

## CHAPTER

# 1

# Incretin Hormones - Pathophysiological Basis of Therapeutic Intervention

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## Historical Perspective

In the excitement of new discoveries, the early work providing the conceptual framework of present therapeutic advances is being conveniently forgotten in most of the recent publications. Last year was the centurian celebration of the 1906 publication by Moore, Edie and Abram entitled “On the treatment of diabetes mellitus by acid extract of duodenal mucous membrane.”<sup>1</sup> It is remarkable that this publication antedates the discovery of insulin by 15 years! The term ‘secretin’ was initially used to define intestinal factors regulating pancreatic secretion. The epoch-making discovery of insulin in 1921 overshadowed the research efforts to define role of intestinal factors till a second revolution of radioimmunoassay of insulin was ushered in 1960 by Berson and Yalow. Using a novel experimental design, McIntyre et al. in 1964<sup>2</sup> observed that an intrajejunal glucose load elicited a significantly higher insulin response than that evoked by an equivalent amount of glucose (isoglycemic load) administered intravenously. Similar observations in the humans soon followed leading to the concept of ‘entero-insular axis’. Our own work in the subhuman primate enlarged this concept to ‘entero-hypothalamo-insular axis’. In a recent review,<sup>3</sup> our earlier work in the context of incretins has been cited :

*‘Based on the experimental data, Bajaj and Chhina proposed in 1976 the existence of Entero-hypothalamo-insular axis. It was conceptualised that in the fasted state, reduced activity in the neurons of the ventromedial hypothalamus with a reciprocally increased activity in those of the lateral hypothalamus would result in the initiation of feeding behavior providing a neural or neurohumoral signal to the  $\beta$ -cell, and initiating what may be termed as the cephalic phase of insulin release. Intestinal motility, blood flow and rate of nutrient absorption would also be altered through the autonomic responses. Food intake would also result in the release of gastrointestinal hormones (presently called Incretins), some of which will further increase insulin secretion from the  $\beta$ -cell. Finally, a rise in blood glucose will directly stimulate the glucose receptor in the  $\beta$ -cell, thus further increasing the levels of circulating insulin and enhancing glucose utilization in the body as well as in the hypothalamic neurons. Presence of food in the intestines and increased glucose utilization by insulin release provided afferent inputs initiating satiety behavior and cessation of food intake.*

## Pathophysiology of Hyperglycemia

In Type 2 diabetes mellitus (T2DM), hyperglycemia is due to : i) insulin resistance in peripheral tissues including muscle, fat and liver ; ii) insufficient pancreatic  $\beta$ -cell function which is reduced by ~ 50% at the time of diagnosis of T2DM ; and

**Table 1 : Biological and Biochemical Characteristics of GIP and GLP-1**<sup>6,7</sup>

GIP	GLP-1
<ul style="list-style-type: none"> <li>• Secreted by K-cells in the proximal gut (duodenum and upper jejunum).</li> <li>• 42 amino acid peptide secreted as a single bioactive form.</li> <li>• Precursor is a 153 amino acid peptide; gene located on chromosome 17.</li> <li>• <i>Stimulates glucose - dependent insulin release.</i></li> <li>• Suppressive effect on glucagon secretion by <math>\alpha</math>-cells <b>not</b> demonstrated.</li> <li>• Does <b>not</b> delay gastric emptying.</li> <li>• Circulating GIP levels are <b>normal</b> or <b>high</b> in Type 2 diabetes mellitus indicating possible GIP resistance.</li> <li>• Enhances beta-cell proliferation and survival in islet cell lines.</li> </ul>	<ul style="list-style-type: none"> <li>• Secreted by L-cells in the distal gut (ileum and colon).</li> <li>• Secreted in two bioactive forms, GLP-1 (7-37) and GLP-1 (7-36).</li> <li>• Product of proglucagon gene located on long arm of chromosome 2 and encoding for enteroglucagon, GLP-1, GLP-2 and other proglucagon derived peptides.</li> <li>• <i>Stimulates glucose - dependent insulin release.</i></li> <li>• Suppresses hepatic glucose output by inhibiting glucagons secretion in a glucose-dependent manner.</li> <li>• Gastric emptying significantly delayed.</li> <li>• Circulating GLP-1 levels are significantly <b>reduced</b> in Type 2 diabetes mellitus.</li> <li>• Enhances beta-cell proliferation and survival in animal models and isolated human islets.</li> </ul>

iii) excess hepatic glucose output due to both a decrease in insulin action *and* an increased glucagon action, primarily contributing to fasting hyperglycemia<sup>4</sup>. Essentially, there is dysfunction of both  $\alpha$  and  $\beta$ -cell, resulting in hypoinsulinemia *and* hyperglucagonemia. It is the dual action of incretins directed at both stimulating glucose-dependent insulin release from the  $\beta$ -cell and inhibiting glucagon secretion from the  $\alpha$ -cell, that provides a rational resolution of the key metabolic dysfunction<sup>5</sup>.

### The incretins

The isolation and characterization of glucose-dependent insulinotropic polypeptide (GIP : previously named gastroinhibitory polypeptide) in 1970, followed by the characterization of glucagon-like peptide 1 (GLP-1) and its truncated form GLP-1 (7 – 36 ) in 1985, led to their recognition as true *incretins*. GLP-1 receptors have been demonstrated in the stomach, intestine and *central nervous system*, in addition to their presence in kidney, heart and lungs. In the context of our earlier hypothesis, it is gratifying to note that GLP-1 receptors have been demonstrated in the neurons in hypothalamus and tractus solitarius, areas involved in regulation of feeding and satiety behavior.

GIP and GLP-1 are principal insulinotropic incretins. While GIP is secreted from K cells in the duodenum and upper jejunum, GLP-1 is secreted from enteroendocrine L-cells located mostly in the mucosa of distal ileum and colon. GIP and GLP-1 are both members of the glucagon peptide superfamily, sharing a close amino acid homology. Table 1 summarizes the important characteristics of these two peptides.

Despite the distal location of L-cells in the GI tract, GLP-1 is released into circulation *within* a few minutes of nutrients ingestion, indicating that such release is more due to neuroendocrine regulation rather than a result of direct contact of nutrients with L-cells. Vagus nerve, through muscarinic receptors, is possibly a major contributing factor, with GLP-1 receptor also located in tractus solitarius. Both GIP and GLP-1 are rapidly degradable by DPP-IV, resulting in inactive or weakly antagonistic peptide fragments. DPP-IV acts by cleavage of the two NH<sub>2</sub>-terminal amino acids of bioactive peptides, *only if* the second amino acid is alanine or proline. Since the second NH<sub>2</sub>-terminal amino acid in GLP-1 is alanine, the peptide is cleaved to a truncated form, GLP-1 (9-36) amide which is essentially inactive. The cleavage is rapid with plasma half-life ( $t_{1/2}$ ) of GLP-1 being only about 1-2 minutes. Both GIP and GLP-1 bind with their respective receptors,

causing an activation of adenylate cyclase via the G-protein and leading to an increase in intracellular cyclic AMP. There is evidence that the activity of endogenous GLP-1 is also mediated through interaction with sensory afferents in the intestines which relay in the brain and modulate efferent vagal fibers which, in turn, regulate several biological actions including gastrointestinal secretions and motility. This is precisely what was proposed by us as *entero-hypothalamo-insular axis* more than thirty years back. Finally, there is suggestive evidence, based on double knockout of GIP and GLP-1 receptors, that smaller loads of rapidly absorbable nutrients preferentially activate GIP, whereas larger meals composed of complex nutrients activate the distal GLP-1. In contrast to the actions of GLP-1, GIP *does not* affect pancreatic  $\alpha$ -cells secretion of glucagon, nor does it delay gastric emptying. It is due to these reasons, amongst several others, that initially only GLP-1 has been considered a viable therapeutic approach in the management of T2DM.

The basic issue as to why there is a defect in the incretin effect in T2DM remains to be fully resolved.<sup>8</sup> Is there a defect in GLP-1 and GIP secretion in T2DM? Is this defect due to a genetic variant in a transcription factor expressed in L cells? Alternatively, is lack of sensitivity of  $\beta$ -cell to glucose also associated with lack of sensitivity to the action of incretins? Or is it a combination of the two defects? Irrespective of the final mechanism, it is obvious that enhancing incretin effect in T2DM may improve metabolic profile and lead to better glycemic control.

### Therapeutic rationale and role of GLP-1

- A. GLP-1 stimulates glucose-induced insulin secretion in isolated pancreatic islets, in the perfused and perifused pancreas, and in whole organism, both in animals and in the human. GLP-1 knockout mice show *fasting* hyperglycemia and following administration of glucose load, abnormal glucose tolerance
- with significantly reduced insulin secretion<sup>9</sup>. In addition to its glucose-dependent effect (approximate threshold  $\sim 4.5$  mM/L), GLP-1 also stimulates insulin gene transcription, thus activating all steps of insulin biosynthesis. Essentially, insulin biosynthesis seems to be coupled with insulin secretion. Finally, GLP-1 has been shown as  $\beta$ -cell trophic, increasing  $\beta$  cell mass. It also promotes the differentiation of precursor cells in pancreatic duct epithelium into  $\beta$  cells. GLP-1 also has an antiapoptotic effect on  $\beta$  cells.<sup>10</sup> It is an exciting speculation whether prolonged administration of GLP-1 analogs (or sensitizers) may protect and preserve functional  $\beta$  cell mass in T2DM.
- B. GLP-1 suppresses glucagon secretion from  $\alpha$ -cells. This effect has been demonstrated in isolated islets, in perfused and perifused pancreas, and in whole organism as in animals and in the human. The inhibitory effect of GLP-1 on glucagon secretion is glucose dependent; this would ensure that exogenous GLP-1 administration (or of its analogs/mimetics) does not lead to impaired glucagon counter regulatory response in hypoglycemia. The precise mechanism(s) underlying GLP-1 induced glucagon suppression remain to be elucidated. Possible suggestive mechanisms include : (i) indirectly mediated (via paracrine effect) through insulin release; (ii) GLP-1 stimulates somatostatin secretion which may in turn suppress glucagon; (iii) a direct effect on  $\alpha$ -cells as GLP-1 receptors are expressed on the membrane of glucagon producing cells. Irrespective of the mechanism(s) involved, GLP-1 inhibition of glucagon secretion plays an important role in glucose regulation as even in those patients with Type 1 diabetes mellitus (who have *no* functioning  $\beta$ -cells), GLP-1 administration decreases blood glucose through inhibition of glucagon and suppression of hepatic glucose production.
- C. GLP-1 reduces caloric intake and enhances satiety, possibly through entero-hypothalamo-

**Table 2 : Physiological Actions of GLP-1**

- Stimulates glucose-dependent insulin secretion.
- Suppresses glucagon secretion.
- Enhances insulin gene transcription and increases insulin biosynthesis.
- Enhances cellular transformation from pancreatic ductal tissues to  $\beta$ -cell tissue.
- Increases  $\beta$ -cell mass by enhancing cellular neogenesis and proliferation.
- Inhibits  $\beta$ -cell apoptosis.
- Stimulates somatostatin secretion.
- Induces satiety through entero-hypothalamo-insular-axis.

insular-axis and related central mechanisms. Significant reduction of food intake leading to lower body weight was observed with prolonged systemic administration of GLP-1 analog in the rhesus monkey, in diabetic db/db mice and in Zucker diabetic fatty rats.<sup>11</sup> In subjects with T2DM, a subcutaneous infusion of GLP-1 for upto 6 weeks resulted in sustained reduction of food intake, associated with a reduction in body weight.

The precise neuroregulatory pathways involved in GLP-1-induced satiety and subsequent weight reduction have not yet been fully elucidated. The possibilities include : (i) GLP-1 acts on intestinal vagal afferents, modulating neuronal transmission through GLP-1 containing neurons in tractus solitarius which in turn project into ventromedial hypothalamus; (ii) GLP-1 may directly reach its receptors located in blood brain barrier-free areas such as area postrema which may relay to hypothalamic areas involved in energy homeostasis; (iii) delayed gastric emptying leading to fullness of stomach may contribute to activation of neuroregulatory mechanisms.

Therapeutic application of the above listed physiological actions (Table 2) opens up a new approach in the management of T2DM.

To realize the therapeutic potential and at the same time to circumvent the problem of rapid

inactivation of GLP-1, two strategies have been successfully explored. Firstly, the use of DPP-IV-resistant GLP-1 receptor agonists (GLP-1 mimetics). Exenatide belongs to this group. The other approach is the use of DPP-IV inhibitors, thus prolonging the action of endogenously released incretin hormone.

### GLP-1 receptor agonists

**Exenatide** is a synthetic peptide originally identified in the lizard *Heloderma suspectum*. It is a 39 amino acid peptide amide : the amino acid sequence partially overlaps that of human GLP-1. Exenatide binds and activates GLP-1 receptor *in vitro*. As a GLP-1 analog, it exhibits incretin-mimetic activity : i) enhances glucose-dependent insulin secretion from  $\beta$ -cells; ii) suppresses glucagon secretion, and iii) slows gastric emptying.

It is administered as a subcutaneous injection, reaching median peak plasma concentration in 2.1 hour. It is predominantly eliminated by glomerular filtration and subsequent proteolytic degradation. Its mean terminal half-life is 2.4 hours. In most subjects, exenatide concentrations are measurable for approximately 10 hours following administration; hence it has to be administered twice daily. In patients with mild to moderate renal dysfunction (creatinine clearance ~ 30 – 80 ml/minute), exenatide clearance was not significantly reduced; hence no dosage adjustment is required. Age, gender, BMI, or hepatic functional status do not affect exenatide pharmacokinetics.<sup>12</sup>

Extensive experience has been generated regarding therapeutic use of *Exenatide* in the management of T2DM.<sup>13,14</sup> Three 30-week, double blind, placebo controlled trials wherein 1446 subjects with T2DM having inadequate glycemic control (mean baseline HbA1c 8.2% - 8.7%) with metformin alone, a sulfonylurea alone, or metformin with a combination of sulfonylurea, were randomized in a placebo group, exenatide 5 mcg bid group, and exenatide 10 mcg bid group. At 30 weeks, when given in combination with metformin, the number of subjects achieving HbA1c  $\leq$  7% were

13%, 31.6% and 46.4% in placebo, 5 mcg bid, and 10 mcg bid treatment groups, respectively. The difference between 2 dosage groups was statistically significant. There was no significant intergroup difference when exenatide was administered with a sulfonylurea, or with a combination of metformin and sulfonylurea. In a subsequent 16-week study, similar data was generated when exenatide was added to a thiozolidinedione regimen.

In another series of 336 metformin-treated subjects treated with either placebo or exenatide 5 mcg or 10 mcg twice daily for a period of 28 weeks, HbA1c (pretreatment 8.2%) decreased by 1% to 1.2% in the 10 mcg treatment group.<sup>15</sup> There was also a significant weight loss in this treatment group, recording average weight loss of ~ 8 pounds (about 3.65 kg). Postprandial glucose showed a significant decline *alongwith* improvement in insulin secretion.

The only contraindication to use of exenatide is known hypersensitivity to this compound. It should also be remembered that exenatide is *not* a substitute of insulin. Therefore, it should not be used in patients with Type 1 diabetes mellitus. The commonest side effect is nausea, especially on initiation of therapy, and gradually disappearing after few weeks of drug usage in majority of patients. Rarely, acute abdominal pain associated with vomiting may follow exenatide use. This is characteristic of acute pancreatitis and warrants urgent medical attention. Other less common side effects include diarrhea, dizziness, headache and dyspepsia.

Similar data has been generated in early clinical trials with *liraglutide*, another GLP-1 analog with longer half-life and therefore ease of administration as a once daily regimen.<sup>16</sup> Finally, a long-acting release formulation of exenatide, *Exenatide LAR*, has been administered as once-weekly regimen in a dose of 0.8 or 2.0 mg in a placebo-controlled phase 2 clinical study in subjects with T2DM inadequately controlled with metformin and/or diet and exercise. A significant decrease in mean HbA1c of 1.4% (0.8

mg. dose) and 1.7% (2.0 mg dose) was observed. HbA1c of  $\leq 7\%$  was achieved in 36% and 86% of subjects receiving 0.8 mg or 2.0 mg. dose, respectively<sup>17</sup>. Mild nausea was the most frequent adverse event; however, no subject withdrew from the treatment group in the study. It was concluded that Exenatide LAR offers the potential of 24-hr. glycemic control and weight reduction with a once-weekly administered treatment regimen when combined with metformin and/or diet and exercise in the management of T2DM.

### DPP-IV Inhibitors

Following animal studies, early clinical investigations have confirmed that DPP-IV inhibition in the human not only increases postprandial but also fasting levels of circulating active GLP-1, with preserved circadian rhythm. As expected, use of DPP-IV inhibitors also increases levels of active GIP.

Presently, extensive clinical data is available with regard to two DPP-IV inhibitors : Sitagliptin (Januvia; Merck) and Vidagliptin (Galvus; Novartis). Of these, Sitagliptin was approved by the FDA in October, 2006 and has recently been approved in the UK also (April, 2007). Several other inhibitors are in various phases of development. Collectively, these are often termed *gliptins* and are categorized as *incretin enhancers*. Table 3 is based on available information in various databases in the public domain :

*Sitagliptin* has been investigated both as *monotherapy*<sup>18,19</sup> in drug-naïve patients as well as in combination with either metformin, or with thiozolidinedione, or with insulin. An 18-week study comprising 521 patients with T2DM who were inadequately controlled (mean HbA1c 8.1%) with diet and/or exercise, were administered Sitagliptin at 100 or 200 mg once daily versus a placebo-administered group. Achieved HbA1c reduction was 0.60% and 0.48% with the two dosage regimens, respectively. Likewise, in another similarly designed study which extended to 24 weeks, mean baseline HbA1c of 8.0% showed a reduction of 0.74% and

**Table 3 : Current Status of DPP-IV Inhibitors**

Name	Company	Stage in development
Sitagliptin (Januvia)	Merck	Approved by FDA
Vildagliptin (Galvus)	Novartis	Pending approval by FDA
Alogliptin	Takeda	Phase III
Saxagliptin	Bristol-Myers Squibb	Phase III
R1438	Roche	Phase II
GRC 8200	Glenmark Pharmaceuticals	Phase II
PSN-9301	OSI Pharmaceuticals	Phase II
TA-6666	Tanabe	Phase II
PHX1149	Phenomix	Phase II

0.94% in the two dosage groups, respectively. Finally, conclusions drawn from a collation of clinical data from the studies using Sitagliptin as monotherapy lead to a number of generalized formulations : i) patients with highest baseline HbA1c levels show the largest reduction in HbA1c; ii) there are no obvious differences in clinical efficacy between younger and older subjects; iii) the degree of obesity in the treated group does not affect effectiveness of treatment; iv) a dosage of 100 mg once daily is both safe and effective. In particular, the reported episodes of hypoglycemia are very low using monotherapy with DPP-IV inhibitors; v) in contrast to body weight reduction following use of GLP-1 analogs, therapy with DPP-IV inhibitors is generally body weight-neutral.

Sitagliptin in *combination* therapy<sup>20</sup> has been evaluated in studies wherein inadequately controlled patients on metformin were administered sitagliptin. In a 6-month clinical trial of 701 patients on treatment with metformin in a dosage > 1.5 gm. per day and with mean HbA1c of 8.0%, addition of 100 mg per day of sitagliptin resulted in reduction of HbA1c by 0.65% compared with placebo. In another study of 1,172 patients extending over 52 weeks, effect of sitagliptin administered in dosage of 100 mg per day, in combination with

metformin was compared with glipizide as an addition to metformin. In both groups HbA1c was reduced by 0.67% from a baseline value of 7.5%. More importantly, two major clinical differences emerged in the two treated groups : i) the number of hypoglycemic episodes was significantly higher in metformin *plus* glipizide group (32%) as compared to metformin plus sitagliptin group (4.9%); ii) there was a significant increase in body weight in subjects on glipizide ( mean weight gain ~ 1.5 kg); in contrast sitagliptin was either weight-neutral or in some patients, there was a decrease in body weight. Sitagliptin has also shown therapeutic efficacy in trials where it was added to pioglitazone. Compared to placebo, pioglitazone plus sitagliptin treated group showed HbA1c reduction of 0.7%.

**Vidagliptin** which is pending approval by FDA has shown equally encouraging results *both* when used as monotherapy,<sup>21,22</sup> or in combination with metformin,<sup>23</sup> or pioglitazone, or when added to insulin-treatment regimen.<sup>24</sup> In the 24-weeks study with insulin-treated group wherein mean duration of diabetes was 14.6 years and mean duration with insulin therapy was 6.3 years, addition of 100 mg. per day of vidagliptin resulted in HbA1c reduction of 0.5% from the pre-vidagliptin value of 8.9%. Hypoglycemic events were less common and less severe when vidagliptin was combined with insulin (33 patients : 113 events; 0 severe event) as compared to insulin alone group (45 patients : 185 events; 6 severe events).

As DPP-IV also cleaves other bioactive peptides with alanine or proline as the second amino acid from the NH<sub>2</sub>-terminal, the possibility of the side effects due to cleavage of physiologically important peptides such as NPY (neuropeptide Y), gastrin releasing peptide and substance P amongst others, could not be ruled out. However, till date no such adverse effects have been reported either in experimental animal studies or in the clinical studies in humans. Thus it is difficult to extrapolate results of cleavage studies *in vitro* to the possible effects *in vivo*. The former primarily deals with pharmacological substrates while the latter is directly related to physiological substrates.

Finally, it must be remembered that DPP-IV is not only an aminopeptidase enzyme but is also immune T-cell activating antigen CD 26. Whether long term administration of DPP-IV inhibitors may result in any organ-specific immune-mediated pathological alterations, shall only be known with long-term follow-up of such patients as well as following chronic toxicology studies in appropriate animal models.

In summary, both sitagliptin and vildagliptin are clinically effective with demonstrable safety profile. Both compounds have similar effects on glycemic control and both are active when administered orally. Nevertheless, two facts emerge from the studies reported thus far. *Firstly*, the administration of exenatide results in enhanced activity at the GLP-1 receptor only while the DPP-IV inhibitors lead to an increase in both GLP-1 and GIP. It is suggested that resistance to GIP as observed in T2DM may be reversible, and a substantial increase in GIP following treatment may contribute to the enhanced therapeutic efficacy. *Secondly*, there is suggestive evidence that metformin itself may increase GLP-1<sup>25</sup>, and the addition of gliptins in a patient inadequately controlled with metformin, results in an enhanced therapeutic synergy. This fact may also be significant in the context of additional biological effects mediated by cyclic AMP system in liver and adipose tissue.

On the basis of very limited personal experience with the use of sitagliptin, the author is convinced of the future potential of gliptins. The possibility that one of the gliptins may emerge as a first-line treatment in combination with metformin in newly diagnosed patients with T2DM remains distinctly plausible and may materialize into recommended future guidelines in the management of T2DM.

### **Incretins : Crystal gazing**

Clinically, the most pertinent and relevant question in a newly diagnosed patient with T2DM is : how best we can preserve beta  $\beta$ -cell mass and function and prevent progressive  $\beta$ -cell failure? What would be the appropriate intervention(s) that may change the natural history of the disease process? In this context,

what is the clinical relevance of the experimental studies which show an enhanced  $\beta$ -cell mass with the use of incretins? Is reduced apoptosis and enhanced  $\beta$ -cell neogenesis as observed in experimental studies, including an *in vitro* study using human  $\beta$ -cell culture hold sufficient promise that may finally lead us to our ultimate objective? There seems to be light at the end of the tunnel, albeit the tunnel is undoubtedly very long. So would be the long-term studies with 'incretins' which may provide realistic answer to this basic question : *whether the early introduction of gliptins in the management schema will preserve and protect  $\beta$  cell function?* An obviously related corollary is the possible role of incretins in impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT). Will their early use prevent or delay the progression of these early stages to overt T2DM? Finally, keeping in view considerations of safety and cost-effectiveness, will such therapeutic interventions be distinctly superior to life style modifications alone or with metformin?

We are indeed passing through an exciting phase of a voyage of scientific discovery and clinical optimism\*.

\* Presently, however, in India and other developing countries, cost factor needs to be seriously considered : present cost of 100 mg per day of sitagliptin is approximately Rs. 250/- per day (Merck US price : \$ 182.25 per 30 tablets).

### **Summary**

Pathophysiology of diabetes mellitus is characterized by relative or absolute insulin deficiency; therefore, most of the therapeutic approaches have thus far been directed to either increasing circulating insulin (insulin administration; sulfonylureas etc.) or to enhance its effectiveness (insulin sensitizers e.g. metformin, thiazolidinediones). However, the resurgence of interest in the earlier concept that excess of glucagon plays a significant role especially in relation to hepatic glucose output and fasting hyperglycemia has refocused the need to develop drugs that inhibit glucagon secretion from  $\alpha$ -cells, in addition to stimulating insulin synthesis/release from the  $\beta$  cells. The availability of incretins fulfills this need. Incretin hormones are defined as peptides of intestinal origin, released

in response to intake of nutrients, and potentiating glucose-induced insulin response while suppressing glucagon release. Incretin effect is mainly due to two peptide hormones : GIP and GLP-1, the latter providing the pivot around which two main therapeutic approaches have been developed. Firstly, development of GLP-1 analogs with longer half life; secondly the inhibitors of dipeptidyl peptidase-IV (DPP IV), the enzyme responsible for rapid degradation of GLP-1. The physiological and pharmacological aspects are highlighted and results of clinical trials of these compounds discussed.

## References

- Moore B, Edie ES, Abram JH. On the treatment of diabetes mellitus by acid extract of duodenal mucous membrane. *Biochem J.* 1906; **1** : 2838.
- McIntyre N, Holdsworth CD, Turner DS. New interpretation of oral glucose tolerance. *Lancet.* 1964 ; **2** : 20-21.
- Bajaj JS. Hypothalamus : A holistic view. *Ann Natl Acad Med Sci.* 2006; **42**: 169-189.
- Bajaj JS, Bajaj M. Insulin Resistance : Pathological Basis and Clinical Significance. *Ann. Natl. Acad. Med. Sc.* 2006; **42** : 45-59.
- Meece J. Pancreatic islet dysfunction in type 2 diabetes: a rational target for incretin-based therapies. *Curr Med Res Opin.* 2007; **23** : 933-944.
- Drucker DJ. Minireview: the glucagon-like peptides. *Endocrinology*, 2001; **142** : 521-527.
- Hansotia T, Baggio LL, Delmeire D, et al. Double incretin receptor knockout (DIRKO) mice reveal an essential role for the enteroinsular axis in transducing the glucoregulatory actions of DPP-IV inhibitors. *Diabetes.* 2004; **53**:1326-1335.
- Drucker DJ. Glucagon-like peptide-1 and the islet  $\beta$ -cell : augmentation of cell proliferation and inhibition of apoptosis. *Endocrinology.* 2003; **144** : 5145-5148.
- Meier JJ, Gallwitz B, Schmidt WE, Nauck MA. Glucagon-like peptide I as a regulator of food intake and body weight : therapeutic perspectives. *Eur J Pharmacol.* 2002; **440** : 269-279.
- Nielsen LL, Young AA, Parkes DG. Pharmacology of exenatide (synthetic exendin-4) : a potential therapeutic for improved glycemic control of type 2 diabetes. *Regulatory Peptides.* 2004; **117** : 77-88.
- Blonde L, Klein EJ, Han J, et al. Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. *Diabetes Obes Metab.* 2006; **8**:436-447.
- Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care.* 2004; **27**:2628-2635.
- DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care.* 2005; **28**:1092-1100.
- Viltsboll T, Zdravkovic M, Le-Thi T, et al. Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. *Diabetes Care.* 2007; **30**: 1608-1610.
- Kim D, MacConell L, Zhuang D et al. Effects of Once-Weekly Dosing of a Long-Acting Release Formulation of Exenatide on Glucose Control and Body Weight in Subjects With Type 2 Diabetes. *Diabetes Care.* 2007; **30** : 1487-1493.
- Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care.* 2006; **29**:2632-2637.
- Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. *Diabetologia.* 2006; **49**:2564-2571.
- Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. *Diabetes Obes Metab.* 2007; **9** : 733-745.
- Pratley RE, Jauffret-Kamel S, Galbreath E, Holmes D. Twelve-week monotherapy with the DPP-4 inhibitor vildagliptin improves glycemic control in subjects with type 2 diabetes. *Horm Metab Res.* 2006; **387** : 423-438.
- Pi-Sunyer FX, Schweizer A, Mills D, Dejager S. Efficacy and tolerability of vildagliptin monotherapy in drug-naïve patients with type 2 diabetes. *Diabetes Res Clin Pract.* 2007; **76** : 132-138.
- Ahren B, Gomis R, Standl E, Mills D, Schweizer A. Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. *Diabetes Care.* 2004; **27** : 2874-2880.
- Fonseca V, DeJager S, Albrecht D, Shirt L, Schweizer A. Vildagliptin as add-on to insulin in patients with type 2 diabetes (T2D). *Diabetes.* 2006; **55** (Suppl 1.): A111.
- Yasuda N, Inoue T, Nagakura T, et al. Enhanced secretion of glucagon-like peptide-1 by biguanide compounds. *Biochem Biophys Res Commun.* 2002; **298**:779-784.
- Drucker DJ. The biology of incretin hormones. *Cell Metabolism.* 2006 ; **3** :153-165.
- Drucker DJ. The role of gut hormones in glucose homeostasis. *J Clin Invest.* 2007; **117** : 24 – 32.