Glucagon like peptide-1: A new therapeutic target for diabetes mellitus


Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana-384001, Gujarat, \(^1\)L.M. College of Pharmacy, Navrangpura, Ahmedabad-380009, Gujarat, India

Correspondence to: Patel Sunita Kanjibhai
E-mail: sunitapatel207@yahoo.com

ABSTRACT

Glucagon-like peptide-1 (GLP-1) is an endogenous peptide secreted from the gut in response to the presence of food. GLP-1 and its longer acting analog exendin-4 have multiple synergistic effects on glucose dependent, insulin secretion pathways of the pancreatic \(\beta\)-cell and on plasticity in neuronal cells. Recently the development of these peptides as a novel therapeutic strategy for non-insulin-dependent (type 2) diabetes mellitus and associated neuropathy has been the focus of much interest. Here we describe the biological actions of GLP-1 and its related analogs.

KEY WORDS: Exendin-4, NIDDM.

Introduction

Non-insulin dependent diabetes mellitus is a progressive disease that is prevalent in the elderly as well as among the youth. Unlike type 1 diabetes, people with type 2 diabetes mellitus might make healthy, even high levels of insulin, but there is a decrease in insulin action on insulin-sensitive tissues.\(^{[9]}\) There is also evidence to indicate that type 2 diabetes, or at least impaired glucose tolerance, is associated with impaired cognition, independent of age. Therefore, the normal, age-related decline in cognitive function might be exacerbated by the development of impaired glucose tolerance and insulin resistance.\(^{[21]}\)

Diabetes has become the major cause of peripheral neuropathy, afflicting some 20% to 30% of type 2 diabetics, for which there is currently no treatment other than strict control of blood glucose levels. A major focus of endocrinology research over the past 5 years has been the development of a new therapeutic strategy for type 2 diabetes and neuropathy, based on the insulinotropic actions of endogenous peptides specifically, glucagon-like peptide-1 (7-36) amide (GLP-1) and glucose-dependent insulinotropic peptide (GIP). They are released from entero-endocrine cells of the gastrointestinal mucosa following the ingestion of nutrients. They regulate nutrient metabolism via effects on insulin release from pancreatic islets, gastric motility and acid secretion, islet cell proliferation and nutrient disposal.\(^{[3-5]}\) Infusion of GLP-1, at pharmacological concentrations, lowers blood glucose in type 2 diabetic and non-diabetic subjects.\(^{[5, \text{6}]}\)

An important regulator of the biological activity of GLP-1 is N-terminal degradation by the common, endogenous, amino peptidase enzyme, dipeptidyl peptidase IV (DPP-IV). This enzyme cleaves GLP-1 at the alanine residue at position 2,\(^{[7]}\) which not only inactivates GLP-1, but also might turn it into an antagonist at the GLP-1 receptor.\(^{[9]}\) Several studies confirm that DPP-IV mediated inactivation of these peptides is a crucial control mechanism that regulates the biological activity of both GIP and GLP-1 in rodents\(^{[8]}\) and humans.\(^{[7], [10]}\) Continuous infusion of the peptide is required to maintain steady-state levels of active GLP-1 in plasma.\(^{[11], [12]}\)

Proposed signaling mechanism for GLP-1

GLP-1 action is mediated by binding to a specific, seven-transmembrane G-protein coupled receptor (GLP-1 receptor) that is coupled positively to the adenyl cyclase (AC) system.\(^{[13], [14]}\) Ligand activation of the Gq subunit of the GLP-1 receptor stimulates AC, which leads to an increase in intracellular cAMP and activation of protein kinase A (PKA). GLP-1 acts directly through the cAMP-PKA pathway to enhance and sensitize \(\beta\)-cells to glucose-stimulated insulin secretion. Glucose metabolism in the \(\beta\)-cell causes an increase in the concentration of ATP and raises the cytoplasmic ATP:ADP ratio, which leads to depolarization of the plasma membrane following closure of ATP-sensitive K\(^+\) channels. This permits opening of voltage-dependent L-type Ca\(^{2+}\) channels and increase cytosolic Ca\(^{2+}\), which triggers fusion of insulin-containing secretory vesicles to the plasma membrane. Exocytosis of insulin follows rapidly. Activation of GLP-1
receptor by GLP-1 leads to an increase in [Ca\(^{2+}\)], as a result of activation of the L-type Ca\(^{2+}\) channel following phosphorylation of PKA and/or mobilization of intracellular Ca\(^{2+}\) stores, an effect that might or might not be PKA dependent.\(^{s15}\) Much is known about the signaling pathways that occur following the binding of GLP-1 to the GLP-1 receptor in pancreatic \(\beta\)-cells but, as yet, little has been confirmed in other cell types.\(^{s16,s17}\) The G\(\beta\)\(\gamma\) dimer activates phosphatidylinositol-3-kinase (PI3K), which subsequently activates mitogen-activated protein kinase (MAPKs) (by a PKC-dependent or independent mechanism).\(^{s10}\) This pathway is associated strongly with the GLP-1-induced proliferative signal in \(\beta\)-cells and the trophic effect in neuronal cells in culture: inhibition of PI3K (with LY294002) or MAPK (with PD98059) results in limited GLP-1-stimulated neurite outgrowth.\(^{s16}\) GLP-1-mediated activation of PI3K and downstream effectors [such as the transcription factor pancreatic and duodenal homeobox gene-1 (PDX-1)] are thought to regulate expression of the gene encoding insulin, \(\beta\)-cell growth, and differentiation of the \(\beta\)-cell phenotype in islet, ductal and exocrine cells.\(^{s18,s19}\) cAMP activates a GTPase of the Ras superfamily, Rap 1, following PKA-dependent phosphorylation. Certainly, cAMP activates multiple intracellular signaling cascades independently of its activation of PKA. An alternative, PKA-independent pathway was recently proposed in \(\beta\)-cells,\(^{s20}\) which involves two types of cAMP-GFs. GPs are activated by binding to cAMP and activation of Rap 1A.\(^{s21}\) Rap 1A inhibits Ras but activates PKG and B-Raf, the latter two events both leading to activation of MAPKs.

### Biological effects of GLP-1

**Insulinotropic action**

The insulinotropic effects of GLP-1 are strictly glucose dependent; it has no effect on insulin secretion at glucose concentrations below 4.5 mM.\(^{s22}\) In addition, GLP-1 strongly potentiates the insulinotropic actions of glucose itself.\(^{s23}\) It enhances all the steps of insulin biosynthesis and transcription of the insulin gene, which provides a continuous, augmented supply of insulin for secretion. Indeed, the expression of genes that are essential for \(\beta\)-cell function, such as glucokinase and Glut 2 are up regulated following GLP-1 treatment. GLP-1 also has trophic effects on \(\beta\)-cells. It both stimulates \(\beta\)-cell proliferation and enhances the differentiation of new \(\beta\)-cells from progenitor cells in the epithelium of the pancreatic duct.\(^{s24,s19}\) Subsequently, Perfetti et al. demonstrated GLP-1 mediated endocrine proliferation in glucose-intolerant aging rats, with a resultant improvement in glucose tolerance.\(^{s12}\) This indicates that GLP-1 might be capable of stimulating the growth of new \(\beta\)-cells in individuals such as type 2 diabetic patients, who have an insufficient number of functioning cells.

**Inhibition of glucagon secretion**

GLP-1 inhibits glucagon secretion in a glucose-dependent manner.\(^{s25,s26}\) Glucagon opposes the effects of insulin on maintaining blood glucose levels, which contributes significantly to the development of hyperglycemia in diabetic subjects. Therefore, injectable glucagon can be used as a treatment for hypoglycemia. However, repeated hypoglycemia often results in the development of a defective counter-regulatory glucagon response.\(^{s13}\) In the hyperglycemic condition, GLP-1 infusion suppresses glucagon secretion which suggests that glucagon suppression is on account of hyperglycemia but not an effect mediated by GLP-1.\(^{s27}\) Thus, the glucose lowering effect of GLP-1 might be a consequence of the inhibition of glucagon secretion but this is not the only mechanism proposed for the hypoglycemic effect of GLP-1, indicating that treatment with GLP-1 is unlikely to interfere with the glucagon mediated defense against hypoglycemia.\(^{s28}\)

**Gastrointestinal effects**

GLP-1 inhibits gastrointestinal secretion and motility, most notably gastric emptying.\(^{s29}\) The speed of gastric emptying response (within a couple of minutes) is indicative of either a neural or endocrine signaling mechanism from the upper gastrointestinal area. GLP-1 is one of the main hormones of the ‘ileal brake’, the primary, inhibitory feedback mechanism that controls the transit of meal through the upper gastrointestinal tract to optimize nutrient digestion and absorption.\(^{s2}\)

During physiological malabsorption, GLP-1 secretion is stimulated and gastric and pancreatic secretions are inhibited.\(^{s28}\) Infusion of GLP-1 during the ingestion of a meal dose-dependently diminishes the insulin responses, rather than enhance them.\(^{s25}\) This is likely to be related to reduced gastric emptying and subsequent decrease in absorption of insulinotropic nutrients.\(^{s29}\) The GLP-1 mediated potentiation of nutrient stimulated insulin secretion might be achieved, in part, through the control of chyme levels in the digestive tract by retarding propulsion and digestion of gastric contents.\(^{s28,s29}\)

**CNS effects of GLP-1**

GLP-1 receptor is expressed in the brains of rodents and humans.\(^{s30,s31}\) GLP-1 receptors are present in the hypothalamic nucleus indicating a role of GLP-1 in the central regulation of food intake. GLP-1 receptor expression has also been demonstrated in the thalamus, brainstem, lateral septum, subfornical organ and the area postrema.\(^{s31,s32}\) In addition to this, specific GLP-1 binding sites are also present in neurons in the caudate-putamen, cerebral cortex, hippocampus and cerebellum at lower densities.\(^{s30,s31,s14}\) Although the stimulus for activation of neuronal GLP-1 receptors in the CNS is unclear, it remains to be established if GLP-1 is produced by neural cells. GLP-1 in the blood stream can enter brain but its function is unknown.\(^{s13,s35}\)

Intestinally derived peptides, such as GLP-1, are classified as both hormones and growth factors-peptides that can regulate diverse cellular processes, including mitosis, growth and differentiation. The recent study shows that GLP-1 can induce the differentiation of neuronal cells in culture in a way that is similar to nerve growth factor; reflects the GLP-1 mediated neogenesis that occurs in pancreatic \(\beta\)-cells.\(^{s16,s24}\)

**Effects of GLP-1 on appetite and food intake**

Recent studies indicate that GLP-1 dose-dependently inhibits feeding behavior in rodents, which can be reversed with exendin, the GLP-1 receptor antagonist. Such satiety-related effects also appear to occur in humans, because peripheral administration of GLP-1 significantly enhances satiety and reduces appetite in both healthy and diabetic subjects, although such effects are transient.\(^{s15,s22,s36-38}\) Whether GLP-1 receptor-mediated signaling pathways are essential for the physiological control of appetite and body weight remains unclear. Certainly, inhibition of gastric emptying might account
for the satiety after GLP-1 administration. Likewise, nutrients in the ileum are thought to have a satiating effect and decrease food intake. Since hypothalamic nuclei that control feeding behavior express GLP-1 receptors it has been suggested that peripheral GLP-1 might exert indirect effects on satiety center in the CNS through neuronal relay mechanisms. However, GLP-1 receptor knockout mice appear to be resistant to the development of obesity.[30, 39] This strongly suggests that GLP-1 receptor signaling is not essential for the long-term control of body weight.

**Neuroprotective effects of GLP-1**

Activation of GLP-1 receptor modulates cell survival in diverse cell types. GLP-1 treatment reduces the number of apoptotic cells in the pancreas of Zucker diabetic fatty rats and db/db mice with an associated increase in the islet size and β-cell mass.[40-42] In addition, GLP-1 also protects against H_{2}O_{2} induced apoptotic cell death in an insulin-secreting cell line.[43] Furthermore, in rat hippocampal neurons in culture, which express functional GLP-1 receptors, GLP-1 and exendin-4 completely protect against glutamate-induced cell death in a manner that is similar to other neurotrophic factors.[43, 44] This provided the first indication of a neuroprotective role for GLP-1 receptor agonists and demonstrates that the antiapoptotic action mediated by GLP-1 might not be restricted to insulin-secreting cells. Although much is known about the signaling pathways involved in apoptotic cell death, the precise mechanism how GLP-1 challenges pro-apoptotic stimuli in diverse cell types is unclear. PI3K, MAPK and cAMP are important signaling molecules involved in GLP-1 mediated cell proliferation and differentiation. Recent studies indicate a role for PI3K-dependent, MAPK-independent signaling in the anti-apoptotic activity of GLP-1.[42]

The amyloid-β peptide (Aβ), cellular oxidative stress and membrane-lipid peroxidation are believed to play important roles in the dysfunction and death of neurons in Alzheimer’s disease. Hippocampal neurons in culture have been exposed to toxic levels of Aβ and iron in the presence and absence of GLP-1 and exendin-4.[45] Both peptides dose-dependently protect neurons against the insults, which indicate possible antiapoptotic and antioxidant actions. Furthermore, GLP-1 and exendin-4 reduce the depletion of choline acetyltransferase immunoreactivity, a marker of acetylcholine-containing neurons in the basal forebrain, in a well-established model of neurodegeneration in rats.[43] Collectively, these data indicate that GLP-1 agonists are likely to play a role in protecting neurons against several types of brain injuries, including excitotoxic and oxidative damage. A study in rats infused with exendin, a GLP-1R antagonist demonstrated decreased neurotoxicity following infusion with beta amyloid protein.[45] In contrast, studies using the rat PC12 pheochromocytoma cell line, which expresses the GLP-1 receptor, suggest that GLP-1 agonists promote neurite outgrowth and NGF-induced differentiation, and may enhance cell survival following withdrawal of NGF depending on the timing of exendin-4 administration. The differentiation actions of GLP-1 were abrogated by the kinase inhibitors LY294002 or PD98059, but the PKA inhibitor H-89 had only modest effects on these actions. Hence, these findings suggest that GLP-1R signaling, perhaps independent of PKA activation, may be neurotrophic in the correct cellular context.[46] A follow-up study from the Greig lab demonstrated that GLP-1, and exendin-4, can completely protect cultured rat hippocampal neurons against glutamate-induced apoptosis, and both GLP-1 and exendin-4 reduced ibotenic acid-induced depletion of choline acetyltransferase immunoreactivity in rat basal forebrain cholinergic neurons.[47] Hence, these results suggest that GLP-1 action in the brain may be neuroprotective, perhaps via activation of anti-apoptotic signaling pathways in specific neurons.[48]

**GLP-1 in learning and memory**

During et al. using a variety of gene therapy, and peptide-based technologies, has shown that activation of CNS GLP-1R signaling enhances associative and spatial learning through GLP-1R. These investigators used a novel N-terminal exendin-4 derivative, [Ser(2)]exendin(1-9), which when administered peripherally, gains access to the CNS, and activates the CNS GLP-1R system. GLP-1R-deficient mice exhibit a learning deficit phenotype which is restored after hippocampal GLP-1R gene transfer. Furthermore, gain of function studies in rats over-expressing the GLP-1R in the hippocampus show improved learning and memory. GLP-1R-deficient mice also have enhanced seizure severity and neuronal injury after kainate administration, with correction after GLP-1R gene transfer in hippocampal somatic cells. Systemic administration of the GLP-1R agonist peptide [Ser(2)]exendin(1-9) in wild-type animals prevent kainate-induced apoptosis of hippocampal neurons.[49]

**GLP-1 and diabetes**

GLP-1 when given as a continuous intravenous infusion is effective in patients with type 2 diabetes by increasing insulin secretion and normalizing fasting as well as postprandial blood glucose;[50] even in advanced type 2 diabetes long after sulfonylurea secondary failure.[51] Unexpectedly, the effects of a single subcutaneous injection of GLP-1 were disappointing. Although high plasma levels of immunoreactive GLP-1 were achieved, insulin secretion rapidly returned to pretreatment values and blood glucose concentrations were not normalized.[52] Nevertheless, the effect of repeated subcutaneous administration on fasting blood glucose was as good as that of intravenous administration.[53] Continuous subcutaneous administration for 6 weeks also reduced fasting and postprandial glucose concentrations and lowered Hba1c concentrations.[53, 54]

The progressive loss of β-cell function and mass is an early feature of type 2 diabetes, eventually leading to insulin dependence in many patients.[55] Intervening early in the course of diabetes or perhaps in the prediabetic state to stimulate β-cell differentiation and/or reduce apoptosis could theoretically halt the progression of the disease. Both GLP-1 and exendin have shown promise in this respect.[56]

**Therapeutic strategies based on GLP-1**

In this review we have highlighted considerable evidence that indicates that activation of the GLP-1 receptor is an important determinant for cell survival, particularly following organ and tissue damage. This makes GLP-1 an attractive therapeutic agent. However such potential is limited by the susceptibility of GLP-1 to proteolytic degradation. Many studies...
have addressed the possibility of manipulating the in vivo survival of GLP-1 as a novel approach to the treatment of diabetes. In this context, two separate approaches can be envisaged:

1) the development of analogs of GLP-1 that are not susceptible to enzymatic degradation and
2) the use of selective enzyme inhibitors to prevent in vivo degradation and enhance the levels of biologically active peptides.\[19\]

**Enzyme-resistant GLP-1 analogs**

Exendin-4 is a GLP-1 receptor agonist, originally isolated from the venom of the Gila monster lizard, which shares 53% sequence homology with native GLP-1. It is resistant to DPP-IV (because of the penultimate NH\(_2\)-terminal is glycine instead of alanine as in GLP-1) and survives longer in the circulation (plasma half-life of 26 min in humans\[27\] compared with 1–2 min for intact biologically active GLP-1\[19\]). In insulin-resistant diabetic mice, repeated administration of exendin-4 for 13 weeks increased plasma insulin and reduced blood glucose and HbA\(_1\text{c}\) concentrations.\[28\] In Zucker rats, 8 weeks of exendin-4 treatment was associated with both reduced glycaemia and insulin levels, suggesting improved glucose tolerance,\[60\] and in addition, body weight gain was reduced. More recently, the effects of exendin-4 were examined in Goto-Kakizaki (GK) rats. In these animals, a genetic neonatal β-cell mass deficit is considered to be the primary defect leading to basal hyperglycaemia and subsequent development of diabetes, but exendin-4 treatment during the first postnatal week (the pre-diabetic period) increases the β-cell mass, with subsequent improvements in glycemic control at adult age.\[30\] In db/db mice, exendin-4, given in the pre-diabetic period, expands the functional β-cell mass via effects on both proliferation and apoptosis, delaying the development of diabetes,\[31\] while neonatal GLP-1 or exendin-4 treatment stimulates β-cell neogenesis in newborn streptozotocin-injected rats (a model of β-cell regeneration), leading to both short- and long-term effects on β-cell mass recovery and glucose homeostasis.\[32\]

In healthy humans, acute intravenous infusion of exendin-4 is insulinotropic and reduces both fasting and postprandial glucose concentrations.\[33\]

Exenatide (AC2993, synthetic exendin-4) has now reached phase 3 of clinical development. In a placebo-controlled study in type 2 diabetic patients, exenatide reduced fasting glucose when given acutely and postprandial glucose when given twice daily over 5 days before breakfast and dinner.\[34\] However, in the 5-day study, there was no significant effect on pre-breakfast fasting glucose levels, suggesting that the duration of action of the previous evening’s dose was insufficient to maintain an antglycemic effect overnight. This was confirmed in a 1-month study, where once-daily injections did not maintain satisfactory glucose control, but twice-daily treatment significantly improved HbA\(_1\text{c}\), relative to pretreatment levels, even though 24-h blood glucose control was not achieved.\[35\] When combined with ongoing oral antidiabetic agents (OAs) (metformin and/or a sulfonylurea) two or three times daily, exenatide leads to further reductions in serum fructosamine and HbA\(_1\text{c}\) compared with OAs alone.\[36\]

LY307161-SR is a sustained release formulation of a DPP-IV-resistant GLP-1 analog. Single daily injection of this compound for 12 weeks significantly improved both fasting and postprandial glucose concentrations in type 2 diabetic patients.\[37\] However, many patients experienced adverse reactions at injection site, leading to reduced compound exposure\[38\], and its development has now been put on hold.

Liraglutide (NN2211; 97% homologous to native GLP-1), is in phase 2 of clinical development. Liraglutide reduces glycaemia in insulin-resistant murine models of diabetes and is associated with increased β-cell mass and proliferation after 2 weeks of treatment.\[39\] Treatment with liraglutide has marked antihyperglycemic effects in rodent models of beta-cell deficiencies, and the in vivo effect of liraglutide on beta-cell mass may in part depend on the metabolic state of the animals.\[40\]

In acute (single-dose) placebo-controlled crossover clinical studies, liraglutide reduces fasting and postprandial glucose concentrations in type 2 diabetic patients\[41\] and is associated with restoration of β-cell responsiveness to physiological hypoglycemia.\[42\] Thus, studies in type 2 diabetic patients indicated that 1 week treatment with once-daily liraglutide significantly reduces 24 h glucose concentrations and improves β-cell function compared with placebo\[43\] and the beneficial effects appear to be maintained with patients showing significant improvements in glycemic control and a trend toward weight reduction after 12 weeks, as compared with sulfonylurea treatment.\[44\] Transient, mild nausea/vomiting was reported but otherwise no serious adverse side effects were noted.

Other approaches involving covalent binding to albumin (e.g., CJC-1131), resulting in a plasma elimination half-life of around 2 weeks in humans (corresponding to the circulating half-life of albumin itself), have also recently been reported.\[45\] CJC-1131 lowers blood glucose in diabetic mice, and the effect persists up to 1 week following discontinuation of treatment.\[46\]

**Enzyme inhibitors**

The alternative approach of inhibiting degradation of endogenous GLP-1, has also been the focus of much interest. A DPP-IV inhibitor, valine-pyrrolidide, eliminated NH\(_2\)-terminal degradation of GLP-1 in vivo, improving the metabolic stability of the intact biologically active peptide and potentiating its insulinotropic and antihyperglycemic effects in anesthetized pigs,\[47\] whereas another inhibitor, isoleucine-thiazolidide, improved glucose tolerance in rats.\[48\] Subsequently, these results were corroborated in acute studies demonstrating that DPP-IV inhibition is effective in animal models of impaired glucose tolerance.\[49\][50] However, valine-pyrrolidide also improves glucose tolerance in mice lacking the GLP-1 receptor,\[51\] suggesting that DPP-IV inhibition may affect other substrates involved in glucose homeostasis. In a 12-week study in Vancouver Zucker diabetic fatty (ZDF) rats, chronic DPP-IV inhibition with isoleucine-thiazolidide was associated with sustained improvements in glucose tolerance and β-cell responsiveness, which appeared to improve with time, and interestingly, by the end of the study, animals had lower body weights.\[52\] Moreover, chronic DPP-IV inhibition improves not only β-cell function, but also both hepatic and peripheral insulin sensitivity.\[53\]

The longer-acting inhibitor, FE 999-011, given twice daily, continuously inhibits plasma DPP-IV activity and was found to
normalize the glucose excursion after oral glucose administration in Zucker obese rats.\textsuperscript{[82]} In ZDF rats, this compound actually delayed the onset of hyperglycemia and restored food and water intake to pre-diabetic levels. Active GLP-1 and pancreatic GLP-1 receptor mRNA levels were increased, suggesting the possibility that the inhibitor led to a GLP-1–mediated improvement in β-cell function.\textsuperscript{[82]}

In human studies, a single dose of DPP-IV inhibitor reduced the glucose excursion in healthy and diabetic subjects.\textsuperscript{[80]} The first chronic study, with two or three times daily administration of the short-acting inhibitor, NVP DPP728, to patients with mild type 2 diabetes gave clinical proof of the concept that DPP-IV inhibition is a viable approach to treating diabetes. Fasting and postprandial glucose concentrations were significantly reduced, and HbA\textsubscript{1c} levels were lowered compared with placebo, even after only 4 weeks of treatment.\textsuperscript{[84]} NVP DPP728 was well tolerated, with only minor adverse events, including pruritis and nasopharyngitis, being reported; which were transient and did not lead to discontinuation of treatment. LAF237, which has now reached phase III clinical development,\textsuperscript{[85]} LAF237 is longer acting than NVP DPP728, and once-daily treatment for 4 weeks significantly improves metabolic control. Fasting and postprandial glucose concentrations and HbA\textsubscript{1c} levels were significantly reduced compared with placebo, insulin secretion was sustained, and postprandial levels of active GLP-1 were increased. Moreover, glucagon concentration was significantly reduced by LAF237,\textsuperscript{[85]} suggesting that GLP-1–mediated inhibition of glucagon secretion in addition to its insulinotropic effects contributes to mediating the effects of DPP-IV inhibition. To date, there are no reports of changes in body weight in humans after DPP-IV inhibitor treatment.

The limited human data suggest that DPP-IV inhibitors are well tolerated, and do not seem to be associated with hypoglycemic events. Four (of 61) patients treated with NVP DPP728 for 28 days reported symptoms suggestive of hypoglycemia, but only 1 had a blood glucose level of <3.3 mmol/L, whereas no hypoglycemic incidence was reported for LAF237.\textsuperscript{[85]} Preliminary studies with LAF237 indicate that it does not significantly increase the risk for hypoglycemia when given together with glibenclamide.\textsuperscript{[80]}

### Conclusion

The studies discussed above support the idea that a GLP-1–based therapy will be a safe and effective treatment for type 2 diabetes. The clinical studies reported so far indicate that this approach, whether achieved by DPP-IV inhibition or by GLP-1 receptor agonists, has the potential to reduce and may be even normalize both fasting and postprandial glucose concentrations without adverse effects such as weight gain. Moreover, the preclinical studies raise the hope that such a therapy may be able to delay or even halt the progression of the disease or possibly even prevent its development by providing a means of safely treating subjects with impaired glucose tolerance. Finally this approach may turn out to be inherently safer than existing insulin secretagogues because of its glucose dependency. Thus, GLP-1 receptor agonists and DPP-IV inhibitors have not been associated with any incidences of severe hypoglycemia even when given in combination with existing oral antidiabetic agents, while when given as monotherapy, virtually no hypoglycemic events have been reported. So GLP-1–based therapy may be a beneficial approach for the management of diabetes.

### References


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