Review Article

Incretion based therapy for type 2 diabetes mellitus

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Abstract

Most existing antidiabetic agents target only one aspect of the pathophysiology of T2DM, and neither tackle the progressive deterioration in beta-cell mass and function nor the hyperglucagonemia that accompanies T2DM. In contrast, incretin-based approaches target both alpha- and beta-cell dysfunction. Studies indicate that incretin-based therapies perhaps because of the potential trophic effects on the pancreatic beta-cells - may halt the progression of disease that inevitably seems to accompany conventional treatment Within the next year many new and promising GLP-1 analogs and DPP4 inhibitors will be introduced to the market, and, the future will elucidate whether these will have the potential of being disease-modifying drugs.

Keywords: DIABETES, GLP1, DPP4

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Received Date: 19/06/2014 Accepted Date: 29/06/2014

Access this article online

Quick Response Code:

Website: www.statperson.com

DOI: 04 July 2014

INTRODUCTION

Diabetes mellitus(DM) is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[1] The World Health Organization estimates that more than 180 million people worldwide have DM, and, as the western lifestyle is making its entry into the developing countries, this number is likely to more than double by 2030.[2,3] with progression of type 2 diabetes over time, β-cell mass and function continue to decline, and Oral Anti-Diabetics drugs become ineffective. Glycemic control may continue to deteriorate even with the addition of second Oral Anti-Diabetic drugs in patients on metformin monotherapy.[4]

No oral antidiabetic agent available today addresses beta cell dysfunction, there is risk of hypoglycemia, weight gain with current therapy.[5] The ideal diabetes treatment should provide effective, sustained glycemic control with negligible risk of hypoglycemia, while improving cardiovascular risk and avoiding weight gain. The glory would be the ability to modify the disease and preventing the decline in beta cell mass. With these concerns in mind, incretin-based therapies offer a practical strategy for glucose control, with many associated metabolic benefits, for patients with sufficient beta cell reserve.

Incretin-Hormone.

There are two incretin hormones: glucagon-like peptide-1 (GLP-1) and glucose- dependent insulin tropic polypeptide (GIP). GLP-1 is a 30-amino acid polypeptide produced in the endocrine L-cells of the intestinal epithelium. L-cells are found throughout the intestinal tract but their density is highest in the ileum and parts of the colon. GIP is a 42-amino acid polypeptide produced in the endocrine K-cells which are more frequent in the proximal small intestine.[6]

Secretion of GLP-1 and GIP

In the fasting state, the plasma concentrations of the incretin hormones is very low, although they are not immeasurable, suggesting that there is a certain basal rate

of secretion. Both incretin hormones are secreted rapidly (within 10-20 min) in response to ingestion of nutrients, with lipids and simple carbohydrates being potent stimulators of secretion.[7] Peak concentrations of GIP and GLP-1 are reached with 15-30 and 30-45 minutes, respectively, after ingestion of glucose. The rapid secretion following ingestion of nutrients - long before the substrates ingested are present in the small intestine - has led to the conclusion of vagus-mediated stimulation of secretion.[8]

Degradation of GLP-1 and GIP.

After the secretion of GIP and GLP-1, both hormones are degraded by the enzyme dipeptidyl peptidase 4 (DPP4).[9] This enzyme, also known as the T-cell antigen CD26, is a serine peptidase found in numerous sites such as the intestinal and renal brush border membranes, hepatocytes and vascular endothelium, as well as in a soluble form in plasma.[10] It cleaves off the two N-terminal amino acids of peptides with a proline or alanine residue, and for the incretin hormones, this abolishes their insulin tropic activity. While GLP-1 is rapidly degraded in the circulation, resulting in a clearance with an apparent half-life of 1-1.5 minute[11], GIP is degraded more slowly, with a half-life for the intact hormone of 7 minutes. The metabolites are eliminated more slowly through the kidneys, with half-lives of 4-5and 17 minutes, respectively.[12]

Action of GLP-1 and GIP.

Receptors for GLP-1 and GIP are found in the pancreatic beta-cell plasma membrane. Both receptors belong to the glucagon subfamily of G-protein- coupled receptors. While GLP-1 not only stimulates beta cell but also prevent apoptosis of beta cell thereby increasing beta cell survival and increasing insulin secretion and sensitivity, it also inhibit glucagon secretion and decreases gastric motility. GIP on the other side produces glucose dependant increases in insulin secretion and promotes peripheral uptake of glucose. The other important functions noted with this hormone are to increase the synthesis of fat molecules in adipose tissue and to inhibit gastric emptying and also gastric acid secretion. Studies have shown that it promotes beta cell proliferation and its survival.

Incretin Effect

The incretin effect refers to the amplification of insulin secretion that occurs when glucose is ingested orally as opposed to infused intravenously in amounts that result in identical glucose excursions.[13] In 1964, *McIntyre et al*. and *Elrick et al*. demonstrated that orally administered glucose evokes a greater insulin response than does intravenously administered glucose, and both groups hypothesized that gut-derived factors could have potentiating effects on insulin secretion after oral ingestion of glucose.[14] A few years later, in1967, this finding was confirmed by *Perley and Kipnis.*[15] They concluded that the insulin response to isoglycemic i. v glucose administration only amounted to 30-40% of that seen after oral glucose. Today, the isoglycemic method used by Perley *and Kipnis* is widely accepted as the method of choice to measure the incretin effect. The effect is defined as the beta-cell secretory response evoked by factors other than glucose itself, and is represented by the difference in responses of the actions of incretin hormones, which are released from the gut in the presence of intraluminal nutritional components. Incretin hormones potentiate glucose-induced insulin secretion and, therefore, play an essential role in the regulation of glucose homeostasis - in particular postprandial glucose levels.

Incretin Based Therapy

There are broadly two groups

Dipeptidyl peptidase 4 inhibiters

Inhibitors of Dipeptidyl Peptidase 4, also known as DPP-4 inhibitors or glyptins, are a class of oral hypoglycemic that blocks DPP-4. Sitagliptiin, Vildagliptin, Saxagliptin, Linagliptin, Dutogliptin, Gemigliptin, Alogliptin are the drugs included in this group

Mechanism of Action

During meal the incretins, glucagon-like peptide 1 (GLP-1) and glucose- dependent gastric inhibitory polypeptide (GIP) are released from the small intestine into the vasculature. The hormones regulate insulin secretion in a glucose-dependent manner. GLP-1 has many roles in the human body; it stimulates insulin biosynthesis, inhibits glucagon secretion, slows gastric emptying, reduces appetite and stimulates regeneration of islet β-cells. GIP and GLP-1 have extremely short plasma half-lives due to a very rapid inactivation. The enzyme responsible for the metabolism is DPP-4. Inhibition of DPP-4 leads to potentiation of endogenous GIP and GLP-1 and hence improves treatment of type 2diabetes.[16]

Pharmakokinetics

After oral administration peak plasma concentration occurs 1-4 hours post dose. The apparent half life is 12 hours .The absolute bioavailability of DPP4 inhibitor is approximately 87%. Mean volume of distribution after intravenous dose is 198 lit. Fraction of plasma protein binding is 38%. It is metabolized mainly by enzyme CYP3A4 with minor contribution from CYP2C8. Elimination is mainly through urine [87%] in unchanged form and also through faeces [13%]. Elimination of DPP4 inhibitors by renal excretion involves active tubular secretion. Administration of DPP4 inhibitors leads to inhibition of DPP4 enzymes activity for 24 hours resulting in 2-3 fold increase in levels of active GLP1,

GIP and insulin, decrease in glucagon concentration. The most common side effects reported in clinical studies were upper respiratory tract infection, sore throat, and diarrhea. There are also reports of isolated incidences of longer-term adverse effects including hypersensitivity reactions and pancreatitis. In theory, DPP-4 inhibitors may allow some cancers to progress, since DPP-4 appears to work as a suppressor in the development of cancer and tumors.[17] 50-100 mg once daily oral administration as monotherapy or in combination with metformin, sulfonylurea and PPAR¥ agonist is the recommended dose. It is used as an adjuvant to diet and exercise to improve glycemic control in type 2diabetes mellitus patients.

Incretin mimetic

The two main candidate molecules that fulfill criteria for being an incretin are Glucagon-like peptide-1 (GLP-1) and Gastric inhibitory peptide (GIP) or glucose-dependent Insulinotropic peptide.

Glucagon-like peptide (glp) analogs and agonists

GLP agonists bind to a membrane GLP receptor.[18] As a consequence of this, insulin release from the pancreatic beta cells is increased.

- Exenatide is the first GLP-1 agonist approved for the treatment of type 2 diabetes. Exenatide has only 53% homology with GLP, which increases its resistance to degradation by DPP-4 and extends its half-life. Typical reductions in A1C values are 0.5-1.0%.[19]
- Liraglutide, a once daily human analogue (97% homology).
- Taspoglutide is presently in Phase III Clinical Trials.
- Exenatide Long-Acting Release. Exenatide given as twice daily injections may not provide complete coverage after midday meals and overnight. In addition several daily injections may be viewed as inconvenient. Therefore, a LAR exenatide formulation for subcutaneous injection in patients with T2DM has recently been developed.

Mechanism of Action

Exenatide is believed to facilitate glucose control in at least five ways:

- It augments pancreas response in response to eating meals; the result is the release of a higher, more appropriate amount of insulin that helps lower the rise in blood sugar from eating. Once blood sugar levels decrease closer to normal values, the pancreas response to produce insulin is reduced.
- It suppresses pancreatic release of glucagon in response to eating, which helps stop the liver from overproducing which prevents hyperglycemia.
- It helps slow down gastric emptying and thus decreases the rate at which meal-derived glucose appears in the bloodstream.
- It has a prolonged effect to reduce appetite, promote satiety via hypothalamic receptors. Most people using Exenatide slowly lose weight, and generally the greatest weight loss is achieved by people who are the most overweight at the beginning of exenatide therapy.
- It reduces liver fat content. Fat accumulation in the liver or non-alcoholic fatty liver disease (NAFLD) is strongly related with several metabolic disorders, in particular low HDL cholesterol and high triglycerides, present in patients with type 2 diabetes

Pharmacokinetics

Following subcutaneous administration, peak plasma concentration is reached in 2.1 hours. Apparent volume of distribution after single dose being 28.3 litres. It is mainly eliminated by renal clearance and terminal half life is 2.4 hours. The recommended dose is 5-10µgm administered twice daily before morning and evening meals .It is to be administered subcutaneously in thigh, abdomen and upper arm The main side effects of exenatide use are gastrointestinal in nature, including acid or sour stomach, belching, diarrhea, heartburn, indigestion, nausea, and vomiting; exenatide is therefore not meant for people with severe gastrointestinal disease. Other side effects include dizziness, headache, and feeling jittery. It also may increase risk of sulfonylurea induced hypoglycemia. Additionally, the FDA has raised concerns over exenatide raising thyroid cancer risk.[21] it is recommended for type 2 diabetes mellitus with poor glycemic control.

Advantages of Incretin Based Therapy

Most significant advantage is the glucose-dependent nature of their insulin tropic effects, which means that incretin-based therapies mimic closely the physiologic insulin profile and are associated with very low rates of hypoglycemia. In addition to this key property, incretin-based therapies do not cause weight gain. In fact, GLP-1 receptor agonists provoke significant weight loss, which is especially important when considered against the weight gain associated with, e.g., sulfonylurea, TZDs, and insulin.[22-25] DPP-4 inhibitors at least are weight neutral.[26] There is also halt in progression, of continuing loss in β-cell function.[27] Studies have also suggested cardio-protective activity of GLP-1.[28] Besides their positive therapeutic effects, incretin-based therapies offer advantages over traditional oral agents and insulin, in

terms of both convenience and reduced side effects, especially with regard to the expected frequency of hypoglycemia and weight gain.

Limitations of Incretin Based Therapy

DPP4 inhibiters also inhibit other member of DPP4 enzyme family like DPP8 and DPP9**.** DPP8 and DPP9 inhibition leads to alopecia, thrombocytopenia and reticulocytopenia. So anti diabetic DPP4 inhibiters should be selective for DPP4 and nonselective for DPP8 and DPP9. But also on costs, which are currently significantly more elevated than with the majority of the other anti-diabetic agents.

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Source of Support: None Declared
Conflict of Interest: None Declared