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DIPEPTIDYL PEPTIDASE-IV INHIBITORS-A NOVEL CLASS OF ANTIHYPERGLYCEMIC DRUGS: CHEMICAL AND PHARMACOLOGICAL PROFILE-A REVIEW

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ABSTRACT

The incretin effect is based on the understanding that oral glucose has a greater stimulatory effect on insulin secretion than that of intravenous glucose. Glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) are incretin hormones which account for higher insulin response after oral versus intravenous administration of glucose. The dipeptidyl peptidase-IV inhibitors are a new class of antihyperglycemic agents which were developed for the treatment of type-2 diabetes by rational drug design, based on an understanding of the underlying mechanism of action and knowledge of the structure of the target enzyme. Although they differ in terms of their chemistry, they are all small molecules which are orally available. Many new drugs are currently in development for the treatment of diabetes, including products with a new mechanism of action such as dipeptidyl peptidase-IV inhibitors.

KEYWORDS: Incretin, GLP-1, GIP, DPP-4, Type-2 diabetes.

1. INTRODUCTION

Diabetes Mellitus is a chronic disorder which is characterized by four metabolic disorders: impaired insulin action, obesity, insulin secretory dysfunction and increased endogenous glucose output.[1] It is the most common endocrine disorder, affecting as many as 200 million people worldwide, with the number estimated to grow to 366 million or more by 2030 affecting both developed and developing countries alike. Type 2 diabetes is the world's fifth leading cause of death according to the World Health Organization.[2] India can be truly called the diabetes capital of the world with reference to the Diabetes Atlas 2009 published by the International Diabetes Federation which estimated diabetic population in India to be around 50.8 million, which is expected to rise to 87 million by 2030.[3] All forms of diabetes have been managed since insulin became available in 1921, and type-2 diabetes may be controlled with medications. Apart from insulin, few other drugs which can be administered orally are also used widely. Commonly known as Oral Hypoglycemic Drugs, they are classified in to different types according to their mode of action. Few major classes of oral hypoglycemic agents extensively used are: insulin secretagogues like sulfonylureas, Sensitizers like biguanides, thiazolidinedione and glucoside inhibitors.[4] Each drug class works on different mechanism of actions, which are briefly presented in Table-1. Insulin secretagogues or sulfonylureas increase the pancreatic insulin secretion by acting on the receptors present in islet cells of pancreas.[5, 6] Meglitinide also act as sulfonylureas, but the binding site is different. They close the K+ channels and open Ca^{2+} channels in the pancreatic beta cells and enhance the insulin production. Biguanides target hepatic insulin resistance, thereby reducing hepatic glucose output and increasing the uptake of glucose by the periphery, including skeletal muscles, enhancing the binding of insulin to its receptors and stimulating insulin mediated glucose disposal.[7, 8]

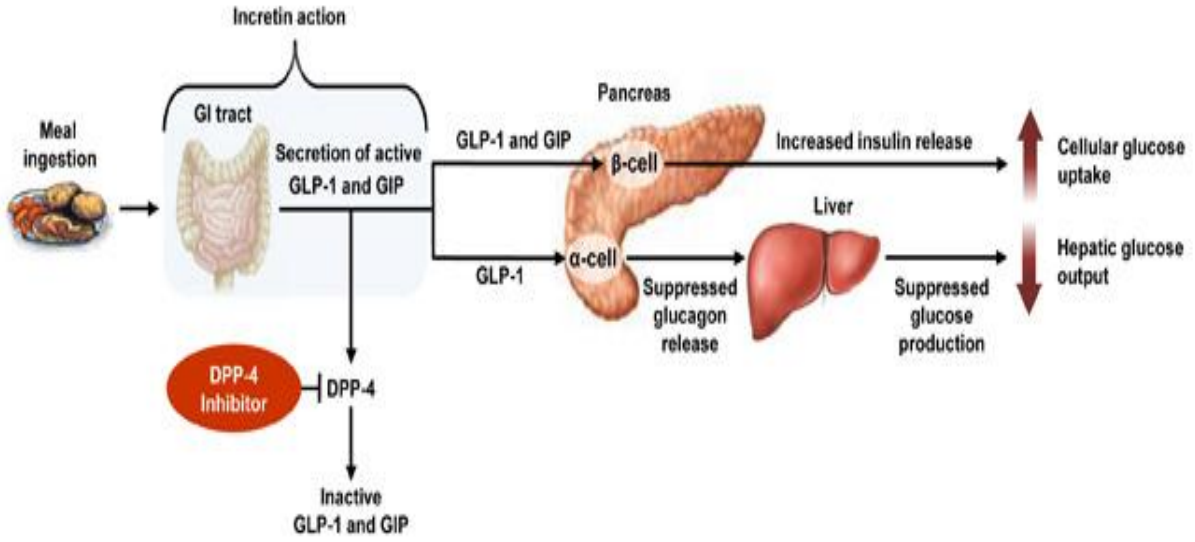
The principle of using DPP-4 inhibitors as therapy of T2DM is now firmly established, and numerous inhibitors are in varying stages of clinical development, with four already approved: sitagliptin in 2006, vildagliptin in 2007 and more recently, saxagliptin in 2009 and alogliptin in 2010 (presently only in Japan).[9, 10] The purpose of this article is to review briefly the leading compounds in the DPP-4 inhibitor class with chemical and pharmacological profile with special emphasis on any features which may help to distinguish between them.

Table 1: Targets for diabetes and their side effects.

Drug group	Members of the group	Targets	References	Side effects	References
Sulfonylureas	Glibenclamide, Glyclopyramide, Glimepride	Stimulating insulin release by pancreatic beta cells	[4]	Hypoglycemia, minor skin, allergy	[6]
Meglitinide	Repaglinide, Nateglinide, Mitiglinide	Stimulate the pancreas to release insulin	[5, 6]	Hypoglycaemia, gastro-intestinal upset	[9, 10]
Biguanides	Metformin, Buformin, Phenformin	Reduce hepatic glucose output and increase the peripheral uptake of glucose	[7, 8]	Nausea, Diarrhea, Gastrointestinal upset	[13]
Thiazolidinediones	Rosiglitazone, Pioglitazone, Troglitazone	Bind to PPARγ	[14]	Fluid retention, edema, weight gain, increased risk of myocardial infraction	[15]
Glucoside Inhibitors	Acarbose, Miglitol, Voglibose	Delay intestinal carbohydrate Absorption	[16]	Flatulence, abdominal discomfort	[15, 16]

2. Mechanism of DPP-4 inhibitor action

Up to now the treatment of type-2 diabetes has been limited primarily to elevation of insulin production, increase of insulin sensitivity, reduction of glucose absorption and replacement of insulin. In the recent years, however, DPP-4 inhibitors (gliptins) emerged. These belong to a novel group of medicines which exert their action by increasing incretin levels.[17] Incretin include glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) which are produced in the intestine and contribute to the physiological regulation of glucose homeostasis in Figure-1. Active endogenous GLP-1 and GIP concentrations increase two- to threefold following a meal. Active GLP-1 and GIP increase the production and release of insulin by pancreatic beta cells. Approximately 60% of the postprandial insulin release is promoted by these two hormones. In addition, GLP-1 also reduces the secretion of glucagon by pancreatic alpha cells, resulting in a decreased hepatic glucose production. These effects are glucose-dependent; GLP-1 stimulates insulin secretion and reduces glucagon production only at a higher blood glucose level. However, the effects of GLP-1 and GIP last only for a few minutes as they are inactivated due to DPP-4.[18]



DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1

Figure 1: Mechanism of DPP-4 inhibitor action.

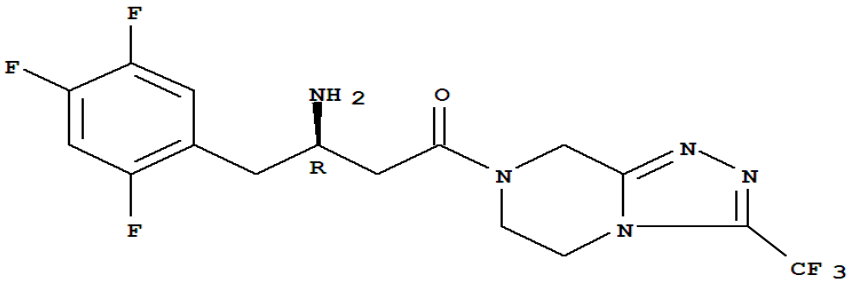
The promising therapeutic potential of GLP-1 as a pharmacological tool for treating type-2 diabetes has been discovered in the 1990. By inhibiting DPP-4, the gliptins increase insulin production and release as well as reduce glucagon levels in a glucose-dependent way, resulting in a decrease of fasting and postprandial glycemia, as well as HbA1c levels.[19] Further, it has the ability to restore the blunted first phase insulin secretion in type 2 diabetes. Also in this respect, their mechanism of action differs from that of the sulfonylureas which stimulate insulin secretion also at low levels of blood glucose and may lead to hypoglycemia.[20]

3. Glucagon-Like Peptide Analogues and Agonists

Long term acting analogues of GLP-1, which maintain the effects of GLP-1andresistant to the action of DPP-IV are also called incretin mimetic. Exenatide is a GLP agonist who enhances glucose-dependent stimulation of insulin secretion, suppresses the inappropriate glucagon secretion and slows down the gastric emptying, and help enhance beta-cell mass.[21, 22] Liraglutide is a human GLP-1 analogue which has 97% homology, has been developed recently and approved by FDA in 2010.[23]

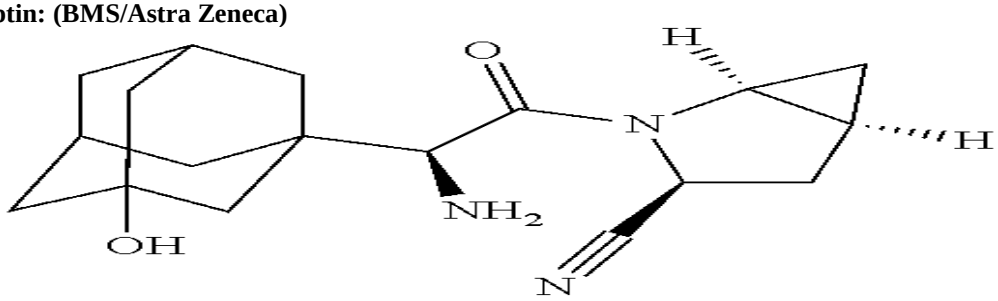
4. Structures of some novel synthetic DPP-IV inhibitors.

(I) Sitagliptin: (Merck)



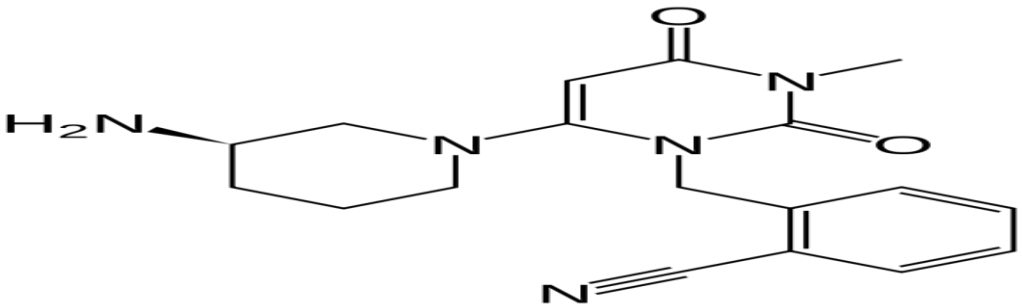
Chemical Name: (R)-4-oxo-4-[3-(trifluoromethly)-5,6-dihydro[1,2,4]triazolo[4,3-α]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenly)butan-2-amine

(II) Saxagliptin: (BMS/Astra Zeneca)



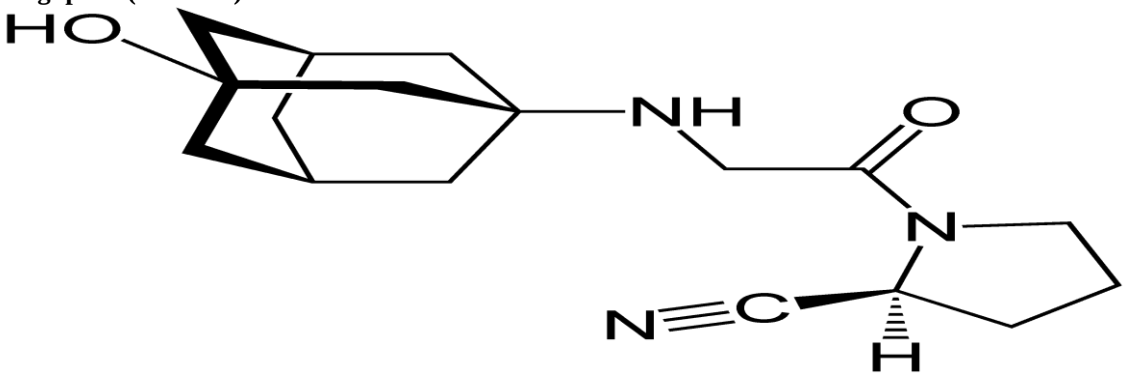
Chemical Name: (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile

(III) Alogliptin: (Takeda)



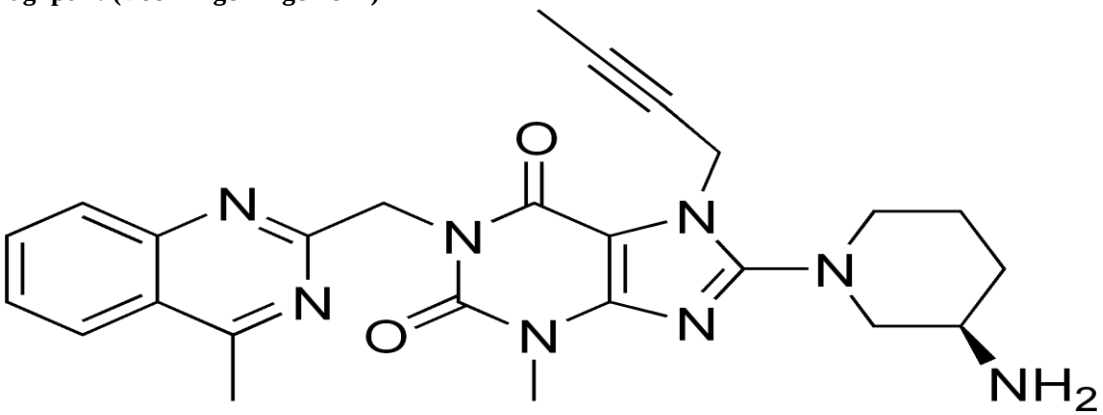
Chemical Name: 2({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzonitrile

(IV) Vildagliptin: (Novartis)



Chemical Name: (S)-1-[N-(3-hydroxy-1-adamantyl)glycyl]pyrrolidine-2-carbonitrile

(V) Linagliptin: (Boehringer Ingelheim)



Chemical Name: 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione

Table 2: Chemistry, metabolism and elimination of dipeptidyl peptidase (DPP)-4 inhibitors.

Inhibitors	Chemistry	Metabolism	Elimination Route
Sitagliptin[24 –26]	*β*-amino acid based	Not appreciably metabolized	Renal (~80% unchanged as parent)
Vildagliptin[27-29]	Cyanopyrrolidine	Hydrolyzed to inactive metabolite (P_{450} enzyme independent)	Renal (22% as parent, 55% as primary metabolite)
Saxagliptin[30, 31]	Cyanopyrrolidine	Hepatically metabolized to active metabolite	Renal (12–29% as parent, 21–52% as metabolite)
Alogliptin[32, 33]	Modified pyrimidinedione	Not appreciably metabolized	Renal (>70% unchanged as parent)
Linagliptin[34, 35]	Xanthine based	Not appreciably metabolized	Biliary (>70% unchanged as parent)

5. Dipeptidyl Protease-IV Inhibitors and Role in Diabetes

Dipeptidyl peptidase-4, also known as adenosine deaminase complexing protein 2 or CD26 (cluster of differentiation 26) is a protein that, in humans, is encoded by the DPP4 gene. The protein encoded by the DPP-4 gene is an antigenic enzyme expressed on the surface of most cell types and is associated with immune regulation, signal transduction and apoptosis. It is an intrinsic membrane glycoprotein and a serine exopeptidase that cleaves X-proline dipeptides from the N-terminus of polypeptides. It is a rather indiscriminate enzyme for which a diverse range of substrates are known. The substrates of CD26/DPP-IV are proline containing peptides and include growth factors, chemokines, neuropeptides, and vasoactive peptides. DPP4 is related to FAP, DPP8 and DPP9. DPP-4 plays a major role in glucose metabolism. It is responsible for the degradation of incretin such as GLP-1.Furthermore, it appears to work as a suppressor in the development of cancer and tumors. CD26/DPP-IV plays an important role in tumor biology, and is useful as a marker for various cancers, with its levels either on the cell surface or in the serum increased in some neoplasms and

decreased in others. DPP-4 also binds the enzyme adenosine deaminase specifically and with high affinity. The significance of this interaction has yet to be established.[36]

Glucagon-like peptide-1 (GLP-1) is a hormone, which is released meals and stimulates insulin release from the pancreas. Its effects are terminated by breakdown by the enzyme dipeptidyl peptidase-IV. Therefore, inhibition of DPP-IV increases GLP-1 levels in the circulation and, hence, insulin release under conditions when it is needed, i.e. after a meal but not during fasting. Consequently, inhibition of GLP-1 inactivation is an insulinotropic principle, which is unlikely to cause hypoglycemia between meals. The lower risk for hypoglycemic events as compared with other insulinotropic or insulin sensitizing agents makes DPP-IV inhibitors very promising candidates for a more physiological treatment of type-2 diabetes.[37] In individuals with type-2 diabetes, the incretin effect appears to be blunted. This blunting has been attributed to 2 factors: GLP-1 levels are lower and GIP exerts a lesser physiologic effect than seen in normoglycemic individuals. Responsiveness to GLP-1 is generally preserved; infusion of GLP-1 to individuals with diabetes has been shown to lower both postprandial and fasting blood glucose levels. The short-term control of hyperglycaemia can be sufficed by intravenous or subcutaneous GLP-1infusions but, the long-term treatment of type 2 diabetes needs a more feasible approach to achieve sustained activation of GLP-1 receptors. Conversely, there appear to be relatively normal levels of GIP in persons with type-2 diabetes, but their physiologic response to GIP is diminished. Whether or not abnormalities in DPP-4 levels or degradative activity exist in patients with diabetes is still unclear.[38]

6. Dipeptidyl peptidase-4 inhibitors in the management of antihyperglycemic

Inhibitors of Dipeptidyl peptidase-4, also DPP-4 inhibitors or gliptins, are a class of oral hypoglycemic that block DPP-4. They can be used to treat diabetes mellitus type-2. The first agent of the class- sitagliptin was approved by the FDA in 2006. Sitagliptin entered the Australian drug market in late 2007 for the treatment of difficult-to-control diabetes mellitus type- 2. Another DPP-4 inhibitor, vildagliptin, was added to the PBS listings in 2010 on the basis of a similar cost-minimization basis to sitagliptin. Their mechanism of action is thought to result from increased Incretin levels (GLP-1 and GIP), which inhibit glucagon release which increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels.

Drugs belonging to this class are

• Sitagliptin (FDA approved 2006, marketed by Merck & Co. under the trade name Januvia),
• Vildagliptin (marketed in the EU by Novartis under the trade name Galvus),
• Saxagliptin (FDA approved in 2009, marketed under the trade name Onglyza),
• Linagliptin (being developed by Boehringer Ingelheim),
• Dutogliptin (being developed by Phenomix Corporation), Phase III
• Gemigliptin (being developed by LG Life Sciences, Korea)
• Alogliptin (developed by Takeda Pharmaceutical Company, whose FDA application for the product is currently suspended as of June 2009).[36]

The administration of DPP-4 inhibitors to individuals with type 2 diabetes has been shown to raise levels of endogenous GLP-1 and GIP, which in turn results in a glucose appropriate increase in insulin secretion and suppression of glucagon release. In patients with type 2 diabetes, administration of DPP-4 inhibitors has been shown to improve markers of insulin processing, including homeostasis model assessment of beta cell function (HOMA-β) and the proinsulin: insulin ratio. Furthermore, there are animal data to suggest that pancreatic beta cell mass may be preserved; beta cells may even be stimulated to grow and proliferate in the presence of these agents. However, no comparable anatomic data in humans are available.[38]

7. DPP- IV Inhibitor using plant source

The use of herbal medicines has recently gained popularity in all over the world for their efficacy in Type2- diabetes and some plants have minor side effects when given in large doses. But there is lack of understanding the actual mechanism of action of these medicines. These medicines are used since centuries in Ayurveda and unani system of medicine and they show more efficacy and fewer or no side effects therefore emphasis should be given on herbal medicine because allopathic system of medicine has failed in providing health to all.[39]

The most commonly studied antihyperglycemic plants are *Opuntia streptacantha*, *Trigonella foenum-graecum*, *Momordica charantia*, *Ficus bengalensis*, *Polygala senega and Gymnema sylvestre*[40] However it is apparent that additional research needs to be undertaken on these and other medicinal plants with hypoglycemic effects because the compounds which are bioactive and their modes of action still remain unclear in most cases. Regarding the stimulation of insulin secretion, one target of interest for the anti diabetic action of these extracts is the serine protease dipeptidyl peptidase-IV (DPP-IV; EC 3.4.14.5) as the DPP-IV inhibition has been shown to be an appropriate treatment for T2DM.[41] DPP-IV specifically removes N-terminal dipeptides from substrates containing proline or alanine as the second residue, altering them into inactive or antagonistic species. Incretin like glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are most important substrates of DPP-IV, which stimulates insulin secretion.[42]

8. CONCLUSION

The development of DPP-4 inhibitors, which potentiate the incretin hormones by inhibiting the enzyme that is responsible for their degradation, has recently emerged as an approach that appears to be promising for the treatment of type-2 diabetes. Although these agents have modest efficacy. they represent an important class of compounds that provide an alternative to other traditional therapies that are used in the management of type-2 diabetes. While they do not appear to lower glucose to a greater extent than existing therapies, when used alone, they offer the potential advantage of a low risk of hypoglycaemia and weight gain. As there is a low risk of hypoglycaemia developing with their use, they may be advantageous in patients who are close to achieving their target HbA_{1c}, but who continually experience elevated glucose levels following a meal.

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