insulin aspart –0.89%). Mean baseline HbA_{1C} value was 8.6%. Taken together, these studies suggest that exenatide is a reasonable alternative to the initiation of insulin treatment, especially for those who are not in an advanced stage of diabetes and may not have sufficient β-cell function for a GLP-1 mimetic to be effective.

Liraglutide is a long acting GLP-1R agonist that was approved in Europe in the spring of 2009 and received marketing authorization on June 30, 2009. Liraglutide contains a Ser 33 Arg amino-acid substitution and has a C16 fatty-acid side chain at Lys 26. This new molecule is DPP-4 resistant and binds to serum albumin, which results in a 11–13 hours half life, in vivo [33]. A single subcutaneous administration results in 24h glucose control and low rates of hypoglycemia. The LEAD program is comprised of six randomized, controlled, double-blind studies conducted in more than 40 countries [34–38]. The program includes 3,800 patients with type 2 diabetes whose blood glucose is inadequately controlled. The results of these trials suggest that liraglutide monotherapy 1.2 mg or 1.8 mg daily, compared to glimepiride monotherapy, was more effective for HbA_{1C} reduction (0.84% and 1.14% versus 0.5% respectively). A 26-week study compared the efficacy of liraglutide versus rosiglitazone in patients inadequately controlled with glimepiride. Liraglutide was more effective at doses 1.2 and 1.8 mg daily than rosiglitazone in reducing HbA_{1C} and fasting plasma glucose.

Data from the head-to-head trial of liraglutide versus glimepiride in patients treated with metformin showed that liraglutide has similar efficacy compared to glimepiride over 26 weeks (about 1% reduction of HbA_{1C} from a baseline value of 8.4%). Liraglutide was also associated with a small decrease in blood pressure, weight loss, less hypoglycemia, but more nausea.

The efficacy of liraglutide has been assessed in comparison with insulin glargine in patients inadequately controlled with glimepiride and metformin. More patients in the liraglutide group achieved the HbA_{1C} target $<7\%$ or $<6.5\%$ (53.1% and 37.1% respectively), than patients in the glargine group (45.8% and 23.6% respectively). In a head-to-head study of liraglutide once daily versus exenatide twice daily, liraglutide 1.8 mg caused a greater reduction in HbA_{1C} than exenatide 10μg twice daily (1.1% versus 0.8% respectively). The reductions in blood pressure and body weight were similar in both groups.

The most common side effect associated with GLP-1 therapy is nausea, which generally diminishes over time, and most patients do not report ongoing nausea after several months of treatment with a GLP-1R agonist. About 50% of patients treated with exenatide develop antibodies. However the antiexenatide antibodies do not seem to be a problem. There are not enough data about antibodies following liraglutide treatment.

Pancreatitis is a rare but severe side effect following treatment with exenatide. There are little clinical data about the incidence of pancreatitis in patients with type 2 diabetes. However it is suggested that the patients with diabetes, who are generally overweight or obese, have a 2.8 fold greater risk of developing pancreatitis and a 1.9 fold greater risk of developing billiary tract disease. Although exendin-4 has been shown to increase amylase release from rat pancreatic acini, no evidence suggested that exendin-4 or GLP-1 alone cause pancreatitis.

Other long-acting GLP-1 agonists include albiglutide and taspoglutide. Albiglutide, originally referred to as Albugon, is a recombinant human albumin-GLP-1 protein that despite its large size and complex structure mimics all of the known GLP-1 actions [39]. Albiglutide can be administered once weekly and possibly less frequently. The phase 3 clinical trial program for albiglutide was commenced in early 2009 and will be comprised of at least 5 trials. Taspoglutide is a once weekly GLP-1R agonist for the treatment of type 2 diabetes.

4. DPP-4 inhibitors

The observation that GLP-1 and GIP are rapidly degraded by DPP-4 fostered the development of DPP-4 inhibitors [40]. DPP-4 inhibitors compounds approved for the treatment of type 2 diabetes include Vildagliptin, Sitagliptin and Saxagliptin. Linagliptin and Alogliptin remain under investigation and other drugs such a Dutogliptin are also in phase 3. DPP-4 inhibitors mimic many of the actions of GLP-1, including insulin stimulation, glucagon inhibition and preservation of β-cell mass [41].

Sitagliptin was approved in the USA on October 2006, for use as monotherapy or combination therapy either with metformin, sulfonylurea or a thiazolidinedione. Vildagliptin was subsequently approved in Europe. DPP-4 inhibitors may be administered orally once or twice daily. The addition of vildagliptin to patients on metformin reduced HbA_{1C} by 0.8% compared to placebo [42]. All DPP-4 inhibitors are selective for DPP-4, but they have different affinity for DPP-4. As DPP-4 is a member of a large class of proteases, there has been considerable attention on the importance of selectivity of DPP-4 inhibitors.

DPP-8 and DPP-9, but not DPP-4 inhibitors, have produced in animals alopecia, thrombocytopenia, reticulocytopenia, gastrointestinal toxicity and high mortality [43]. To date,

DPP-4 inhibitors have shown sustained effectiveness and a safe profile.

There is a great interest in whether DPP-4 inhibitors and GLP-1R agonists' treatment will be associated with sustained long-term control of HbA_{1C}, and improvement in β-cell function. On the other hand, patients with type 2 diabetes have increased risk of cardiovascular morbidity and mortality. The observation that GLP-1R agonists improve myocardial function and survival of cardiomyocytes highlights the need for further studies.

Incretin mimetics show great promise for the treatment of type 2 diabetes. However, long term clinical studies are needed to permit a better understanding of the role of these drugs in the treatment of type 2 diabetes.

Conflict of interest

The author has no conflicts of interest to report.

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