# Historical Overview of Incretin Based Therapies

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## Abstract

A set of physiological responses is activated following meal intake, providing neural and endocrine signals regulating the digestion, absorption and assimilation of ingested nutrients, in which incretin plays an important role. It is believed that the incretin effect is mediated mainly by two incretin hormones: gastric inhibitory polypeptide (GIP) and glucagon-like peptides (GLP)-1. Shortly following release from gut L cells, GLP-1 is rapidly degraded by dipeptide peptidase-4 (DPP-4) to GLP-1(9–36) or GLP-1(9–37) amide, which inactivates native GLP-1. Because of the short plasma half-life of native GLP-1, about 2 minutes, long-acting derivatives should be developed to make GLP-1 treatment therapeutically relevant.

It has been demonstrated that DPP-4 inhibition can protect GLP-1 and GIP from degradation, resulting in enhanced insulinotropic activity of infused GLP. Currently, DPP-4 inhibitors on the market are mainly sitagliptin and vildagliptin. Both inhibitors have significant antidiabetic effects when given in monotherapy and can result in further improvements in glycaemic control when given in combination with other antidiabetic agents such as metformin, sulfonylurea (SU) and thiazolidinediones (TZDs). Exenatide is the first GLP-1 receptor agonist that has been approved for use as an adjunctive therapy to improve glycaemic control in patients with type 2 diabetes who are not adequately controlled with metformin/SU mono- or combination therapy. Liraglutide is the first once-daily human GLP-1 analogue. In July 2009, Victoza® (liraglutide) was approved by the European Medicines Agency (EMA) in the treatment of type 2 diabetes mellitus to achieve glycaemic control. In January 2010, the U.S. Food and Drug Association (FDA) approved Victoza® as an adjunct therapy to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. It has been shown in different trials that at suggested therapeutic doses of 1.2 mg and 1.8 mg, liraglutide can lower glycated haemoglobin A1c ($HbA_{1c}$) by 1.0–1.5% points as mono- or combination therapy in approximately two-thirds of subjects. GLP-1 receptor agonist showed a greater effect than the DPP-4 inhibitor in reducing postprandial glucose (PPG) concentrations, a more potent effect in increasing insulin secretion and decreasing postprandial glucagon secretion, a relatively greater effect in reducing caloric intake, and it decreased the rate of gastric emptying.

Overall, available evidence supports the use of incretin-based therapies in diabetes patients requiring effective glycaemic and body weight control while minimising the risk of hypoglycaemia.


## The Discovery of Incretin Hormones and Incretin Effect

A set of physiological responses is activated following meal intake, providing neural and endocrine signals regulating the digestion, absorption and assimilation of ingested nutrients, in which incretin, mainly GIP and GLP-1 (Table 1), plays an important role.[1]

The existence of incretins was postulated in the early 20th century when Murce administered duodenal extract in patients with diabetes and demonstrated reduction in glucosuria. However, the identity of the putative incretin factor(s) remained elusive until the purification and characterisation of the first incretin, GIP, was discovered in 1973. GIP is a peptide of 42 amino acids, produced predominantly in duodenal K cells in the proximal small intestine, and can inhibit acid secretion in denervated gastric pouches.[2] Soon after its discovery, insulinotropic properties of GIP were further exposed.[3] The predominant stimulus for GIP secretion is nutrient intake. Circulating levels of GIP are low in the fasting state and rise within minutes of food ingestion.

An early animal experiment has shown that gut extracts from rats have insulinotropic activity. However, removal of GIP from gut extracts did not eliminate such effects. This finding indicates that the insulinotropic activity of rat gut extracts can only be partially related to GIP, and additional insulinotropic gut factors may also be released following oral glucose.[4] Using GIP antiserum, Alam MJ et al. measured circulating GIP levels in 18 healthy volunteers, and 13 type 2 and 9 type 1 diabetes patients following ingestion of 75 g of glucose.[5] Besides the significant difference in blood glucose and insulin levels observed between healthy and diabetes patients, circulating GIP levels at all time-points and integrated incremental GIP over 120 minutes were not different among various groups. Results from this study implicated that gut-derived biological active factor other than GIP also played a significant role in the pathogenesis of the disease.

A decade later, a second peptide with incretin activity was

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**Table 1 : GLP-1 and GIP**

| GLP-1<br>Glucagon-like peptide 1 | GIP<br>Gastric inhibitory polypeptide |
|---|---|
| Is released from L cells in ileum and colon | Is released from K cells in duodenum |
| Stimulates insulin response from beta cells in a glucose-dependent manner | Stimulates insulin response from beta cells in a glucose-dependent manner |
| Inhibits gastric emptying | Has minimal effects on gastric emptying |
| Reduces food intake and body weight | Has no significant effects on satiety or body weight |
| Inhibits glucagon secretion from alpha cells | Does not appear to inhibit glucagon secretion from alpha cells |
| Deficient in type 2 diabetes | Normal levels but decreased responsiveness in type 2 diabetes |

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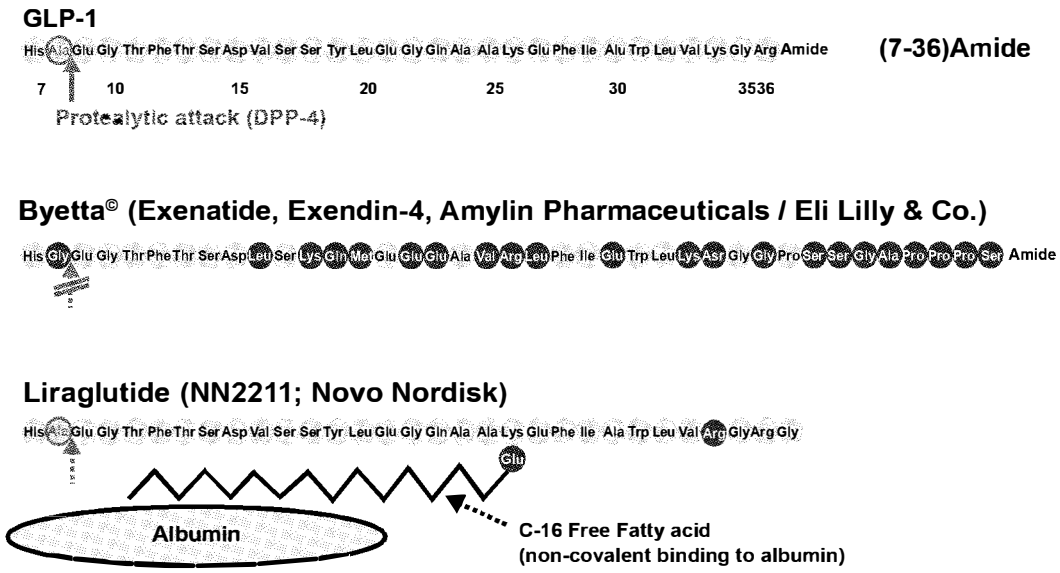


**Fig. 1 : Molecular structure of native GLP-1, exenatide & Liraglutide**

identified after cloning and characterising of the proglucagon gene. Proglucagon is a pro-hormone containing two separate peptides: GLP-1 and -2.[6] Only the amino acid sequence of GLP-1 (Figure 1) after residue 7 shows the similarity to glucagon and to other biologically active members of the incretin family, particularly GIP.[7] Circulating concentration of GLP-1 after a meal is about 10-fold lower than that of GIP. GLP-1 is rapidly degraded by DPP-4 into GLP-1(9–36) or GLP-1(9–37) amide following its release from gut L cells, which are an inactive form of native GLP-1.[8] In addition, the remaining proportion of GLP-1 or GIP will be rapidly cleared from the kidney. In circulation the plasma half-life ($t_{½}$) of GLP-1 is about 1–2 minutes.[9]

The effects of GLP-1 are mediated after binding to its specific plasma membrane receptors that belong to the 7 trans-membrane-domain receptor family coupled to G-proteins.[10] GLP-1 receptors are expressed in the gastrointestinal tract, endocrine pancreas ($\alpha$ and $\beta$ cells), lung, kidneys, heart and several areas of the brain (hypothalamus, nucleus of the solitary tract, area postrema).

It is shown that GLP-1(7-36) is a more potent insulin secretagogue than GIP *in vitro*.[11, 12] It has been shown in both preclinical and human studies that, *in vivo*, GLP-1 can stimulate insulin secretion in a glucose-dependent manner.[12, 13] Other biological effects, which include inhibiting glucagon secretion, decelerating gastric emptying and reducing food intake with GLP-1, were also demonstrated. Furthermore, previous studies indicated that GLP-1 promoted enhanced glucose disposal in peripheral tissues. In addition, activation of the incretin receptors on $\beta$ cells resulted in other longer term effects such as enhanced $\beta$-cell proliferation and promoted resistance to $\beta$-cell apoptosis.[14]

Interestingly, GLP-1 may also have other beneficial effects that are independent from its effects on glucose metabolism. Animal studies showed that GLP-1 protected myocardial cells from ischemic and reperfusion injury, prevented endothelial dysfunction, promoted endothelium in dependent artery relaxation and increased diuresis and natriuresis.[15] In subjects with type 2 diabetes, studies showed that GLP-1 reduced systolic blood pressure (SBP) and deceased plasma concentrations of triglyceride and plasminogen activator inhibitor (PAI-1) and brain natriuretic peptide (BNP), which are considered biomarkers of cardiovascular diseases.[16]

## Summary of Native GLP-1 Studies

A single-centre, randomised, parallel, double-blind, placebo-controlled trial was conducted in 40 hospitalised patients who were randomised to receive continuous infusions of either placebo or native GLP-1 at 4 or 8 ng/kg/min for either 16 or 24 h per day over 7 days. Results demonstrated that continuous infusion of native GLP-1 dramatically lowered both fasting and postprandial glucose concentrations without any sign of tachyphylaxis over 7 days.[17] However in this study, it was not possible to completely normalise plasma glucose concentrations within the therapeutic window. This study demonstrated that native GLP-1 should be given continuously to obtain the most optimal glycaemic control.

Because of the short plasma half-life of native GLP-1, there is a need to develop long-acting derivatives to make GLP-1 treatment clinically relevant.

## DPP-4 Inhibitors

DPP is an enzyme secreted from endothelial cells that rapidly degrades both GIP and GLP-1. It has been demonstrated that inhibiting DPP-4 activity can effectively protect GIP from degradation, resulting in enhanced insulinotropic activity of infused GIP.[17] Furthermore, in the presence of the DPP-4 inhibitor (valine-pyrrolidide), the proportion of intact GLP-1 released from the perfused porcine ileum is increased under both basal and stimulated conditions.[18] In the light of these findings, DPP-4 inhibitor has been proposed as a new therapy for the treatment of type 2 diabetes.[19]

The main DPP-4 inhibitors on the market are sitagliptin (Januvia, Merck & Co., Inc.) and vildagliptin (Galvus, Novartis AG). Both inhibitors have good oral bioavailability and a relatively long duration of action. Once-daily dosing of DPP-4 inhibitors can give 70–90% inhibition of plasma DPP-4 activity over a 24-h period. DPP-4 inhibitors (glycated haemoglobin $A_{1c}$ [$HbA_{1c}$] reduction by 0.7%) can be administrated as monotherapy and result in further improvement in glycaemic control when given in combination with other antidiabetic agents including metformin, SU and TZDs.[20] Ahren et al. demonstrated that after 12 weeks' oral administration with DPP-4 inhibitor, vildagliptin in patients with type 2 diabetes, long-term glycaemic control,

**Table 2 : GLP-1 receptor agonist and DPP-4 inhibitors**

| | GLP-1 receptor agonist | DPP-4 inhibitors |
|---|---|---|
| Administration | Subcutaneous | Oral |
| $t_{½}$ | up to 24 h/d | 3–6 h (meals) |
| GLP-1/receptor agonist concentration | Pharmacological | Close to physiological |
| Action through | GLP-1 receptor (exclusively) | GLP-1 receptor, GIP-receptor and others |
| GLP-1 receptor activation | Pharmacological GLP-1R potentiation | Enhancement of endogenous GLP-1 and GIP |
| $HbA_{1c}$ reduction | -0.8–1.8% | ≈-0.5–1.1% |
| Weight change | Satiety and weight loss | Weight neutral |
| Beta-cell mass effects (animal experiments) | Robust | Probable |
| Adverse events | Nausea and vomiting | Well tolerated |

prandial plasma glucose, as well as fasting plasma glucose were significantly reduced.[21]

Previous clinical trials also indicated that a DPP-4 inhibitor such as vildagliptin improved acute β-cell function by showing that oral administration with vildagliptin increased insulin response in relation to the glucose response after meal ingestion,[22] and increased estimated insulin secretory rate after meal ingestion.[23, 24]

It was shown in clinical trials that both vildagliptin and sitagliptin were tolerable and safe with an adverse events profile similar to that of placebo-administered patients. Also, the reported numbers of hypoglycaemia were very low during DPP-4 treatment. Unlike GLP-1 receptor agonist or human GLP-1 analogue, most studies with DPP-4 inhibitor reported that the drug had no effect on blood pressure. Moreover, in contrast to the reduction in body weight seen after treatment with GLP-1 analogues, DPP-4 inhibitors were body weight neutral.[25]

DPP-4 inhibitors may be considered as an additional choice and possible alternative treatment to currently available antidiabetic agents in type 2 diabetes. However, long-term safety and efficacy data are still required.

## GLP-1 receptor agonist

Exenatide (Figure 1) has been developed by Amylin Pharmaceuticals, Inc. and Eli Lilly and Company for diabetes treatment under the name Byetta●. It is a synthetic peptide, and originally identified in the lizard Heloderma spectum. As a GLP-1 receptor agonist (designating a synthetic replica of exendin 4), exenatide is administered twice daily.[26] Exenatide received FDA approval as an adjunctive therapy to improve glycaemic control in patients with type 2 diabetes who are inadequately controlled with metformin, SU and TZD mono- or combination therapy.

Clinical trials with exenatide demonstrated that exenatide stimulated insulin secretion in a glucose-dependent manner, and suppressed glucagon secretion, slowed gastric emptying and reduced food intake in patients with type 2 diabetes. It also showed that exenatide administration improved long-term glycaemic control.[27] Exenatide may delay or even halt the progression of type 2 diabetes due to its effect on β-cell mass and function. However, this effect has to be further evaluated in long-term clinical trials.

The most common adverse effects experienced by patients who were treated with exenatide were nausea and vomiting. However, incidence of gastrointestinal adverse effects was significantly reduced with step-wise dose escalation of exenatide. Currently there are no reports of hypersensitivity reactions to exenatide. Yet the amino acid sequence of exenatide shares slightly more than 50% of its identity with human native GLP-1.[28] This may explain why the second most reported adverse event associated with exenatide therapy was antibody formation. Approximately 40–67% of patients treated with exenatide had positive anti-exenatide antibody titres at the end of the study.[29, 30] In another open-label, single-arm, multicentre, 24-week study in patients who were re-exposed to exenatide, an anti-exenatide antibody was developed in more than 70% of patients.[31] Among those who developed an antibody, around 40% of patients did not have $HbA_{1c}$ reduction. However, the study design limitations (overall sample size and disparity between subgroups) and the dissimilar diabetes treatment at study initiation do not allow for conclusions to be drawn on the $HbA_{1c}$ findings.

Pancreatitis has been reported as a rare side effect of exenatide therapy principally through post-marketing surveillance. A summary of the first 30 cases of individuals taking exenatide who developed acute pancreatitis was published in 2008.[32] The authors noted that in at least 90% of these subjects, there were other factors that could predispose the individuals to pancreatitis. Analysis of pancreatitis in subjects with type 2 diabetes notably suggests that their risk is increased threefold over nondiabetic subjects.[33] Since only a fraction of this risk could be attributed to biliary pancreatitis, it seems likely that other factors such as obesity and hypertriglyceridemia might contribute to the increased risk in this population.

A recent study compared the effects of GLP-1 receptor agonist exenatide with that of DPP-4 inhibitor sitagliptin on postprandial glucose (PPG) concentrations, insulin and glucagon secretion, gastric emptying, and caloric intake.[34] Although limited by the short treatment duration (2 weeks), the study showed that the GLP-1 receptor agonist had a better effect than the DPP-4 inhibitor in reducing PPG concentrations (Table 2). Furthermore, exenatide was more potent in terms of increased insulin secretion, decreased postprandial glucagon secretion and reduced caloric intake as compared with sitagliptin. Results also indicated that in contrast to exenatide, sitagliptin had no effect on gastric emptying.

## Human GLP-1 analogue

Liraglutide (Figure 1) is a once-daily human GLP-1 analogue, which has been developed by Novo Nordisk.

In liraglutide, lysine at position 34 of human native GLP-1 is substituted by arginine, and a palmitic acid chain (C-16) is attached to an ε-amino group of lysine at position 26 via glutamate spacer. Liraglutide has 97% amino acid homology with the human GLP-1 peptide and is produced by a recombinant DNA technology in Saccharomyces cerevisiae.

In July 2009, Victoza● was approved by EMA in the treatment of type 2 diabetes mellitus to achieve glycaemic control in combination with 1) metformin or SU, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or SU, or 2) metformin and SU or metformin and TZD in patients with insufficient glycaemic control despite dual therapy. In January 2010, the FDA approved Victoza● as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. In

**Table 3 : Liraglutide vs. exenatide**

| | Liraglutide | Exenatide |
|---|---|---|
| Homology with native GLP-1 | 97% | 50% |
| Administration | Injection once daily | Injection twice daily |
| Glucose-dependent insulin secretion and glucagon | Yes | Yes |
| Slows gastric emptying | Little | Yes |
| Effect on $HbA_{1c}$ | 0.9–1.6% | 1–1.6% |
| Effect on body weight | Weight loss | Weight loss |
| Effect on FPG | Good | Modest |
| Effect on PPG | Modest | Good |
| Effect on CVD risk factors | Improvement | Improvement (with weight loss) |
| Common side effects | Some nausea | Nausea |
| Pancreatitis | Rare | Rare |
| Rodent medullary thyroid cancer | Signal | Little or no signal |

India, Victoza® is approved for "use in type 2 diabetes". So it can be used in monotherapy as well as in combination with other antidiabetic agents. At the suggested therapeutic doses of 1.2 mg and 1.8 mg in several phase 3 trials, liraglutide lowered $HbA_{1c}$ by 1.0–1.5% in approximately two-thirds of patients when administered as monotherapy or in combination with other oral antidiabetic drugs (OADs).[23] The magnitude of $HbA_{1c}$ reduction was significantly greater with liraglutide than with a number of currently available type 2 diabetes treatments. A significant reduction in weight and a decrease in SBP were documented across a number of the phase 3 trials.

Liraglutide was generally well tolerated. The most common adverse events with liraglutide treatment were related to the gastrointestinal system, and the most frequently reported side effect was nausea. These adverse events were mostly mild and occurred during the initial period of treatment. Development of an anti-liraglutide antibody was rare. In addition, no neutralising effect of such an antibody was observed in the clinical trials.

In preclinical carcinogenicity studies, liraglutide was associated with a dose-dependent increase in the frequency of thyroid C-cell tumours in rats and mice.[35] Calcitonin was measured in the liraglutide phase 3a trials as a marker to monitor thyroid C-cell mass. There were no clinical signals of increased C-cell tumours (i.e., medullary thyroid carcinoma) with liraglutide in humans and non-human primates. In the controlled clinical trials, increases in calcitonin levels occurred in a slightly higher percentage of the patients treated with liraglutide than in control patients; although the increases represented shifts from below to slightly above the assay's detection limit (0.7 ng/L), calcitonin levels were still within normal ranges.[36] Furthermore, data from a long-term study did not reveal any notable difference in mean calcitonin levels between liraglutide and control groups over 2 years of follow-up. The FDA concluded that increases in the incidence of carcinomas among rodents translated into a low risk for humans, because statistically significant increases occurred only at drug exposure levels many times those anticipated in humans, and the increase in cancers did not affect overall survival rates. However, it is difficult to extrapolate findings from studies in animals to humans. To further explore possible associations between medullary thyroid cancer and liraglutide use, the FDA exercised its authority under the Food and Drug Administration Amendments Act to require additional studies in animals and the establishment of a cancer registry to monitor the annual incidence of medullary thyroid cancer over the next 15 years.

Another safety concern is a possible increased risk of pancreatitis attributable to drugs that act through the GLP-1 pathway.[36] This concern arises from post-marketing reports submitted to the FDA Adverse Event Reporting System regarding pancreatitis associated with the use of exenatide and sitagliptin, both of which act through this pathway. In the phase 2 and phase 3 trials of liraglutide, there were seven cases of pancreatitis reported among the 4257 patients treated with liraglutide, and only one case in the 2381 patients in the comparator group. The small number of events makes it difficult to draw conclusions about causation, but this imbalance, along with concerns about exenatide and sitagliptin, led the FDA to require the sponsor to perform post-approval mechanistic studies in animals and to conduct an epidemiologic evaluation using a large insurance-claims database. Prescribers and patients should be aware that the common side effects of liraglutide include nausea and vomiting, but persistent or severe nausea and vomiting should be carefully evaluated since they may be early manifestations of pancreatitis and therefore warrant prompt discontinuation of liraglutide treatmentRecently, in a 26-week randomised, parallel-group, multinational, open-label trial, clinical efficacy and safety of liraglutide was compared with exenatide.[37] In this trial, 464 adults with type 2 diabetes, who were inadequately controlled on maximally tolerated doses of metformin, SU or both, were treated. Results showed that liraglutide reduced mean $HbA_{1c}$ significantly more than exenatide with a difference of 0.33%. More patients achieved a $HbA_{1c}$ value of less than 7% in the liraglutide group than exenatide (54% *vs.* 43%). Both drugs resulted in similar weight loss, and were well tolerated, but nausea was less persistent and minor hypoglycaemia less frequent with liraglutide than with exenatide (Table 3).

In addition, recombinant albumin-GLP-1 fusion proteins have been developed that mimic the full range of GLP-1 actions. Albiglutide is one example: it stimulates GLP-1 receptor–dependent pathways coupled with glucose homeostasis and gastrointestinal motility, improves insulin secretion and reduces blood glucose.[38] Little clinical information is currently available regarding this drug's safety in humans. Taspoglutide is a matrix-free sustained-release formulation for GLP-1 now being converted for phase 3 studies.

Semaglutide (NN9535) is a once-weekly human GLP-1 analogue that is being developed by Novo Nordisk for the treatment of type 2 diabetes. Semaglutide lowers blood glucose through stimulating release of insulin and lowers body weight. The phase 2 programme with more than 400 people was completed in 2009. Novo Nordisk is also developing an oral GLP-1 (NN9924) to increase the convenience of GLP-1 treatment of type 2 diabetes. It is more resistant to enzymatic degradation, and its first phase 1 clinical trial started January 2010.

In conclusion, available evidence indicates that unlike current antidiabetic treatments, incretin-based therapies possess great potential in offering effective glycaemic and weight control to patients with type 2 diabetes. This new therapeutic modality does not increase the risk of hypoglycaemia. However, more data on long-term safety and the cost-effectiveness analysis of such treatment are still needed.

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