Review Article

NEW DRUG THERAPY FOR TYPE 2 DIABETES MELLITUS: DPP-IV INHIBITORS

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Accepted on: 16-12-2010; **Finalized on:** 15-02-2011.

ABSTRACT

Drugs inhibiting the enzyme Dipeptidyl peptidase-IV are under development in preclinical and clinical studies. These drugs have potential to treat the Type 2 diabetes mellitus. DPP-iv enzyme inhibits rapidly the incretin hormones Glucagon like peptide-1 which is released after food administration to increase insulin level. DPP-IV inhibitor drugs are orally bioactive and after administration stabilize endogenous GLp-1 level and induce insulin secretion in glucose dependent manner. Drug sitagliptin is approved by US FDA. And other drugs like vidagliptin, saxagliptin are under development and late stages of clinical trials. So, DPP-IV inhibitors drugs are good choice for treatment of T2DM with very less side effects.

Keywords: Dipeptidyl peptidase-IV, Glucagon like peptide-1, type 2 Diabetes, Incretin.

INTRODUCTION

Now a day, most of people are becoming victim of diabetes with large proportion. International Drug Federation (IDF) projection showing that 246 millions adults are having diabetes and it will increase to 389 millions until 2025. 50 % of total death takes place due to cardiovascular problem[1,2]. Global burden of T2DM is increasing day by day, hence there is necessity of novel drugs to decrease the disease progression and maintain control on it[3]. There are large no. of therapies are present but they are not becoming successful to control hyperglycemia for longer period. T2DM is characterized by combination of[4,5]:

1) insulin resistance
2) impaired insulin secretion

As T2DM is complex disease; many patients are inadequately treated due to shortcomings of present therapies. In T2DM, there is progressive loss of β-cell function which secrets insulin, treatment becoming less effective over time. Incretin hormones GLP-1 and GIP, stimulates insulin secretion and play important role in glucose homeostasis[6,7]. In T2DM, effect of GLP-1 is preserved while effect of GIP is severely impaired[8,9]. So in T2DM, GLP-1 mimetic can be given to secret insulin but it has short half life. Enzyme Dipeptidyl peptidase-IV i.e. DPP-IV degrades the GLP-1 [10-14].

Since hormone is rapidly inactivated by DPP-IV, there are two therapies emerged to overcome this degradation problem[15]

1) long acting DPP-IV resistant analogues of GLP-1
2) DPP-IV inhibitors

This review will focus on DPP-IV inhibitors as new approach to treat T2DM and its future direction.

GLP-1[16-20]

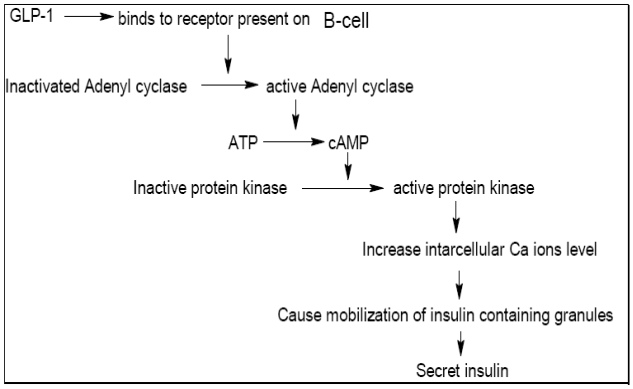
GLP-1 is secreted from endocrine L-cells of intestinal mucosa after food ingestion. It is polypeptide of 30 amino acids. It stimulates insulin secretion; it is shown to stimulate β-cell proliferation and differentiation.

It helps in preserving pancreatic β-cell and its function. GLP-1 has short half life because it undergoes rapid degradation by enzyme DPP-IV inhibitors,

Functions of GLP-1 in patient with T2DM are:

1) glucose dependent suppression of glucagons
2) decrease rate of gastric emptying
3) decrease food intake, appetite and body weight
4) cardiac protective effects
5) inhibit apoptosis of β-cell in response to extern al toxic stimuli

Mechanism of action of GLP-1 to secret insulin:



In T2DM, there is continuous deterioration of β-cell mass but GLP-1 is capable of preventing this and even give rise to β-cell mass.

GLP-1 MIMETIC[21-23]

Therapeutic agents that are agonist of GLP-1 receptor, mimics the function of GLP-1.these agents are given intravenous S.C. continuously. They have side effects like nausea and vomiting. Continuous i.v. of GLP-1 has capacity to normalize blood glucose concentration in T2DM but it is degraded rapidly by DPP-IV and not practicable for clinical use.

Plasma half life: 1-2 min.

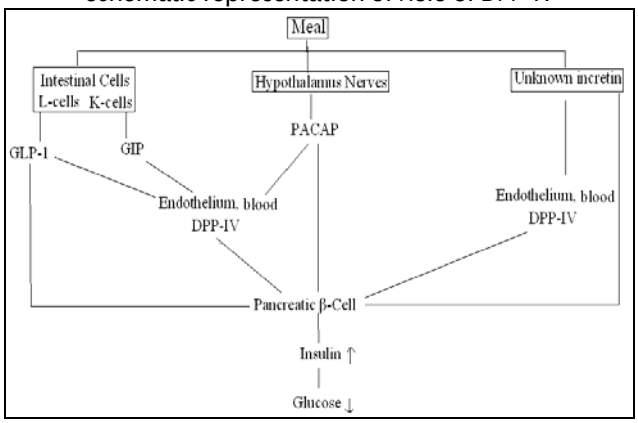
Metabolic clearance test: 5-10 L/min.

DIPEPTIDYL PEPTIDASE IV[15-18]

Enzyme DPP-IV is serine protease and breaks two amino acids from small protein having alanine or proline at penultimate position. DPP-IV is also known as T-cell antigen CD26. This is found in renal and intestinal brush border membrane and present in soluble form in plasma.

DPP-IV is also has unique enzymatic specificity in cleaving dipeptide from neuropeptide, chemokines and hormones. Thus it is involved in regulation of function of immune endocrine and nervous system.

Schematic representation of Role of DPP-IV

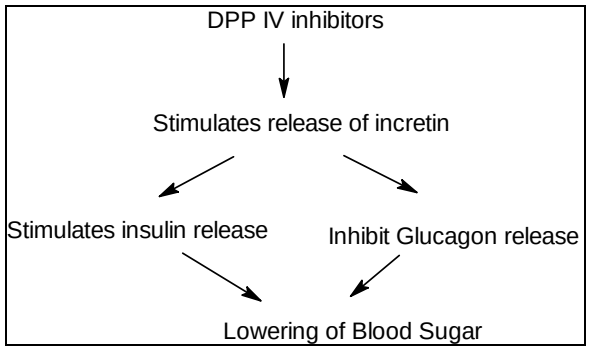


DIPEPTIDYL PEPTIDASE IV INHIBITORS[24-29]

DPP-IV acts via enhancing the incretin, hence represents new approach to treat T2DM. It is new class of oral hypoglycemic agent, increase pancreatic β-cell function and clinical course of T2DM. Therapeutic agents, DPP-IV inhibitors, can increase endogenous GLP-1 level and enhance incretin action.

These agents are orally bioavailability, having low molecular weight and high bioavailability. it is competitive reversible inhibitor of DPP-IV produce 90% inhibition during a day.

They enhance or double the active form of GLP-1 and GIP that enhance incretin action.



Several orally active DPP-IV inhibitors developed to treat T2DM,

1) Sitagliptin, 2) vildagliptin, 3) saxagliptin, 4) alogliptine, 5) denagliptine

OTHER EFFECTS OF DPP-IV INHIBITORS[25-27]

DPP-IV inhibitors prolong action of hormones peptide YY, GHRH, neuropeptide Y and substance P, Chemokines such as stomatol cell derived factor-1 (CXCL 12) and macrophage derived chemokine (CCL 22). So side effects due to prolongation of these messengers are:-

1) Neurogenic inflammation (due to neuropeptide Y and substance P)
2) increase in blood pressure (due to neuropeptide Y)
3) enhanced general inflammation and allergic reaction (due to chemokines)

Enzymes which are mostly related to DPP-IV are:

1) Fibroblast activation protein-α
2) DPP-II
3) DPP-8
4) DPP-9

Inhibition of DPP-8 and DPP-9 related to production of some toxic effects. Hence DPP-IV must have specific action.

Levels of GLP-1 secretion are lower than normal in fatty person and type 2 diabetic patients, so treatment with DPP-IV inhibitors restore endogenous active GLP-1. Increased level of active GLP-1, results in increased β-cell mass and which secrets insulin.

So the GLP-1 agonist and DPP-IV inhibitors are complement to one another, suggesting that combination of two agents are beneficial. In addition to GLP-1, DPP-IV inhibitors also cleave peptide like GIP and PACAP (it is one of the type of incretin).

DPP-IV INHIBITOR DRUGS

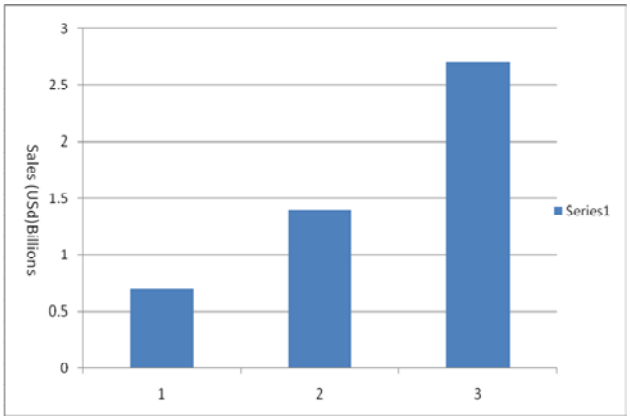
1) Sitagliptin (Merck's Januvia)[30-35]

It was approved by US FDA in oct. 2006 used as monotheropy or with metformin. It was introduced in US market in 2006 and in Europe in 2007.Generaly primary importance is selectivity. Sitagliptin exhibits > 2600 time's higher affinity for DPP-IV than structurally related DPP-VII

and DPP-IX enzymes. In phase-I drug-drug interaction studies, Sitagliptin did not alter the pharmacokinetic of other oral hypoglycemic agents including metformin or sulphonylureas and these drugs did not alter the pharmacokinetic properties of sitagliptin.

When efficacy and safety of these drugs studied then they are not studied for patient age below 18 years but it was suggested that these drugs are also safe for patient's age below 18 years. Because DPP-IV inhibitors increase the action of GLP-1 by stimulating pancreatic insulin secretion, it is contraindicated in patient with type 1 diabetes and not intended to use in diabetic ketoacidosis.

Chart 1: worldwide sales of Januvia



1: 2007, 2: 2008, 3: 2009

Chart 2: Prevalence of Diabetes bye age group, 2007

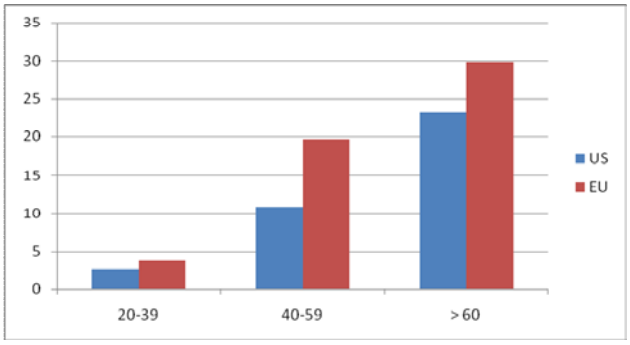
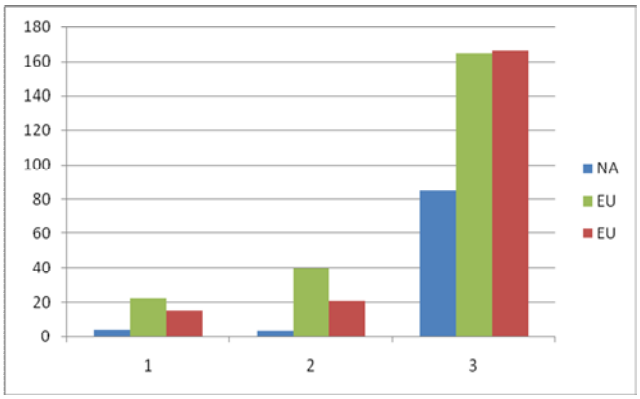


Chart 3: Estimated prevalence of Diabetes by Age Group, 2025



1: 20-39, 2: 40-59, 3: 60-79

2) Vildagliptin (Galvus)[32-33]

It is in late phase clinical development. It is used as monotherapy or in combination with metformin, pioglitazine. Most common adverse effects are nasopharyngitis, headache and dizziness. It is also give some episodes of hypoglycemia.

3) Saxagliptin (Onglyza)[33-34]

These drugs are used single or in combination with other hypoglycemic drugs. In combination they are used with metformin or thiazolidinediones. The incidence of side effects was no higher when saxagliptin was added to metformin therapy.

CONCLUSION

DPP-IV inhibitors are novel class of antidiabetic drugs having potential to increase β cell function and clinical course of Type 2 diabetes mellitus. These produce no weight gain. Main advantages of drugs are they are given orally with very less gastrointestinal side effects like vomiting and nausea. To overcome the increasing problem of Type 2 diabetes mellitus, DPP-IV inhibitor is the most useful way to treat it. Mainly these drugs are given orally and most of drugs are target specific. These agents are having some drawbacks due to its action on peptide YY, GHRH, Neuropeptide Y etc. But these effects are negligible as compared to its antidiabetic activity.Thse drugs inhibits enzyme dipeptidyl peptidase which cause the metabolism of GLP-1 which is responsible for insulin secretion. DPP-IV inhibitors drugs like Sitagliptin, vildagilptin, saxagliptin are used nowadays. Sitagliptin is drug approved by US FDA in 2005. Other drugs are in late phases of clinical trials.

So there is necessary to make research on these DPP-IV inhibitors and to produce some more analogues because they have ability to restore insulin secretion with increasing β-cell mass.

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