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Dipeptidyl Peptidase-IV: A Brief Review.

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Review Article

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ABSTRACT

Diabetes mellitus-2 [NIDDM/T2D] is a metabolic disorder that is characterized by Insulin resistance and hyperglycemia. DPP IV inhibitors have been investigated as new target for T2D treatment. DPP IV inhibition improves the impaired insulin secretion and decrease postprandial concentrations of glucagon by enhancing the incretin hormone levels of Glucagon like peptide-1(GLP-1) and Glucose dependent insulinotropic polypeptide (GIP). Many research activities in this area resulted in the introduction of Sitagliptin and Vildagliptin (Only in Europe) and few active molecules entered into clinical trials, for example Alogliptin. Treatment of this metabolic disorder especially in the early stages of the disease by DPP IV inhibition has been recognized as a validated and large numbers of inhibitors are currently in various stages of preclinical or clinical development. This review summarizes the development of DPP IV inhibitors, molecular mechanism, and etc.

INTRODUCTION

Diabetes is an emerging epidemic of the 21st century and has become a major health problem throughout the globe. It is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. After digestion, glucose passes into the bloodstream, where it is used by cells for growth and energy. For glucose to get into cells, insulin must be present. Insulin (51 amino acid residue) is a hormone produced by the pancreas, a large gland behind the stomach (Pancreas) [1, 2]. In diabetes, the pancreas either produces little or no insulin, or the cells do not respond appropriately to the insulin that is produced. Glucose builds up in the blood, overflows into the urine, and passes out of the body. Thus, the body loses its main source of fuel even though the blood contains large amounts of sugar. The three main types of (Chart-1) diabetes are (1) Type-1diabetes(T1D) (2) Type-2 diabetes(T2D) (3) Gestational diabetes, Out of this T2D, often called Non-Insulin Dependent Diabetes and is the most common form of diabetes, affecting 90% - 95% people in the world. Metabolic syndrome is associated with a markedly increased incidence of coronary, cerebral and peripheral artery disease. The current oral hypoglycemic agents against T2D include metformin, sulfonylurea, thiazolidinedione and α-glycosidase inhibitors, although effective in increasing insulin secretion, are associated with undesirable side effects, Weight gain, edema, gastrointestinal toxicities and hypoglycemia are the few side effects of existing oral antidiabetic agents. List of existing oral antidiabetic agents along with their molecular target, mechanism of action and adverse effects related to their use are summerised in Table 1. Patients having T2D are at high risk of vascular complications including coronary heart disease, stroke, hypertension, peripheral vascular disease, neuropathy, retinopathy and nephropathy [2]. According to World Health Organization (WHO) this public health problem affecting 366 million people by 2030. Inhibition of Dipeptidyl Peptidase IV (DPP IV) has emerged as a new treatment for T2D. Inhibition of DPP-IV has shown to increase the half life of GLP-1 and to prolong the beneficial effects of incretin hormone. Moreover, DPP-IV inhibitors did not show the undesirable side effects, as observed in other oral antidiabetic agents [2, 3].

Chart 1: Classification Diabetes

Types of Diabetes	
Type-1	Type-2
Insulin dependent diabetes(IDDM)	Non insulin dependent diabetes (NIDDM)
Caused by destruction of beta cells	Caused by target cell resistance to insulin
Appears in childhood appears to reduce the number of insulin receptor	Mostly appears in obese person, obesity
Dependent on insulin replacement	Treated with oral hypoglycemic drugs

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Table 1: DPP-IV inhibitors status and availability

Drug	Chemical nature	Status	Trade name	Pharmaceutical company
Sitagliptin	B-amino acid based blockbuster drug	Approved in the United States and Europe	Januvia™, Janumet®	Merck & Co., Inc
Saxagliptin (BMS-477118)	Methanoprolinenitrile based inhibitor	Approved in the United States and Europe	Onglyza™	Bristol-Meyers Squibb/AstraZeneca
Linagliptin	---	Approved in United States and Europe	Ondero® , Tradjenta™	Boehringer Ingelheim
Vildagliptin	Cyanopyrrolidine based inhibitor	Approved in Europe	Galvus®	Novartis AG
Alogliptin (SYR-322)	Non-peptidomimetic series drug	Under investigation	Nesina®	Takeda Pharmaceutical Company Limited
Dutogliptin (PHX-1149)	Boronic acid based inhibitor	Phase III	Not officially disclosed	Phenomix/Forest Laboratories, Ind.
Melogliptin (GRC-8200)	Fluropyrrolidine based inhibitor	Phase II	Not officially disclosed	Glenmark Pharmaceuticals, Europe
Teneligliptin (MP-513)	Cyanopyrrolidinebased inhibitor	Phase II (Japan) Phase III(US/EU)	Not officially disclosed	Mitsubishi Tanabe Pharma Corporation.
Denagliptin (GW-823093)	Cyanopyrrolidine based bis-aryl inhibitor	Phase II	Not officially disclosed	Glaxosmith Kline Pharmaceuticals Ltd
K-579	Pyrrolidine carbonitrile derivative	-----	-----	Tocris Bioscience
ABT-341	Alkylcyanopyrrolidine based inhibitor	-----	-----	Abbott laboratories

Incretin System

Incretins are a group of gastrointestinal hormones released during meals from gut endocrine cells. They cause an increase in the amount of insulin released from β-cells of the Islets of Langerhans after intake of food, they also inhibit glucagon release from the α-cells of the Islets of Langerhans. The incretin hormones include glucagon-like peptide-1(GLP-1) and glucose dependent insulinotropic polypeptide (GIP). Both hormones contribute to insulin secretion from the beginning of a meal and their effects are progressively amplified as plasma glucose concentration rises. In response of food ingestion GLP-1 (7-36 amide) is a 30 amino acid polypeptide which is rapidly secreted into the small intestine and the colon. Half life of GLP is 1- 1.5 minutes and shortly after its secretion it is rapidly degraded by the enzyme DPP-IV, by cleaving the two N-terminal residues ogGLP-1[4,5]. K cells of the duodenum are responsible to release GIP with the response of nutrient ingestion and also enhance glucose-stimulated insulin secretion. Half life of GIP is 5-7 minutes [6,7,8,9].

Dipeptidyl Peptidase-IV Inhibitors

Dipeptidyl peptidase IV (DPP IV) was identified in 1966 by Hopsu-Hovu and Glenner as glycylproline napthylamidase and was purified from rat liver and pig kidney in 1967 and 1968, respectively. The first inhibitor were characterized in the late 1980s and 1990s [10]. DPP-IV is circular membrane protein with ubiquitous expression, its activity has been recorded in rats, mice and humans in epithelial cells of the intestine, kidney, liver, lung, thymus, spleen and etc. It is also known as the T-cell antigen CD26, a serine exopeptidase. Members of protease family include DPP I-IV; DPP IV is a key regulator of incretin hormones. DPP IV is a non classical serine protease, membrane associated peptidase of 766 amino acids, widely distributed in numerous tissues and DPP-IV inhibitors prevents the degradation of GLP-1 and increases its concentration in blood [11,12].

Mechanism of Action

DPP-IV is a 766 amino acid amino peptidase. It is a tetramer with each subunit comprising of two domains, N-terminal β-propeller domain & C-terminal catalytic domain. The active site of the enzyme is covered by the β-propeller domain or a side opening formed at the interface of β-propeller domain and catalytic domain [13]. Based on In-vitro studies DPP-IV has a preference to cleave X-proline dipeptides at the N-terminus of polypeptides. GLP-1 and related glucagon family members contain alanine at this position [13].

DPP-IV inhibitors competitively inhibit the enzyme DPP IV, this enzyme breaks down the incretin GLP-1 and GIP, which are released in response to a meal. By preventing GLP-1 and GIP inactivation, insulin secretion increases and suppresses the release of glucagon by the pancreas which brings the blood glucose levels to normal. As the blood glucose level attained normal, the amount of insulin released and glucagon suppressed diminishes and prevents hypoglycemia which is seen with some oral hypoglycemic agents [15].

There are three class of DPP-IV inhibitors are under investigation, reversible product analogue inhibitors (pyrrolidines and thiazolidines), covalently modifying product analogues (Cyanopyrrolidines) and reversible non-peptidic heterocyclic inhibitors (xanthines and aminomethylpyrimidines) [14,15].

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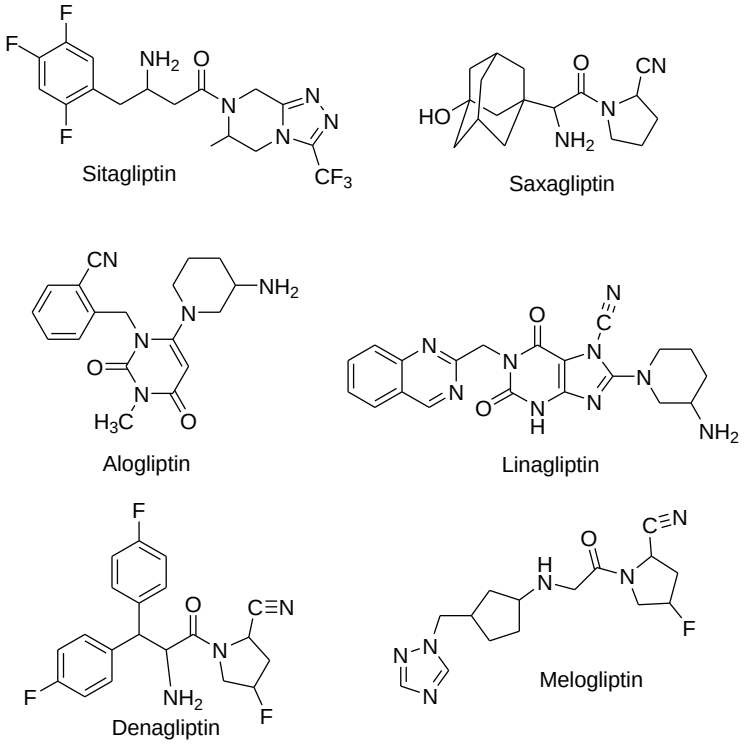
Sitagliptin (JANUVIA ™):

Sitagliptin (Figure-1) (Merck Pharmaceuticals, USA) is a highly potent, competitive; a highly selective triazolopiprazine based reversible inhibitor of DPP-IV enzyme. It is the first compound of its class introduced in the market and its chemical structure is (2R)-4-oxo-4[3-(trifluoromethyl)-5,6-dihydro[1,2,4]-triazolo-[4,3]-pyrazin-7-(8H)-yl]-1-(2,4,5-trifluorophenyl)-butan-2-amide. In October 2006, the US FDA approved sitagliptin as monotherapy and in combination with other oral diabetic medications, metformin, pioglitazone to improve blood glucose controlin T2D [16, 17]. In March 2007 it was approved in European Union. The normal dose is 100mg at once a day. Currently it is approved in 42 countries as an anti-diabetic agent [18, 19].

Figure.1: Structures of selected DPP-IV inhibitors



Pharmacokinetics and Drug Interaction

38% of sitagliptin is bound to plasma protein and its bioavailability is approximately 87%. Its halflife is 8-14hours, it undergoes metabolism via CYP3A4 and CYP2C8. Dose of sitagliptin should not be changed when it is combined with other antidiabetic drugs (metformin/glitazones). Elimination is mainly through urine.

Combination of sitagliptin with pioglitazone results in peripheral oedema. According to reports on glitazones, it posses cardio toxic effect. Although sitagliptin is not as likely to cause hypoglycemia as other oral diabetes medications [20,21,22].

Side Effects

Side effects of sitagliptin are cold, stuffy nose, diarrhea, headache, skin irritation, anaphylaxis, angioedema, hypersensitivity and rashes.

Vildagliptin (Galvus®):

Vildagliptin (Figure-1) is a potent, selective and orally active 2nd generation pyrrolidine based reversible inhibitor of DPP-IV. Reversible binding forms a complex with DPP-IV, causing its inhibition. Its chemical structure is (S)-1-[N-(3-hydroxy-1-adamantyl) glycyl]pyrrolidine-2-carbonitrile. In December 2011, the EU FDA approved Vildagliptin as monotherapy and in combination with other existing oral antidiabetc agents (metformin, sulfonylureas and glitazones) to treat T2D [23]. The approval of Galvus in the US remains uncertain, however presently it is using in 37 countries as an antidiabetic agent [23, 24].

Pharmacokinetics and Drug Interaction

Vildagliptin bioavailability is 85% and rapidly absorbed within 1-2 hours. It undergoes metabolism via CYP450, with a half life of 1.5-4.5 hrs but it does not appear to induce or inhibit the CYP450 enzyme. Dose of 50mg to be taken twice daily. So, Vildagliptin dose frequency is higher than Sitagliptin. Vildagliptin is used as a monotherapy or in combination with metformin [25, 26, 27,

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[31] (50mg of Galvus and 850mg of metfomin) and rosiglitazone [30]. Major antidiabetic action appears to be an enhancement of glucose stimulated insulin release, mediated via increasein GLP-1 levels. Most of the published evidence shows that Vildagliptin 50mg/day is more effective in reducing both fasting plasma glucose and postprandial plasma glucose [25,26,27,28,29,30,31].

Side effects

Head ache, dizziness, upper respiratory infection, high blood pressure, nose and throat infection, pain in the extremities. Swelling of the face, lips, mouth, tongue and allergic reaction known as anaphylactic shock.

Saxagliptin (Onglyza™)

Saxagliptin (Figure-1) was approved by US Food and Drug administration in July 2009 and by European Medicines Evaluation Agency in October 2009 for use as monotherapy or in combination for the treatment of T2D [32, 33]. Its chemical structure is (1S, 3S, 5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo hexane-3-carbonitrile.The combination product of saxagliptin/ metformin was approved in November 2010 [33]. Presently it is using in 68 countries as anti diabetic agent. It is also approved to use as monotherapy (Dose of 50mg) and in combination with other drugs, metformin (100mg), sulfonyl urea and glitazones [34, 35, 36, 37, 38, 39, 40, 41].

Pharmacokinetics and Drug interactions

Saxagliptin is a cyannopyrrolidine P-glycoprotein (P-gp) substrate. It is metabolized hepatically by cytochrome P450 (CYP) 3A4/5 to an active metabolite, 5-hydroxy saxagliptin [34]. This active metabolite is also a selective, reversible, competitive DPP-4 inhibitor. According to reports on saxagliptin, it does not inhibit the T-cell activity in *In vivo* study [38, 39, 40, 41].

Linagliptin (Tradjenta™)

Linagliptin (Figure-1) (Boehringer Ingelheim Research) is a structurally novel dipeptidyl-peptidase-4 (DPP-4) inhibitor[42]. Its chemical structure is 1H-Purine-2, 6-dione -8- [(3R)-3-amino-1-piperidinyl] - 7 - (2-butyn-1-yl) - 3, 7-dihydro-3-methyl-1-1[(4-methyl-2-quinazolinyl)-methyl]. In May 2011, US FDA approved Linagliptin for clinical use. Combination of linagliptin plus metformin (Jentadueto, Eli Lilly) was approved for clinical use on February 2012 [43, 44, 45].

Pharmacokinetics and Drug Interaction

Dose of 5mg to be administered daily and its bioavailability is 30% of the administered drug[45]. 90% of linagliptin is excreted in unchanged form. According to reported datas on Combination therapy of linagliptin with other diabetic drugs (metformin, sulfonylurea, glitazones) were also showed significant reduction of blood glucose level. Combination of linagliptin plus metformin hydrochloride received approval from US FDA on February 2012 [46, 47, 48].

Alogliptin (Nesina ®)

Alogliptin (Figure-1) is an orally available quinazolinonebased noncovalent inhibitor of DPP 4.It is under investigation in the US for the treatment of T2DM. It is being sold in Japan. It failed to receive the approval from European FDA; on April 2012 regulators of Europe have agreed to review its T2D therapy of Alogliptin. Regard this in the month of April, the FDA issued a second complete response letter for the drug and fixed dose combination of alogliptin with pioglitazone [49, 50].

CONCLUSION

DPP-IV inhibitors are a novel class of orally available molecules for the treatment of type 2 diabetes. Even though they are structurally different, they share a common mechanism of action by extending half-life endogenous Incretins and potentially reduce blood glucose level. Because GLP-1 secreted in glucose-dependent manner, DPP-IV inhibitors which prolong its half-life.

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