

CHAPTER

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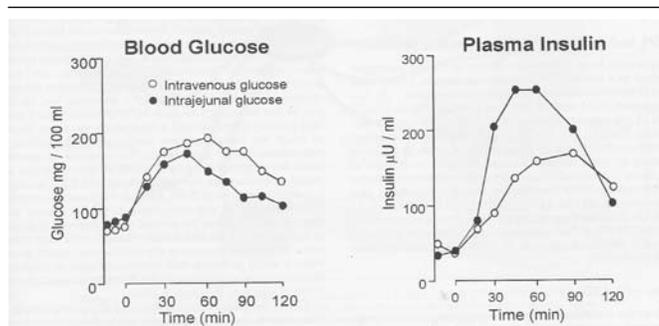
Glucagon Like Peptide 1 – Related Analogs

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Insulin release from the beta cells is influenced by nutrients (both carbohydrates and non-carbohydrates), hormonal factors including gut hormones and neural factors. Of all these insulin secretagogues, glucose availability is the major physiological determinant of insulin secretion. The insulin secretory response is greater after oral administration of glucose than after intravenous glucose administration (Fig – 1), an indication that absorption of glucose by way of gastro-intestinal tract stimulates the release of hormones and other mechanism that ultimately enhance the sensitivity of the beta cell to glucose. This phenomenon is known as ‘Incretin effect’ and is facilitated by gut hormones.

Glucagon is secreted from α cells and functions predominantly during the fasting state to maintain

Figure 1 : Incretin Effect



Adapted from Joslin’s Textbook of Diabetes Mellitus (14th edition).

blood glucose levels by the mobilization of glucose from glycogen stores in peripheral tissues such as muscle and liver. Excessive production of glucagon contributes to hyperglycemia and thus approaches that antagonize glucagon action in subjects with diabetes are being actively investigated. Two aspects of the gut have interested the diabetologists over the past 30 years. They are the incretin effect and the occurrence of glucagon-producing L-cells in the gut. The incretin effect is the amplification of nutrient-induced insulin secretion by hormones from the gut particularly GIP (gastric inhibitory peptide) and GLP 1 (glucagon like peptide 1)¹ [Fig – 2]. Of these two peptides, GLP 1 is the most potent and efficacious insulinotropic hormone¹. The

Figure 2 : Nutrients and Gut Hormones

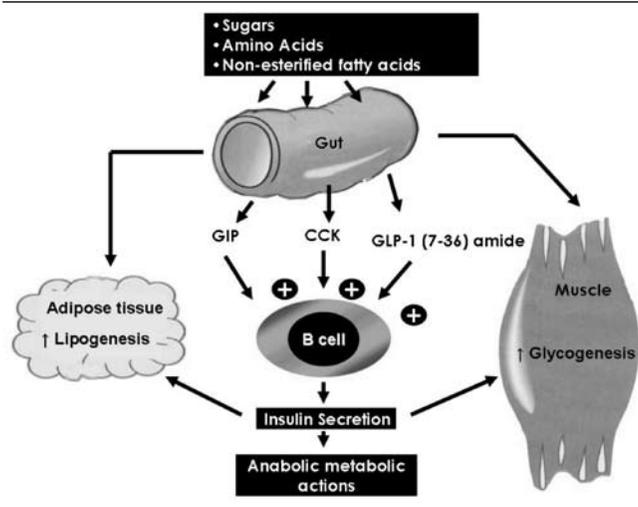
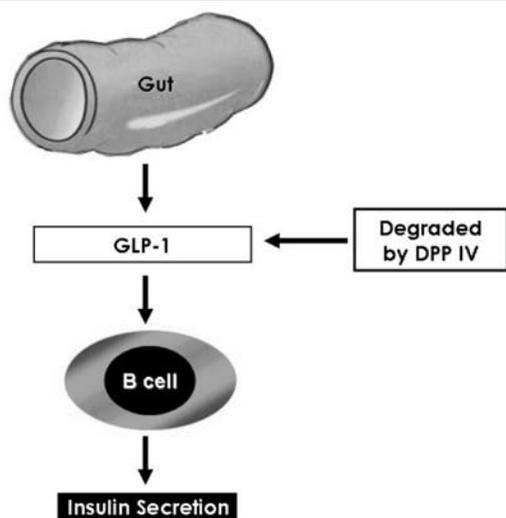


Figure 3 : Nor GLP I Action (Short Life) Enzyme resistant GLP I Analog



insulinotropic actions of GLP 1 appear to be due to an increase in the insulinogenic index, such that the same degree of insulin secretion is produced at lower glucose levels. The incretin effect is markedly impaired or absent in patients with type 2 diabetes because of decreased secretion of GLP 1.

The glucagon like peptides are secreted in response to feeding. Glucagon like peptide 1 (GLP 1) and gastric inhibitory polypeptide (GIP) comprise the intestinal ‘incretin’ hormones released from the intestine in response to feeding and augment glucose stimulated insulin secretion from the β cells^{2,3}. GLP 1 also enhances insulin stimulated glucose uptake in peripheral tissues (muscle, fat, liver), suppresses glucagon secretion, induces satiety, and promotes the growth and differentiation of new b cells in the pancreas. These antidiabetic properties of GLP 1 have prompted considerable interest in the therapeutic potential of GLP 1 for the treatment of diabetes.

The regulation of secretion of GLP-1 from the L-cells in the gut is complex and appears to involve combination of nutrient, hormonal and neural stimuli. There are atleast three potential sites where insulin secretion can be modulated by peptides. Firstly GLP-1 binds to receptors on pancreatic β -cells and thus affects the ion channels that regulate the membrane potential by activation of

adenylate cyclase, thereby stimulating cyclic AMP production and calcium influx. Secondly they may influence the mobilization of intracellular calcium stores notably the endoplasmic reticulum and thus cytosolic calcium concentration. Thirdly they may modify the calcium sensitivity of the contractile protein interactions that lead to the release of insulin secretory granules. Cyclic AMP and calcium stimulate rapid release of insulin from the cells and induce transcription of the insulin gene, thereby replenishing insulin stores. GLP-1 also activates receptors in neurons located in the hypothalamus, resulting in a reduction in food intake; thus, GLP-1 has an important role in controlling energy balance. GLP-1 receptors are also located on neurons in brain regions, such as the hippocampus, that are involved in learning and memory.

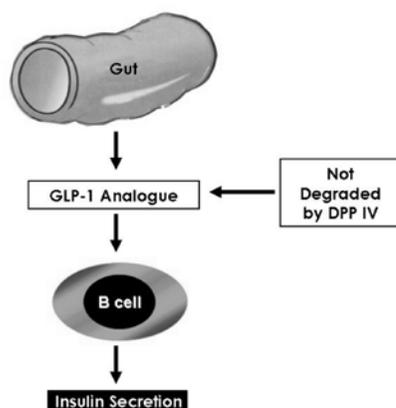
GLP I and diabetes treatment

GLP-1 powerfully inhibited glucagon secretion⁴. Furthermore, GLP-1 not only stimulated glucose-induced insulin secretion, but also all steps of insulin biosynthesis and insulin gene expression⁵. GLP- 1 also turned out to have powerful effects on gastrointestinal secretion and motility^{6,7}, and it was shown that inhibition of gastric emptying had strong effects on postprandial glucose excursions⁸ in healthy subjects and patients with type 2 diabetes⁹. In addition, GLP-1 was shown to inhibit appetite and food intake, both in healthy individuals¹⁰, and in patients with type 2 diabetes¹¹. These gastrointestinal ‘ileal brake’ effects of GLP-1 may in fact be the most important actions of the hormone under physiological conditions¹².

GLP-1 had dramatic effects on insulin secretion and blood glucose in patients with type 2 diabetes and was capable of completely normalizing fasting blood glucose levels, even in patients with long-standing type 2 diabetes and HbA1c levels of 11%¹³⁻¹⁶.

GLP I Preparation

Metabolic control in Type 2 DM can be restored or greatly improved by administration of exogenous GLP 1. Initial preparation of GLP 1 was ineffective

Figure 4 : Analog-Toprolong GLP I Action

when injected subcutaneously or intravenously as its effect on insulin and blood glucose was both transient and weak^{17,18}. The explanation for this was that the molecule is broken down extremely rapidly after both subcutaneous and intravenous administration¹⁹⁻²¹. Mechanism involved in the degradation of GLP 1 is the ubiquitous enzyme, dipeptidyl peptidase IV (DPP-IV)¹⁹.

The degradation is truly extensive, which means that the peptide has a plasma half-life of 1 to 2 min and a clearance of 5 to 10 l/min. (Fig 3). For practical diabetes treatment, there were now three possibilities: (a) to provide GLP-1 continuously; (b) to develop stable analogs of GLP-1 or agonists of the GLP-1 receptors; and (c) to try to inhibit the enzyme, DPP-IV.

Enzyme resistant GLP I Analog

Exenatide (Byetta®)

GLP-1 peptide is almost immediately degraded by dipeptidyl peptidase IV (DPP IV) and therefore has little clinical value. DPP IV resistant analogs (incretin mimetics) have been identified. Exendin-4 is a GLP-1 receptor agonist originally isolated from the venom of the Gila monster and is resistant to DPP-IV degradation and survives longer in circulation (Fig 4).

Exenatide (Synthetic Exendin-4, Byetta®) is a 39 amino acid peptide incretin mimetic agent that exhibits its gluoregulatory activities similar to the mammalian incretin hormone GLP 1. These

actions include glucose dependent enhancement of insulin secretion, restoration of first phase insulin response, suppression of inappropriately high glucagon secretion, slowing of gastric emptying, and reduction of food intake. Exenatide has acute effects on pancreatic β cell responsiveness to glucose and leads to insulin release only in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia.²² Exenatide's glucose dependent enhancement of insulin secretion may be mediated by exenatide binding to the pancreatic GLP 1 receptor.²³

The collective gluoregulatory effects of Exenatide (Byetta®) complement the actions of existing therapies, making it an excellent treatment option for combination therapy. The effects of Exenatide (Byetta®) on the β cell to enhance glucose dependent insulin secretion and restore first phase insulin secretion are unique. It is also apparently cleared in the kidneys only by glomerular filtration²⁴.

Exenatide (Byetta®) is found to be more stable and when given twice daily subcutaneously in type 2 diabetic patients reduces blood glucose. Exenatide is initiated as 5 mcg twice a day and up-titrated to 10 mcg twice a day. Following subcutaneous administration to patients with type 2 DM, exenatide reaches median peak plasma concentration in 2.1 hours.

Long term use of Exenatide (Byetta®) in combination with metformin, sulfonylurea, or both, reduced both fasting and postprandial plasma glucose concentrations in a statistically significant, dose dependent manner through week 30.^{25,26,27} Patients with type 2 diabetes receiving Exenatide (Byetta®) 10 mcg BID experienced placebo corrected A1c changes of -0.9 to -1.0%, with 34% to 46% of patients achieving A1c target levels of $\leq 7\%$ by significantly reducing both fasting and postprandial plasma glucose concentrations^{25,26,27}. Improvements in glycemic control with Exenatide (Byetta®) were achieved with the added benefit of reduction in

body weight in most patients^{25,26,27}. Adverse effects were mild and generally gastrointestinal.

Treatment with Exenatide (Byetta®) for 1 year resulted in sustained reductions in A1c and progressive reductions in body weight. Patients in the 5 mcg BID Exenatide (Byetta®) treatment arm showed changes from baseline to week 30 of -0.8% in A1c and -1.6kg in body weight. Upon shifting to 10 mcg BID during the extension, changes from baseline to week 52 were -1.0% in A1c and -3.1 kg in body weight. Patients in the 10mcg BID Exenatide (Byetta®) treatment arm showed changes from baseline to week 30 of -0.9% in A1c and -2.1 kg in body weight, and changes from baseline to week 52 of -1.1% in A1c and -3.2 kg in body weight²⁸.

Exenatide thus represents an efficacious supplement to failing conventional oral antihyperglycemic agents, and the sustained effect observed in the extension studies and its continued weight-lowering effects must be considered.

Liraglutide

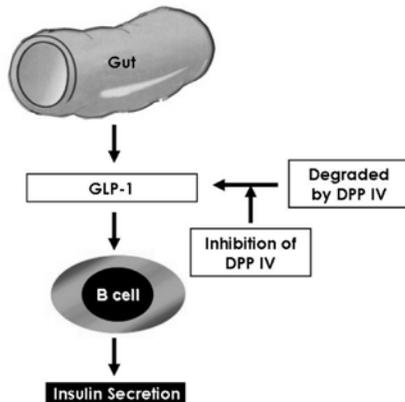
Other analogs currently in clinical development include slightly modified versions of the GLP 1 molecule that attach to albumin, thereby acquiring the pharmacokinetic profile of albumin.

Liraglutide is a potent, long-acting GLP-1 analog. The peptide is based on the structure of native GLP-1. The modifications include an amino acid substitution (replacement of lysine with arginine at position 34) and an attachment of a C16 acyl chain via a glutamoyl spacer to lysine at position 26. Liraglutide is administered as an isotonic solution for injection by the subcutaneous route; it is slowly absorbed with a time to maximum concentration (Tmax) of ~ 10 – 14 h and half-life ($t_{1/2}$) of ~ 11 – 13 h²⁹, making it suitable for once-daily injection. The long half-life of liraglutide is believed to be based on albumin binding and an ability to form micellar-like aggregates in the subcutis, resulting in prolonged absorption and elimination as well as DDP IV stability. It has been proven that liraglutide provides 24-h glycemic control³⁰. No

effect of gender or age has been seen with respect to the pharmacokinetics of liraglutide³¹.

The glucoregulatory mode of action of liraglutide in patients with Type 2 diabetes mellitus includes a glucose-dependent enhancement of insulin secretion and suppression of glucagons secretion together with a slowing of gastric emptying after both single and multiple injections. In addition, liraglutide has been shown to promote increased β -cell mass in animal models of Type 2 diabetes mellitus.^{32,33} In Phase II studies in patients with Type 2 diabetes mellitus on diet or oral antidiabetic treatment as monotherapy, liraglutide injected once daily significantly lowered fasting plasma glucose (FPG) concentrations, improved β -cell function and reduced body weight with a very low risk of hypoglycemia.^{34,35} The risk of hypoglycemia during GLP-1 treatment is very low. Liraglutide induced hypoglycemia do not impair the glucagon response or the general hypoglycemic counter-regulatory responses and liraglutide has not been proven to be insulinotropic at hypoglycemic plasma glucose concentrations.³⁶ Preclinical studies have shown that liraglutide lowers blood glucose, body weight and food intake in a broad selection of animal models.^{32, 37-39}

Recent data from a randomised, double-blind, parallel- group trial including 165 patients with Type 2 diabetes mellitus administered higher doses of liraglutide (0.65, 1.25 or 1.9 mg) for 14 weeks and demonstrated that liraglutide is capable of decreasing FPG levels between 2.7 mM (0.65 mg) and 3.4 mM (1.25 and 1.9 mg) on average when compared with placebo.³⁵ All three doses of liraglutide lowered both pre and postprandial self-monitored blood glucose levels. Interestingly, in the same study, a decrease in levels of HbA1c of ~ 1.7 percentage points was noted and $\sim 50\%$ of the patients with Type 2 diabetes mellitus managed to reach the goal level of $< 7\%$ in HbA1c set by the American Diabetes Association (ADA)⁴⁰ when receiving the 2 highest doses of liraglutide (1.25 and 1.9 mg) compared with only 5% in the placebo group.³⁵ In the highest liraglutide dose group (1.9

Figure 5: GLP 1 Action – Protected by DPP IV Inhibitors

mg), change from baseline in body weight was -2.99 and -1.21 kg compared with placebo³⁵. The most frequently reported side effects involve the gastrointestinal system during liraglutide treatment. Gradual dose escalation of liraglutide successfully reduced the proportion of subjects experiencing dose-limiting nausea.

Liraglutide as an add-on therapy to metformin was evaluated by Nauck *et al.* Following 5 weeks of treatment, HbA1c was significantly reduced relative to baseline in all of the groups except the group receiving metformin as a monotherapy. Furthermore, combination therapy with liraglutide plus metformin resulted in significantly greater reductions in HbA1c than liraglutide or metformin monotherapy⁴¹. Liraglutide in combination with metformin induced a clinically and statistically significant weight loss (2.9 kg) compared with metformin plus glimepiride.

DPP IV Inhibitors

Inhibitors of DPP IV have also proved effective in protecting endogenous GLP 1 from degradation.

The therapeutic use of inhibitors of DPP-IV, the enzyme responsible for inactivation of GLP-1 (Fig 5), as an antihyperglycemic agent was first proposed based on the finding that GLP-1 seems uniquely sensitive to cleavage by DPP-IV.⁴² DPP-IV inhibitors improve beta cell function and peripheral tissue sensitivity. This reduces both

fasting and postprandial glucose concentration and thus A1c. Another important consideration is that insulin levels are not elevated during inhibitor treatment.^{43,44} The DPP-IV inhibitors are given orally.

GLP 1 invariably inhibits gastric emptying whereas DPP IV inhibitors have little effect on gastric emptying. It has been established that nausea will be elicited when circulating concentrations of active GLP 1 exceeds 60 pmol/l which can be initially reached after subcutaneous injections of GLP 1 or GLP 1 mimetics. However this effect has never been seen when DPP IV inhibitors are used. In contrast to the results obtained with the GLP-1 analogs, no change in body weight was seen with DPP-IV inhibition.

The main effects of DPP IV inhibitors are mediated by GLP 1. One of the more important therapeutic effects of GLP 1 may be the inhibition of glucagon secretion, which also seems to be the case for DPP IV inhibitors – a striking similarity. Protection of GLP 1 is a major contributor to the effects of DPP IV inhibition.

The binding kinetics, type of inhibition and selectivity with respect to other peptidases for the inhibitor (now called vildagliptin) has been reported.⁴⁵ Januvia (Sitagliptin) is one of the marketed preparations under this category.

When comparing liraglutide with the orally administered DPP IV inhibitors (sitagliptin or vildagliptin), the effect of liraglutide seems to be more pronounced with the DPP IV inhibitors being weight neutral with an effect on HbA1c levels in the range of ~ 0.6 – 1%.⁴⁶⁻⁴⁸ The reason for this difference is most likely to be due to the substantially greater concentrations obtained when using a GLP-1 analog.

Protective effects of GLP I

The GLP-1-based therapies possess a unique potential: GLP-1 has trophic effects on beta cells⁴⁹. Not only does it stimulate beta cell proliferation^{50,51}, it also enhances the differentiation of new beta cells from progenitor cells in the pancreatic duct epithelium⁵² and, most importantly, GLP-1

is capable of inhibiting apoptosis of beta cells including human beta cells.⁵³

GLP-1 improves postprandial lipidemia, presumably as a result of delayed gastric emptying and insulin-mediated inhibition of lipolysis. Thus, by lowering both glucose and lipid concentrations, GLP-1 administration may reduce the cardiovascular risk in patients with type 2 diabetes.⁵⁴

GLP 1 based therapy should be started as early in the clinical course as possible, before beta cell function has deteriorated to unacceptable levels.

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