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Review article

Incretins: based therapy for type -2 Diabetes mellitus (T2DM)

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ABSTRACT

The treatment of type 2 diabetes mellitus is metformin and sulfonylurea (SU) as first-line anti-diabetic therapies for many years. It is the first line treatment though the combination results in a progressive decline in [beta]-cell function. There is 50% decline in [beta] cell by 3 years in diabetic patients so there is requirement of an additional pharmacological agent to maintain the glycosylated hemoglobin (HbA1c) <7.0% (UKPDS). Gliptins represent a novel class of agents that improve beta cell health and suppress glucagon, resulting in improved post-prandial and fasting hyperglycemia. They function by augmenting the incretin system (GLP-1 and GIP) preventing their metabolism by dipeptidyl peptidase-4 (DPP-4). They are not only efficacious but also safe as they do not cause significant hypoglycemia, and are weight neutral.

1. Introduction

The treatment of type 2 diabetes mellitus (T2DM) particularly in the overweight patient is Metformin and in both lean and overweight patient is sulfonyurea (SU), as first line anti-diabetic therapies worldwide. Before 1995, sulfonyurea (SU)was the most popular anti-diabetic therapy in the USA (United States). Sulfonyurea increases insulin secretion in a glucose-independent manner, causing severe and unpredictable hypoglycaemia. Hypoglycaemia occurs particularly if the meal is delayed or if its carbohydrate quantity reduced. The use of metformin only became popular in the US after 1995. They continue to remain mainstay therapy despite their problems they are best suited to deal with the original pathogenic triumvirate theory for T2DM proposed by Ralf Defranzo. The triumvirate theory includes qualitative and quantitative beta cell failure, insulin resistance at level of liver and peripheral tissue. This was true since there was no agent that could help improve health of the beta cell and cause insulin release in a glucose dependant manner. This all changed once it was known about the incretin system in the pathogenesis of T2DM. Dearrangement of the incretin system has been implicated in progression of beta-cell failure so a therapy that can augment this system has been shown to promote beta cell health and insulin release in a glucose-dependent manner[1-5].

Metformin therapy has been associated with several advantages such as non-hypoglycemic, weight-loss promoting, anti-ischemic to cardiac tissue, improvement in non-alcoholic hepatosteatosis, anti-neoplastic , also its use has been associated with gastrointestinal adverse effects, limiting its use, particularly in the non-overweight patient[2, 6]. Use of SU's on the other hand although effective in lowering plasma glucose can be associated with variable severities of hypoglycemia, weight gain, beta-cell death, and possibly adverse cardiac outcomes as proposed originally by the UKPDS and later by other groups[2, 7].

The UKPDS was the first to show that the combination of SU and metformin resulted in a progressive decline in [beta]-cell function and by 3 years up to 50% of diabetic patients can require an additional pharmacological agent to maintain the glycosylated hemoglobin (HbA1c) <7.0%[2, 5]. Moreover, the percentage of diabetic patients classified as adequately controlled while mostly on these therapies still remains a challenge with a majority (> 50%) of diabetic patients having a HbA1c > 7%[8] From the above data it seems clear that existing popular therapies are not only ineffective but are associated with a significant amount of morbidity (weight gain and hypoglycemia). So the need of the population is a refreshing class of drugs whose effects is on hyperglycemia , without adversely affecting the survival of beta-cells, weight and free of hypoglycemia, GLIPTINS might just close to that class.

1.1 Pathophysiology

Type 2 DM is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production, and

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abnormal fat metabolism. In the early stages of the disorder, glucose tolerance remains near-normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. IGT, characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately, beta cell failure ensues.

2. What are incretins

It is intestine secretion insulin.

Definition

Gut derived factors that increase glucose stimulated insulin secretion.

Two hormones

(1). glucagon-like peptide-1 (GLP-1)
(2). glucose-dependent insulinotropic polypeptide (GIP)

In 1930 La Barre described a greater effect of oral rather parenteral glucose in increasing insulin secretion. In 1986 Nauck demonstrated that a glucose infusion graded to achieve plasma glucose levels identical to those achieved with oral glucose led to a insulin response that was only one fourth of that in comparison of oral glucose. This led the researchers to come to a conclusion that this is due incretin effect due to incretin hormone. There are two main incretin hormones in humans, GIP (glucose-dependent insulinotropic peptide; also known as gastric inhibitory peptide) and GLP-1 (glucagon-like peptide-1). Both hormones are secreted by endocrine cells that are located in the epithelium of the small intestine. The release of incretin hormone is regulated in a similar way as other digestive tract hormones. As the glucose concentration increases in the small intestine, it stimulates the release of incretin. Incretins are released in the circulation to reach their target tissue: the pancreatic beta cells. Incretin stimulation of beta cells causes them to secrete *more insulin* in response to the same amount of blood glucose**[9,10].**
This has generated an interest among the researchers in developing incretin-based therapies for the treatment of type 2 diabetes mellitus. As it is well known that type 2 diabetes mellitus is due to insulin resistance, which is due to decreased responsiveness of tissues to insulin, and so it may lead to a relative insulin deficiency. In most of the advanced cases of type 2 diabetes mellitus there is a defect in insulin secretion.

2.1 Incretins and their actions

Glucagon-like peptide-1 (GLP-1)

It is secreted by L cells in the distal gut (ileum and colon). It stimulates release of insulin in glucose-dependent manner. It suppresses hepatic glucose output by inhibiting glucagon secretion in a glucose-dependent manner. It enhances β cell proliferation and survival in animal models and also delays gastric emptying.

Glucose-dependent insulinotropic polypeptide (GIP)

It is secreted by K cells in the proximal gut (duodenum). It stimulates release of insulin in glucose-dependent manner. It also helps in proliferation of β cell and its survival and delays gastric emptying.

2.2 Incretins in diabetes

The clinical relevance of the incretin system came to light when it was recognised that the incretin response is markedly attenuated in people with type 2 diabetes. There is decreased response of GLP-1 with respect to food intake leading to hyperglycaemia in these patients through a relative reduction in postprandial insulin response, the subsequent failure of glucagon suppression and a lack of appetite suppression. The concentration of GIP is near normal, but its effect on insulin secretion is diminished. These observations uncovered a new therapeutic strategy for type 2 diabetes - that of promoting the activity of the incretin system. Two pharmacological approaches have been taken to enhance the incretin effect in type 2 diabetes.

One approach is to administer GLP-1 'analogues' (GLP-1 receptor agonists) that are resistant to cleavage by DPP4. The other approach is to inhibit DPP4 activity. This effectively increases the half life and therefore the circulating concentrations of the incretins. The effectiveness of both approaches suggests that there is no significant reduction in GLP-1 sensitivity in subjects with diabetes. GLP-1-Based Agents Incretins are GI hormones that are released after meals and stimulate insulin secretion. The two best known incretins are GLP-1 and GIP. Although these peptides share many similarities, they differ in that GIP is not effective for stimulating insulin release and lowering blood glucose in persons with type 2 diabetes, whereas GLP-1 is effective. Consequently, the GLP-1 signaling system has been a successful drug target.

Both GLP-1 and glucagon are products derived from preproglucagon, a 180–amino acid precursor with five separately processed domains (Drucker, 2006). An amino-terminal signal peptide is followed by glicentin-related pancreatic peptide, glucagon, GLP-1, and glucagon-like peptide 2 (GLP-2). Processing of the protein is sequential and occurs in a tissue-specific fashion. Pancreatic -cells cleave proglucagon into glucagon and a large C-terminal peptide that includes both of the GLPs. Intestinal L-cells and specific hindbrain neurons process proglucagon into a large N-terminal peptide that includes glucagon or GLP-1 and GLP-2. GLP-2 impacts the proliferation of epithelial cells lining the GI tract. Teduglutide, a GLP-2 analog, is under development as a treatment for short bowel syndrome and has received orphan drug designation for the treatment of short bowel syndrome from the U.S. FDA and the European Medicines Agency.

Given intravenously to diabetic subjects in supraphysiologic amounts, GLP-1 stimulates insulin secretion, inhibits glucagon release, delays gastric emptying, reduces food intake, and normalizes fasting and postprandial insulin secretion. The insulinotropic effect of GLP-1 is glucose dependent in that insulin secretion at fasting glucose concentrations, even with high levels of circulating GLP-1, is minimal. The effects of GLP-1 to promote glucose homeostasis and the glucose dependence of these effects are beneficial aspects of this signaling system for treating type 2 diabetes. GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase IV (DPP-4), with a plasma t1/2 of 1-2 minutes; thus, the natural peptide, itself, is not a useful therapeutic agent.

Two broad strategies have been taken to applying GLP-1 to therapeutics, the development of injectable, DPP-4 resistant peptide agonists of the GLP-1 receptor, and the creation of small molecule inhibitors of DPP-4.

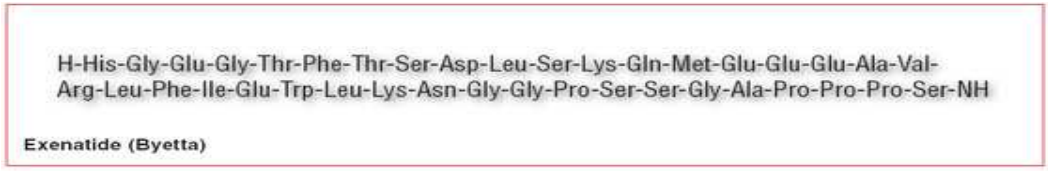
GLP-1 Receptor agonists

Several GLP-1 agonists are in advanced phases of development but currently two GLP-1 receptor agonists that have been approved for treatment diabetic patients in the U.S. Exendin-4 is a naturally occurring reptilian, Gila Monster peptide of 39 amino acids with considerable homology to GLP-1. It is a potent GLP-1 receptor agonist that shares many of the physiological and pharmacological effects of GLP-1. It is not metabolized by DPP-4. Plasma t1/2 of 2-3 hours following subcutaneous injection. Importantly, exendin-4 cause's glucose-dependent insulin secretion, delayed gastric emptying, lower glucagon levels, and reduced food intake.

Exenatide (BYETTA), synthetic exendin-4, is the first GLP-1 agonist approved for use as monotherapy and as adjunctive therapy for type 2 diabetes patients,who do not achieve glycemic control with metformin, sulfonylurea, the combination of metformin and sulfonylurea, or thiazolidinedione. In clinical trials, exenatide, alone or in combination with metformin, sulfonylurea, or thiazolidinedione, was associated with improved glycemic control, as reflected in an ~1% decrease in HbA1C, and weight loss that averaged 2.5-4 kg (Amori et al., 2007).Amino acid sequence of Exenatide

Exenatide:
HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS

GLP-1: HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG



Liraglutide is a second GLP-1 receptor agonist. Structurally, liraglutide is nearly identical to native GLP-1, with Lys34 to Arg substitution and addition of a -glutamic acid coupled to a C16 fatty acyl group. The fatty acid side chain permits binding to albumin and other plasma proteins,this leads to extended t1/2 permitting once a day administration. The pharmacodynamic profile of liraglutide mimics GLP-1 and exenatide, and in clinical trials liraglutide caused both improvement in glycemic control and weight loss. In a single comparative trial, liraglutide reduced A1C~30% more than exenatide.

There are a number of other GLP-1 receptor agonists in development. A sustained-release form of exenatide, exenatide LAR, is being tested as a once-weekly injection. This compound is composed of exenatide in microspheres with the biodegradable polymer D,L lactic-co-glycolic acid. In phase 3 studies, exenatide LAR shares the pharmacodynamic properties of exenatide but may be more potent (Kim et al., 2007). Other long-acting GLP-1 receptor agonists in advanced stages of development include albiglutide, a recombinant protein fusion of GLP-1 and albumin; taspoglutide, a modified GLP-1; lixisenatide, a modified exendin-4 based molecule; and CJC-1134, an exendin-4/albumin conjugate. These agonists all have extended half-lives relative to exenatide and liraglutide and may be suitable for once-weekly injection. The distinguishing feature among the drugs currently available or under investigation is their pharmacokinetics and the exposure time to the GLP-1 receptor.

2.3 Mechanism of action

All GLP-1 receptor agonists works through a common mechanism,which is activation of the GLP-1 receptor. GLP-1 receptors are expressed by cells in the peripheral and central nervous system, the heart and vasculature, kidney, lung, and GI mucosa. Binding of agonists to the GLP-1 receptor activates the cAMP-PKA pathway and several GEFs (guanine nucleotide exchange factors) (Drucker, 2006). GLP-1 receptor activation also initiates signals through PKC and PI3K, and it alters the activity of several ion channels. In cells, the end result of these actions is increased insulin biosynthesis and exocytosis in a glucose-dependent manner.

2.4 Absorption, distribution, metabolism, excretion, and dosing

Exenatide is given as a subcutaneous injection twice daily, before meals. Exenatide is rapidly absorbed, peak concentrations is reached in ~2 hours. It undergoes little metabolism in the circulation, and has a volume of distribution of nearly 30 L. Clearance of the drug occurs primarily by glomerular filtration,

glomerular filtration, with tubular proteolysis and minimal reabsorption. Exenatide is marketed as a pen that delivers 5 or 10 g; dosing is typically started at the lower doses and it is increased based on the response to therapy.

Liraglutide is given as a subcutaneous injection once daily. A peak level is reached in 8-12 hours and the t1/2 is 12-14 hours. There is little renal or intestinal excretion of liraglutide, and clearance is primarily through the metabolic pathways of large plasma proteins. Liraglutide is supplied in a pen injector that delivers 0.6, 1.2, or 1.8 mg of drug. We start the treatment with low dose and generally advanced to the two higher doses based on clinical response.

2.5 Adverse effects and drug interactions

Intravenous or subcutaneous administration of GLP-1 causes nausea and vomiting in a dose-dependent manner. Gastro-intestinal side effects occur at higher doses which are needed to regulate blood glucose. Based on data from clinical trials, up to 40-50% of subjects given a GLP-1 receptor agonist report nausea at the initiation of therapy. Because the GI side effects of these drugs decreases over time, most affected patients are able to continue a course of therapy. The activation of the GLP-1 receptor can delay gastric emptying; thus exenatide and other drugs of this class should be used with caution with other compounds that affect gastric emptying. Moreover, GLP-1 agonists may alter the pharmacokinetics of drugs that require rapid GI absorption, such as oral contraceptives and antibiotics.

The combination of exenatide or liraglutide with sulfonylurea drugs causes an increased rate of hypoglycemia compared to sulfonylurea treatment alone. Because of the high degree of renal clearance, exenatide should not be given to persons with moderate to severe renal failure (creatinine clearance <30 mL/minute). There is no current recommendation for dose adjustments of other GLP-1 receptor agonists for decreased renal function. Exenatide has also been rarely associated with acute renal failure. Based on surveillance data, there is a possible association of exenatide treatment with pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis. There is currently no mechanism to explain this association, and cases linking exenatide to pancreatitis are rare.

2.6DPP-4 Inhibitors

Mechanism of action

DPP-4 is a serine protease that is widely distributed throughout the body, expressed as an ectoenzyme on endothelial cells, on the surface of T-lymphocytes, and in a circulating form. DPP-4 cleaves the two N-terminal amino acids from peptides with a proline or alanine in the second position. Although there are many potential substrates for this enzyme, it seems to be especially critical for the inactivation of GLP-1 and GIP (glucose-dependent insulinotropic polypeptide; gastric inhibitory peptide)[9].

2.7 Dosage forms

Several agents provide nearly complete and long-lasting inhibition of DPP-4, thereby increasing the proportion of active GLP-1 from 10-20% of total circulating GLP-1 immunoreactivity to nearly 100%. Two of these, sitagliptin (JANUVIA) and saxagliptin (ONGLYZA), are now available in the U.S.; a third, vildagliptin, is available in the E.U.; a fourth compound, alogliptin, is in advanced stages of clinical trials. Sitagliptin and alogliptin are competitive inhibitors of DPP-4, whereas vildagliptin and saxagliptin bind the enzyme covalently. Despite these differences, all four drugs can be given in doses that lower measurable activity of DPP-4 by >95% for 12 hours. This causes a greater than 2-fold elevation of plasma concentrations of active GIP and GLP-1 and is associated with increased insulin secretion, reduced glucagon levels, and improvements in both fasting and postprandial hyperglycemia. Inhibition of DPP-4 does not appear to have direct effects on insulin sensitivity, gastric motility, or satiety, nor does chronic treatment with DPP-4 inhibitors affect body weight. DPP-4 inhibitors used as monotherapy in type 2 diabetic patients, reduced HbA1c levels by an average ~0.8%. These compounds are also effective for chronic glucose control when added to the treatment of diabetic patients receiving metformin, thiazolidinediones, sulfonylureas, and insulin. The effects of DPP-4 inhibitors in combination regimens appear to be additive. The recommended dose of sitagliptin is 100 mg once daily. The recommended dose of saxagliptin is 5 mg once daily.

2.8 Absorption, distribution, metabolism, and excretion

DPP-4 inhibitors are absorbed effectively from the small intestine. They circulate in primarily in unbound form and are excreted mostly unchanged in the urine. DPP-4 inhibitors do not bind to albumin, nor do they affect the hepatic cytochrome oxidase system. Both sitagliptin and saxagliptin are excreted renally, and lower doses should be used in patients with reduced renal function. Sitagliptin has minimal metabolism by hepatic microsomal enzymes. Saxagliptin is metabolized by CYP 3A4/5 to an active metabolite. The dose saxagliptin should be lowered to 2.5 mg daily when co-administered with strong CYP3A4 inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).

2.9 Adverse effects and drug interactions

There are no consistent adverse effects that have been noted in clinical trials with any of the DPP-4 inhibitors. With few exceptions the incidence of adverse effects in drug-treated and placebo-treated patients has been similar. DPP-4 is expressed on lymphocytes; in the immunology literature, the enzyme is referred to as CD26. Although there is some evidence of minor effects on in vitro lymphocyte function with DPP-4 inhibitors, there is no evidence from clinical studies of major adverse effects in humans. This area bears scrutiny as more patients are treated with these compounds[14].

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