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15

Role of Incretin, Incretin Analogues and Dipeptidyl Peptidase 4 Inhibitors in the Pathogenesis and Treatment of Diabetes Mellitus

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1. Introduction

Type 2 diabetes mellitus (T2DM) is increasing in prevalence worldwide, and is expected to affect 440 million people by 2030 (IDF, 2009). Despite the development and use of several medications to control patients' blood glucose levels, the effective management of T2DM continues to be a challenge to physicians. In order to achieve HbA1c targets (<7.0%), patients must reach desirable fasting (90 mg/dL - 130 mg/dL) and postprandial glucose levels (<180 mg/dL) (American Diabetes Association, 2006). However, two thirds of patients with T2DM remain unable to reach the HbA1c targets (Koro, 1988; Fan, 2006).

Blood glucose levels are dependent on the dynamic processes of hepatic production of glucose and skeletal muscle use of glucose. Treatment strategies designed to improve these processes have as a result the improvement in patient's glycemic status. Different agents are currently available, providing physicians with several options for the management of T2DM. These clinical therapies include insulin and oral drugs that are classified as insulin sensitizers (e.g., biguanides and thiazolidinediones), insulin secretagogues (e.g., sulfonylureas and meglitinides), and alpha-glucosidase inhibitors. Newer treatment agents, incretin mimetics and dipeptidyl peptidase 4 (DPP-4) inhibitors, have been recently added to clinicians' therapeutic choices (Drucker, 2003; Drucker, 2006a).

2. The incretin effect

The concept that gut factors stimulate pancreatic endocrine secretion was hypothesized soon after secretin was discovered in 1902 (Kieffer, 1999). In 1906, this notion was tested by giving gut extracts to patients with diabetes, which reduced their glycosuria (Moore, 1906). In the 1920s, based on studies in dogs, the term incretins was introduced for the gastrointestinal hormones released in response to food ingestion (Zunz, 1929). These hormones are responsible for approximately 60% of the insulin secretion following a meal and for the so-called incretin effect. The incretin effect describes the phenomenon that oral glucose leads to

a greater insulin response than an isoglycaemic intravenous glucose load (McIntyre, 1964; Nauck, 1986).
There are two major incretins: glucosedependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). In this chapter we will focus on GLP-1 actions, since this molecule is preserved in patients with T2DM.

3. Physiological actions of GLP-1

GLP-1 is a product of the glucagons gene, which is expressed in pancreatic α-cells and in L-cells, located mostly in the lower small intestine and colon. GLP-1 concentrations increase as early as 5 to 10 minutes following ingestion of carbohydrates and lipids, well before the nutrients pass into the lower gut where most L-cells are located (Eissele, 1992; Deacon, 1995). Once released from L- cells, GLP-1 is rapidly metabolized by a widely distributed serine protease, DPP-4, resulting in a half-life of 1 to 2 minutes in the circulation. DPP-4, which is located on endothelial cells as well as in soluble form in plasma, cleaves the two N-terminal amino acids from GLP-1, causing a substantial loss of insulinotropic activity (Deacon, 1995; Vahl, 2003).
GLP-1 stimulates insulin secretion of the β-cells and inhibits glucagon secretion from the α-cells. Both actions occur in a glucose-dependent manner and lead to a normalisation of postprandial and fasting hyperglycaemia (Drucker, 2006b). In the gastrointestinal tract, GLP-1 has a direct effect on motility and slows gastric emptying. This effect contributes to a normalisation of postprandial hyperglycaemia and explains why long-term treatment with GLP-1 receptor agonists leads to weight loss (Drucker, 2006b). Under hypoglycaemic conditions the counter-regulation by glucagon is not affected and insulin secretion is not stimulated and, therefore, GLP-1 does not elicit hypoglycaemia (Drucker, 2006b).
Except for its antidiabetic actions, recent findings have shown that application of GLP-1 receptor agonists led to an improvement in cardiovascular parameters (reduction of systolic blood pressure, beneficial effects on myocardial ischaemia in animal models, positive effects on left ventricular function in heart failure) (Papazafiropoulou, 2011). In addition, animal studies in rodents and isolated human islets showed beneficial long-term actions of GLP-1 to β-cell mass (Fehmann, 1992; Brubaker, 2004). Whether these findings will have a positive effect on preventing T2DM progression is not known yet.

4. Incretins and the pathogenesis of T2DM

In T2DM patients the incretin effect is diminished. Incretins does not act as an insulinotropic hormones under chronic hyperglycaemia in T2DM. However, GLP-1 is still able to stimulate insulin secretion under hyperglycaemia in T2DM (Drucker, 2006). In addition, the effects of GLP-1 on gastric emptying and glucagon secretion are maintained in patients with T2DM (Nauck, 1993a).
A study confirmed that the incretin effect is reduced in patients with T2DM (Knop, 2007). Another study showed a significant reduction in the incretin effect and the GLP-1 response to oral glucose in T2DM patients compared with individuals with normal or impaired glucose tolerance (Muscelli, 2008). Notably, impaired actions of GLP-1 may be partially restored by improved glycemic control (Knop, 2007). The findings from a study of obese diabetic mice suggest that the effect of GLP-1 therapy may be caused by improvements in β-cell function and insulin sensitivity, as well as by a reduction in gluconeogenesis in the liver (Lee, 2007).

Several studies in T2DM patients have shown that synthetic GLP-1 administration induces insulin secretion, (Nathan, 1992; Nauck, 1993a) slows gastric emptying, and decreases inappropriately elevated glucagons secretion (Nauck, 1993a; Kolterman, 2003). Acute GLP-1 infusion studies showed that GLP-1 improved fasting and post prandial plasma glucose concentrations (Nathan, 1992; Nauck, 1993b). Long-term studies showed that this hormone exerts euglycemic effects, leading to improvements in HbA1c, and induces weight loss (Zander, 2002).

5. T2DM and incretin-based therapies

The incretin-based therapies offer a good alternative choice to the established antidiabetic compounds due to their satisfying antihyperglycaemic efficacy, their lack of risk of hypoglycaemia and their positive effects on body weight. In order to utilise GLP-1 action for T2DM, two options are presently available:

1. GLP-1-receptor agonists (or GLP-1 mimetics) as injectable compounds
2. DPP-4 inhibitors as orally active substances

6. GLP-1-receptor agonists

6.1 Exenatide

Exenatide is the synthetic form of exendin-4, a peptide first discovered in the saliva of the gila monster (heloderma suspectum) in 1992. It has a 53% amino acid sequence homology to human GLP-1 and is a GLP-1 receptor agonist (Eng, 1992). It is administered subcutaneously twice daily. A slow release formulation for once-weekly administration (Exenatide LAR [long-acting release]) is presently in clinical phase III studies (Drucker, 2008). Exenatide has a prolonged half-life in comparison to native GLP-1 of approximately 3.5 h. After subcutaneous injection sufficient plasma concentrations are reached for 4–6 hours (Kolterman, 2005).

In clinical studies exenatide lowered the HbA1c by 0.8–1.1% (Buse, 2004; DeFronzo, 2005). Exenatide in combination with metformin (Kendall, 2005), sulfonylurea (DeFronzo, 2005), or both (Buse, 2004) resulted in significant mean HbA1c reductions from baseline ranging from –0.77% to –0.86%. Patients also had statistically significant reductions in mean body weight from baseline (–1.6 kg to -2.8 kg). Comparative studies with insulin showed that effects of exenatide on glycaemic parameters are comparable to the improvement seen with insulin therapy (Heine 2005; Gallwitz, 2006; Barnett, 2007; Nauck, 2007). The comparative studies with insulin showed a difference in weight development of 4–5 kg in 30 weeks between the insulin and exenatide treated groups (Heine 2005; Barnett, 2007a; Nauck, 2007a).

An improvement of β-cell function [measured with HOMA-β (homeostatic modelling assessment of beta cell function) and the proinsulin: insulin ratio] was also observed in the clinical studies. First phase of insulin secretion was restored after an intravenous glucose bolus under treatment with exenatide (Gallwitz, 2006; Barnett, 2007b).

Severe hypoglycaemic events were only observed in exenatide-treated patients who had received combination therapy with sulfonylurea. For this reason a reduction in the dosage of sulfonylurea should be considered when initiating exenatide therapy. In the comparative studies comparing exenatide with insulin treatment, the incidence of nocturnal hypoglycaemic events was lower in the exenatide-treated patients (Gallwitz, 2006; Barnett, 2007).

The most frequent adverse events with exenatide were fullness and nausea. Nausea was the most common reason to stop therapy; with 2–6.4% drop-outs in the clinical studies with exenatide (Gallwitz, 2006; Barnett, 2007). Escalating the dose of exenatide from 5 μg to 10 μg after 4 weeks led to a transient increase in nausea which diminished with continued exposure to the higher dose (Gallwitz, 2006; Barnett, 2007).

In approximately 40% of exenatide-treated patients, anti-exenatide antibodies can be detected. However, over a time period of at least 3 years, these antibody titres did not have any obvious effect on glycaemic control (Drucker, 2008). Cases of acute pancreatitis have been reported since exenatide has been used (Ahmad, 2008; Cure, 2008). In total, the incidence of pancreatitis was low and similar to the elevated risk of pancreatitis that was observed in obese T2DM patients (Dore, 2009).

Exenatide is predominantly eliminated by glomerular filtration followed by proteolytic degradation (Yoo, 2006). Exenatide should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min) or end stage renal disease. Additionally, caution should be applied when initiating or increasing doses of exenatide in patients with moderate renal impairment (creatinine clearance 30–50 ml/min) (Gallwitz, 2006; Barnett, 2007).

6.2 Liraglutide

Liraglutide is the first human GLP-1 analogue. It has two modifications in the amino acid sequence of native GLP-1 and an attachment of a fatty acid side chain to the peptide. It is injected subcutaneously once daily (Agerso, 2002). Liraglutide lowers blood glucose, body weight and food intake in animal models (Sturis, 2003). In clinical studies in approximately 4,200 T2DM patients liraglutide was efficacious and safe (Marre, 2009; Nauck, 2009; Zinman, 2009). In animal studies with diabetic rodents, liraglutide has been shown to increase β-cell mass.

Liraglutide in monotherapy in newly diagnosed T2DM patients led to HbA1c reduction of 0.9–1.1% in a dose of 1.2 or 1.8 mg once daily respectively, over a period of up to 2 years (Garber, 2008). In other studies, the same doses of liraglutide effectively lowered glycaemic parameters in various combinations with oral antidiabetic agents by approximately 1.0–1.5% (Garber, 2008; Garber, 2009).

Liraglutide treatment led to a significant weight loss (Deacon, 2009a; Vilsboll, 2009). The weight loss was accompanied by a more pronounced loss in visceral fat than subcutaneous fat (Deacon, 2009a; Vilsboll, 2009). Furthermore, systolic blood pressure was lowered by 2–6 mmHg in the liraglutide-treated patients. This effect was independent of the weight loss, as the reduction of blood pressure was already observed early on in therapy, when weight loss had not yet occurred (Garber, 2008; Garber, 2009; Zinman, 2009).

The incidence of hypoglycaemic episodes was comparable to placebo in all studies, where no sulfonylurea was used in the combination with liraglutide (Deacon, 2009a; Vilsboll, 2009). Gastrointestinal symptoms were also common, but nausea and vomiting were reported for a short period at the beginning of therapy (Buse, 2009). In the liraglutide clinical trials, there was no evidence of neutralizing antibodies (Garber, 2008; Garber, 2009; Zinman, 2009).

Animal studies showed that a rare type of thyroid cancer known as medullary thyroid cancer was associated with liraglutide in mice and rats, although the relevance of this finding to humans remains unknown. FDA has stipulated that liraglutide be contraindicated in patients

with a personal or family history of medullary thyroid cancer and in patients with multiple endocrine neoplasia syndrome type 2 (US Food and Drug Administration, 2010).
Data on the pharmacokinetic profile of liraglutide in mild to moderate renal impairment showed no alteration of the profile (Deacon, 2009a; Vilsboll, 2009).

7. DPP-4 Inhibitors

7.1 Sitagliptin

Sitagliptin was the first DPP-4 inhibitor approved for the T2DM treatment. The recommended dose of once-daily oral sitagliptin is 100 mg. At this dose, sitagliptin can inhibit ~80% of endogenous DPP-4 activity over a 24-hour period (Herman, 2005). Increases in HOMA-β ranging from 4% to 20% have been shown in the sitagliptin trials.
In the monotherapy trials, sitagliptin compared to placebo, resulted in statistically significant improvements in HbA1c and fasting glucose (Aschner, 2006; Raz, 2006; Scott, 2007). Sitagliptin given as add-on therapy to metformin (Charbonnel, 2006) resulted in similar HbA1c and fasting glucose reductions as in the monotherapy trials. The same result was observed, in a 24-week trial, when sitagliptin was added to pioglitazone vs pioglitazone and placebo (Rosenstock, 2006). In another study, reductions from baseline in HbA1c and fasting glucose were similar when sitagliptin was compared to glipizide, (Nauck, 2007). Increases in HOMA-β ranging from 4% to 20% have been shown in the sitagliptin trials.
Sitagliptin therapy has been shown to be weight neutral in all clinical trials except in one study in which sitagliptin given with metformin resulted in weight reduction of 1.5 kg after 52 weeks of treatment (Nauck, 2007b). The most common side effects of sitagliptin were headache, arthritis, nasopharyngitis, respiratory or urinary tract infections and rarely skin reactions (Aschner, 2006; Raz, 2006; Rosenstock, 2006). The incidence of hypoglycemia was low in these trials (<2%) and was similar to the placebo arms. Dose reduction of sitagliptin has been recommended for patients with moderate or severe renal insufficiency or end stage renal disease (Bergman, 2007).

7.2 Vildagliptin

Vildagliptin also acts by inhibiting circulating DPP-4 activity. It is available as a 50 mg twice-daily in combination with metformin, sulfonylurea or pioglitazone. Vildagliptin has been studied as monotherapy (Ristic, 2005; Pratley, 2006; Dejager, 2007), in combination with other oral antidiabetic agents (Ahren, 2004; Fonseca, 2007; Rosenstock, 2007), and against active comparator therapies including glitazones (Rosenstock, 2007) and metformin (Schweizer, 2007) Vildagliptin therapy was associated with an increase in HOMA-β (11% and 23%) in two monotherapy trials (Ristic, 2005; Pratley, 2006).
In placebo-controlled trials, vildagliptin monotherapy reduced HbA1c (range 0.5% to 0.9%) and fasting glucose (14.4 mg/dL to 19.8 mg/dL) from baseline. The HbA1c reductions observed with monotherapy were statistically significantly greater than placebo in all trials. In clinical studies testing vildaglitpin in monotherapy or combination therapy with metformin, glimepiride, pioglitazone or insulin, vildagliptin was able to decrease the HbA1c by approximately 0.5–1.0% (Ahren, 2008; Pratley, 2008; Barnett, 2009). Vildagliptin therapy was associated with an increase HOMA-β (11% and 23%) in two monotherapy trials (Ristic, 2005; Pratley, 2006), but improvement relative to placebo was only observed in one trial (Ristic, 2005).

Vildagliptin has a good safety and tolerability profile and the most common adverse events are flu-like symptoms, headache, dizziness, and rarely liver enzyme elevations. Vildagliptin, like the other DPP-4 inhibitors, is weight-neutral. The incidence of hypoglycemia was low in trials with vildagliptin and similar to the placebo (Fonseca, 2007; Rosenstock, 2007). No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥50 ml/min). Vildagliptin should not be used in patients with hepatic impairment, including patients with pre-treatment alanine aminotransferase or aspartate aminotransferase >3x the upper limit of normal.

7.3 Saxagliptin

Saxagliptin also acts by inhibiting circulating DPP-4 activity and is available as a 5 mg once-daily in combination with metformin, sulfonylurea or pioglitazone. Saxagliptin causes a reduction in HbA1c by 0.7–0.9%. Fasting plasma glucose is also lowered dose dependently lowered by saxagliptin (Rosenstock, 2008). In a study with drug-naïve patients, saxagliptin lowered all glycaemic parameters significantly (Rosenstock, 2009). As an add-on medication to a therapy with either metformin or glitazone, saxagliptin also led to significant metabolic improvements (Chacra, 2009; Deacon, 2009b; DeFronzo, 2009).

Saxagliptin did not cause hypoglycaemia, was well-tolerated and was weight-neutral. A meta-analysis of clinical phase III studies with saxagliptin showed favourable data on the development of cardiovascular events (Wolf, 2009).

8. In conclusion

Incretin-based therapies offer an alternative treatment option for T2DM patients by targeting pancreatic β-cell dysfunction. Both GLP-1 receptor agonists and DPP-4 inhibitors have been shown to be effective in improving glycemic control in patients with T2DM. They appear to be well tolerated, have a low risk of hypoglycaemia, lead to weight reduction or have a neutral effect on weight.

Choice of therapy should be based on a patient's profile and preference, with consideration given to the unique characteristics of the GLP-1 receptor agonists and DPP-4 inhibitors. The most patient-relevant and striking difference between the incretin-based therapies is that GLP-1 receptor agonists are injectable agents, while DPP-4 inhibitors are effective orally. GLP-1 receptor agonists offer more robust HbA1c level reductions and the potential for weight loss. Nausea, the most common adverse event observed with GLP-1 receptor agonist therapy is not observed in treatment with DPP-4 inhibitors. Advances in the investigation of incretin therapies will further improve treatment outcomes for patients with T2DM and help them reach target goals.

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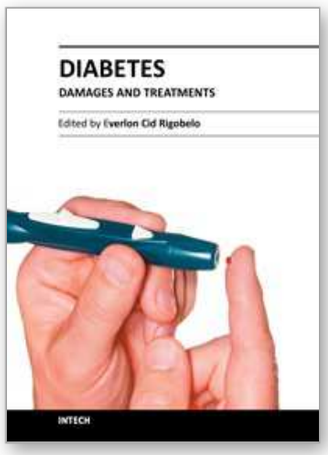

Diabetes - Damages and Treatments

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Over the last few decades the prevalence of diabetes has dramatically grown in most regions of the world. In 2010, 285 million people were diagnosed with diabetes and it is estimated that the number will increase to 438 million in 2030. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the serum glucose concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. Hopefully, this book will be of help to many scientists, doctors, pharmacists, chemicals, and other experts in a variety of disciplines, both academic and industrial. In addition to supporting researcher and development, this book should be suitable for teaching.

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