Special Article

Incretins: The Novel Therapy of Type 2 Diabetes

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Type 2 diabetes mellitus is a worldwide health problem. Adequate glycemic control can help to prevent many chronic diabetic complications. Despite the availability of several classes of oral hypoglycemic agents and insulin, many patients fail to achieve adequate glycemic control. Incretins are gut hormones produced in response to ingestion of nutrients. Glucagon-like peptide-1 (GLP-1), one of the incretin hormones, has pleiotropic actions on the control of blood glucose. Clinical trials with the incretin mimetic and Dipeptidyl peptidase-IV inhibitors demonstrate promising results in the improvement of glucose homeostasis.

Keywords: *Incretins, GLP-1, DPP-IV inhibitors, Type 2 diabetes*

J Med Assoc Thai 2008; 91 (6): 943-54
Full text. e-Journal: *http://www.medassocthai.org/journal*

Type 2 diabetes mellitus (DM) is a growing problem in most parts of the world. WHO has predicted that the incidence of type 2 DM patients will reach 300 million by the year 2030[1]. The microvascular and macrovascular complications of diabetes account for the morbidity and mortality in type 2 diabetic patients. Despite the fact that good glycemic control can reduce these diabetic complications, most diabetic patients still have inadequate glycemic control. Nowadays there are many kinds of hypoglycemic agents, but most of them are associated with side effects that limit their uses. Sulfonylureas and insulin are associated with hypoglycemia and weight gain. Thiazolidenediones cause edema and weight gain. Biguanides and alpha glucosidase inhibitors account for gastrointestinal side effects. Moreover, because of the progressive deterioration of beta cells function, monotherapy gradually results in therapeutic failure over time. Therefore, a novel therapy for diabetic patients is still needed.

Gastrointestinal glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones released in response to nutrient ingestion. Incretin hormones were discovered from the observation that insulin responses to an oral glucose load exceeded those measured after intravenous administration of an equivalent amount of glucose. This phenomenon was named the "incretin effect"[2]. Normally incretin hormones are responsible for 70% of the postprandial insulin secretion but in diabetic patients, the incretin effect decreases to 30%. GLP-1 secretion in diabetic patients is found to reduce but its ability to stimulate insulin secretion (insulinotropic actions) still remains[3]. Contrary to GLP-1, the GIP effect in type 2 diabetic patients on insulin secretion is impaired. GLP-1 has been demonstrated to regulate insulin and glucagon secretion, decrease gastric emptying time, increase satiety, and decrease body weight. Moreover, GLP-1 has been found to enhance pancreatic beta cell mass through the stimulation of beta cell proliferation and neogenesis in healthy and diabetic rodents[4,5]. Therefore, GLP-1 has become the attractive agent in clinical research studies for the development of new antidiabetic medications.

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GLP-1 Physiology

GLP-1 secretion

GLP-1 was first discovered in 1984. It is synthesized from L-cells in the small intestine through post translational processing of the pro-glucagon gene[6] GLP-1 secretes rapidly after a meal and the secretion increases in proportion to the meal size. During fasting state, basal GLP-1 secretion is also observed in low level (5-10 pM). After a meal, the secretion is biphasic.

The early phase begins within a few minutes of eating and lasts up to 1 hour, followed by the second phase that lasts up to 120 minutes postprandially[7]. Studies in rodents suggest that the first phase GLP-1 secretion is mediated through neuroendocrine pathways involving the vagus nerve, leptin, gastrin- releasing peptide and gastrin inhibitory factor[8,9], whereas the later phase is directly induced by the contact of nutrients with L-cells in the distal ileum and the colon. In humans, L-cells are also present in the duodenum, so the early rise of GLP-1 can be explained by the rapid stimulation of L-cells in the duodenum[10,11]. However, the precise contributions of the proximal and distal L-cells to the rapid rise in plasma GLP-1 remain unclear. In addition to glucose, other nutrients, such as: free fatty acids, peptides and other forms of sugar can also stimulate GLP-1 secretion, but only the mechanism of glucose and fructose stimulated GLP-1 secretion is well understood. First, glucose and fructose are transported into L-cells by sodium/glucose cotransporter and glucose transporter-5 respectively. Then glucose metabolism results in the closure of ATP-linked potassium (K_{ATP}) channels and depolarization of cell membranes. Finally, calcium influxes into the cell and leads to GLP-1 secretion[12].

GLP-1 actions

GLP-1 exerts actions by binding to its receptors in the pancreas (delta cells and beta cells), brain, and heart. However, the presence of these receptors remains controversial in pancreatic alpha cells, adipose tissue and muscle. GLP-1 receptor is a seven membered transmembrane receptor coupled to the G-protein G_S, which stimulates the adenylyl cyclase system. The activation of the G- protein coupled receptor causes an increase in the intracellular cAMP level, which results in an activation of protein kinase A (PKA) and exchange protein directly activated by cAMP (EPAC). GLP-1 has been shown to stimulate insulin secretion *in vitro* and *in vivo* and also to up regulate insulin gene expression and promote insulin biosynthesis[13]. The mechanism by which GLP-1 induces insulin secretion in beta cells is as follows. First, GLP-1 induces K_{ATP} channels closure that results in membrane depolarization. After the depolarization, calcium influx into beta cell and causes insulin secretion[14] (Fig. 1).

GLP-1 signaling induces differentiation and maturation of the progenitor cells into beta cells[15,16]. The activation of cAMP and phosphatidyl inositol 3-kinase by GLP-1 also results in beta cell proliferation and prevents beta cell apoptosis, which in turn, causes an increase in beta cell mass. Recent data shows that GLP-1 promotes beta cell neogenesis and increases beta cell mass in healthy and diabetic rodents[4,5].

GLP-1 has pleiotropic actions on the control of blood glucose and exerts its actions on various organs including the pancreas, brain, stomach, muscle and the cardiovascular system (Fig. 2).

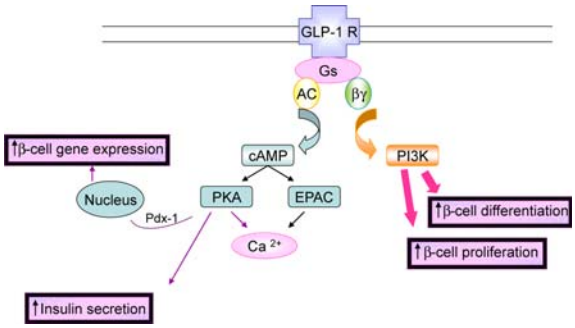

Fig. 1 GLP-1 signaling. Binding of GLP-1 to its receptors in beta cells results in an increase in intracellular cAMP, activates PKA and EPAC, and causes insulin secretion. GLP-1 also increases PDX1 activity and regulates beta cells gene expression. The activation of PI3K system leads to beta cell proliferation, differentiation and protect beta cells against apoptosis. GLP1-R, GLP-1 receptor; AC, adenylyl cyclase; PI3K, phosphatidyl inositol 3-kinase; PKA, protein kinase A; EPAC, exchange protein directly activated by cAMP

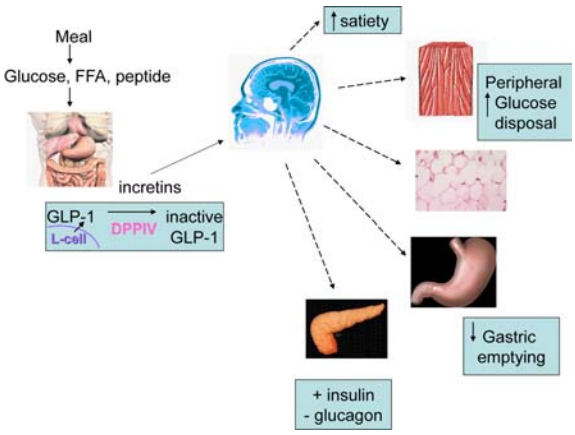

Fig. 2 GLP-1 actions on pancreas and extrapancreatic organs

The actions of GLP-1 on pancreas are summarized below:

1. GLP-1 enhances insulin biosynthesis and secretion from beta cells in a glucose dependent manner. This action occurs when blood glucose level is higher than 72 mg/dl (4 mmol/l), and disappears when blood glucose falls below the normal range.

2. GLP-1 restores first phase insulin secretion that is impaired or lost in type 2 diabetic patients.

3. GLP-1 stimulates beta cell proliferation and prevents beta cell apoptosis; therefore enhancing beta cell survival in both rodent and human islets.

4. GLP-1 inhibits glucagon secretion in a glucose dependent manner. These effects may be mediated directly via its receptor on alpha cells[17] or indirectly by the inhibitive effect of insulin and somatostatin secretion[18].

The actions of GLP-1 on extrapancreatic organs are as followings.

1. GLP-1 acts centrally, through GLP-1 receptor located in the brain, to promote satiety, decrease food intake and decrease body weight[19,20]. GLP-1 also causes a reduction of the neurotoxic form of amyloid beta peptide, suppresses neurodegenerative cascade[21,22] and promotes learning and memory[23].

2. GLP-1 delays gastric emptying time, which helps to control the postprandial glucose homeostasis. This effect seems to be regulated by neural mechanisms initiated by vagal afferent nerves[24].

3. GLP-1 also promotes peripheral glucose disposal at muscle and adipose tissue[25] by increasing insulin sensitivity.

4. Cardiovascular effects of GLP-1 include antihypertensive action and vasorelaxation in rodents and type 2 diabetic patients[26,27].

GLP-1 metabolism

The circulating plasma half-life of GLP-1 is very short, approximately 1-2 minutes. GLP-1 is rapidly degraded mainly by dipeptidyl peptidase IV (DPP-IV), while the roles of other proteases, such as neutral endopeptidase, in an inactivation of GLP-1 are under investigation. DPP-IV is a transmembrane enzyme, presents at the highest level in the kidney, liver, brain, and intestine, especially in the enterocytes brush border. DPP-IV can also be found as a soluble form in the plasma. This enzyme removes the two N-terminal amino acids, histidine, and alanine, from GLP-1 yielding an inactive metabolite.

After GLP-1 is secreted from intestinal L-cell, it is degraded rapidly by DPP-IV expressed on the endothelial cells of the intestinal capillaries. Consequently, only 25% of GLP-1 secreted enters the portal circulation in an intact form. Passage through the liver inactivates 40% of the remaining active GLP-1; therefore, only 10-15% of the entire GLP-1 secreted can enter the systemic circulation and pancreas (Fig. 3)

GLP-1 in type 2 diabetes

The GLP-1 effects are known to reduce in patients with type 2 diabetes resulting in low insulin secretion and high blood glucose level after a meal[28]. Recent studies have demonstrated that plasma level of GLP-1 are reduced in type 2 diabetic patients and in patients with impaired glucose tolerance, as compared to that of normal subjects (Fig. 4). Severity of diabetes

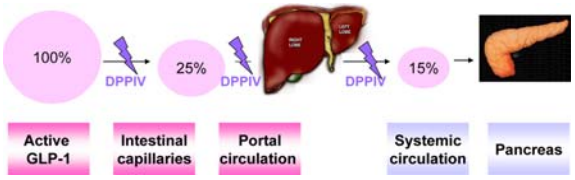

Fig. 3 GLP-1 metabolism**.** GLP-1 is degraded rapidly by DPP-IV expressed on the endothelial cells of the intestinal capillaries. Twenty five percent of the GLP-1 secreted enters the portal circulation in an active form. Forty percent of the remaining active GLP-1 is inactivated by liver; therefore, only 10-15% of the entire GLP-1 secreted can enter the systemic circulation and pancreas**.** DPP-IV, Dipeptidyl peptidase IV

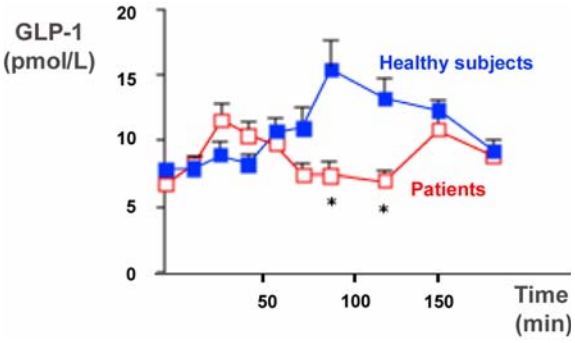

Fig. 4 Postprandial plasma levels of GLP-1 in type 2 diabetic patients are lower than healthy subjects
Data shown as mean ± SD
* $p < 0.05$
Adapted from Vilsboll T, et al
Diabetes 2001; 50: 609-13[3]

and body mass index have been suggested to have an influence on GLP-1 secretion, consistent with previous findings that secretion of GLP-1 is decreased in patients with morbid obesity[29]. However, the mechanism of GLP-1 reduction in obesity is unclear. Intravenous infusion of GLP-1 can increase insulin secretion and normalize both fasting and postprandial blood glucose in type 2 diabetic patients[30], even in patients who have advanced diseases or failure to sulfonylurea treatment. Furthermore, the effect of repeated subcutaneous administration of GLP-1 on fasting blood glucose is as good as that of intravenous infusion.

Therapeutic approaches based on GLP-1

Since GLP-1 actions remain preserved in diabetic patients, studies on the development of novel antidiabetic therapies have focused on GLP-1. Moreover, the fact that the rapid inactivation of GLP-1 contributes to a short half-life of GLP-1, two strategies for circumventing this rapid inactivation have been successful to date.

1. The development of GLP-1 receptor agonists that are resistant to the DPP-IV enzyme (GLP-1 mimetics).

2. The development of the substances to inhibit DPP-IV enzyme, thus prolonging the half-life of GLP-1 (DPP-IV inhibitors).

1. GLP-1 mimetics

GLP-1 mimetics have been developed by substituting some of the amino acids in GLP-1 molecule or changing the peptide structure to reduce the binding affinity of the enzyme to the analogues. Several GLP-1 are currently undergoing human clinical trials (Table 1)[31]:

1.1 Exendin 4 (Exenatide)

Exendin 4 was isolated from the saliva of a lizard, *Heloderma suspectum* (Gila monster). It shares 53% homologues to human GLP-1. Amino acid in position two is substituted from alanine to glycine, allowing exendin 4 to resist to DPP-IV. Exenatide, synthetic exendin 4, shares particular glucoregulatory activities to GLP-1, including, glucose-dependent insulin secretion[32], delaying gastric emptying time and reduction of food intake, restoration of the first phase insulin secretion and promoting beta cell differentiation, and islet neogenesis. Exenatide has a circulating

Table 1. Structure and Half-life of GLP-1 mimetics

Compound	Structure	Principles of GLP-1 prolongation	Half-life in human	Clinical phase and dose
Exenatide	Exendin 4	Inherent in exendin 4 amino acid sequence	4-5 h	FDA approved 2005, 5/10 μg twice daily
Liraglutide	(γ-l-Glutamyl (*N*-α-hexa-decanoyl))-$Lys^{26}Arg^{34}$-GLP-1(7-37)	Self-association and albumin binding	11-15 h	Phase II completed, once daily
CJC-1131	d-$Ala^{8}Lys^{37}$[2-[2-[2-maleimidopropionamido (ethoxy) ethoxy] acetamide-GLP-1(7-37)	*In vivo* covalent conjugation to albumin	10-12 days	Phase I/II, once daily
ZP-10	-	Inherent in exendin 4 sequence and added C-terminal stability	-	Phase I/II, acute dosing only
Albugon	-	Genetic fusion protein with albumin	-	Preclinical
BIM-51077	-	Enzymatically stabilized GLP-1 analogue	-	Preclinical

Adapted from Arulmozhi DK, Portha B. Eur J Pharm Sci 2006; 28:96-108[31].

half-life of 60-90 minutes, with increases in plasma concentrations lasting up to 4-6 hours after a single subcutaneous injection.

In Phase III clinical trials, adding exenatide 5-10 μg subcutaneously for 30 weeks can significantly decrease fasting and postprandial blood glucose in type 2 diabetic patients suboptimally controlled with maximum dose of thiazolidenediones, metformin and/or sulfonylurea[33-35]. Exenatide 10 μg decreased HbA_{1C} by 1% as compared to placebo. It also caused a reduction of body weight by 1.5 kg when adding to sulfonylurea or thiazolidenediones, and by 3 kg when adding to metformin. The decrease in body weight also led to an improvement in blood pressure and lipid profile[34]. Patients continuing in an open-label extension lost more weight, with the total weight loss reaching 4-5 kg after 80 weeks[36]. The most common side effect of exenatide is gastrointestinal (nausea, or more rarely vomiting and diarrhea). However, exenatide was rarely discontinued because of side-effects, and the symptoms lessened with a continuation of therapy. Forty to fifty percent of patients receiving exenatide develop antibodies with weak binding affinity and low titers[33-35]. Antibody formation has not been associated with impaired antidiabetic effectiveness in most of those treated. However, the drug might not be as effective in the patients with high-titer antibodies.

An open-label study in diabetic patients ineffectively controlled with metformin and sulfonylurea shows that the addition of exenatide results in better control of postprandial blood glucose, especially after breakfast and dinner, compared to the addition of insulin glargine. Whereas, the addition of glargine results in greater reduction of fasting blood glucose. However, exenatide or glargine reduced HbA_{1C} level equally by 1.1% over 26 weeks[37].

In April 2005, Exenatide was approved by US FDA as an adjunctive treatment in type 2 diabetic patients who have not achieved adequate glycemic control with metformin, sulfonylurea, or thiazolidendione. The drug is self-administered as a fixed-dose 5 and 10 μg subcutaneous injection via prefilled pen device prior to morning and evening meals. Exenatide may be approvable as a monotherapy pending a 6-month FDA review of any additional data that support such an indication. In October 2007, US FDA warned of a potential link between exenatide and pancreatitis. The warning was based on data from 30 postmarketing reports of acute pancreatitis in exenatide-treated patients. Exenatide should be discontinued if pancreatitis is suspected and permanently discontinued upon diagnostic confirmation unless another etiology is identified.

1.2 Liraglutide (NN221)

Liraglutide is created by substituting lysine with arginine at amino acid position 34 and adding an acyl chain to native GLP-1. The acyl moiety promotes non-covalent binding to albumin, thereby reducing access to NH_2-terminal by DPP-IV and allowing the molecule to escape from renal infiltration. Liraglutide is found to be 97% homologues to human GLP-1. It has a half-life of 10-14 hours after administering subcutaneously in humans, and once daily administration is adequate for sufficient activity throughout the day[38].

Liraglutide has been shown to be equipotent to GLP-1 in activating GLP-1 receptors *in vitro* and has proven to be efficient in acute and chronic administration to *db/db* and *ob/ob* mice, the genetic animal models of diabetes[39]. Liraglutide has multiple glucoregulatory actions including stimulate insulin secretion, suppress glucagon action, delay gastric emptying time and enhance beta cell mass and function[40,41].

Liraglutide administered 0.45-0.75 mg/day for 3 months in type 2 diabetic patients has been shown to reduce HbA_{1C} level comparable to that of maximum dose of glimeperide[42]. Another study comparing liragutide 0.75 mg/day with metformin 2 gram per day also demonstrated comparable hypoglycemic efficacy[43]. A 14-week randomized controlled trial comparing liraglutide monotherapy with placebo in patients with type 2 diabetes demonstrated significant improvement in glycemic control. Liraglutide 1.90 mg decreased HbA_{1C} by 1.74% compared with placebo. Body weight decreased by 1.21 Kg and there was no report of major and minor hypoglycemic episodes[44].

The beta cell function study using proinsulin: insulin ratio demonstrated significant improvement in the Liraglutide 0.75 mg/day group compared with placebo. Weight was maintained with a tendency to decrease and the risk of hypoglycemia was very low. A few subjects reported mild headache and gastrointestinal side effects, two thirds of which were resolved within a few days. No antibody formation against liraglutide was detected in the 12-week trial[42,45].

1.3 CJC-1131

CJC-1131 is a GLP-1 analogue using chemical linker to form covalent binding with albumin and create GLP-1-albumin complex. The GLP-1 albumin complex retains GLP-1 actions but resists the DPP-IV enzyme. CJC-1131 has a longer duration of action because it

conjugates covalently to lysine 34 of the albumin and thereby acquires the half-life of albumin. The study in diabetic mice found that CJC-1131 can lower blood glucose level and the effect persists up to 1 week following discontinuation of treatment[46].

A clinical trial in patients with type 2 diabetes treated with CJC-1131 demonstrated that CJC-1131 could reduce glucose and body weight. Mild to moderate transient nausea is the most common side effect. There is no report of neutralizing antibodies in humans[47].

Limitation of GLP-1 analogues

1. GLP-1 analogues have to be administered by subcutaneous or intravenous injection. There is no oral form available.

2. The stability of GLP-1 analogues is limited by time, temperature, and pH. However, liraglutide and exenatide are reported to be stable[48].

3. GLP-1 analogues are potentially immunogenic. Antibodies to 36-residue natural peptides such as neuropeptideY can be produced in rabbits without high molecular mass carriers[49]. However, so far, none of the reported compounds were found to be immunogenic.

4. GLP-1 analogues cause nausea and vomiting. In rodents, GLP-1 can also increase heart rate and blood pressure, however these side effects have not been observed in humans[50].

2. Dipeptidyl peptidase IV inhibitors

DPP-IV is a glycoprotein consisting of 766 amino acids in humans, and 767 amino acids in rats. There is an 85% identity between human and rat sequences[51]. DPP-IV was first discovered in 1966 in rat liver[52]. It is highly expressed in the kidney, especially glomerular basement membrane and proximal convoluted tubule[53].

DPP-IV is a membrane bound homodimeric class II protein with a molecular weight of 110-150 kDa/subunit. In addition to its protease function, DPP-IV also has receptor properties and can act as an extracellular binding protein. Because of its three dimension structures, DPP-IV cannot react to peptides larger than 80 amino acids or smaller than 30 amino acids[54]. Most of the DPP-IV substrates are neuropeptides which include neuropeptide Y, substance P, gastrin releasing peptide, pituitary adenylate cyclase activating peptide (PACAP). The other substrates are involved in immune responses, such as macrophage-derived chemokine, monocyte chemoactive protein, regulated-on-activation normal T cell expressed and secreted (RANTES) protein. Substrates are gastrointestinal hormones such as, enterostatin, insulin like growth factor 1, peptide YY, glucagon-like peptide-1, glucagon-like peptide-2, and glucose dependent insulinotropic peptide.

The rationale for using DPP-IV inhibitors for the treatment of type 2 diabetic patients based on animal studies showing that animals with defective in DPP-IV activity or has DPP-IV gene deletion are resistant to develop high fat diet-induced glucose intolerance[55,56]. In preclinical studies, DPP-IV inhibitors mimic many of the actions ascribed to GLP-1 analogues, including stimulation of insulin, inhibition of glucagon, and preservation of beta cell mass through stimulation of cell proliferation and inhibition of apoptosis. By contrast, DPP-IV inhibitors are generally not associated with a decrease in gastric emptying time and weight loss. DPP-IV inhibitors that have been under development are listed in Table 2.

2.1 Vildagliptin (LAF237)

It has been observed that acute administration of vildagliptin inhibit plasma DPP-IV activity in a dose dependent manner. This inhibition led to a marked increase in the glucose-stimulated level of intact GLP-

Table 2. Characteristics of DPP-IV inhibitors

Compounds	Clinical phase	Compound type	Dose range in clinical trial
Sitagliptin (MK-0431)	FDA approved (Oct 2006)	Non-covalent, reversible	25-200 mg OD
Vildagliptin (LAF237)	Pre-registered by FDA (Feb 2006)	Covalently modifying	25-100 mg OD/bid
Saxagliptin (BMS477118)	Phase III	Covalently modifying	10 mg OD
Alogliptin	Phase III	Not available	Not available
Denagliptin	Phase III	Not available	Not available
TA6666	Phase II	Non covalent, reversible	Not available
PSN9301	Phase II	Non covalent, reversible	Not available

1, an increase of glucose stimulated insulin secretion and a marked decrease in glucose excursion following an oral glucose challenge. Vildagliptin is reported to inhibit DPP-IV and improve beta cell function *in vitro* and in type 2 diabetic patients[57,58].

Four weeks treatment of vildagliptin 100 mg per day has been shown to reduce fasting blood glucose, postprandial blood glucose, plasma glucagon and HbA_{1C} significantly compared with placebo. Furthermore, postprandial GLP-1 level also increased significantly compared with placebo[59]. Twelve weeks of vildagliptin treatment in type 2 diabetic patients, who have been treated with metformin, can reduce HbA_{1C} by 0.8% compared with placebo and this effect was maintained during an open-label extension for 52 weeks[43]. Another study in type 2 diabetic patients using vildagliptin 50 mg and 100 mg once daily for 12 weeks, HbA_{1C} decreased significantly compared with placebo (-0.56% and -0.53% respectively)[60]. In a 52-week head to head study versus metformin, vildagliptin 100 mg daily reduced HbA_{1C} comparable to metformin 2 gm/day (-1% and -1.4% in vildagliptin and metformin group respectively). The decrease in HbA_{1C} sustained throughout a 1-year treatment in both metformin and vildagliptin monotherapy, although a gastrointestinal event was two folds higher in the metformin group[61]. Similarly, vildagliptin was as effective as rosiglitazone in glycemic reductions in a 24-week randomized controlled trial. However, body weight did not change in the vildagliptin group but increased in the rosiglitazone treated group[62]. Vildagliptin also produces clinically significant reductions in HbA_{1C} as an add-on therapy in patients already treated with metformin, glimepiride, or insulin[63,64].

2.2 Sitagliptin (MK-0431)

In a randomized placebo-controlled study, sitagliptin 25-600 mg single dose markedly and dose dependently inhibited plasma DPP-IV activity. Sitagliptin 50 mg inhibit DPP-IV activity by 80% over a 12-hour period and sitagliptin 100 mg or greater inhibit DPP-IV activity by 80% over a 24-hour period[65]. Sitagliptin increases post meal GLP-1 level by 2 folds compared with placebo. Clinical studies have demonstrated that sitagliptin is well tolerated at a dosage of 100 mg/day, either as monotherapy, or in combination with metformin or pioglitazone, without significant hypoglycemia or weight gain[66-68]. Sitagliptin was approved by US FDA for the treatment of type 2 diabetes in October 2006 either as monotherapy, or as an add-on treatment to either metformin, sulfonylurea, or thiazolidenediones. The usual dose is 100 mg daily. However, patients with renal impairment may require a reduction in dose to 50 mg daily when creatinine clearance is between 30-50 ml/min or to 25 mg daily when creatinine clearance falls below 30 ml/min.

2.3 Saxagliptin (BMS-477118)

Saxagliptin 0.3-3 μmol/kg significantly improved glucose tolerance in diabetic mice. Saxagliptin inhibited rat plasma DPP-IV activity up to 4 hours in an *ex vivo* study[69]. It has been shown that saxagliptin has a potent 24-hour DPP-IV inhibition after single dose and effectively lowered HbA_{1C} in a 12-week phase II trial at 10 mg dose. Further studies are ongoing.

Limitations of DPP-IV inhibitors

1. DPP-IV is a pleiotropic enzyme that inactivates a variety of peptides. Furthermore, it acts as a binding protein of fibronectin and adenosine deaminase, and is a co-stimulator for T-cell activation. Therefore, in addition to prolongation of incretins actions, DPP-IV also prolongs the action of hormones peptide YY, growth hormone releasing hormone, neuropeptide Y, substance P, chemokines such as stromal cell-derived factor-1 (CCXCL 12) and macrophage-derived chemokine (CCL 22). Potential side effects resulting from prolongation of these peptides include an increase of neurogenic inflammation (from substance P, neuropeptide Y), and enhancement of general inflammation and allergic reactions (chemokines). However, there is no report of such side effects in preclinical animal or clinical human studies to date[70].

2. Several enzymes, such as DPP-2, DPP-8, DPP-9, have similar catalytic activities as DPP-IV. These enzymes might interfere with the activity of DPP-IV. DPP-2 is a lysosomal peptidase cleaving only small peptides so it does not cleave GLP-1. DPP-8, DPP-9 are cytosolic enzymes, which cleave chromogenic DPP-IV substrates, but their physiologic functions have not yet been explored. Inhibition of DPP-8 and DPP-9 seems to be responsible for toxic effects such as alopecia, thrombocytopenia, enlarged spleen in rats, and gastrointestinal toxicity in a dog study[71]. However, vildagliptin and sitagliptin, which are highly selective to DPP-IV, seem to be well tolerated in preclinical studies. Long-term safety of DPP-IV inhibitors should be closely monitored.

3. DPP-IV is a ubiquitous cell-membrane protein, expressed in many tissues, including lymphocytes, which has raised some concerns about their long-term effects, especially on immune function. In addition,

recent meta-analysis showed that DPP-IV inhibitors had an increased risk of infection (risk ratio 1.2 [95% CI, 1.0-1.4] for nasopharygitis and 1.5 [95% CI, 1.0-2.2] for urinary tract infection), and headache (risk ratio 1.4 [95% CI, 1.1-1.7])[72].

Comparison of GLP-1 analogues and DPP-IV inhibitors

1. DPP-IV can be administered orally but GLP-1 mimetics have to be administered parenterally.

2. DPP-IV inhibitors slightly increase endogenous GLP-1 (approximately 2 times) but GLP-1 mimetics increase GLP-1 several folds above physiologic range. Side effects of GLP-1 mimetics include nausea, and vomiting. These effects seem to depend on the level of GLP-1 so DPP-IV inhibitors do not produce these side effects. Since GLP-1 mimetics delay gastric emptying time, caution should be made when using with drugs that need to be absorbed rapidly. DPP-IV inhibitors are very well tolerated. There is no report of an increase risk in gastrointestinal side effects. However, there is a concern of an increased risk of certain infection and long-term safety data are still unavailable.

3. GLP-1 mimetics promote significant weight loss compared to the comparators. Weight loss with exenatide and liraglutide are progressive and dose-dependent. In contrary, DPP-IV inhibitors are weight-neutral.

4. The hypoglycemic effect of exenatide was similar to vildagliptin. However, liraglutide has been reported to reduce HbA_{1C} better than vildagliptin and sitagliptin did.

5. In rodents, vildagliptin promotes beta cell neogenesis and improves glucose tolerance as efficiently as exenatide does, suggesting that GLP-1 mimetics and DPP-IV inhibitors could slow the progression of type 2 diabetes by increasing functioning beta cell mass. It is difficult to estimate the protective effects of GLP-1 on beta cell mass in humans. However, an improvement in beta cell function, as measured by homeostasis model assessment of beta cell function (HOMA-B) or by proinsulin:insulin ratio, has been observed in patients treated with vildagliptin and exenatide suggesting that these compounds may slow beta cell failure.

6. Exenatide has been shown to reduce cardiovascular risk factors related to diabetes as well as vildagliptin, which can reduce blood pressure in type 2 diabetic patients.

Comparison of clinical safety and efficacy of GLP-1 mimetics and DPP-IV inhibitors are shown in Table 3[25].

Table 3. Comparison of safety and efficacy of GLP-1 mimetics and DPP-IV inhibitors

	GLP-1 mimetics Exenatide	DPP-IV inhibitors Sitagliptin
Administration	Injection	Oral
GLP-1 concentration	> 5 folds	2-3 folds
Signaling	GLP-1 receptor agonists	DPP-IV substrates
Drug interactions	Drugs require rapid gastrointestinal absorption	No
Homology with human GLP-1	53%	-
Duration of elevated GLP-1 (hr)	4	24
Recommended dose	5-10 μg sc bid	100 mg po OD
Expected decrease in HbA_{1C}	0.5-1.0%	0.5-0.8%
Delays gastric emptying time	Yes	No
Blood pressure	Decrease	Not described
Body weight (Kg)	-4.7	Neutral
Antibody formation	Yes (38%)	No
Side effects	Nausea/vomiting	Well-tolerated but may increase risk of certain infection
Hypoglycemia	36%	Comparable with placebo
Non-responders	12%	No

Adapted from Combettes MM. Curr Opin Pharmacol 2006 ;6:598-605[25]

Conclusion

GLP-1 mimetics and DPP-IV inhibitors are novel antidiabetic agents, which have been shown to reduce HbA_{1C} level up to 1 year. Both agents can be used as monotherapy or as combination therapy. GLP-1 mimetics cause weight reduction but their limitations are the potential immunogenicity and need to be administered parenterally. The most frequent side effects are nausea and vomiting. DPP-IV inhibitors, in contrary, can be taken orally and are well tolerated. There are no reports of serious side effects in humans. However, DPP-IV inhibitors have no effect on weight loss. Further long-term studies are required to determine whether GLP-1 based therapies can protect beta cell and retard the progression of type 2 diabetes.

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อินครีติน: การรักษาแบบใหม่ในผู้ป่วยเบาหวานชนิดที่ 2

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โรคเบาหวานชนิดที่สองเป็นปัญหาสำคัญของหลายๆ ประเทศทั่วโลก การควบคุมระดับน้ำตาลในเลือดให้ดีสามารถช่วยป้องกันภาวะแทรกซ้อนเรื้อรังจากโรคเบาหวานได้ แม้ว่าในปัจจุบันจะมียาที่ใช้ในการรักษาโรคเบาหวานอยู่หลายชนิดแต่ผู้ป่วยส่วนใหญ่ยังไม่สามารถควบคุมระดับน้ำตาลให้อยู่ในเกณฑ์ที่เหมาะสมได้ อินครีตินเป็นฮอร์โมนที่ผลิตจากลำไส้ภายหลังรับประทานอาหารและมีผลช่วยลดระดับน้ำตาลในเลือดได้โดยออกฤทธิ์ผ่านหลายกลไก ปัจจุบันมียาที่พัฒนามาจาก glucagon-like peptide-1 (GLP-1) ซึ่งเป็นอินครีตินชนิดหนึ่ง ได้แก่ ยา GLP-1 mimetic และ Dipeptidyl peptidase-IV inhibitors จากการศึกษาพบว่ายาทั้งสองตัวสามารถลดระดับน้ำตาลในเลือดได้ดี