NOVEL APPROACH OF MANAGEMENT OF DIABETES MELLITUS WITH DPP IV AND INCRETIN

Bhapkar R., Ganu G*, Garud A, Kshirsagar A.

Padmashree Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune- 411018 India.

ABSTRACT

At the present time, DPP IV is considered one of the most promising therapeutic targets for the treatment of T2DM. A large number of clinical trials have shown that DPP IV inhibitors appear to be well tolerated, with a low incidence of significant adverse effects, including hypoglycemia, weight gain, and gastrointestinal side effects. In addition, DPP IV inhibitors also improved the glycaemic control either as monotherapy or as combination therapy with other antihyperglycemic drugs. Incretin mimetics and dipeptidyl-peptidase IV inhibitors offer unique benefits for patients with type 2 diabetes as they are still in clinical studies and there will be a few years before they can be approved for routine use in type 2 diabetic patients. Glitins increase nutrient-stimulated insulin secretion in type 2 diabetes with low-risk of hypoglycemia and without weight gain. They are positioned as add-on therapy to metformin or a thiazolidinediones, and to-date the first gliptins, sitagliptin has shown antihyperglycemic efficacy with good tolerability.

Keywords: DPP IV, type 2 diabetes, incretins, antihyperglycemic, glycaemic control.

INTRODUCTION

Sitagliptin and vildagliptin are both investigational agents belonging to the “Dipeptidyl peptidase IV (DPP-IV) inhibitor” drug class. These drugs are currently under FDA review for the treatment of type II diabetes. Both agents work to lower blood glucose in diabetes by inhibiting the breakdown of substances called “incretin hormones”. These hormones are released in response to food and subsequently stimulate the pancreas to release insulin, which reduces blood sugar. Sitagliptin and vildagliptin produce antihyperglycemic by blocking incretin breakdown. Advantage of these drugs is that they have a low potential to cause hypoglycemia, a serious condition associated with diabetes medications that results in excessively low blood sugar levels. In clinical trials, treatment with both agents has resulted in meaningful reductions in glycated Hb (HbA1C) (long term measure of average blood sugar levels) with few side effects. Both
medications have been studied up to 1 year, alone and in combination with other antidiabetic medications, and both are appropriate for once daily dosing [1].

**Incretin concept**

The incretins are a group of agents that stimulate insulin production from β cells in the presence of glucose. GLP-1 is being used as a therapy for T2D. Other effects of these agents are to inhibit the apoptosis of β cells, and enhance the differentiation of pancreatic precursors into β cells. This result in enhancement of the β cell mass, both in the pancreas of diabetic rats, and human fetal pancreas transplanted into rats. While exendin-4 has been used to enhance the function of allografted adult human islets, it is probable this effect is due to the inhibition of apoptosis rather than the formation of new β cells. There are no data on whether exendin-4 enhances β cell mass in humans. GLP-1 has a short half-life and is rendered inactive by the enzyme DPP-IV. Sitagliptin is a DPP-IV inhibitor that recently entered clinical practice as a therapy for type 2 diabetes. It acts to delay the metabolism of GLP-1. As with the incretins, this agent also acts to increase β cell mass in rodents. Whether this class of drugs will cause β cell regeneration in people with type 2 diabetes is unknown [2].

Gastrointestinal glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin tropic polypeptide (GIP) are ‘incretin hormones’ released from the gut after a meal and are responsible for 70% of postprandial insulin secretion. In diabetic patients, GLP-1 secretion and GIP action are impaired, and the above-mentioned incretin effect is decreased to 30%. GLP-1 contributes to the normalization of elevated glucose levels through regulation of insulin and glucagon secretion, gastric emptying, satiety and body weight. Finally, GLP-1 can enhance pancreatic β-cell mass through the stimulation of β-cell proliferation and neogenesis in healthy and diabetic rodents. GIP has a similar insulinotropic effect to GLP-1 at glucose concentrations between 5.5 mM and 7.8 mM. However, GIP does not suppress glucagon secretion, and its effects on feeding behavior, if any, are unknown. Collectively, these characteristics render GLP-1 more attractive than GIP as a target for the treatment of type 2 diabetes. The fact that GLP-1 is rapidly degraded by dipeptidyl peptidase IV (DPP IV) in vivo, however, reduces its usefulness in treating patients. Thus, to improve therapeutic efficacy, two approaches can be used the development of GLP-1 analogues resistant to degradation by DPP IV or the development of DPP IV inhibitors. This review focuses on the knowledge recently gained.
on GLP-1 biology, which should permit a better understanding of new drug candidates based on GLP-1 therapy\cite{3}. One such approach is based on the action of the incretin hormone glucagon-like peptide 1 (GLP-1) (Table1). Incretins, the best understood of which are GLP-1 and glucose-dependent insulinotropic peptide (GIP), the gut peptides released in response to nutrient ingestion that increase insulin and metabolized by Dipeptidyl peptidase IV. It is secreted in response to meal ingestion and normally functions in the so-called ileal brake, i.e. inhibition of upper gastrointestinal motility and secretion when nutrients are present in the distal small intestine. It also induces satiety and promotes tissue deposition of ingested glucose by stimulating insulin secretion. In addition, GLP-1 has been demonstrated to promote insulin biosynthesis and insulin gene expression and to have trophic effects on the $\beta$ cells. The trophic effects include proliferation of existing $\beta$ cells, maturation of new cells from duct progenitor cells and inhibition of apoptosis. This review summarizes recent research results for the pharmacological approaches based on GLP-1 towards antidiabetic therapy.

Due to the DPP IV inhibition by DPP IV showing the various action on body like stimulation of insulin secretion, suppression of glucose secretion, delay the gastric empty time, increase the insulin sensitivity, appetite suppression, increase the $\beta$ cell mass, glucose disposal enhancement.\cite{4}

**TABLE 1: ACTIONS OF THE INCRETIN HORMONE ON VARIOUS PARAMETERS**

<table>
<thead>
<tr>
<th>SR.NO.</th>
<th>PROCESS</th>
<th>ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Insulin secretion</td>
<td>Stimulation</td>
</tr>
<tr>
<td>2.</td>
<td>Glucagon secretion</td>
<td>Suppression</td>
</tr>
<tr>
<td>3.</td>
<td>Gastric emptying</td>
<td>Delay</td>
</tr>
<tr>
<td>4.</td>
<td>Insulin sensitivity</td>
<td>Increase (indirect)</td>
</tr>
<tr>
<td>5.</td>
<td>Appetite</td>
<td>Suppression</td>
</tr>
<tr>
<td>6.</td>
<td>$\beta$ Cell mass</td>
<td>Increase</td>
</tr>
</tbody>
</table>

New target for diabetes:

Despite good compliance to treatment, the glycaemic control of T2D deteriorates progressively. Hence, new therapeutic agents are continuously being developed to help
our diabetes population. Recent studies have shown that early intervention at prediabetes state and beta cell protection with insulin sensitizers may improve the prognosis of diabetes. DPP IV inhibitors, which act via enhancing the incretins, represent another new therapeutic approach to the treatment of type 2 diabetes. GLP-1 and GIP are account for the majority of incretin action. GLP-1 is a gut hormone that plays a key role in glucose homeostasis via its incretin effect. GLP-1 is produced from the enteroendocrine L-cell of small intestine and is secreted in response to meal and nutrients. It stimulates insulin release from the pancreatic islets in a glucose dependent manner. It restores the defective first and second phases of insulin response to glucose in type 2 diabetes patients in animal models, GLP-1 and its analogs are shown to stimulate β-cell proliferation and differentiation. These may help in preserving the pancreatic beta cell mass and function, and thus have beneficial effect in the prognosis of type 2 diabetes. However, GLP-1 has a very short half-life. These are therapeutic agents that can block the breakdown of DPP IV enzyme (DPP IV inhibitor), and increase the endogenous GLP-1 level and thus enhances the incretin action. Sitagliptin is a potent and highly selective DPP IV inhibitor. The gut hormones GLP-1 and GIP are both incretin hormones that are released postprandially and markedly augment glucose-stimulated insulin secretion through sensitizing the β-cell action of glucose. GLP-1 also exhibits other effects of importance to glucose homeostasis, viz., inhibiting glucagon secretion, delaying gastric emptying, and stimulating insulin biosynthesis Fig.1.

The short half-life of GLP-1 has prompted development of alternate strategies to harness the potent antidiabetic activity of GLP-1. One approach is to inhibit DPP IV activity, thereby prolonging the circulating half-life of endogenous GLP-1. DPP IV (or CD26) is an enzyme that is found throughout the body in both plasma and the endothelial lining of several organs, such as the kidney, liver, and intestine. It cleaves a number of biologically active peptides, including GLP-1, which is degraded from the active form of GLP-1, i.e. GLP-17–36 amide, yielding GLP-19–36 amide. DPP IV also degrades GIP through a similar mechanism, removing the two first NH₂ terminal amino acids therefore, by inhibiting this enzyme will prolong the circulating half-life of the two most important incretins. Interestingly, the degradation product of GLP-1, GLP-19–36 amide, has been
shown to exhibit GLP-1 receptor antagonistic properties suggesting that DPP IV inhibition increases the level of an antagonist, GLP-19–36 amide.

Figure 1
GLP-1 actions in peripheral tissues GLP-1 acts directly on the endocrine pancreas, heart, stomach, and brain, whereas actions on liver and muscle are indirect.

Why DPP IV?
Pharmacokinetics and pharmacodynamics DPP IV inhibitors have demonstrated excellent bioavailability in rats, mice, and monkeys (from 60% to 90%, according to species). Studies on Type 2 diabetic patients and healthy volunteers have shown rapid absorption [maximum concentration (Cmax) observed within 1-2 h] and >90% of DPP-4 inhibition persists for more than 12 hrs after administration. The strength and duration of inhibition does not change with age, gender or body mass index. DPP IV inhibitors are oral agents that prolong the bioactivity of native GLP-1 and GIP by inhibiting the proteolytic activity of the DPP IV enzyme. DPP IV inhibitors have been shown to elevate
active GLP-1 levels 2 to 3fold by providing up to 90% inhibition of plasma DPP IV activity over 24 hours in vivo.[10]

Combination therapy:

The DPP IV inhibitors have been assessed as monotherapy and in conjunction with insulin, metformin, sulfonylureas, and thiazolidinediones in patients with T2D. Although the DPP IV inhibitors have been shown to improve glycemic control, as with most other new agents used in the treatment of diabetes, data have not been published addressing the effects of the DPP IV inhibitors on key outcome measures such as mortality, diabetes complications, or health related quality of life.

Mechanisms of DPP IV inhibitor:

DPP IV has a well-established physiological role in the regulation of the incretin hormones, GLP-1 and GIP. In animals that are genetically deficient in DPP IV or with pharmacological treatment with a DPP IV inhibitor, increased active GLP-1, GIP and improved glucose tolerance were observed. Increased insulin and decreased glucagon levels were also observed both in DPP IV deficient mice and, upon pharmacological treatment with inhibitors, in rodents and humans, consistent with the role of this enzyme in incretin regulation and metabolic control. DPP IV inhibitors do not improve glucose tolerance in mice deficient in both GLP-1 and GIP receptors, indicating that these incretins are exclusively responsible for the improved glucose tolerance that is observed in these animals. Taken together, these data unequivocally establish that these incretins are endogenous substrates for DPP IV. This enzyme has been implicated in the regulation of peptides in addition to GLP-1 and GIP, including growth-hormone-releasing hormone (GHRH), glucagon-like peptide 2 (GLP-2), pituitary adenylate cyclase-activating polypeptide (PACAP) and gastrin-releasing peptide (GRP). Several neuropeptides and chemokines are also in vitro substrates for this enzyme. Although many of these peptides are cleaved efficiently in vitro, it is difficult to determine if these peptides are regulated in vivo by DPP IV largely because suitable assays for measurement of the endogenous levels of the putative substrates and products are not available. Further work will be required to obtain a comprehensive understanding of the biology of this enzyme. DPP IV deficient mice are healthy and fertile, and thus if other proteins and/or peptides are regulated by this enzyme, there are no obvious important consequences related to growth
and development, reproductive capacity or health. Moreover, the results of clinical studies indicate that selective DPP IV inhibitors are well tolerated and do not suggest any functions for this enzyme beyond its role in metabolic control (Fig.2 and Fig.3) \(^{[9,11]}\).

**Figure 2**
Mechanism of DPP IV

**Figure 3**
Incretin hormone GLP-1
Drug interaction:

Co administration of the DPP IV inhibitors with several other antidiabetic agents and other drugs including metformin, Glyburide, Pioglitazone, Rosiglitazone, Simvastatin, digoxin, warfarin has not revealed any drug interactions.

Efficacy and safety of DPP IV inhibitors:

The efficacy and safety of DPP IV inhibitors as monotherapy have been evaluated in a number of clinical trials. In these studies, DPP IV inhibitors have been well tolerated and have demonstrated weight neutrality rather than weight loss, which has been seen with the GLP-1 receptor agonists. DPP IV inhibitors have proved to be generally safe and well tolerated in clinical trials. Sitagliptin is primarily excreted via renal elimination; thus the dosage must be adjusted in patients with moderate-to-severe renal insufficiency or end stage renal disease. Hypoglycemia and gastrointestinal adverse events appear to be infrequent. A meta-analysis reported that DPP IV inhibitors may be associated with a 1.2-fold increased risk of infection for nasopharyngitis, a 1.5 fold increased risk for urinary tract infection, and a 1.4 fold increased risk for frequency of headache. In post marketing studies of sitagliptin, severe skin reactions, including some cases of Stevens-Johnson syndrome, have been reported. As most trials with DPP IV inhibitors are of 30 weeks duration, longer follow-up is needed to establish the long-term safety of these agents.

Adverse events:

Severe hypoglycemia was reported in only 2 patients receiving DPP IV inhibitors in all the trials. There was no difference in reported mild to moderate hypoglycemia between DPP IV inhibitors and a comparator group. The studies reported no risk of adverse gastrointestinal events such as diarrhea, nausea or abdominal pain compared to placebo. There was a slight increased risk of nasopharyngitis of 6.4% against 6.1% for comparator, and an increased risk of urinary tract infection of 3.2% against 2.4% for comparator for both DPP IV inhibitors. Headache was also more common with 5.1% for DPP IV versus 3.9% with comparator. Overall DPP IV inhibitors were very well tolerated with low absolute rates of adverse events.
CONCLUSION

At the present time, DPP IV is considered one of the most promising therapeutic targets for the treatment of T2DM. A large number of clinical trials have shown that DPP IV inhibitors appear to be well tolerated, with a low incidence of significant adverse effects, including hypoglycemia, weight gain, and gastrointestinal side effects. In addition, DPP IV inhibitors also improved the glycaemic control either as monotherapy or as combination therapy with other antihyperglycemic drugs. However, a limited number of long-term clinical studies have been published on the adverse effects of DPP IV inhibitors. Moreover, it is uncertain whether the promising findings on β-cell neogenesis and apoptosis reported in animal studies will apply to humans in a clinical setting. It is also unclear whether DPP IV inhibitors can play a role in the pre diabetic patient and in the progression of diabetes. Therefore, further research will be required to understand the full potential of DPP IV as an anti-diabetic target. Therefore beneficial effect of the presented group of agents on body mass constitutes additional advantage. Incretin mimetics and dipeptidyl-peptidase IV inhibitors offer unique benefits for patients with type 2 diabetes they are still in clinical studies and there will be a few years before they can be approved for routine use in type 2 diabetic patients. Glitpins increase nutrient-stimulated insulin secretion in type 2 diabetes with low-risk of hypoglycemia and without weight gain. They are positioned as add-on therapy to metformin or a thiazolidinediones, and to-date the first glitpin, sitagliptin has shown antihyperglycemic efficacy with good tolerability.

REFERENCES


For Correspondence:
Ganu G.
Padmashree Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune- 411018 India.
contact no :- 09665016806
Email: ganu.gayatri@gmail.com