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DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITION: A NOVEL APPROACH FOR THE TREATMENT OF TYPE II DIABETES MELLITUS

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ABSTRACT

Diabetes Mellitus is a metabolic disorder characterized by hyperglycemia. The prevalence of Diabetes is on the rise, more alarmingly in the developing nations. It is projected that as many as 40-45% of persons aged 65 or older have either Type II Diabetes or its precursor state, Impaired Glucose Tolerance (IGT). The current therapeutic strategies for Type II Diabetes are relatively limited, and involve insulin therapy for Type I Diabetes and Oral Hypoglycemic Agents (OHAs) such as Sulfonylureas, Metformin and the Thiazolidinediones as the primary line of treatment for Type II Diabetes. Combination therapy with one or more of these agents is also a viable option. A wide variety of therapeutic approaches are now being examined for Type II Diabetes. Dipeptidyl peptidase IV (DPP IV), a key regulator of incretinhormones, glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), remains an attractive target in diabetes as it enhances glucose (nutrient) dependent insulin secretion. The present review will give an insight into the development of several DPP-4 inhibitors and their potential prospects in the treatment of Type II Diabetes Mellitus.

KEYWORDS:Type II Diabetes, Incretins, DPP-4, DPP-4 inhibitors

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INTRODUCTION

Diabetes mellitus is the only noninfectious disease designated as an epidemic by the World Health Organization (1) and is primarily characterized by insulin resistance or decreased insulin sensitivity. Some of the contributing factors for type 2 diabetes (T2D) include, body cell resistance to insulin, impaired beta cell functioning, sedentary life styles, obesity, genetics etc. which lead to abnormal glycemic control (2). Consequently, the increased and sustained plasma glucose levels progress into a number of diabetic complications viz. retinopathy, neuropathy, atherosclerosis and coronary artery disease. (3). The prevalence of T2D is increasing worldwide.(4) According to WHO, about 194 million people worldwide are affected by T2D and the number is projected to be 366 million by 2030 (5). The current therapeutic strategies for T2D (6) fail to address the progressive nature of the disease and are associated with undesirable side effects (7). Therefore, there is a growing demand for the development of new drugs to treat T2D. Inhibition of Dipeptidyl Peptidase-4 (DPP-4) is one of the approaches that have gained a lot of importance in the treatment of T2D over the last few years as it promotes/enhances glucose (nutrient) dependent insulin secretion. The present review focuses on the characteristics of DPP-4 that makes it a unique target and will also touch upon the development of some DPP-4 inhibitors. Several DPP-4 inhibitors have been developed, with five already approved in the USA, Europe and/or Japan (Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin and Linagliptin) and many more waiting in the pipeline to be launched in the market.

The Incretin hormones

The hormones, glucose dependent insulinotropic polypeptide (GIP) and glucagon like peptide (GLP-1) are collectively termed as the incretins. These hormones promote the growth of pancreatic beta cells and also help in their survival. The first incretin to be identified, glucose-dependent insulinotropic polypeptide (GIP), was purified from porcine intestinal extracts had potent insulinotropic actions in human beings. GIP is a 42-aminoacid hormone synthesized in duodenal and jejunal enteroendocrine K cells in the proximal small bowel. (8, 9) The second incretin hormone, glucagon-like peptide-1 (GLP-1) was identified after the cloning of the cDNAs and genes encoding proglucagon. GLP-1 exists in two circulating equipotent molecular forms, GLP-1(7-37) and GLP-1(7-36) amide, although GLP-1(7-36) amide is more abundant in the circulation after eating. It is produced mainly in the intestinal L-cells, located in the distal portion of the small intestine. (10)

Role of DPP-4 in Pathogenesis of T2D

Ingestion of food results in the release of incretins, which regulate insulin in a glucose-dependent fashion. 11 Incretins also control gastric emptying, induction of satiety as well as regeneration and differentiation of islet beta cells. (12,13) The structures of glucagon- like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) reveal that these peptides are the ideal substrates for DPP-4. (14). DPP-4 rapidly degrades these incretins by cleaving them from the N-terminus, transforming them into inactive species. GLP-1 (7-36) amide (active form) is rapidly converted to the inactive GLP-1 (9-36) while GIP (1-42) is rapidly converted to the inactive GIP (3-42) form by DPP-4. (15**)**. Thus, inhibition of DPP-4 will ensure increased action of the incretins which will consequently lead to sustained insulin secretion. (16)

DPP-4: A multifaceted enzyme

DPP-4 is a serine protease that cleaves N-terminal dipeptides from polypeptides having Pro (or Ala) at the penultimate position. (17, 18) In humans, the highest levels of DPP-4 are found in the bone marrow and the brush border of the small intestine and kidney proximal tubules. Structurally, it is an integral membrane

protein consisting of a hydrophobic N-terminal domain, a transmembrane region, and a C-terminal domain containing the catalytic triad that acts on oligopeptides by selectively removing N-terminal dipeptides. (19) DPP-4/ CD26 primarily consist of 766 amino acid residues. (20) Cross-linking and ultracentrifugation studies have shown that DPP-4 exists as a dimmer both in vivo and in vitro. (21.) It has been proposed that this homodimerization is essential for its serine protease activity. (22) DPP-4, which is identical to CD26, a marker for activated T cells; is likely to be involved in modulating certain immune functions. (23, 24)

Related Isoforms

In addition to DPP-4, family members include quiescent cell proline dipeptidase (QPP/ DPP-7), DPP-8, DPP-9, fibroblast activation protein, attractin, and DPP-4 beta. Except for DPP-4, the functions of these enzymes are unknown. Nonetheless, based on their preference for cleavage after H_2N-X-Pro in vitro, they are likely to be involved in at least some of the biological processes that appear to be regulated by proline-specific NH_2-terminal processing. (25). DPP-7 appears to be identical to DPP-2 and is located in the intracellular vesicles.(26) Selective inhibition of QPP produced reticulocytopenia in rats. (25) DPP-8 (27) and DPP-9 (28) are soluble, cytoplasmic enzymes that are ubiquitously expressed. DPP-8 has 51% homology with DPP-4 at the amino acid level. Selective inhibition of DPP-8/9 produced alopecia, thrombocytopenia, reticulocytopenia, enlarged spleen, multi organ histopathological changes, and mortality in rats while it produced gastrointestinal toxicity in dogs. (25) Thus, selective inhibition of DPP-4 over these isoforms may prove to be very important for identifying potentially safe and well tolerated drugs to treat T2D.

An overview of DPP-4 Inhibitors

A general classification of DPP-4 inhibitors based on their structural features has been shown in Fig. 1. Inhibitors can be divided into two major classes, i.e., peptidomimetic and non-peptidomimetic series. The first series can be further sub divided into (a) glycine based inhibitors (alpha-series) and (b) beta-alanine-based inhibitors (beta-series). A prototype example of an inhibitor belonging to each class has been listed in Table. 1 In the case of alpha-series, the pyrrolidine derivatives have been widely explored as DPP IV inhibitors due to DPP-4's specificity for substrate having an amino-terminal proline at C-2 which can be further divided as reversible and irreversible depending upon the substitution at C-2 of the pyrrolidine ring. The beta- series was generally developed from a lead obtained via high-throughput screening (HTS). (29) The non-peptidomimetic series represents a diverse class of compounds, which in spite of its distinct structural features; interact well at the active site of DPP-4. (30)

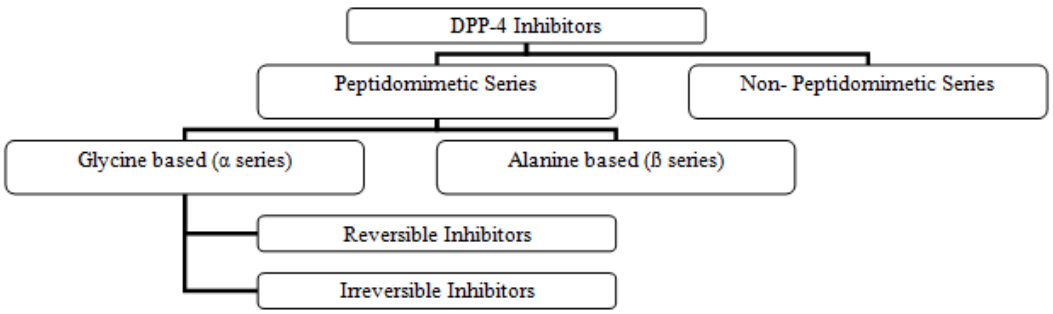

Figure 1
Classification of DPP-4 Inhibitors

Table 1
Examples of DPP-4 Inhibitors as per their classification

Class	Example
Reversible Inhibitors (α series)	2- cyano pyrrolidine Derivatives (31)
Irreversible Inhibitors (α series)	Diaryl Phosphonate ester Derivatives(32)
ß series	Triazolopiperazine Derivatives (33)
Non-Peptidomimetic Inhibitors	Benzimidazole Derivatives (34)

Pharmacodynamic and pharmacokinetic profiles of several DPP-4 inhibitors

Several DPP-4 inhibitors are on the market or in trials as listed in Table. 2. DPP-4 inhibitors reported in literature are all orally available, show good absorption and have good affinity for DPP-4.

Sitagliptin (JANUVIA)

a triazolopiperazine derivative**,** developed by Merck and Co., was approved in 2006 and is a potent and selective inhibitor of DPP-4. It shows good bioavailability (87%) and has a half-life between 8-14 hours. It is 38% bound to plasma proteins and undergoes limited metabolism via CYP3A4 and CYP2C8. Elimination is mainly through urine. (35) In clinical trials of 1-year duration, Sitagliptin improved glycemic control by reducing both fasting and postprandial glucose concentrations, leading to clinically meaningful reductions in glycosylated hemoglobin levels. Monotherapy with Sitagliptin 100mg daily decreases mean HbA1c by 0.6-0.79% (mean difference from placebo). When used in combination with metformin or pioglitazone, the mean reduction in HbA1c is 0.7% and 0.9% respectively. Sitagliptin is considered to be weight neutral and lipid neutral. Adverse effects include upper respiratory tract infection, stuffy or running nose, sore throat, headache and diarrhea. (36)

Vildagliptin (GALVUS)

a cyanopyrrolidine derivative by Novartis, is the second DPP-4 inhibitor approved for human use and is indicated in T2D (37). Vildagliptin is a potent, selective, reversible and orally bioavailable DPP IV inhibitor. (38) In healthy human volunteers, Vildagliptin is rapidly absorbed with 85% bioavailability and a half-life of about 90 minutes. However, sustained DPP IV inhibition was observed for more than 10 hrs. It is available as a 50mg and a 100mg tablet with recommended dose of 50mg once daily if used in combination with Metformin/Glitazones/Sulfonylureas. Most common adverse events include nasopharyngitis, headache and dizziness. (30)

Saxagliptin (ONGLYZA)

a methanoprolinenitrile derivative, by Bristol/Myers Squibb(BMS), is also a potent selective long acting DPP-4 inhibitor with better stability and several benefits when compared with other gliptins (39). Oral absorption of saxagliptin in humans is high (≥ 75%) as demonstrated in a mass balance study using 50mg saxagliptin. Absorption is not affected by alterations in gastric pH and is not affected by food. Saxagliptin and its major metabolite BMS-510849 do not bind to plasma proteins in in vitro serum, which has also been confirmed by the mass balance study that also suggests that saxagliptin and its related compounds are not retained in the body to a substantial extent. The biotransformation of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). Renal excretion is an important route of clearance for saxagliptin. In the placebo-controlled Core Phase 3 studies, upper respiratory tract infections (URI), headache and UTI were the adverse events that were more frequent (≥5% and without any thresholds between treatment groups) among subjects treated with the recommended dose of saxagliptin (5 mg) as compared to placebo. At a higher dose of saxagliptin (10 mg), the additional adverse effects of URI,

nasopharyngitis, nausea, arthralgia, headache, and anxiety were more common in subjects receiving saxagliptin 10 mg, based on criteria of >1% difference relative to placebo(40)

Alogliptin (SYR-322)

a pyrimidine derivative, by Takeda Pharmaceuticals, is a potent (IC50<10nM) and selective inhibitor (selectivity >10,000overDPP-8and-9) (41). In a double blind placebo-controlled study, when used as a mono-therapy, alogliptin 12.5 and 25mg once daily resulted in a significant reduction of HbA1c by 0.6%, and was weight neutral.(42).Several studies showed that alogliptin in combination with other oral antidiabetic agents also improve glycemic control. In a randomized, double-blind trial, the administration of 12.5 and 25mg alogliptin for 26 weeks in patients inadequately controlled by the sulphonylurea glyburide (mean baseline HbA1c 8.1%) led to a further reduction of HbA1c levels by 0.53 and 0.39%, and fasting glucose by -8.4 and -4.7mg/dL(43)

Linagliptin (BI-1356)

also known as Ondero, a dihydropurinedione based inhibitor, developed by Boehringer Ingelheim, is a long acting orally available DPP-4 inhibitor. It is well tolerated, with a low renal excretion and a terminal half-life around 180 hrs (44). Linagliptin was evaluated as monotherapy or add-on therapy and has shown clinically meaningful improvement of glycemic control in T2D. In a randomized, placebo-controlled, phase III trial, Linagliptin improved glycemic control (HbA1c -0.69 % from baseline, -1.01% in the patients with a baseline HbA1c > 9%). Apart from being very potent (IC50=1nm) and weight neutral, it also enhances beta cell functioning.(45)

Dutogliptin tartarate

(PHX-1149), by Phenomix Corp., a boronic acid derivative, exhibited good safety profile. A 28-day phase 2a clinical trial of PHX-1149 in 174 T2D patients, demonstrated that the drug was well tolerated and met its primary endpoint of reduction in postprandial glucose levels. In April 2007, a 12-week phase 2b clinical trial study was initiated and in May 2008, positive results were reported regarding the safety of the drug.(46)

Carmegliptin (R-1579)

developed by Roche, is a benzo[a]quinolizine derivative and a potent inhibitor of DPP-4(IC 50=6.8nM). Carmegliptin exhibits a unique pharmacokinetic profile, with no metabolism and balanced renal and hepatic excretion. Clinical phase 1 and 2 studies have indicated its suitability as a safe oral anti-diabetic agent with once-daily administration(47)

Melogliptin

(GRC-8200), developed by Glenmark Pharmaceuticals Ltd., is a potent (IC50=1.61nM) and selective (selectivity~10,000-fold over DPP-2) DPP-4 inhibitor. Melogliptin has a good pharmacokinetic profile with 50-95% bioavailability. Phase I and Phase II studies have suggested that the drug is safe, efficacious and weight neutral. (48,49) Few DPP-4 inhibitors like MP-513, AMG-222, KRP-104, SK-0403, RO-0730699, BMS-686117, TAK-100, SSR-162369, ABT-279, GW-1853, LY-2463665 and S-40010 have already completed their pre-clinical studies and are currently under various stages of clinical investigations.

Table 2
Summary of DPP-4 Inhibitors at various developmental stages

DPP-4 Inhibitor	Company	Status
Sitagliptin	Merck and Co.	Launched
Vildagliptin	Novartis	Launched (Europe)
Saxagliptin	Bristol-Myers-Squibb/ Astra Zeneca	Phase III
Alogliptin	Takeda	Phase III
Linagliptin	Boehringer Ingelheim	Phase III
Dutogliptin	Phenomix Corp	Phase III
Carmegliptin	Roche	Phase II
Melogliptin	Glenmark	Phase II
MP-513	Mitsubishi Tanabe	Phase II
AMG-222	Alantos Pharmaceuticals And Amgen	Phase II
KRP-104	Active X Biosciences Inc.	Phase II
SK-0403	Sanwa Kagaku Kenkyushu	Phase II
RO-0730699	Roche Holding AG	Phase II
BMS-686117	Bristol-Myers-Squibb Co.	Phase I
TAK-100	Takeda	Phase I
SSR-162369	Sanofi-Aventis Deutschla ND GMBH	Phase I
ABT-279	Abbott Laboratories	Phase I
GW-1853	GlaxoSmithKline	Pre-clinical studies completed
LY-2463665	Eli Lilly and Co.	Pre-clinical studies completed
S-40010	Servier	Pre-clinical studies completed

CONCLUSION

Most of the existing therapies fail to tackle weight gain, severe hypoglycemia on prolonged use and beta cell dysfunction. The development of DPP-4 inhibitors, therefore, seems to be an attractive approach for the treatment of T2D as it may halt the progression of the disease; something that has not been achieved till date with other conventional therapies. Several findings from the clinical studies are indeed very promising. DPP-4 inhibitors are expected to provide an opportunity in specifically controlling postprandial hyperglycemia in T2D patients. To conclude, comprehensive studies are needed to give a clear insight about the long term effects of DPP-4 inhibition *in vivo* and the effects of DPP-4 inhibitors on T-cell signaling and immune functions *in vivo*.

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