Dipeptidyl peptidase IV (DPP IV): a novel emerging target for the treatment of type 2 diabetes

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Abstract

The enzyme, dipeptidyl peptidase IV (DPP IV), is a novel target for the treatment of type 2 diabetes. Dipeptidyl peptidase IV inhibition improves the impaired insulin secretion and decrease postprandial concentrations of glucagon by enhancing the incretin hormone levels glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide/gastric inhibitory polypeptide (GIP). Recently, DPP IV inhibitors have attracted more and more attention, several of which have entered pre-clinical and clinical trials, and one has received approval for use as an anti-diabetic agent. Among the DPP IV inhibitors, two leading agents (sitagliptin and vildagliptin) have been shown to be effective in reducing glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG) in patients with type 2 diabetes. This review summarizes the evidence supporting DPP IV inhibitors as potential antidiabetic agents.

Keywords: dipeptidyl peptidase IV, DPP IV inhibitors, type 2 diabetes, incretin hormone

INTRODUCTION

Diabetes mellitus is a metabolic disorder, which is considered as a major public health issue all over the world. Recent WHO calculations indicate that worldwide almost 3 million deaths per year are attributable to diabetes. By the year 2025, it is projected that about 333 million people will suffer from the disease, with type 2 diabetes mellitus (T2DM) representing approximately 90-95% of the diagnosed cases[1].

Type 2 diabetes mellitus (T2DM) is a chronic disease, which is characterized by several pathophysiologic defects including insulin resistance, excess hepatic glucose production and progressive pancreatic β cell dysfunction[2]. It can cause a number of complications such as peripheral vascular insufficiencies, neuropathy, retinopathy and end stage renal disease. Besides lifestyle intervention, treatment of T2DM consists of some oral antihyperglycaemic drugs and insulin(Table 1)[3]. Although much effort has been made to delay the natural progression of T2DM, it remains inadequately controlled in most parts of the world. Moreover, the existing agents may also be associated with an increased risk of adverse events. Therefore, there is a need for more effective therapies to improve glycaemic control and maintain pancreatic islet function. Among the numerous possible targets, the development of dipeptidyl peptidase IV inhibitors which can prevent the degradation of the incretin hormones appears to be one of the most attractive, rational agents for the treatment of T2DM[4]. In this review, we present a summary of the data available on the two leading agents (sitagliptin and vildagliptin), clarifying the relationship between DPP IV and T2DM.

INHIBITION OF THE INCRETN HORMONES TO IMPROVE GLYCEMIC CONTROL IN T2DM

Incretin hormones, which are released from the gut, play a significant role in glucose homeostasis in healthy
subjects\(^5\). It has been estimated that the incretins are responsible for 50-70% of postprandial insulin release\(^5,6\). The key factors of incretin effects are glucose-dependent insulinotropic polypeptide (GIP), also known as gastric inhibitory polypeptide (GIP), and glucagon-like peptide 1 (GLP-1). GIP is a 42-amino-acid peptide produced by enteroendocrine K cells, which are located in the duodenum and jejunum, while GLP-1 is produced by enteroendocrine L cells, which are also located in the duodenum, but are mainly found in the distal small bowel and colon\(^7\). Considerable research has shown that GIP and GLP-1 are released into the circulation within minutes after the ingestion of a meal containing glucose or fat and this correlates with insulin secretion\(^8\).

Both GIP and GLP-1 exert a marked effect on \(\beta\) cells through their binding with specific receptors which belong to the seven transmembrane domain G protein-coupled receptor (GPCR) family. The GLP-1 receptor was cloned from a rat pancreatic islet cDNA library\(^9\), while the GIP receptor was cloned from a rat cerebral cortex cDNA library\(^9,10\). After binding to their specific receptors expressed on the islet \(\beta\) cells, GIP and GLP-1 hormones transmit signals to the Gs protein which rapidly dissociates into \(\alpha\)s and \(\beta\gamma\) subunits. Subsequently the \(\beta\gamma\) subunits can stimulate adenylate cyclase (AC). The activation of AC results in conversion of ATP into cAMP, which then activates the protein kinases A (PKA) to increase endoplasmic reticulum (ER) calcium release\(^11\). The incretins synergize with glucose to stimulate insulin secretion by inhibiting the activity of K-ATP channels which are consistently thought to be cAMP/PKA-dependent\(^12\). However, the mechanism of action of PKA on the K-ATP channels is not completely understood. The closure of K-ATP channels mediated by the incretins results in membrane depolarization and increases the Ca\(^{2+}\) influx through voltage-dependent Ca\(^{2+}\) channels (VDCCs). Finally, the whole process triggers exocytotic release of insulin-containing granules (Fig. 1).

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Site of Action</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>Metformin</td>
<td>Liver, Skeletal muscle</td>
<td>Gastrointestinal effects (abdominal pain, nausea, diarrhea) Lactic acidosis</td>
</tr>
<tr>
<td>Sulfonlurea</td>
<td>Gliclazide</td>
<td>Pancreatic (\beta) cells</td>
<td>Hypoglycemia, Weight gain, Hypersensitivity reactions</td>
</tr>
<tr>
<td>(\alpha)-Glucosidase Inhibitor</td>
<td>Acarbose</td>
<td>Small intestine</td>
<td>Gastrointestinal effects (flatulence, diarrhea, abdominal discomfort)</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Pioglitazone</td>
<td>Skeletal muscle, Liver, Fat</td>
<td>Edema, Weight gain, Anemia</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>Pioglitazone</td>
<td>Pancreatic (\beta) cells</td>
<td>Hypoglycemia, Weight gain</td>
</tr>
<tr>
<td>Insulin</td>
<td>NPH PZI</td>
<td>Pancreas, Fat, Liver, Skeletal muscle</td>
<td>Hypoglycemia, Weight gain, Injection-site sensitivity</td>
</tr>
</tbody>
</table>

Table 1  Target tissues and adverse effects of antidiabetic drugs

![Fig. 1 Schematic representation of the signaling pathways resulting in \(\beta\) cell insulin secretion following glucose exposure and GPCR binding\(^12-14\)](image-url)
Besides increasing insulin secretion, other physiological actions of GLP-1 and GIP are gradually being recognized. In α cells, GLP-1 inhibits glucagon secretion, probably indirectly via somatostatin secretion and via its effect on insulin release\[13\]. In the β cells, GLP-1 and GIP have been shown to promote cell proliferation and survival\[16\]. Some other antidiabetic actions of the incretin hormones are as follows: 1) inhibition of food intake and weight gain\[6\], 2) retardation of gastric emptying which can attenuate the meal-associated increases in blood glucose\[17\], 3) promotion of insulin-stimulated incorporation of fatty acids into triglycerides\[10\]. For more detailed information on the actions of GLP-1 and GIP, refer to the review by Hansotia and Drucker\[6\].

The half-life of active GLP-1 is less than 2 minutes and that of GLP-1 is ~7 minutes\[10\]. These hormones can be completely and rapidly inactivated by DPP IV. The truncation of the peptides by cutting the N-terminal dipeptide end results in biologically inactive peptides that are incapable of stimulating insulin secretion\[19\]. Thus, inhibition the enzyme DPP IV in order to prevent the degradation of the incretin hormones has become a promising therapeutic strategy.

**DPP IV ENZYME:A RATIONAL TARGET TO TREAT DIABETES**

Dipeptidyl-peptidase IV (CD26; EC3.4.14.5) is a 766 amino acid membrane-associated, serine-type protease which cleaves off a dipeptide from the N-terminal end of peptides with a proline or alanine residue at the penultimate position\[20\]. The enzyme is widely distributed in numerous tissues such as kidney, intestine, liver, spleen, placenta, adrenal glands, lymphocytes, and endothelial cells\[21\]. The DPP IV inhibitors exert their function of controlling hyperglycemia in T2DM by improving the stability and action of incretins.

Numerous animal studies support the concept of DPP IV inhibition as a strategy for the treatment of diabetes in the clinical setting. Nagakura’s group has reported that DPP IV-deficient F344/DuCrj rats show improved glucose tolerance via enhanced glucose-dependent insulin secretion when compared with DPP IV-positive F344/Jcl rats\[22\]. The study of mice lacking CD26 (DPP IV) has suggested that total lack of CD26 is surprisingly tolerable. These knockout animals have normal blood glucose levels in the fasted state, and reduced blood glucose excursions following a glucose challenge\[23\]. Reim and colleagues reported that long-term DPP IV inhibition in mice improves glucose intolerance through improved islet function, mediated by increased GLUT-2 expression\[24\]. Importantly, rodents lacking DPP IV showed a low risk of hypoglycemia. The initial proof-of-concept of DPP IV inhibitors for diabetes treatment in humans came from the clinical study done by Ahren and colleagues\[25\]. They chose 93 patients with a history of T2DM diagnosed at least 12 weeks, administered with an active DPP IV inhibitor, NVP DPP728, 100mg tid or 150mg bid for 4 weeks. The results showed that the fasting plasma glucose levels, as well as prandial glucose excursion, were decreased and HbA1c levels were significantly reduced compared with placebo. This agent was well-tolerated in all groups. Subsequently, several longer acting DPP IV inhibitors were developed and have undergone preclinical and clinical trials (Table 2).

**Table 2**  DPP-IV Inhibitors that have entered clinical trials (Information on the Clinical phase obtained from ClinicalTrials.gov: http://www.clinicaltrials.gov)

<table>
<thead>
<tr>
<th>DPP-IV inhibitor</th>
<th>Company</th>
<th>Clinical phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin(MK-0431)</td>
<td>Merck</td>
<td>Approved</td>
</tr>
<tr>
<td>Vildagliptin(LAF-237)</td>
<td>Novartis</td>
<td>Filed</td>
</tr>
<tr>
<td>Saxagliptin(BMS-47711B)</td>
<td>Bristol-Myers Squibb</td>
<td>Phase III</td>
</tr>
<tr>
<td>Alogliptin(SYR-322)</td>
<td>Takeda Global Research &amp;</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Development Center, Inc</td>
<td></td>
</tr>
<tr>
<td>PHX1149T</td>
<td>Phenomix</td>
<td>Phase III</td>
</tr>
<tr>
<td>GW823093</td>
<td>GlaxoSmithKline</td>
<td>Phase III</td>
</tr>
<tr>
<td>GW823093C</td>
<td>GlaxoSmithKline</td>
<td>Phase II</td>
</tr>
<tr>
<td>PHX1149</td>
<td>Phenomix</td>
<td>Phase II</td>
</tr>
<tr>
<td>KRP-104</td>
<td>ActivX Biosciences, Inc</td>
<td>Phase II</td>
</tr>
<tr>
<td>SYR619</td>
<td>Takeda Global Research &amp;</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Development Center, Inc</td>
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</table>

**CLINICAL PROGRESS OF DPP IV INHIBITORS**

The DPP IV inhibitors are orally active, small molecular weight drugs that inhibit >90% of plasma DPP IV activity for over 24 hours in vivo\[26\]. These agents increase active incretin levels by preventing their rapid degradation. Thus, DPP IV inhibitors are dependent on endogenous incretin secretion, and they may be effectively employed early in type 2 diabetes\[27\]. Several DPP IV inhibitors have been developed, of which vildagliptin...
and sitagliptin are currently in late-stage development and have been approved for use, respectively. Both agents exhibit a high degree of selectivity for DPP IV. Furthermore, both vildagliptin and sitagliptin show slow, tight-binding inhibition kinetics of DPP IV and efficiently inhibit plasma DPP IV activity.

**Vildagliptin**

Vildagliptin (Galvus®, Novartis) ([Fig. 2](image)) is a potent, selective, and competitive inhibitor of DPP IV [28]. The agent is mainly hydrolyzed to the inactive metabolite LAY151 and then both active and inactive forms are eliminated by the kidneys [29]. The US Food and Drug Administration (FDA) has asked Novartis to provide additional safety data for patients with renal impairment before Vildagliptin can be approved.

A randomized, double-blind study (100 mg daily, n=18) versus placebo (n=19), administered to patients with mild T2DM. The conclusion was that DPP IV inhibition improved metabolic control by reducing glucagon levels. However, the insulin levels were not altered in spite of the lower glycemia [30]. In a 12-week, double-blind, dose-ranging study 279 patients with mean HbA1c levels between 6.8 and 10.0% of total hemoglobin, and fasting plasma glucose (FPG) between 6.1 and 15 mmol/L, were randomized to receive vildagliptin in different doses (25-100 mg daily). Compared with placebo, HbA1c values were significantly reduced by 0.43% (P = 0.003) and 0.4% (P = 0.004) with dosages of 50 mg and 100 mg once daily, respectively [31]. At a higher dose of 100 mg twice daily for 4 weeks, vildagliptin decreased the degragation of GLP-1 and improved β-cell function in diabetic patients [32]. Matikainen et al have reported that treatment with vildagliptin (50 mg bid) for 4 weeks improved postprandial plasma triglyceride after a fat-rich meal [33].

A randomized, double-masked study examined the effects of vildagliptin monotherapy (25 mg, bid, n = 70) versus placebo (n = 28), in subjects with a mean baseline HbA1c of 8.0%. It was found that vildagliptin improved glycemic control and reduced HbA1c by 0.6% [34]. Another study performed in drug-naïve patients with type 2 diabetes showed that vildagliptin monotherapy for 24 weeks was well-tolerated and provided similar clinical benefit when given at a 100 mg qd dose or a 50 mg bid dose [35]. Additional evidence for the efficacy and tolerability of vildagliptin was obtained from a multicentre, placebo-controlled, 52-week study involving 306 drug-naïve patients with mild hyperglycaemia (HbA1c = 6.2-7.5%, and FPG ≈ 7.1 mmol/L). Vildagliptin 50 mg daily was well-tolerated and significantly reduced HbA1c, FPG and prandial plasma glucose (PPG) relative to placebo [36]. The effect of vildagliptin therapy was evaluated by Utzschneider and colleagues in patients with impaired fasting glucose (IFG) (n = 22), administered with placebo for 2 weeks followed by vildagliptin for 6 weeks and then placebo for 2 weeks. It was found that vildagliptin, 100 mg once daily, improved β-cell function and insulin sensitivity in subjects with IFG [37].

**B. Combination therapy**

Vildagliptin has also been reported to improve glycaemic control by add-on combination therapy. The first trial was conducted to assess efficacy and tolerability of the vildagliptin versus placebo in patients with a mean baseline fasting glucose of 9.8 mmol/L and a mean baseline HbA1c of 7.8%. The patients had been on metformin treatment for a mean of 29 months. The results showed that during the initial 12-week core study period, HbA1c levels in the vildagliptin/metformin group (n = 56) was reduced by 0.7% compared to the placebo/metformin group (n = 51). During the following 40-week extension period, HbA1c increased by 0.066% per month in placebo/metformin group (n = 29) but only by 0.013% per month in vildagliptin/metformin group (n = 42). The study also showed that the addition of vildagliptin to patients treated with metformin could effectively prevent deterioration of glycemic control [38]. It took over 1 year to assess the effects of vildagliptin on β-cell function and insulin sensitivity. A total of 57 patients (vildagliptin plus metformin, n = 31; metformin plus placebo, n = 26) completed the entire study. The conclusion indicated that HbA1c and FPG decreased in the vildagliptin/metformin group while these indicators increased in the placebo/metformin group, with the between-group differences of -1.0% ± 0.2% (P < 0.001) and -0.9 ± 0.3 mmol/L (P = 0.016), respectively. In addition, the post-meal insulin sensitivity was significantly increased in the vildagliptin/metformin group compared to the placebo/metformin group [39].
During a 24-week study, the patients inadequately controlled with metformin monotherapy were additionally given 50 mg vildagliptin daily (n = 177), 100 mg vildagliptin daily (n = 185), or placebo (n = 182). Vildagliptin was well tolerated and showed a clinically significant, dose related improvement in glycemic control by decreasing FPG and HbA1c [40]. The open-label study in healthy volunteers conducted by Yan-Ling He et al demonstrated that the vildagliptin/ metformin (50/1000 mg) fixed-dose combination tablet can be taken with meals without altering the pharmacokinetics of the DPP IV inhibitor, vildagliptin [41].

Another study compared the effects of vildagliptin at 50 or 100 mg daily with placebo when used as an add-on therapy to pioglitazone at 45 mg daily in 463 patients who had a mean baseline HbA1c of 8.7%. The results showed that HbA1c was reduced by 1.1% in the vildagliptin 100 mg daily group and by 0.8% in the vildagliptin 50 mg daily group, versus a 0.3% reduction in the placebo group [42]. A 24-week trial examined the effect of vildagliptin (n = 144; 50 mg twice daily) and placebo (n = 152) when added to insulin therapy. The patients were inadequately controlled by insulin (HbA1c = 7.5-11%). The results suggested that vildagliptin in combination with insulin reduced HbA1c by 0.7%, whereas insulin alone reduced HbA1c only by 0.2% [43].

**Sitagliptin**

Sitagliptin (Januvia®, Merck Pharmaceuticals) (Fig. 3) was approved by the U.S. Food and Drug Administration (FDA) in October 2006 as monotherapy for the treatment of T2DM. The FDA also approved a sitagliptin/metformin fixed-dose combination (Janumet™, Merck & Co.) in April 2007 as adjunct therapy to diet and exercise to improve glycemic control in adult patients with T2DM.

![Chemical structure of sitagliptin](image)

**Fig. 3** Chemical structure of sitagliptin

**A. Monotherapy**

A number of clinical trials have evaluated the safety and efficacy of sitagliptin monotherapy for the treatment of T2DM. Scott et al examined the efficacy and tolerability of sitagliptin as monotherapy in a randomized, double-blind, placebo-controlled and dose-ranging study for the duration of 12 weeks. The patients (n = 743) with T2DM and a mean baseline HbA1c of 7.9% had inadequate glycemic control on diet and exercise, and were randomized to receive 1 of 6 treatments: placebo (n = 125), sitagliptin 5 mg b.i.d. (n = 125), sitagliptin 12.5 mg b.i.d. (n = 123), sitagliptin 25 mg b.i.d. (n = 123), sitagliptin 50 mg b.i.d. (n = 124), or glipizide 5 mg daily (n = 123). The results showed that sitagliptin led to significant reductions in HbA1c (-0.38% to -0.77%) and FPG (8.64 mg/dL to 26.1 mg/dL) relative to placebo. Among all the sitagliptin doses, sitagliptin 50 mg twice daily demonstrated the greatest efficacy in glycemic control. Sitagliptin was also well tolerated, with the incidence of hypoglycemia and weight gain adverse effects similar to placebo and lower than glipizide [44].

The efficacy of sitagliptin as a monotherapy in patients between the ages of 18 and 75 years with T2DM was examined by Aschner and colleagues in a randomized, placebo controlled, 24-week, double-blind study. The patients (n = 741) with a mean baseline HbA1c of 8.0% were randomized to receive sitagliptin 100 mg/d (n = 238), sitagliptin 200 mg/d (n = 250) or placebo (n = 253). Sitagliptin 100 mg/d and 200 mg/d therapy achieved statistically significant efficacy with the placebo-subtracted reductions in HbA1c values from baseline (-0.79% and -0.94%, respectively) and FPG levels from baseline (-17.1 mg/dL and -21.3 mg/dL, respectively). Moreover, 2-h postprandial glucose was reduced by 46.7 mg/dL and 54.1 mg/dL compared with placebo for patients treated with sitagliptin 100 and 200 mg, respectively. Sitagliptin also improved β-cell function, which was assessed by the proinsulin/insulin ratio and the homeostasis model assessment of β-cell function (HOMA-β) [45].

**B. Combination therapy**

Sitagliptin has also been evaluated in various add-on combination therapies. In a multinational, randomized, placebo-controlled, double-blind study, Raz and associates evaluated the effects of sitagliptin added to metformin in patients with moderately severe (HbA1c values of 8-11%) T2DM. Patients receiving other oral antihyperglycemic agents (OHAs) took metformin as monotherapy which was then titrated to a tolerated and stable dose ≥ 1,500 and ≤ 2,550 mg/d. These patients then entered a metformin dose-stable run-in period of 6 weeks, while patients taking metformin monotherapy at a stable dose of at least 1,300 mg daily directly entered the 6-week metformin dose-stable run-in period. After the run-in period, patients with HbA1c between 8% and 11% continued into a 2-week placebo run-in period. All the patients (n = 190) were randomized to receive
the addition of sitagliptin 100 mg (n = 96) or placebo (n = 94) once daily for 30 weeks. The results demonstrated that at week 18, HbA1c, FPG and 2-h PPG were reduced from the baseline by 1.0%, 32.4 mg/dL and 68.4 mg/dL, respectively, when compared with placebo. Placebo-subtracted differences in LS mean (95% CI) changes in HbA1c and FPG from baseline were -1.0% (-1.4% to -0.6%) and -25.2 mg/mL (-37.8 mg/dL to -12.6 mg/dL) at week 30[40].

Rosenstock et al assessed the efficacy and tolerability of sitagliptin added to ongoing pioglitazone therapy in patients who have inadequate glycemic control with a stable dose of pioglitazone alone. After pioglitazone monotherapy dose titration /dose stabilization periods and 2-week placebo run-in period, all patients (n = 353) were receiving ongoing pioglitazone (30 or 45 mg/d). Then patients were randomized in a 1:1 ratio to receive sitagliptin 100 mg once daily or placebo for 24 weeks. The mean baseline HbA1c value and FPG levels were 8.1% and 168.3 mg/dL in the sitagliptin group and 8.0% and 165.6 mg/dL in the placebo group, respectively. A total of 307 patients adequate glycemic control. Study at week 24, sitagliptin therapy was associated with significant reductions in HbA1c values (P < 0.001) and FPG levels (P < 0.001) compared with placebo. The between-group difference in LS mean (95% CI) changes from baseline in HbA1c and FPG were -0.70% (-0.85% to -0.54%) and -17.7 mg/mL (-24.3 to -11.0), respectively. There was no statistically significant difference in the incidence of hypoglycemia and body weight change between the sitagliptin group and placebo group[47].

Safety and tolerability of DPP IV inhibitors

A great many studies have shown that both vildagliptin and sitagliptin are safe and well-tolerated as monotherapy or as combination therapy. In most studies, the frequency of hypoglycemia and body weight gain were similar to that with placebo, and the clinical adverse events were generally mild, transient, and self-limited[48,49]. Compared with GLP-1 mimetics, DPP IV inhibitors have no significant adverse gastrointestinal side effects, such as abdominal pain, nausea and diarrhea[50]. In two of the studies, hypertension was reported in patients receiving vildagliptin, although the cases were not thought to be drug-related[48]. Moreover, no electrocardiogram abnormalities were observed during treatment with DPP IV inhibitors.

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 prediabetic 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.

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