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ORIGINAL ARTICLE

INCRETIN MIMETICS: NEW AGE DRUGS FOR TYPE 2 DIABETES MELLITUS

DEEPIKA TIKOO* AND MEENAKSHI GUPTA
Department of Pharmacology, Sri Guru Ram Das Institute of Medical Sciences & Research, Amritsar, Punjab-143001, India

ABSTRACT:

Type 2 diabetes mellitus is a fast growing global epidemic and its prevalence has increased in the 21st century. The rise in blood glucose levels is associated with complex pathogenesis which includes a significant reduction of the incretin effect. In patients with type 2 diabetes, glucagon like peptide-1 secretion may be impaired. In depth understanding of the role of incretin hormones in glucose homeostasis has led to the development of incretin-based therapies that target gastrointestinal hormone action of incretin and cause significant glucose-lowering effects, promote weight loss (or are weight-neutral), inhibit glucagon secretion and protect beta cells. They represent a new tool to be used as an add on therapy to older ant diabetic drugs which by themselves have not been successful in retarding the progression of the disease.

Keywords: Diabetes mellitus, incretin, glucagon like peptide-1.

INTRODUCTION

Diabetes mellitus is a spectrum of common metabolic disorders caused by genetic and environmental factors which contribute to its pathogenesis. The number of people with diabetes is increasing due to population growth, aging, increasing prevalence of obesity and physical inactivity (Wild *et al.,* 2004, Powers, 2008). The current armamentarium of drugs used for treating diabetes include biguanides (metformin), sulphonylureas (glyburide, glimiperide, glipizide, gliclazide), thiazolidinediones (pioglitazone), meglitinides (nateglinide, repaglinide), alpha glucosidase inhibitors (miglitol, acarbose, voglibose) and insulin. Sulfonylureas and meglitinides are insulin secretagogues while biguanides and thiazolidinediones are known as insulin sensitizers. Alpha glucosidase inhibitors decrease the amount of glucose which is absorbed as the carbohydrates. The latest in the development of anti-diabetic drugs are incretin based therapies which restore incretin activity and may reduce the patho-physiologic consequences of diabetes.

Corresponding Author: e-mail: dtikoo@gmail.com

Patho-physiology of Diabetes Mellitus

Diabetes mellitus is classified on the basis of pathogenesis which causes hyperglycemia and the two broad categories are type 1 and type 2 diabetes mellitus. Type 1 diabetes mellitus occurs due to destruction of pancreatic islet β cells, mainly due to an autoimmune process which can cause complete or near total insulin deficiency. Type 2 diabetes mellitus is a progressive, debilitating metabolic blood glucose disorder due to multiple metabolic abnormalities including impaired insulin secretion, insulin resistance, loss of beta cell function, impaired regulation of glucagon secretion and disturbed incretin physiology (Powers 2008, Andukuri *et al.,* 2009). Incretins maintain glucose homeostasis along with other hormones like insulin, glucagon and amylin. They are released in response to a meal by enteroendocrine cells in the intestine. Incretin dysfunction, along with other defects, has been implicated in contributing to the pathogenesis of type 2 diabetes mellitus (Campbell *et al.,*

2011). A new paradigm of drugs thus have been developed which are based on the actions of the incretins and are injectable long-acting stable analogues of glucagon like peptide-1 (GLP-1) known as incretin mimetics.

Incretin Mimetics

The incretin effect is the rise in insulin secretion which is more pronounced in response to oral glucose bolus as compared to equivalent intravenous glucose bolus (Elrick *et al.,* 1964, McIntyre *et al.,* 1965) .Incretins are gastrointestinal hormones released after meals which can cause an augmentation of insulin secretion. The two best known hormones that fulfill this criterion are glucose-dependent insulinotropic peptide (GIP) and GLP-1. GIP is a 42-amino acid peptide synthesized and released from enteroendocrine K cells located mostly in the duodenum and upper jejunum. Function of GIP is to induce insulin secretion, which is stimulated primarily by hyperosmolarity of glucose in the duodenum (Thorrens, 1995). GLP-1, is derived from proglucagon , a 180 amino acid precursor and exists in two bioactive forms, GLP-1 (7-36) amide and GLP-1 (7–37) with GLP-1 (7–36) comprising up to 80% of the GLP-1 in circulation (Chia, 2009). Together, the insulinotropic effect of GLP-1 and GIP accounts for up to 60% of the insulin secreted after eating food and plays a very important role in promoting glucose homeostasis and GLP-1 in addition may have the potential to improve pancreatic beta cell function. GLP-1 also suppresses pancreatic glucagon secretion, enhances glucose disposal, slows gastric emptying, promotes satiety, preserves islet integrity and enhances resistance of beta cells to apoptosis. (Meier *et al.,* 2003, Drucker, 2006, Gallwitz, 2006, Nielsen *et al.,* 2004, Campbell et.al 2010). GLP-1 has a very short half life of 1-2 minutes and is quickly metabolized by dipeptidyl-peptidase 4 (DPP-4) enzymes and neutral endopeptidase (NEP) (Kieffer *et al.,* 1995, Meier *et al.,* 2004, Sharma and Sharma, 2011).

Hence being a natural peptide, it itself is not a useful therapeutic agent. In diabetics, the normal incretin effect is lost and GLP-1 secretion is reduced. The response of beta cells to exogenously administered GLP-1 has been found to be three to five times lower in patients with type 2 diabetes mellitus as compared to healthy people (Kjems *et al.,* 2003, Chia, 2009).

Pharmacology

Incretin mimetics or GLP-1 analogs are structurally altered chemical versions of GLP-1. They boost GLP-1 to supra physiological levels by activating GLP-1 receptor which is a seven-member trans-membrane G protein-coupled receptor. GLP-1 receptors are expressed in pancreatic islets, brain, heart, kidney, and the gastrointestinal tract. When GLP-1 binds to its receptor, it activates cAMP-PKA pathway and several guanine nucleotide exchange factors which in turn alters the activity of several ion channels. In beta cells, it causes an increase in insulin biosynthesis and exocytosis in a glucose dependant manner. (Thorens *et al.,* 1993, Powers 2011). When GLP-1 is infused in patients with type 2 diabetes mellitus, it stimulates insulin secretion and lowers glucose levels but unlike sulfonylureas, it has modest insulin stimulating effect at normoglycemic levels. Thus GLP-1 is associated with a low risk of hypoglycemia (Masharani, 2010). The GLP-1 analogs available are exenatide, liraglutide, taspoglutide and lixisenatide.

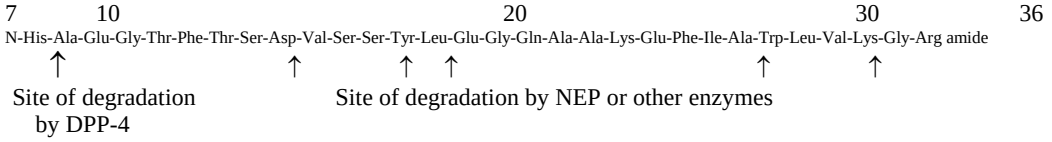

Fig. 1: Amino acid sequence of GLP-1 (7-36) (Chi Y *et al.,* 2008)

Exenatide

Structure & pharmacokinetics

Exenatide was the first marketed GLP-1 analog which was approved by FDA in April 2005 as an adjunctive therapy for type 2 DM with metformin or sulfonylurea (IItz, 2006). It is a synthetic version of a peptide exendin-4 originally found in the saliva of the Gila monster (*Heloderma suspectum*). Unlike native GLP-1, exenatide has a Glycine 8 in place of an Alanine8 of the N-terminus, which renders it resistant to the action of DPP 4 enzyme.

1 **10**
N-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-
11 **20**
Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-
21 **30**
Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-
31 **39**
Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser- amide

Fig 2: Amino acid sequence of Exenatide (Chi Y *et al.,* 2008)

It reaches a maximum plasma concentration in approximately 2 hours, and the mean half-life ranges from 3.3 - 4 hours (Powers, 2008, Chia 2009). It is administered subcutaneously at a dose of 5µg twice daily, one hour before a meal and can be increased to a maximum of 10µg twice a day. It is equally absorbed from arm, abdomen, or thigh injection sites and duration of action is upto 10 hours (Powers 2008, Nolte 2009). Based on animal studies, the bioavailability of exenatide after subcutaneous injection has been estimated to be between 65% and 75%. The drug is predominantly eliminated by glomerular filtration followed by proteolytic degradation (Bray, 2006). It should not be used in patients taking insulin.

Clinical studies

Administration of exenatide once- or twice-daily by subcutaneous injections, in ten type 2 diabetes mellitus patients who were insulin naïve showed improvement in HbA1c ($P<0.009$) after one month of treatment (Egan *et al.,* 2003). In another study, exenatide alone or in combination with metformin, sulfonylurea or thiazolidinedione, was associated with modest reduction in HbA1c of about 1% (Amori, 2007). Exenatide long acting release (LAR) is in phase 3 development. Exenatide LAR is formulated with exenatide and poly (d,l lactic-co-glycolic acid) microspheres, a biodegradable medical polymer commonly used in extended drug release formulation. Once weekly subcutaneous injection is thought to be the desired dosing frequency (Drucker *et al.,* 2008). It was seen in one of the studies that HbA1c of ≤ 7% was achieved in 77 % of patients treated with exenatide LAR (once weekly) compared to 61% of those taking exenatide twice daily. Adverse events reported were pruritis at injection site, nausea, vomiting, diarrhea, dizziness, headache, dyspepsia, decrease in appetite, hypoglycemia (mainly when combined with a sulfonylurea), increased sweating. Exenatide delays gastric emptying, so it should be administered at least one hour before taking other drugs like digoxin, lovastatin, lisinopril, anti-infectives and oral contraceptives (Kaushal *et al.,* 2006, Bray, 2006, Levien *et al.*, 2009).

Liraglutide

Structure & pharmacokinetics

Liraglutide is an acylated human GLP-1 analogue while is nearly identical to it with lysine 34 to arginine substitution and an addition of a C-16 free-fatty acid derivative at lysine 26. (Mudaliar, 2007; Chia, 2009). The free-fatty acid side chain promotes binding to albumin and other plasma proteins leading to delayed absorption rate from the injection site and extended plasma half life of 11-13 hours. It was approved for use by US FDA in January 2010 and in Europe in 2009 (Parks and Rosebraugh, 2010). Liraglutide is indicated for adjunctive therapy along with metformin, sulfonylurea or their combination and like exenatide is administered by subcutaneous route. Liraglutide has been shown to lower blood glucose, cause weight loss, and improve beta cell functioning on adding it to metformin and thiazolidienedione in the treatment of type 2 diabetes mellitus.

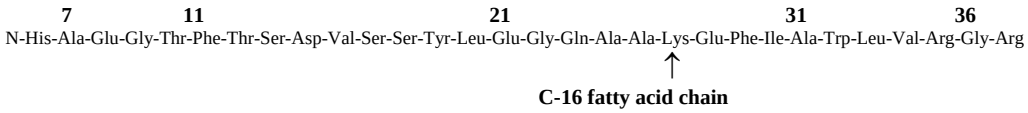

Fig 3: Amino acid sequence of Liraglutide (Chi Y *et al*., 2008)

Clinical studies

In a single comparative trial, liraglutide once a day reduced HbA1c levels to around 30% more than exenatide twice a day and was better tolerated too (Buse *et al.,* 2009). In another 12 week clinical trial in 193 patients with type 2 DM, 0.75 mg liraglutide subcutaneously daily caused equivalent reductions of HbA1c compared with glimepiride and the treatment was associated with a weight reduction of 0.39 kg, whereas patients treated with glimepiride experienced a mean weight gain of 0.94 kg. (Madsbad *et al.,* 2004 , Mudaliar, 2007). FDA has expressed some serious concerns about safety of liraglutide. Data from preclinical studies in rodents suggested that liraglutide was associated with increase in the risk of thyroid C-cell focal hyperplasia and C-cell tumors. Its relevance to humans still is unknown and a data from a long-term study did not show any notable difference in mean calcitonin levels between liraglutide and control groups over 2 years of follow-up. So the FDA concluded that statistically significant increases in cancer occurred only at drug levels many times those used in humans but careful monitoring in humans and additional animal studies should be carried out. There were some cases of pancreatitis reported in phase 2 and 3 studies with liraglutide but such small data is difficult for forming any conclusion so the patients need to be aware that persistent nausea and vomiting with liratglutide need careful evaluation and it should be discontinued if signs of pancreatitis appear (Parks and Rosebraugh, 2010). More and more post approval clinical trials will give us a better picture about their safety profile.

Taspoglutide & Lixisenatide

Structure & pharmacokinetics

Another GLP-1 analog taspoglutide has 93% homology with native polypeptide where amino acids 8 and 35 of the native GLP-1 peptide are substituted with aminoisobutyric acid to prevent DPP-4 and protease-mediated cleavage at the N- and C-terminus, respectively. It is to be injected subcutaneously once weekly and is also effective given bi-weekly (Retterstol, 2009). Lixisenatide is a modified exendin-4 based molecule with a short half-life of 2–4 hours, and it is classed as a short-acting GLP-1-receptor agonist but despite that it is intended for once-daily dosing as it has a strong binding affinity to the GLP-1 receptor.

Clinical studies

Phase II trials have shown that weekly administration of a slow-release formulation of taspoglutide was associated with enhanced glycemic control, reduction in body weight and improved beta cell function. Mild gastrointestinal adverse effects were reported and apart from that it is generally well tolerated (Arjona, 2008).Various clinical studies with lixisenatide have shown beneficial effects on HbA1c when combined with commonly used anti-diabetic agents. As there is limited data with the intended once-daily 20 µg subcutaneous dosing, so further evaluation of lixisenatide as add-on to various anti-hyperglycemic treatments is required. There was no increased risk of hypoglycemia while beneficial weight reduction was seen. Adverse effects were similar to other GLP-1 receptor agonists, the most frequent being gastrointestinal. Due to the pronounced effect of lixisenatide on postprandial plasma glucose it seems rational to combine it with long-acting basal insulin analogs, so as to achieve

additive effects on glycemic control (Barnett, 2011).

CONCLUSION

The prevention and management of type 2 diabetes mellitus is a major health challenge and these newfound class of drugs seem to have a promising future as they have the potential to retard the disease process in type 2 diabetes mellitus and have less chance of hypoglycemic episodes. However, they will need continuous monitoring both in long-term efficacy and safety controlled trials to further assess their effectiveness in glycemic control and safety profile. A better understanding for initiation of treatment in type 2 diabetes and adjusting it with the older medications in order to provide appropriate care and safety for the well-being of the patients can reduce the enormous health burden & economic cost associated with the disease.

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