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Review Article

ROLE OF DPP-IV INHIBITORS IN TREATMENT OF TYPE II DIABETES

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ABSTRACT
Emerging as an epidemic of the 21st century type II diabetes has become a major health problem throughout the globe. Known treatments of type II diabetes mellitus have limitations such as weight gain and hypoglycaemias. A new perspective is the use of incretin hormones and incretin enhancers. Incretin mimetics are a new class of pharmacological agents with multiple antihyperglycemic actions that mimic the actions of incretin hormones such as glucagon-like peptide (GLP)-1. DPP-4, a protease that specifically cleaves dipeptides from proteins and oligopeptides after a penultimate N-terminal proline or alanine, is involved in the degradation of a number of neuropeptides, peptide hormones and cytokines, including the incretins GLP-1 and GIP. Based on preliminary clinical data, incretin mimetics and DPP-IV inhibitors show potential for treating type II diabetes.

KEYWORDS: Type II diabetes, GLP-1, DPP-IV

INTRODUCTION

The metabolic syndrome (MS) is diagnosed by a cluster of clinical parameters including central obesity, atherogenic dyslipidemia, raised blood pressure and hyperglycemia. Visceral obesity, hepatic steatosis and insulin resistance (IR) have been proposed as unifying mechanisms, yielding a prothrombotic and proinflammatory state[1]. Consequently, patients with MS are at increased risk of micro- and macro-vascular complications (e.g. coronary artery disease (CAD), stroke, renal failure, blindness and lower extremity amputation) and progression to type II diabetes (T2D). Diabetes mellitus is a group of metabolic diseases characterized by increased blood glucose levels resulting from defects in insulin secretion, insulin action, or both. Diabetes is commonly described as a metabolic disorder of glucose metabolism. Type II diabetes mellitus (T2DM) is characterized clinically by hyperglycemia and insulin resistance. In T2DM, hyperglycemia results both from an impaired insulin secretory response to glucose and decreased insulin effectiveness in stimulating glucose uptake by skeletal muscle and in restraining hepatic glucose production (insulin resistance). Though T2DM is not the result of genetic alternations in the insulin receptor or the glucose transportor, however genetically determined postreceptor intracellular defects likely play a role. The resulting hyperinsulinemia may lead to other common conditions such as obesity (abdominal), hypertension, hyperlipidemia and coronary artery disease (the syndrome of insulin resistance). In T2DM, β-cell mass is normal, however pancreatic islet amyloid resulting from deposition of amylin is found in a higher percentage, however, its relationship to pathogenesis is not well established. Before diabetes develops, patients generally lose the early insulin secretory response to glucose and may secrete relatively large amount of proinsulin (Figure 1)[2].

Currently Available Therapy for the Treatment of Type II Diabetes

Diet, exercise, drug and insulin are the options for diabetic control. It is estimated that about half of the new diabetic patients can be adequately controlled by diet and exercise. Anti-diabetic drugs treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide and pramlintide, all are administered orally and are thus also called oral hypoglycemic agents or oral

antihyperglycemic agents. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors. A list of these agents along with their mechanism of action and adverse effects are summarized in table 1. Due to their adverse side effects most of these treatments are considered to be unsatisfactory in terms of prevention of complications and preservation of quality of life. Thus, there is an imperative need for novel therapeutic approaches for glycemic control that can complement existing therapies and possibly attempt to preserve normal physiological response to meal intake. One of the desirable approaches to achieve this goal would be to identify agents that promote/enhance glucose (nutrient)-dependent insulin secretion like incretin hormone.

THERAPEUTIC APPROACHES BASED ON INCRETIN HORMONE

Incretins are a group of gastrointestinal hormones that cause an increase in the amount of insulin released from the beta cells of the islets of Langerhans after eating, even before blood glucose levels become elevated. They also slow the rate of absorption of nutrients into the blood stream by reducing gastric emptying and may directly reduce food intake. As expected, they also inhibit glucagon release from the alpha cells of the Islets of Langerhans. The two main candidate molecules that fulfill criteria for an incretin are glucagon-like peptide-1 (GLP-1) and Gastric inhibitory peptide (aka glucose-dependent insulinotropic peptide or GIP). Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). There are two strategies for circumventing the rapid inactivation of GLP-1 have been successful to date. One is the development of GLP-1 receptor agonists, which are not substrates for DPP-IV and show only low affinity for the enzyme, thereby avoiding the rapid degradation and thus ensuring prolonged circulation time. Second strategy is to inhibit the enzyme DPP-IV, thus preventing the degradation of GLP-1 and allowing the daily fluctuations of GLP-1 levels that follow each meal to be augmented[3].

DIPEPTIDYL PEPTIDASE IV INHIBITORS

Dipeptidyl peptidase (DPP)-IV inhibitors are a new approach to the treatment of type II diabetes. DPP-IV is a member of a family of serine peptidases that includes quiescent cell proline dipeptidase (QPP), DPP8 and DPP9; DPP-IV is a key regulator of incretin hormones. Enzymes within this family have a rare substrate specificity, cleaving N-terminal dipeptides from regulatory factors containing proline or alanine in the penultimate position[4]. DPP4 was first identified in 1966 by Hopsu-Havu and Glenner as glycylproline naphthylamidase[5] and was purified from rat liver and pig kidney in 1967 and 1968, respectively[6, 7]. Dipeptidyl peptidase-IV (DPP-IV) inhibitors increase blood concentration of the incretin GLP-1 (glucagon-like peptide-1) by inhibiting its degradation by Dipeptidyl peptidase-IV (DPP-IV) (Figure 2)[8].

Mechanism of action

DPP-IV inhibitors competitively inhibit the enzyme Dipeptidyl peptidase-IV. This enzyme breaks down the incretins GLP-1 and GIP (glucose-dependent insulinotropic polypeptide), gastrointestinal hormone that are released in response to a meal[9]. By preventing GLP-1 and GIP inactivation, GLP-1 and GIP are able to potentiate the secretion of insulin and suppress the release of glucagon by the pancreas. This drives blood glucose levels towards normal. As the blood glucose level approaches normal, the amounts of insulin released and glucagon suppressed diminishes thus tending to prevent an "overshoot" and subsequent low blood sugar (hypoglycemia) which is seen with some other oral hypoglycemic agents.

DPP-IV distribution and function

DPP-IV selectively cleaves two amino acids from peptides, such as GLP-1 and GIP which have proline or alanine in the second position (Figure 3)[10, 11]. At the active site of the protease there is a characteristic motif of three amino acids, Asp-His-Ser. DPP-IV is the CD26 T-cell activating antigen which is widely distributed in human organs and tissue. Tissues which strongly express DPP-IV include the exocrine pancreas, sweat glands, salivary and mammary glands, thymus, lymph nodes, biliary tract, kidney, liver, placenta, uterus, prostate, skin and the capillary bed of the gut mucosa where most GLP-1 is inactivated locally. DPP-IV is attached to the plasma membrane of the endothelia of almost all organs in the body. It

is also present in body fluids, such as blood plasma and cerebrospinal fluid, in a soluble form. DPP-IV inactivates GLP-1 and GIP very rapidly. Regarding GIP and GLP-1, alanine and proline are crucial for biological activity, so elimination of these amino acids leads to formation of metabolites that are inactive. Thus, preventing the degradation of the incretin hormones GIP and GLP-1 by inhibition of DPP-IV is an exciting therapeutic strategy[12].

Importance of developing selective DPP-IV inhibitors

Development of small molecules as selective inhibitors of DPP-4 is a major challenge. Although experimental results obtained using nonselective DPP-4 inhibitors implicated a role for DPP-4 in the control of immune regulation, transplantation biology, cancer cell growth, and metastasis[13, 14], there is limited data for similar studies using highly selective DPP-4 inhibitors that have been generated for the treatment of type 2 diabetes. More recent experiments comparing the actions of DPP-4 selective versus nonselective inhibitors suggest that preferential inhibition of DPP-8/9 and quiescent cell proline dipeptidase (QPP) in vivo was associated with a species- and tissue-specific profile of different toxicities. Inhibition of DPP-8/9 produced alopecia, thrombocytopenia, splenomegaly, thrombocytopenia, and multiorgan pathology, leading to death in rats and gastrointestinal toxicity in dogs. Moreover, similar toxicities were observed in wild-type and DPP-4$^{-/-}$ mice treated with DPP-8/9 inhibitors. In contrast, inhibition of the related enzyme QPP produced reticulocytopenia in rats, whereas selective inhibition of DPP-4 was not associated with detectable toxicity in rats or dogs[15]. Similarly, inhibition of DPP-8/9, but not DPP-4, was associated with reduction of mitogen-stimulated proliferation of human mononuclear cells in vitro[16]. Curiously, some but not all DPP-4 inhibitors have been reported to produce skin lesions in monkey studies. The extent to which these findings reflect differential selectivity of specific agents for the monkey enzymes and whether the lesions are completely attributable to non–DPP-4 dependent mechanisms remains poorly understood. Collectively, these findings illustrate that data obtained using nonselective DPP inhibitors needs to be interpreted with caution in regard to the putative role of DPP-4 in the development of specific organ pathologies.

VARIOUS CLASSES OF DPP-IV INHIBITORS

In respect of current clinical developments of the thousands of individual compounds prepared in the mean time, three classes of DPP-IV inhibitors are under investigation namely reversible product analogue inhibitors (e.g. pyrrolidines and thiazolidines), covalently modifying product analogues (e.g. cyanopyrrolidines) and reversible non-peptidic heterocyclic inhibitors (e.g. xanthines and aminomethylpyrimidines) (Figure 4). Because of the different modes of action (non-covalent reversible or transiently covalently modifying inhibitors), two treatment principles currently under investigation are mealdependent administration of short acting DPP-IV inhibitors with the goal to minimize potential side effects or long acting inhibitors with once a day dosing potential[17, 18].

Table 2 lists various DPP-IV inhibitors in various stages of clinical development[19].

SITAGLIPTIN (MK-0431)

Sitagliptin (Januvia) is the first compound of its class introduced in the market as a DPP-4 inhibitor. Its chemical structure is (2R)-4-Oxo-4[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]1-(2,4,5-trifluorophenyl)butan-2-amide (Figure 4). In October 2006, the U.S. Food and Drug Administration (FDA) approved sitagliptin as monotherapy and as add-on therapy to either of two other types of oral diabetes medications, metformin orthiazolidinediones to improve blood glucose control in patients with type II diabetes when diet and exercise are not enough[20]. In March, 2007 it was approved in European Union. Sitagliptin is currently approved in 42 countries[21]. The normal dose is 100 mg once a day[22].

Pharmacokinetics

Bioavailability of sitagliptin is approximately 87%. Halflife is between 8-14 hours. It is 38% bound to plasma proteins. It undergoes limited metabolism via CYP3A4 and CYP2C8. Elimination is mainly through urine. The dose should not be changed when it is combined with other antidiabetic drugs (e.g. metformin or glitazones). In kidney malfunction or even renal failure the dose of sitagliptine has to be reduced one half or one fourth or sitagliptin should even no longer be used[20, 23]

Side effects: Side effects of sitagliptin are cold (running nose), stuffy nose and diarrhoea, also sore throat, headache and arthralgias were observed. Recently, postmarketing reports of anaphylaxis, angioedema, and rashes, including Stevens- Johnson syndrome, in sitagliptin-treated patients have emerged.

Drug interaction: The combination of sitagliptin with pioglitazone results in peripheral oedema (4%). Glitazones probably posses a cardiotoxic effect (increased heart attack) and worsening of heart failure[24]. It is not sure whether the increase of cardiotoxic effects is only a result of this combination therapy. Although sitagliptin is not as likely to cause hypoglycemia as some other oral diabetes medications, be careful while prescribing any other drug that can potentially lower blood sugar, such as: probenecid, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin or other salicylates, sulfa drugs, a monoamine oxidase inhibitor (MAOI) or beta-blockers[23]. An interaction with any antidiabetic drugs has not been observed[25].

VILDAGLIPTIN (LAF237)

Vildagliptin (Galvus) is a new oral anti-hyperglycemic agent (anti-diabetic drug) of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. Its chemical structure is (S)-1-[N-(3-hydroxy-1-adamantyl)glycyl]pyrrolidine-2-carbonitrile (Figure 4).

Clinical evidence: Sitagliptin and Vildagliptin are different in molecular structure and in pharmacokinetics. The in vitro actions have translated into significant effects in improving glycaemic control in type II diabetic patients, as illustrated by the clinically meaningful reductions in HbA1c (by 0.8%) observed over 24 weeks[26] and 1 year[27] when a monotherapy of 100 mg/day is used. Vildagliptin is used as a monotherapy or in combination with metformin (50 mg together with 850 mg metformin). Vildagliptin (as sitagliptin) may be used as monotherapy in patients who cannot tolerate metformin or sulfonyureas. Vildagliptin's major antidiabetic mechanism of action appears to be an enhancement of glucose-stimulated insulin release, mediated via an increase in GLP-1 levels[28, 29]. Most of the published evidence shows that vildagliptin 50 mg/day or 100 mg/day is more effective than placebo in reducing both fasting plasma glucose and postprandial plasma glucose. Vildagliptin improves glucose dependent pancreatic A-cell function in type 2 diabetes mellitus, as shown by reduced glucagon levels in the postmeal period[30, 31]. The reduction in glucagon/insulin ratio is associated with reduced endogenous glucose production during both the postprandial period and the postabsorptive period[32]. These results illustrate the dual effects of vildagliptin to improve glucose tolerance during meals and to directly reduce fasting hepatic glucose production. The combination of vildagliptin 50 mg once or twice daily plus metformin caused a significant decrease of HbA1c compared with metformin alone, and a significantly greater proportion of patients achieved levels <7.0%[33].

Adverse effects: The adverse effects of vildagliptin were headache, nasopharyngitis, dizziness, peripheral edema, increased sweating and cough. Similar rates of these adverse effects were reported in the placebo groups. Hypoglycaemias are rare in response to vildagliptin combined with pioglitazone (0.3%) but were higher with pioglitazone being used alone (1.9%). Pioglitazone increased body weight (1.4 kg) which is further increased using a combination with 100 mg vildagliptin (2.7 kg).

Dosage: Vildagliptin (Galvus) can be prescribed to patients with type II diabetes at a dosage of 50 mg once daily in combination with a sulfonylurea, or 50 mg twice daily with metformin or a thiazolidinedione such as pioglitazone. Vildagliptin should not be used by patients with impaired kidney function or being dialysed or having a severe liver disease.

SAXAGLIPTIN (BMS-477118)

Bristol-Myers Squibb (BMS) is developing saxagliptin (BMS-477118; pyrrolidine-based structure), an oral DPP-IV inhibitor, for a potential once-daily treatment of type II diabetes. In early structure-activity relationships (SAR) studies, BMS has investigated a series of 3,4- and 4,5-disubstituted methanoprolinenitrile dipeptide mimetics and found that compounds with the highest degree of betabranching had the greatest stability. The stable compounds have demonstrated some anti-diabetes activities by suppressing postprandial glucose elevation[34-36]. Several patents have been filed for BMS-477118 including the specific process for preparation of intermediates involved in the production of saxagliptin, including the enzymatic process allowing for a faster procedure and the isolation of crystalline forms without the use of ammonium hydroxide[37-39]. In addition, saxagliptin has been shown

not to inhibit T-cell activity in vivo[34]. In some clinical studies, saxagliptin exhibited several beneficial effects: for example, 10 mg qd patients showed glucose and HbA1c lowering, and good toleration of the drug. Phase III trials (both as a monotherapy and in combination with other oral agents) were initiated during late 2005 with results expected soon.

ADVANTAGES OF DPP-IV INHIBITION THERAPY[22]

- Oral administration
- Long acting
- Effect less strong compared with incretin mimetics (except decrease in HbA1c)
- Monotherapy or adjunctive therapy
- Increase in endogenous GLP-1 concentrations
- Inhibited glucagon secretion
- Stimulated insulin secretion
- No change in fasting glucose
- Slight reduction in prandial glucose
- Drug overdose is non-toxic (except liver toxicity and QT prolongation for vildagliptin)
- Weight neutral (no effect)

CURRENT & FUTURE DEVELOPMENTS

The therapeutic potential of inhibitors of post-proline cleaving enzymes like DPP-IV has been the focus of recent pharmaceutical research. The DPP-IV inhibitors are evaluated being as monotherapy or in combination with other antidiabetic drugs, e.g. metformin, thiazolidinediones, and/or PPAR γ agonists. Although human trial results in type II diabetes with DPP-IV inhibitors look promising, the lack of selectivity, i.e. inhibition of the structurally related enzymes DPP-8 and DPP-9, has been a potential concern. Based on the crystal structure resolved, it is expected to develop certain therapeutic agents such as small peptide via binding to the catalytic binding site as a ‘‘substrate-selective’’ DPP-IV inhibitor[40, 41]. Recently, one exiting finding is to show the activity of such DPP-IV inhibitors is due in part to their specific absorption by the small intestinal di- and tripeptide uptake transporter, PEPT1, thus establishing a system for optimizing the orally active peptidomimetic drugs such as amino acid-based DPP-IV inhibitors. The beneficial effects of DPP-IV inhibitors on treatment for type II diabetes not only offer advantages over the current therapies but also provide more therapeutic applications beyond the treatment for diabetes due to the biological diversity of DPP-IV.

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Table 1: Currently available therapy for treatment of type II diabetes

Class	Mechanism	Drugs	Adverse effects
Sulfonylureas	These drugs stimulate the insulin secretion by stimulating β-cells of islets of Langerhans	Tolbutamide, Acetohexamide, Tolazamide, Chlorpropamide, Glipizide, Glibenclamide	hypoglycemia, weight gain
Biguanides	These drugs stimulate glucose utilization by muscles & they also suppress degradation of insulin	Metformin, Phenformin	gastrointestinal disturbances, lactic acidosis
Thiazolidinediones	These drugs produce improvement in insulin sensitivity	Troglitazone, Rosiglitazone, Pioglitazone	weight gain, oedema, anaemia
α-Glucosidase Inhibitors	These drugs inhibit α-glucosidase; an enzyme that increases absorption of glucose at the gastrointestinal tract	Acarbose	gastrointestinal disturbances

Table 2: DPP-IV inhibitors in various stages of clinical development

Name	Company	Stage in development
Sitagliptin (Januvia)	Merck	In market
Vildagliptin (Galvus)	Novartis	In market
Alogliptin	Takeda	Phase III
Saxagliptin	Bristol-Myers Squibb	Phase III
PSN-9301	OSI pharmaceuticals	Phase II
R1438	Roche	Phase II
TA-6666	Tanabe	Phase II
PHX1149	Phenomix	Phase II
GRC 8200	Glenmark Pharmaceuticals	Phase II
SYR-619	Takeda	Phase I
TS-021	Taisho Pharmaceuticals	Phase I
SSR 162369	Sanofi-Aventis	Phase I
ALS 2-0426	Alantos Pharmaceuticals	Phase I

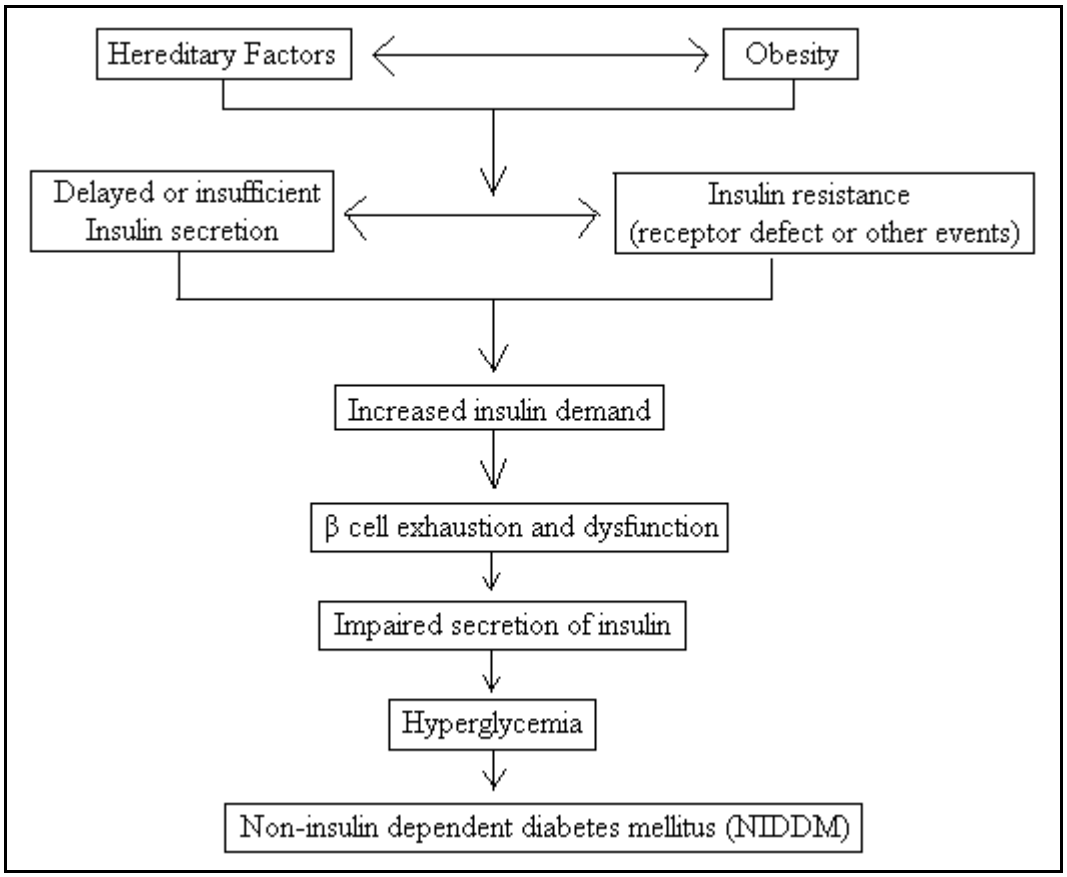

Figure 1: Pathogenesis of Type II Diabetes Mellitus

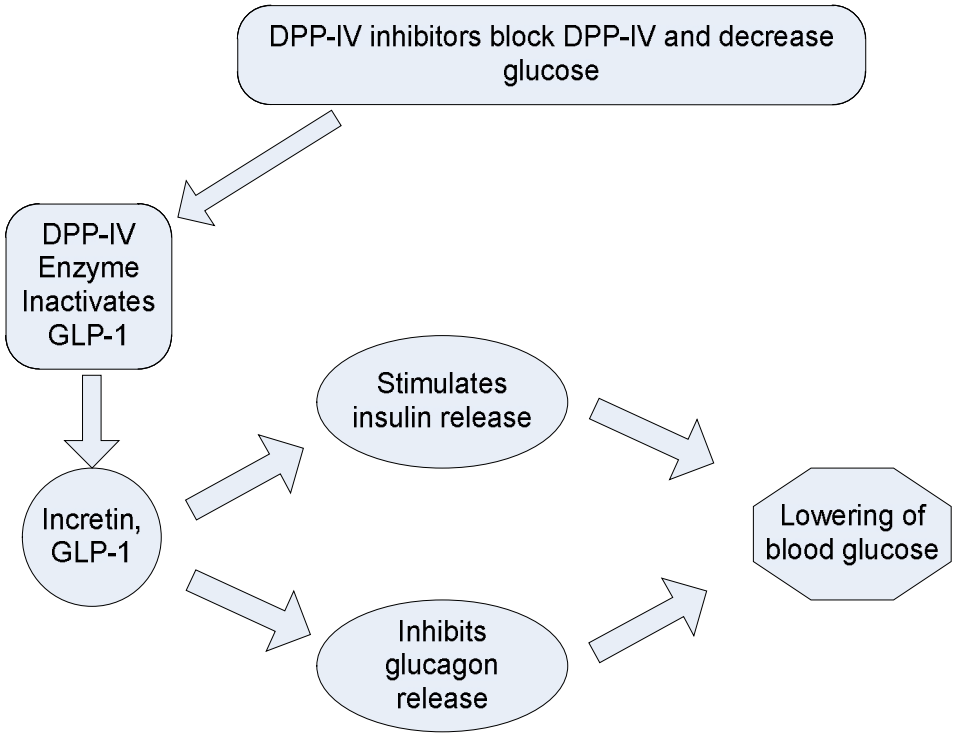

Figure 2: Mechanism of Action of DPP-IV Inhibitors

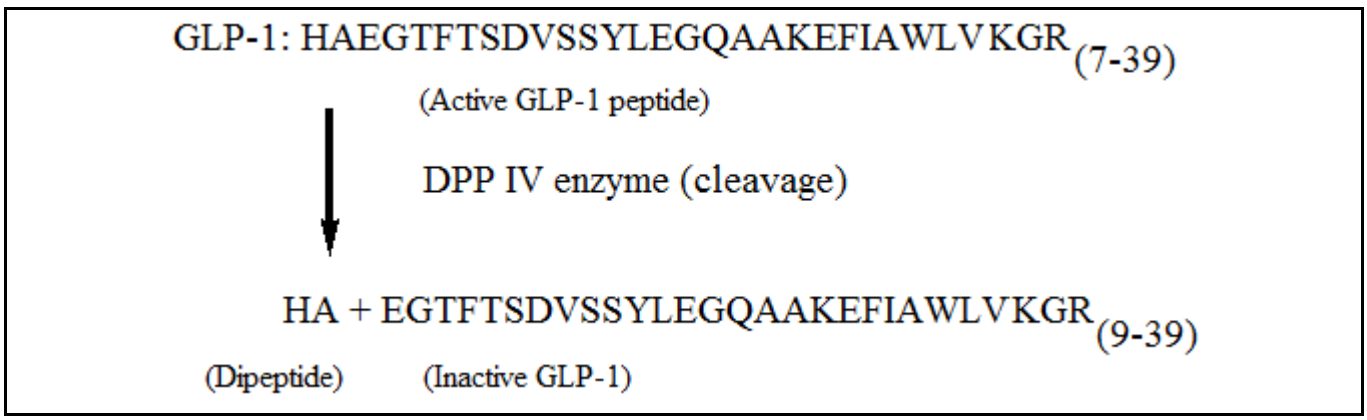

Figure 3: DPP-IV Cleaves Two Amino Acids from the N-Terminal end of Peptides, such as GLP-1

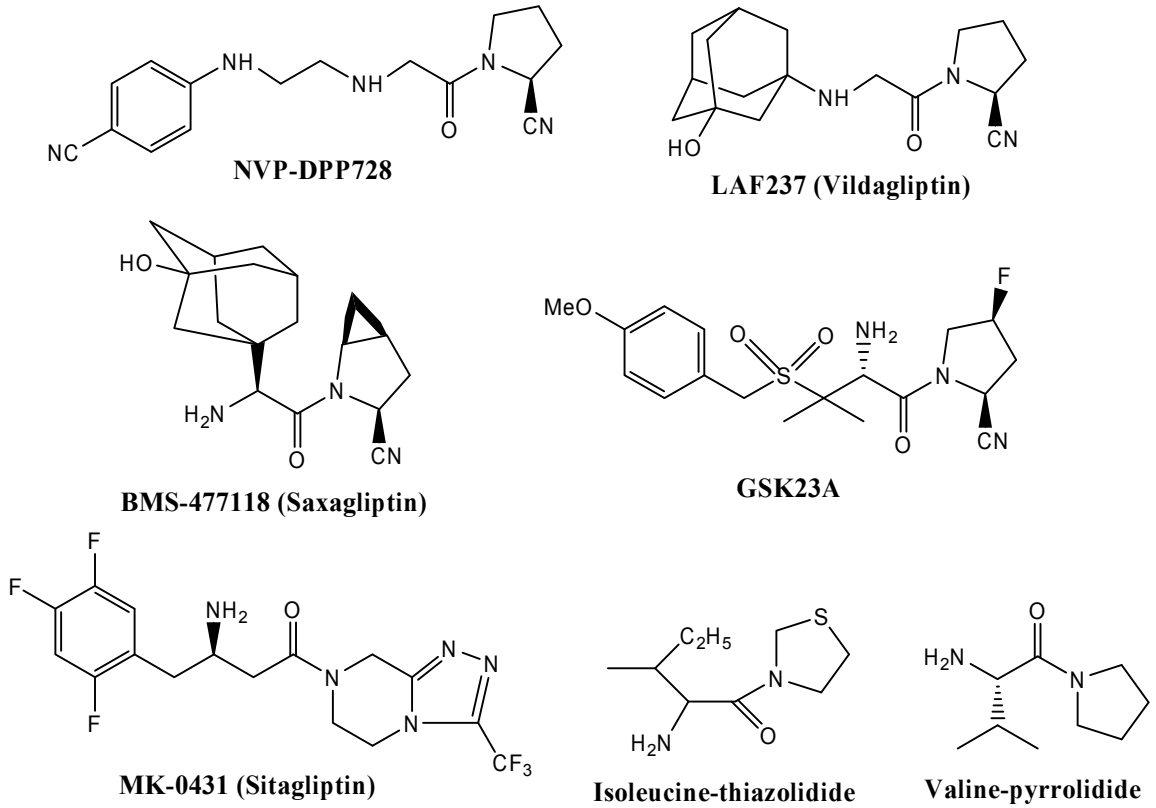

Figure 4: Structures of DPP-IV inhibitors

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