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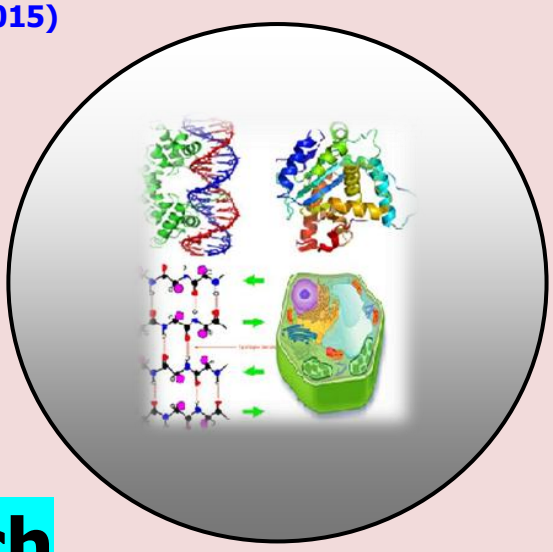

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RESEARCH PAPER

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Glucagon like Peptide-1 Receptor Agonists and its Analogues in the Management of type 2 Diabetes Mellitus Patients: An Overview

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ABSTRACT

The incretin based therapies plays a key role in mentainance of glucose homeostasis, predominantly enhance insulin secretion and inhibition of glucagons secretion in type 2 diabetes mellitus(T2DM). Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones secreted by the enteroendocrine cells of the gut in response to the ingestion of nutrients, stimulate glucose-dependent insulin secretion, pancreatic beta-cell proliferation, inhibits gastric emptying, reduces appetite and food intake. The remedial approaches for enhancing incretin action include degradation-resistant Glucagon like peptide-1(GLP-1) receptor agonists (incretin mimetics) and inhibitors of dipeptidyl peptidase-4 (DPP-4) activity (incretin enhancers). GLP-1 induced insulinotropic effect is mediated by GLP-1 receptor (GLP-1R), resulting in activation of adenylate GLP-1R with a greater affinity compared to other peptides such as GIP and glucagon which are also able to bind to GLP-1R. Stimulation of GLP1R leads to activation of Gs-adenylyl cyclase-cAMP-PKA pathway, resulting in increased insulin synthesis and release in pancreatic cells. Native GLP-1 is degraded within 2 to 3 min in the circulation. Therefore, various GLP-1R agonists (GLP-1RAs) have been developed to prolong their vivo actions by suppressing glucagon production and normalizing postprandial and fasting glucose levels. GLP-1 analogs include exenatide, lixisenatide, albiglutide, dulaglutide, liraglutide and exenatide extended-release, have been shown to stimulate insulin secretion with an incretin-mimetic mechanism, beta-cell dysfunction, maintain glucose homeostatis, defective insulin secretion and augmented glucagon release in the T2DM patients. With lifestyle modifications, in non-alcoholic and alcoholic fatty liver disease, viral hepatitis, liver fibrosis, obesity and inflammation, it reduces transaminase levels to improve blood lipid levels, cutting down the fat content to promote fat

redistribution, directly decreasing fatty degeneration of the liver, reducing the degree of liver fibrosis and improving inflammation. This review also emphasizes the effects of GLP-1RAs on bone metabolism and weight management associated with T2DM.
Keywords: Glucagon, Peptide-1, Agonists, Analogues and Diabetes mellitus patients.

INTRODUCTION

There is a global pandemic of type 2 diabetes mellitus (T2DM) and progression of disease and long term complications impose a major health burden. The older hypoglycemic drugs, though control hyperglycemia but have minimal effect on disease progression and long term cardiovascular complications. To maintain the adequate glycemic control and prevention of long term secondary complications in the treatment of T2DM patients is a central challangable goal due to progressive nature of disease (Inzucchi et al., 2012). A long term glycemic control often cannot be sustained by currently available oral hypoglycemic agents including incretins-based therapy, thus, an additional treatment modalities for maintaining normoglycemia in T2DM patients are urgently needed. The glucoregulatory effects of incretins are the basis for new therapies currently being developed for the treatment of T2DM that plays a key role in mentainance of glucose homeostasis (Inzucchi et al., 2012). The first incretin hormone identified as glucose-dependent insulinotropic polypeptide (GIP) was purified from porcine intenstinal extract, showed weak effects on gastric acid secretion but more potent insulinotropic actions in human (Elirch et al, 1964). GIP is a 42-aminoacid hormone synthesized in duodenal and jejunal enteroendocrine K cells in the proximal small bowel (Drucker and Nauck, 2006). A second incretin hormone, glucagon-like peptide-1 (GLP-1) was indetified after cloning of the cDNAs and genes encoding the proglucagon (Figure 1). GLP-1 is a 30- amino acid peptide derived from a large proglucagin precursor that encodes not only GLP-1 but also the related proglucagon-derived peptides. It exists in two circulating equipotent molecular forms, GLP-1(7-37) and GLP-1(7-36) amide, but, GLP-1(7-36) amide is more abundant in the circulation after a meal which is mainly secreted by enteroendocrine Langerhans (L) cells in the distal ileum and colon. It has been shown that plasma levels of GLP-1, like GIP, increases within minutes of eating. Therefore, a combination of endocrine and neural signals probably promote the rapid stimulation of GLP-1 secretion well before digested food transits through the gut to directly engage the L cell in the small bowel and colon. Also, the proximally located L cells in the duodenum and jejunum have also been described but, the precise contributions of the proximal and distal L cells to the early rapid increase in plasma GLP-1 remains unclear. Plasma levels of GLP-1 are low in the fasted state which increases rapidly after meal (Drucker and Nauck, 2006). The circulating levels of intact GLP-1 and GIP decrease rapidly because of enzymatic inactivation, mainly dipeptidyl peptidase-4 (DPP-4) and renal clearance (Orskov et al., 1993).

DPP-4 is essential for incretin inactivation, and mice with targeted inactivation of the DPP-4 gene have raised levels of plasma GIP and GLP-1, increased insulin secretion and reduced glucose excursion after glycaemic challenge (Marguet et al., 2000). As a result of DPP-4 activity, intact, biologically active GLP-1 represents only 10–20% of total plasma GLP-1(Deacon et al., 1995). The proglucagon gene is expressed in the α-cells of pancrease, neuroendocrine L-cells of the small intestine, Brain, the vascular system, the heart and kidney (Alan, 2011). Plasma level of bioactive GLP-1 in normal fasting humans are 5-10 pmol/L which increases by two to three-fold after a carbohydrate meal. GLP-1 contains an NH2-terminal alanine at position 2, making it a substrate for cleavage by DPP-4. Therapeutic approaches for enhancing the incretin action include degradation resistant GLP-1 receptor agonists (incretin mimetics) (Drucker and Nauck, 2006). Clinical studies have shown that replacement therapy with metabolically stable GLP-1 mimetic greatly improves management of hyperglycemia, nearly correcting blood glucose regulation in some patients. For example, treatment with either accented or liraglutide declines fasting hyperglycemia and results in sustained lowering of glycosylated A1C (A1C) levels (Alan, 2011).

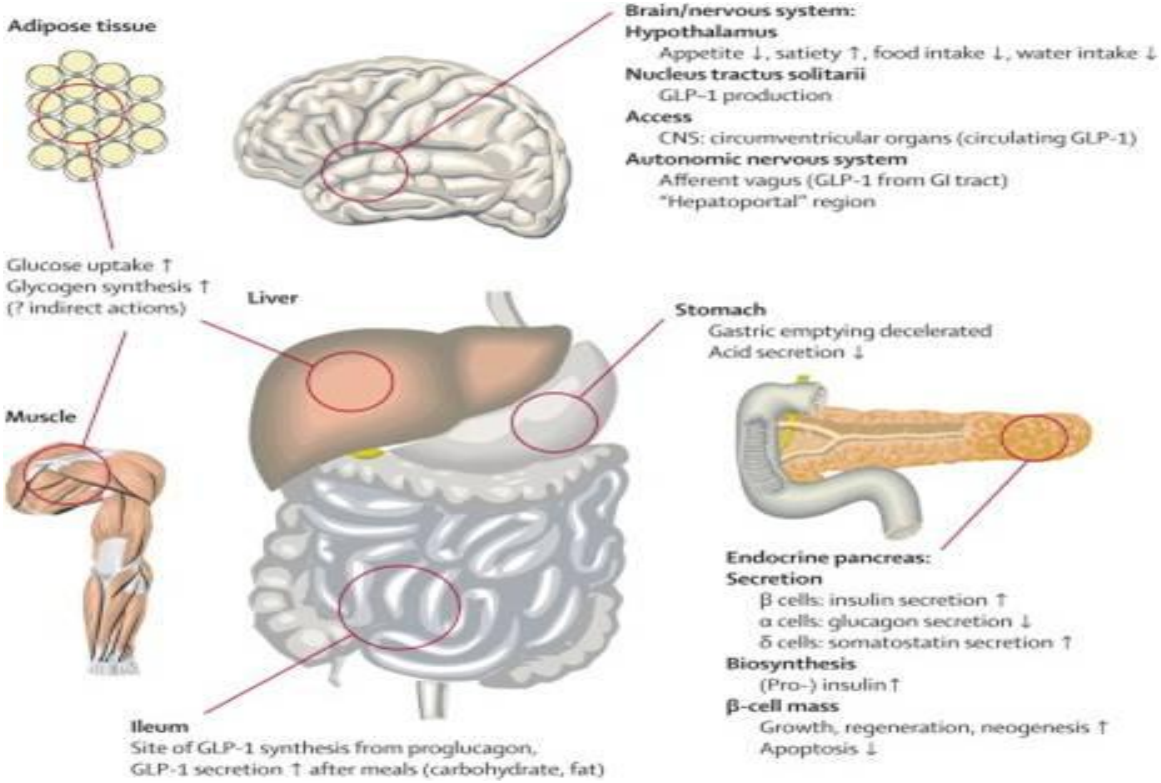


Figure 1. Physiology of GLP-1 secretion and action on GLP-1 receptors in different organs and tissues (Ref: Drucker & Nauck, 2006).

Preclinical studies revealed other potential benefits of GLP-1 receptor agonist treatment in individuals with type 2 diabetes which causes the promotion of β-cell proliferation (Drucker and Nauck, 2006) and reduces the β-cell apoptosis (Alan, 2011). The biochemical parameters which inform the appropriate choice of GLP-1 receptor include efficacy, safety, tolerability and versatility in combination with insulin (Sanjay, 2014). It has been reported that a supraphysiological dose of GLP-1 enhances the beta cells responses to glucose in patients with type 2 diabetes and in 4 week of near normalization of blood glucose further improves this effect (Hojberg et al., 2008). Unfortunately, GLP-1 analogues are peptides requiring administration by subcutaneous injection.

The GLP-1 receptor is a member of the class B/II family of seven transmembrane G protein-coupled receptors (GPCRs) that include receptors for peptide hormones such as secretin, GLP-1, GIP, glucagon, vasoactive intestinal peptide (VIP), corticotropin-releasing factor (CRF), calcitonin, and parathyroid hormone (PTH) (Kyle et al., 2010, Grace Flock et al., 2011, Machado et al., 2017). Interaction of endogenous peptide hormones with their receptors typically involves large receptor:ligand binding sites and is often initiated by receptor NH2-terminal ectodomains (ECDs). This extracellular structure interacts with COOH-terminal residues of cognate ligands and positions the NH2-terminus of the ligand to interact with critical determinants in receptor transmembrane regions, thereby activating heterotrimeric G-proteins and subsequently adenylylcyclase (Kyle et al., 2010). More recent findings have expanded the spectrum of GLP-1 receptor agonists work by mimicking the action of the endogenous incretin GLP-1, which acts to control glycemia via several pathways, including stimulation of insulin secretion, inhibition of glucagon secretion, delay of gastric emptying and induction of satiety (Grace Flock et al., 2011). In occasional cases where weight loss is seen as an essential aspect of therapy, treatment with GLP-1 receptor agonist might be very useful (Machado et al., 2017). GLP-1 receptor agonists are generally associated with weight reduction and DPP-4 inhibitors are usually weight neutral. Glucagon like peptide-1 receptor is an ideal target in the development of incretin–based therapies for diabetes and obesity (Fracanzani et al., 2010).

GLP-1 receptor agonist led us to believe that a small molecule approach to class B G-protein coupled receptor agonism is no longer a fantasy but a reality. Incretin-based therapies, including GLP-1 analogues and DPP-4 inhibitors, have been shown to reduce glycated hemoglobin (HbA1c), restore glucose homeostasis and improve glycemic control. The DPP-4 inhibitors, used as monotherapy or in combination with other antidiabetic drugs, have shown promising new treatment option, especially for patients with early-stage T2DM and more severe hyperglycemia. Recently, the nonalcoholic fatty liver disease (NAFLD) has continued to rise, and considered as a leading cause of chronic liver damage. It encompasses a variety of deseases ranging from simple hepatic steatosis, approximately 10%-25% of NAFLD cases will progress to non-alcoholic steatohepatitis (NASH), while 10%-15% of NASH cases will develop into hepatocellular carcinoma (Zhang et al., 2014) NAFLD is associated with obesity, T2DM, dyslipidemia and cardiovascular diseases, thus, there has been an increasing interest in the role of GLP-1RAs in NAFLD treatment. In fact, recent studies have found that GLP-1RAs can regulate lipid metabolism in the liver under pro-inflammatory conditions. Therefore, we review the effects of GLP-1RAs on NAFLD and inflammation with the aim of extending the use of GLP-1RAs to the treatment of NAFLD (Wang Jue and Xiao Ruiping, 2014). The purpose of this review is to provide an overview of GLP-1RAs and its analogues that are participating in the improvement in glucose homeostasis in T2DM, NAFLD, NASH and bone metabolism.

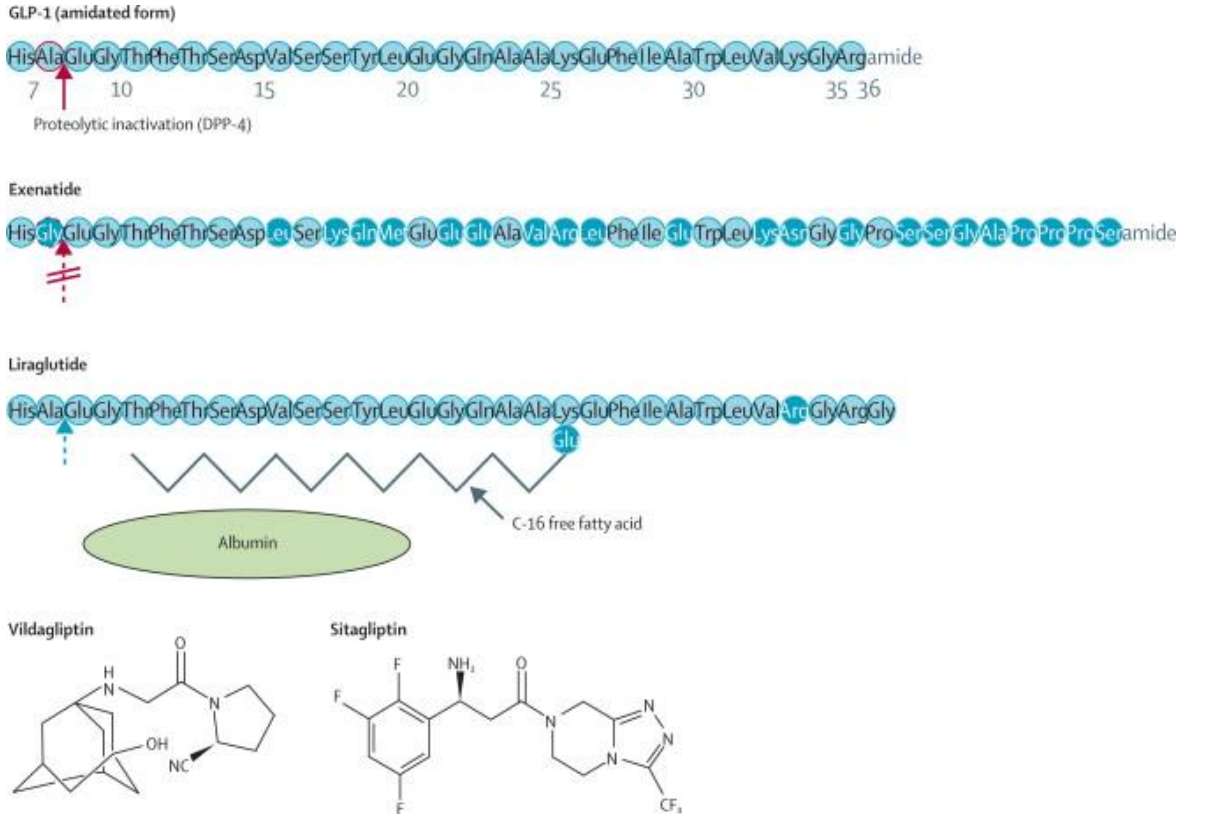


Figure 2. Structure of GLP-1, GLP-1R agonists exenatide and liraglutide, and DPP-4 inhibitors vildagliptin and sitagliptin (Drucker and Nauck, 2006).

Crystal Structure of GLP-1 in Complex with the Extracellular Domain of the GLP-1 receptor

The GLP-1 receptor belongs to class B of the G-protein-coupled receptors, a subfamily characterized by a large N-terminal extracellular ligand binding domain. Exendin-4 and GLP-1 are 50% identical, and exendin-4 is a full agonist with similar affinity and potency for the GLP-1 receptor.

(Wang Jue and Xiao Ruiping, 2014) have been recently shown the crystal structure of the GLP-1 receptor extracellular domain in complex with the competitive antagonist exendin-4. Interestingly, the isolated extracellular domain binds exendin-4 with much higher affinity than the endogenous agonist GLP-1. They have solved the crystal structure of the extracellular domain in complex with GLP-1 to 2.1 A resolution. The structure shows that important hydrophobic ligand-receptor interactions are conserved in agonist- and antagonist-bound forms of the extracellular domain, but certain residues in the ligand-binding site adopt a GLP-1-specific conformation. GLP-1 is a kinked but continuous helix from Thr 13 to Val 33 when bound to the extracellular domain. They have been supplemented the crystal structure with site-directed mutagenesis to link the structural information of the isolated extracellular domain with the binding properties of the full-length receptor. The data support the existence of differences in the binding modes of GLP-1 and exendin-4 on the full-length GLP-1 receptor (Figure 3).

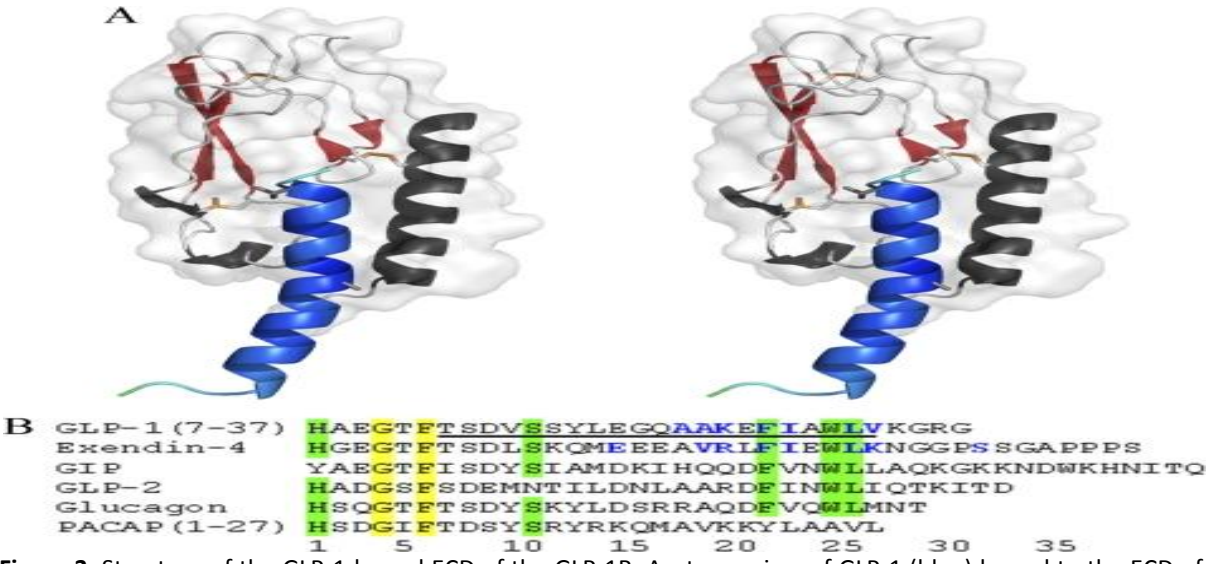
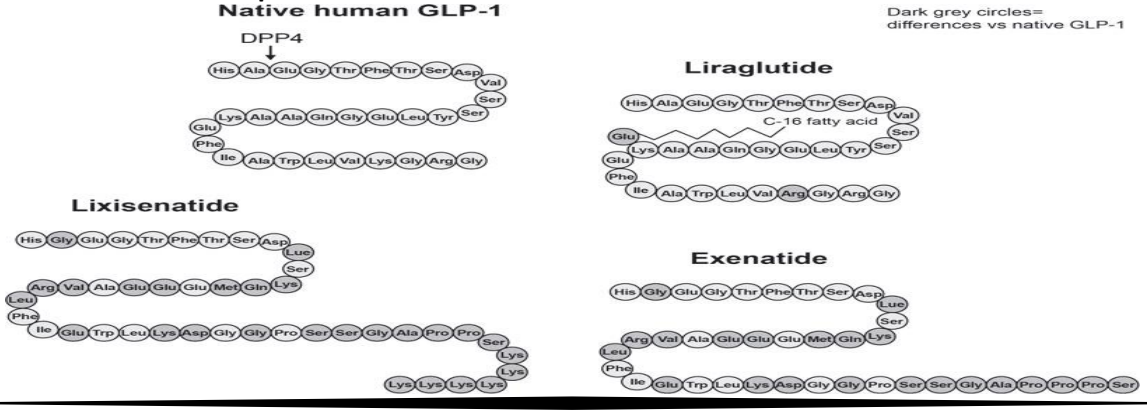


Figure 3. Structure of the GLP-1-bound ECD of the GLP-1R. A, stereo view of GLP-1 (blue) bound to the ECD of the GLP-1R (-helix in Black -strands in red, and loops in gray). Disulfide bridges are shown as orange sticks. Residues Cys 62–Asp 67 (1) and Ala70–Gly75 (2) constitute the first region of antiparallel -sheets, and the second region is comprised of residues Gly 78 –Ser 84 (3) and His 99 –Thr 105 (4), which is shown in red. Our final structure contains GLP-1 residues Gly 10*–Gly 35*. The residues that interact with GLP-1R ECD lie within Ala 24* and Val 33 *, which are shown as sticks. B, sequence alignment of GLP-1, exendin-4, GIP, GLP-2, glucagon, and PACAP (1–27). Fully conserved residues are highlighted in yellow, and partially conserved residues are high-lighted in green. The residues of GLP-1 and exendin-4 that interact with GLP-1R ECD are colored blue. The underlined residues symbolize residues of GLP-1 in -helical conformation when bound to the ECD. Residue number 1 of exendin-4 corresponds to residue number 7 of GLP-1(Wang Jue and Xiao Ruiping, 2014).

Structure of GLP-1 Receptor



Structure of Native GLP-1 and GLP-1 Receptor agonist

GLP1R is a G protein-coupled receptor (GPCR) involved in insulin synthesis and regulation; thus, it is an important drug target for treatment of diabetes. A characteristic structural feature of this family is a long and structurally complex extracellular amino-terminal domain (N-domain) containing six conserved cysteine residues that form disulfide bonds important for stabilizing the folded protein. The N-domain is connected to a juxtamembrane domain (J-domain) of the seven membrane-spanning α-helices with intervening loops and a C-terminal tail. Methods were developed for the structures of GPCRs since the late 1990s. The earlier methodology, denoted as MembStruk, focused on sequential optimization of the seven TM helices starting from a homology template (Wang Jue and Xiao Ruiping, 2014). More recently, a method was developed, denoted as GEnSeMBLE, that is directed at a combinatorially complete set of helix rotations and tilts (Dan Donnelly 2012). To offer a structural basis, we predicted the transmembrane (TM) bundle structure of GLP1R bound to the peptide Exendin-4 (Exe4; a GLP1R agonist on the grocery store for treating diabetes) using the MembStruk method for scanning TM bundle conformations. It was used protein–protein docking methods to combine the TM bundle with the X-ray crystal structure of the 143-aa N terminus coupled to the Exe4 peptide. This complex was subjected to 28 ns of full-solvent, full-lipid molecular dynamics and was found 14 strong polar interactions of Exe4 with GLP1R, of which 8 interactions are in the TM bundle (2 interactions confirmed by mutation studies) and 6 interactions involve the N terminus (3 interactions found in the crystal structure).it was also found that10 important hydrophobic interactions, of which 4 interactions are in the TM bundle (2 interactions confirmed by mutation studies) and 6 interactions are in the N terminus (6 interactions present in the crystal structure). Therefore, the predicted structure agrees with available mutagenesis studies. Structural information regarding GLP-1 receptor agonist is also available primarily from NMR studies. (Christina et al., 2010) The data are uniform with other class B1 GPCR ligands (Petra Rovó et al., 2014) in that GLP-1 (7-36) and exendin-4 peptides are likely α-helical in structure with disordered N-termini, although the artificial environment in which these subjects are conducted must be utilized to qualify any interpretation of the experimental data. (Lagerstrom and Schioth, 2008) GLP-1 receptor agonist approved to treat T2DM is liraglutide (NN2211). In this molecule, a “fatty acid derivatization” strategy was used to prolong the *in vivo* action of GLP-1. This approach attaches a fatty acid moiety to GLP-1 in order to facilitate GLP-1 binding to serum albumin. Liraglutide is acylated on Lys26 with a covalently attached palmitoyl (C16:0) chain (Lagerstrom and Schioth, 2008). As this modification enables binding to albumin, GLP-1 is then sterically protected from DPP4 degradation .(16)A complicating factor in understanding and determining the structure of family B GPCRs may be their tendency to form oligomers. (Kirkpatrick et al., 2012, Dan Donnelly, 2012, Runge et al., 2003) For example, a predicted lipid-exposed face of TM4 of the secretin receptor has been implicated in functionally relevant oligomerization Disruption of this interface using eitherpeptides derived from the sequence of TM4, or site-directed mutagenesis of Gly 243 and Ile 244, demonstrated that the oligomerization mediated by the lipid-exposed face of TM4 was important for the full potency of secretin. (Petra Rovó, 2014, Hsin-Chieh Tang and Calvin Yu-Chian Chen 2014, Laburthe et al., 1996). The cloning of GLP-1R suggested the presence of a signal peptide at the extreme N-terminus, and this was shown to be required for the receptor’s synthesis in HEK-293 cells Cleavage of the signal peptide was essential for correct processing and trafficking, such that only the mature and fully glycosylated receptor reached the plasma membrane. The N-glycosylation of GLP-1R had previously been demonstrated in RINm5F cells with glycopeptidase F reducing the apparent molecular weight from 63 to 51 kDa and tunicamycin reducing detectable receptor expression but not ligand affinity. (Laburthe et al., 1996, Fredriksson et al., 2003, Laburthe et al., 2007, Castro et al., 2005, Hoare, 2005, Nicolaus et al., 2006).

In recombinant CHO cells, mutation of any two of the three N-glycosylation sites resulted in disruption of receptor trafficking to the plasma membrane. Therefore, it appears that GLP-1R is a glycoprotein, and that the glycosylation, together with the cleavage of the signal peptide, is an essential process in the correct trafficking and processing of the receptor.

Physiological activities

A number of good effects have been reported during the intravenous administration of GLP1 (7–36) amide, the major biologically active form of GLP1. Yet, then the native GLP1 peptide does not appear to be suitable for long-term treatment of patients with T2DM, primarily owing to its low stability in vivo. GLP17–36 amide has a half-life of only ~2–3 min, and is inactivated by the enzyme DPP4, (Elizabeth et al., 2012) necessitating continuous administration of the peptide for sustained activity. A proof-of-concept study has been conducted with the aim of overcoming the short half-life of GLP-1 (7–36) amide (Vanita et al., 2012). The results convincingly concluded the efficacy of this peptide in improving glycemic control and body weight during continuous subcutaneous infusion of the hormone via a mini-pump (Adriano Maida et al., 2009). Several other approaches have been used to prolong the biological action of GLP1 in patients. Alternative approach to constant administration of GLP-1 (7–36) amide is the inhibition of DPP4, thereby decreasing degradation of GLP-1, which produces plasma concentrations of the intact endogenous peptide. A number of GLP1 receptor agonists have been produced and can be classified as either short-acting or long-acting compounds, whereas the short-acting receptor agonists are characterized by large-amplitude variations in plasma peptide levels when administered at typical intervals, (Hui et al., 2005) treated with the long-acting compounds at their typical administration intervals leads to a more consistent, supraphysiological activation of the GLP1 receptor (Suda et al., 1989). These pharmacokinetic differences between short-acting and long-acting analogues have fundamental implications for the mode of action, efficacy and tolerability of these compounds. One method that has been accepted to extend the in vivo half-life of GLP-1 is to take over the peptide resistant to cleavage by DPP4. By exchanging amino acids at the second and third N terminal positions of the peptide, cleavage by this enzyme is reduced (Wettergren et al., 1998, Suzuki et al., 1989, Gromada et al., 2004, Sinclair and Drucker, 2005). The short-acting GLP1 receptor agonists exenatide and lixisenatide are examples of agents in which this molecular modification has been applied. Nonetheless, because the intact peptide is still subject to renal elimination, (Levy, 2006) resistant to cleavage by DPP4 alone can simply prolong the half-life of GLP1 to a special extent. A second strategy to sustain the actions of GLP1 is based on the binding of the peptide to plasma albumin, which can also prevent renal filtration of GLP1 (Combettes, 2006). Albumin binding can be enhanced in a noncovalent fashion, for instance via the attachment of fatty acid side chains to the peptide, as in the long-acting GLP1 receptor agonist liraglutide. The fatty acid side chain promotes noncovalent conjugation of liraglutide to plasma albumin, with only ~1% of the peptide circulating in an unbound mode. Association with albumin can also be induced covalently by fusing the GLP1 molecule with albumin, the approach used in the output of some other long-acting GLP1 receptor agonist, albiglutide resulting elimination kinetics are determined by either the rate at which GLP-1 dissociates from plasma albumin (as in the case of liraglutide), or by the plasma half-life of the albumin–GLP-1 conjugate (as in the case of albiglutide) (Toft-Nielsen, 2001). In a third long-acting GLP1 receptor agonist, dulaglutide, conjugation with the Fc fragment of IgG has been used to improve the pharmacokinetics and extend the duration of action of GLP1. In addition, GLP1 can be distributed together with chemicals, such as zinc, that delay absorption of the peptide from the subcutaneous tissue. Clinical development of the GLP1 receptor agonist taspoglutide utilized this method, although development of this drug was blocked in 2010 owing to an increased incidence of adverse gastrointestinal effects and hypersensitivity reactions (Tokuyama et al., 2004). In a similar approach, the GLP-1 peptide can be coupled to microspheres that confer protracted release of the peptide from the subcutaneous depot.

The long-acting GLP-1 receptor agonist exenatide-LAR (long-acting release) acts through this mechanism (Theodorakis et al., 2006). These various chemical modifications of GLP-1 explain the individual pharmacokinetic properties of the different GLP-1 receptor agonists that are available for the treatment of type 2 diabetes mellitus or are in clinical development. As a general rule, GLP-1 receptor agonists can be subdivided into short-acting or long-acting compounds. The individual characteristics of the drugs and their effects are described (Baggio et al., 2004). The physiological actions of endogenous GLP-1 on glucose metabolism have been studied using continuous infusion of a potent GLP-1R antagonist, exendin, Ex-9. Post-meal glucose homeostasis is tightly regulated as a result of GLP-1action since elimination of this action causes a decline in quality of glucose tolerance (Nauck et al., 1993). Nevertheless, interpretation of the gist of the GLP-1R blockade on insulin response during meal or oral glucose studies is complicated due to increased glaucoma as a consequence of the Ex-9 infusion. Studies with glucose or meal ingestions during fixed blood glucose concentrations with a hypoglycemic clamp has demonstrated that blocking endogenous GLP-1 reduces postprandial insulin secretion by 30-40 %and increases glucagon release (Nauck et al., 2002). These findings indicate that endogenous GLP-1 has a significant insulinotropic effect in healthy humans, and important glucagonostatic properties as well. Of note, the proportional contribution of the GLP-1 effect to postprandial insulin secretion is similar in patients with well controlled T2DM and age- and weight-matched controls despite an absolute decrease in beta-cell function in the diabetic individuals (Vilsboll and Holst, 2004). The insulintropic effect of GLP-1 does not appear to be mediated through alteration in gastric emptying since endogenousGLP-1, unlike pharmacological levels of GLP-1 or GLP-1 agonists, has only modest effects on the rate of nutrient passage from the abdomen to the small intestine (Adrian et al., 1985).

Mode of action of GLP-1 Receptor Agonists

The function of GLP-1 is going through a receptor called G protein coupled receptors (GPCRs). Later binding of GLP-1 to its receptor in pancreatic β-cells, it increases the intracellular concentration of camp and induces the exocytosis of insulin by PKA-dependent and PKA-independent signaling mechanism (Wong et al., 2013). Activated PKA and camp-guanine nucleotide exchange factor II both are found to raise a lot of molecular events which are participating in the regulation of insulin secretion by GLP-1 (Schirra et al., 2006). GLP-1 blocked the KATP as well as Kv channels and hence increases the β-cell mass and induces the membrane depolarization. These changes translate into the activation of the voltage-gated Ca2+ channels with influx of Ca2+ and initiation of Ca2+-dependent insulin exocytosis (Salehi et al., 2008). Inhibition in the Kv-channels by GLP-1 is indispensable for the repolarization of the β-cells (Salehi et al., 2010). The anti-apoptotic effects of GLP-1 are the final results of the activation of cAMP and PI3-Kinase. Activation of CREB and its interaction with the coactivator TORC2 protein (transducer of regulated CREB activity) activates the cAMP signaling pathways and upregulates the expression of IRS-2 (insulin receptor substrate-2) which leads to the activation of PI3-Kinase (Nicolaus et al., 2011). Activated PI3 Kinase transmitted the signal by the two pathways: one is MAPK/PKC and another is AKT/PKB. Activation of PKC and MAPK is responsible for β-cell proliferation, whereas ERK and MAPK linked to the β-cell differentiation.

Therapeutic value of GLP-1 Receptor Agonist and Analogues

GLP-1 increases the insulin synthesis and reduced glucagon secretion, therefore GLP-1 improved the glucose homeostasis by reducing hyperglycemic condition. But native GLP-1 has a diminished life span in the plasma, because GLP-1 is a breakdown by DPP-4 at position 8 (alanine) and peptide bonds that are contiguous to the Arg or Lys residues, are frequently breakdown by serine protease.

It is known that Lys residues at 34 positions are sensitive to such protease (Pratley et al., 2010) Change in these sites may enhance the half life of GLP-1. Hence pharmacological mimetics have been developed with improved stability. Therapeutic of GLP‑1 analogues can be sorted as follows-

Glycemic control

Study on human suggest that when the acute intravenous administration of peptide to patients with type-2 diabetes reduces postprandial blood glucose and meal-related insulin requirements (Buse et al., 2009). Short and long-term follow-up of intravenous or subcutaneous treatment of GLP-1 was also set up to increase promising lowering in blood glucose level in diabetes. Regular treatment of GLP-1 by subcutaneous therapy in type-2 diabetic patient for 6 weeks significantly decrease fasting blood glucose by 4.3 mmol/L as well as hemoglobin A1c (HbA1c) by 1.3% and found to improve in the secretion of insulin (Blevins et al., 2011). In vivo GLP-1 treatment has been hampered by the low plasma half-life and fast renal clearance of the natural hormone (Ellard et al.,). Hence it is necessary to evolve long-acting GLP-1 analogues that are insensitive to GLP-1 or DPP-4 agonist, known as DPP-4 inhibitors in the treatment of Type-2 diabetes. The therapeutic promise of liraglutide is evident from preclinical data. Liraglutide showed the potential to provide good glycaemic control without the risk of hypoglycaemia and, as with exenatide, but not dipeptidylpeptidase-4 inhibitors, to mediate weight loss. Although these benefits have subsequently been studied clinically, beta-cell mass can be directly studied only in animal models. In common with other incretin-based therapies, liraglutide showed the potential to modulate the progressive loss of beta-cell function that drives the continuing deterioration in glycaemic control in patients with type 2 diabetes. Body weight was lowered by a mechanism involving mainly lowered energy intake, but also potentially altered food preference and maintained energy expenditure despite weight loss.

DPP-4 Inhibitors

DPP-4 inhibitors are being used clinically in combination with most other oral antidiabetic agents (including sulfonylureas, thiazolidinediones, and metformin) in patients failing to achieve adequate glycaemic control, or who wish to limit weight gain. A number of inhibitors of the enzyme DPP-4, which regulates the bioactivity of native GLP-1, have been developed but only few of these agents (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin) are available for clinical use (Linagliptin et al., 2012**)** Either as monotherapy or an add-on to oral agents, DPP-4 inhibitors reduce mean HbA1c by approximately 0.5% to 0.8% (Astrup et al., 2013, Boss, 2010, Imeryüz et al., 1997), a clinical effect somewhat less than that reported with the GLP-1 receptor agonists. DPP-4 inhibitors lower blood glucose without a significant increase or reduction in body weight (0.2 to 0.8 kg) (Imeryüz et al., 1997). Data demonstrating extraglycemic effects of DPP-4 inhibitors such as benefits on lipids, blood pressure, or markers of inflammation are very limited. There is no evidence that DPP-4 inhibitor therapy results in significant body weight, appetite, or food intake reductions. Trials with vildagliptin have shown modest improvements in triglycerides and high-density lipoprotein cholesterol (4.8% and 10.6%, respectively, in combination with a thiazolidinedione), as well as reductions in systolic and diastolic blood pressure (Imeryüz et al., 1997). On the opposite to GLP-1 receptor agonists, DPP-4 inhibitor therapy is generally well tolerated, with no significant gastrointestinal or systemic side effects having been reported in clinical trials. A favorable tolerability profile means that DPP-4 inhibitor therapy can be safely administered to patients with a range of comorbidities. However, dosage adjustments of sitagliptin are recommended in patients with moderate-to end- stage renal disease, because it is cleared by the kidney while both sitagliptin and vildagliptin are contraindicated in patients with severe hepatic dysfunction but no sitagliptin dosage adjustment is needed in patients with mild-to-moderate hepatic insufficiency.

Postmarketing reports of sitagliptin-associated serious hypersensitivity reactions, including anaphylaxis, angioedema, Stevens-Johnson syndrome, and hepatic enzyme elevations have been noted. On the other hand, the elimination of another oral DPP-4 inhibitor linagliptin, that was approved in the United States and Europe, is primarily non-renal and dose adjustment is not required even in patients with mild, moderate or severe hepatic impairment.

Cross the blood brain barrier and enhance neurogenesis

Type 2 diabetes is a risk factor for Alzheimer's disease (AD), most likely associated with an impairment of insulin signalling in the brain. Thus, drugs that enhance insulin signalling may have healing potential for AD.ide (Victoza) and exenatide (Byetta) are novel long-lasting analogues of the GLP-1 incretin hormone are currently available to treat diabetes. Thus, drugs that enhance insulin signalling may have healing potential for AD. Numerous in vitro and in vivo studies have shown that GLP-1 analogues have a range of neuroprotective properties. GLP-1 Rs are expressed in the hippocampal area of the brain an important site of adult neurogenesis and maintenance of cognition and memory formation. Therefore, if GLP-1 analogues can cross the blood brain barrier, diffuse through the brain to reach the receptors and most importantly activate them, their neuro protective effects may be realized.

A new avenue for adrresing cardiovascular comorbidites in T2DM.

Exenetide has been shown to increase heart rate and depress heart rate variability in mice following i.c.v. administration. however, in a small, 12-week, placebo controlled study of patients with type 2 diabetes, exenatide produced a decrease in systolic blood pressure (-3.5mmHg) but a small non significant increase in heart rate 92.1 beats /minute (Imeryüz et al., 1997). The mean increase in heart rate observed in clinical trials of liraglutide or exenatide-LAR ranges between 2 bpm and 5 bpm. In a direct comparison of exenatide and liraglutide, the increase in heart rate was significantly greater in patients receiving liraglutide than in those receiving exenatide (3.28 bpm versus 0.69 bpm). (Rauch et al.) In patients receiving exenatide-LAR, mean heart rate increases of 4.1 bpm and 4.0 bpm have been reported (Nauck et al., 2011). By contrast, the findings of a trial in which short-acting exenatide was administered to patients twice daily did not show a significant increase in heart rate. (Fehse et al., 2005) In another direct comparison, long-acting liraglutide was associated with a mean heart rate increase of 5.3 bpm, whereas short-acting lixisenatide led to a mean heart rate reduction of 3.6 bpm. (Becker et al., 2010) Thus, continuous activation of the GLP-1 receptor seems to result in a greater increase in heart rate than intermittent stimulation. The mechanism underlying this increase in heart rate has not yet been completely clarified. Decreases in body weight or a reflex mechanism triggered in response to the blood-pressure-lowering effect of GLP1 receptor agonists do not appear to be plausible explanations, because both effects are similarly found with short-acting and long-acting GLP1 receptor agonists. On the basis of information from studies in rodents, inhibition of vagus nerve signaling by GLP1 might underlie the increase in heart rate. (Ratner et al., 2009) whether the increase in heart rate induced by GLP1 receptor agonists might result in an increased incidence of cardiovascular consequences, including heart failure or arrhythmia, cannot be estimated at this period in time.in time. Preliminary cardiovascular safety analyses of data on liraglutide and exenatide have even registered a movement towards a decrease in cardiovascular events (Endocrinology, 2003).

N**europrotective effects**

GLP-1 receptors are expressed widely in the central and peripheral nervous systems, and evidence is suggesting that they are active. GLP-1 and exendin-4 mediate differentiation in PC12 cells and protect neurons from damage in vitro, through the activation of the GLP-1 receptor and a cascade involving cAMP.

GLP-1 and a receptor agonist offer protective effects in neuronal cells in addition to in insulin secreting cells, by coupling to trophic and antiapoptotic signalling pathways (Edwards et al., 2001). Some studies indicate that intracerebroventricular (i.c.v.) injection of GLP-1 and infusion of exendin-4 attenuate then neuronal apoptosis and nerve injury induced by kainite (O'Donovan et al., 2004) and pyridoxine (DeFronzo et al., 2008) in vivo. GLP-1 or exendin-4 also retarded neuron degeneration and stimulated cell proliferation by attenuating the toxicity of amyloid-b and oxidative challenge, findings that reinforce the potential value of incretins in treating Parkinson's disease and Alzheimer's disease (Farr and Adeli, 2012). We recently proposed that a DPP-IV inhibitor might prevent peripheral nerve degeneration in an induced diabetes model by enhancing the endogenous levels of GLP-1 (Eng et al., 1992). Therefore, GLP-1-receptor activation mediated by GLP-1 or exendin-4 has been implicated in various processes, including the mediation of cyclic AMP, the action of neurotrophic factors and the antiapoptosis pathway in a sort of nerve insults.

Type of GLP-1 receptor agonist

Short- acting GLP 1 receptor agonists

Exenatide, Lixisenatide

Resistance to cleavage by DPP4 confers a plasma half-life of ~2–4 h for the short acting GLP-1 receptor agonists, exenatide and lixisenatide (Nielsen et al., 2004). As a consequence, these compounds activate the GLP-1 receptor for only ~6 h after each injection. The recommended dosing intervals are twice daily for exenatide (before breakfast and dinner) and once daily for lixisenatide (typically before breakfast), meaning that only modest efficacy can be expected in the fasting state, after lunch, and during the night (during which periods plasma levels of these drugs decline to baseline levels) (Kendall et al., 2005). Not surprisingly, the effects of these drugs on fasting glucose levels or fasting measures of insulin, secretion (such as the Homeostasis Model Assessment-B index) are less pronounced than those of long-acting analogues. (Buse et al., 2004, Defronzo et al., 2005) By contrast, the rapid increases in plasma levels of these short-acting receptor agonists lead to substantial retardation of gastric emptying, thereby markedly blunting postprandial glucose excursions after breakfast, in the case of exenatide and lixisenatide, and before dinner, in the case of exenatide (Heine et al., 2005, Buse et al., 2011, Christensen et al., 2009). Although the two short-acting receptor agonists stimulate insulin secretion in the fasting state and under experimental conditions, including hyperglycaemic clamp, their effects on postprandial blood glucose levels do not seem to be mediated by stimulation of insulin secretion (Ratner et al., 2010). In fact, postprandial insulin secretion is actually dose-dependently reduced by exenatide and lixisenatide, (Distiller and Ruus, 2008) a finding that is consistent with the results of experiments in which GLP-1 was infused at the time of meal ingestion (Figure 2) (Gerich et al., 2010, Ratner et al., 2011, Rosenstock et al., 2011). Indeed, the postprandial reduction of blood glucose levels induced by short-acting GLP-1 receptor agonists seems to primarily result from delayed gastric emptying, which leads to a decreased rate of glucose entry into the duodenum and, subsequently, into the circulation (Madsen et al., 2007). This slowed absorption of glucose is of great relevance when considering treatment with these drugs, because the evidence shows that postprandial glucose excursions are determined by the rate of glucose delivery into the duodenum rather than by the total amount of glucose delivered (Buse et al., 2011). This mechanism explains why short-acting GLP-1 receptor agonists seem to exert an insulin-lowering effect in the postprandial state despite the well-characterized insulinotropic effect of GLP-1 itself (Degn et al., 2004, Flint et al., 2011). However, even though controlled studies indicate that these drugs reduce mean postprandial insulin levels in most patients, they might still exert an insulinotropic effect after meal consumption in some souls, including patients with overt hyperglycemia or alterations of the autonomous neural system of the cat gut, other consequence of the delay in gastric emptying in patients treated with short-acting GLP-1 receptor agonists might be a reduction in postprandial blood lipid levels. Indeed, acute intravenous

infusion of GLP-1 significantly lowers postprandial levels of free fatty acids and triglycerides (Tang-Christensen et al., 2001). However, few studies have yet been undertaken to specifically examine the effects of GLP-1 receptor agonists on postprandial blood lipid profiles (Turton et al., 1996). The reduction in postprandial blood lipid levels observed in patients receiving incretin-based therapies could involve additional actions, such as reduced production of chylomicrons or hepatic VLDL, or enhanced chylomicron clearance, all of which would lead to decreased lipid levels (Meeran et al., 1999).

Exenatide (synthetic exendin-4)

Exendin-4 was discovered in a search for biologically active peptides in venom from the Gila monster (*Heloderma suspectum*) (Seino et al., 2004, Matthews et al., 2008, Bush et al., 2009). This reptilian protein shares approximately 50% amino acid sequence identity with mammalian -1 and is resistant to DPP4-mediated degradation. The half-life of exenatide, an identical synthetic version of exendin4, has been estimated to be ~2.4 h, 42 with plasma concentrations remaining elevated 4–8 h following a single subcutaneous injection. (Reusch et al., 2009) Exenatide is approved for the treatment of type 2 diabetes mellitus. At a dose of 10 µg twice per day, exenatide reduces HbA1c concentrations by 0.8–1.5 % (Ørskov et al., 1996, Rosenstock et al., 2009). In particular, exenatide lowers postprandial glucose levels after breakfast and dinner to a much greater degree than after lunch. The half-life of this agent is also short for the before-breakfast injection to also extend the lunch-related glucose excursion. In patients with type 2 diabetes mellitus, the exenatide-induced decrease in fasting plasma glucose levels is inferior to that induced by the long-acting receptor agonists, liraglutide and exenatide LAR (Stewart et al., 2009, Glaesner et al., 2010, Barrington et al., 2011, Barrington et al., 2011). Mean body-weight reductions observed in patients treated with exenatide range from 2 kg to 3 kg (Barrington et al., 2011). The most frequently reported adverse effects of exenatide are nausea and vomiting, which occur in ~40–60 % and ≤10 % of patients, respectively (Umpierrez et al., 2011). Antibodies against exenatide have been detected in ~40–60 % of patients treated with the drug (Diamant et al., 2010). The clinical relevance of these antibodies cannot be known with certainty, but in the majority of patients, their presence does not seem to impair the efficacy of exenatide. However, in patients with high antibody titers, the exenatide-induced reduction in HbA1c level was significantly smaller than in patients with low titers of antibodies (Bergenstal et al., 2010). GLP-1 is 5-10 times more potent than GLP-1R agonist as notice in in vivo models. Although extending-4 share 53% sequence identity with GLP-1 and is equipotent at the GLP-1R, yet it is resistant to DPP-4 cleavage (Blevins et al., 2011), because resistance is held upwards by the presence of glycine at 2 position (Richard et al.,). The half-life of exendin4 has been judged to be ~2.4 hand indicated as twice or three times daily dosing to achieve therapeutic serum concentrations (Fineman et al., 2010). Exendin-4 were found to decrease HbA1c level in diabetic patient and effect was similar to done by metformin and sulfonylureas (Marre et al., 2009, Michael et al., 2009, Zinman et al., 2009). Exendine-4 improved the health of β-cell and increase synthesis of insulin. Exendine-stimulated decrease in the fasting plasma glucose levels is inferior to that enhanced by the long-acting receptor agonists (liraglutide and exenatide-LAR) in diabetic patients (Montanya and Sesti et al., 2009). Exendine-4 also found to reduce the body weight (2-3 kg) in diabetic patient (Astrup et al., 2009).

Lixisenatide

Lixisenatide, like exenatide, is a GLP-1 receptor agonist based on exendin-4. The peptide differs from exendin-4 in that two amino acids at the C-terminal end have been exchanged for seven different amino acids (Pratley et al., 2009). Similarly to exendin-4 and exenatide, lixisenatide is protected against cleavage by DPP4 owing to an amino acid substitution at the second N-terminal position (Stewart et al., 2009). The *in vivo* half-life of lixisenatide is 3–4 h, so large-amplitude fluctuations in circulating plasma concentrations occur after once-daily subcutaneous administration (Werner et al., 2010).

However, even though the half-life of this compound suggested that multiple daily doses would be necessary for adequate glycaemic control, initial dose-finding studies revealed only small differences in HbA1c reduction when 20 µg lixisenatide was administered once or twice per day (−0.69% versus −0.75%) (Christensen, et al., 2009). For this reason, once-daily administration of lixisenatide has been used in subsequent studies. In preclinical studies, lixisenatide significantly delayed gastric empting, thereby blunting glucose excursions after oral glucose ingestion (Ratner et al., 2010). Similar to findings in patients receiving exenatide, administration of lixisenatide before a meal leads to a marked reduction in postprandial plasma glucose concentrations, accompanied by a dose-dependent reduction in plasma insulin concentration (Distiller and Ruus, 2008). These findings strongly suggest that the effects of lixisenatide on postprandial glycaemic control are primarily mediated via a delay in gastric emptying (Ratner et al., 2011). However, the effects of lixisenatide on fasting plasma glucose levels seem to be smaller than those seen in individuals treated with long-acting GLP-1 receptor agonists. Interestingly, despite the short half-life of lixisenatide, modest reductions in blood glucose levels were also observed following lunch and dinner in patients injecting lixisenatide once per day, before breakfast (Rosenstock et al., 2011). In phase III clinical trials, lixisenatide treatment led to a decrease in plasma HbA1c levels of 0.7–1.0 %, which was accompanied by a decrease in body weight of 1–3 kg (Anthony, 2011). The incidence of nausea was lower in patients receiving lixisenatide once daily than in those who received exenatide twice per day (25% versus 35 %, respectively) (Werner, 2010). There were also fewer episodes of symptomatic hypoglycemia in patients who were taking lixisenatide than in those taking exenatide (2.5% versus 7.9%, respectively (Irl, 2014).

Long-acting GLP-1 receptor agonists

Albiglutide, Dulaglutide, Exenatide-LAR, Liraglutide, CJC-1134 and CJC-1131

Plasma levels of the long-acting GLP-1 receptor agonists—albiglutide, exenatide-LAR, dulaglutide and liraglutide—are all continuously elevated throughout the periods between doses at their respective recommended injection intervals. These drugs provide better glycaemic control than the short-acting GLP-1 receptor agonists, as patients have higher insulin levels in the fasting state (and presumably during the night) following administration of long-acting receptor agonists (Luc, 2014). The consistently high plasma levels of long-acting GLP-1 receptor agonists result in greater reductions in plasma HbA1c levels than those observed with the intermittent activation of the GLP-1 receptor resulting from administration of short-acting compounds (Bolli and Owens, 2014, Ulrich, 2013, Vishal Gupta, 2013). The long-acting compounds in all likelihood have a bigger force on blood glucose levels than short-acting receptor agonists because they are also effective during the night and early morning, when the interval between doses of short-acting receptor agonists is long and the plasma concentration of these drugs decreases (Asger et al., 2014). Significantly, the modality of action of long-acting GLP1 receptor agonists differs from that of the short-acting compounds. For example, unlike the short-acting compounds, the long-acting GLP1 receptor agonists do not appear to cause a strong effect on gastric motility when administered for a long term (Mikkel Christensen, 2009). This lack of an effect on the rate of gastric emptying of the long-acting GLP-1 receptor agonists is probably due to tachyphylaxis, meaning that the effect of these compounds on gastric emptying decreases rapidly with time owing to their, As a consequence, long-acting GLP-1 receptor agonists do not lower postprandial glucose excursions to the same extent as do short-acting compounds (Vivian et al., 2012). Consistent with this concept, postprandial insulin concentrations are increased by the long-acting compounds (Mikkel et al., 2011) but decrease after administration of short-acting GLP-1 receptor agonists(134) The appetite-suppressing action of GLP-1 has long been thought to be secondary to its role in delaying gastric emptying (Justin et al., 2014). However, reductions in body weight observed in individuals receiving a short-acting GLP-1 receptor agonist are

comparable to those seen in patients treated with long-acting compounds (Ratner et al., 2010, Pinget et al., 2013). This finding suggests that the reduction of body weight induced by GLP-1 is probably largely independent of gastric emptying and is, instead, primarily mediated by its central actions on receptors in the hypothalamus and other areas of the CNS. In line with this theory, direct intracerebroventricular administration of GLP-1 consistently and strongly suppresses food intake in rodents (Eng et al., 1992, Kendall et al., 2005, Buse et al., 2004). Significantly, although the decrease in body weight appears to be sustained during long-term treatment with long-acting GLP1 receptor agonists, the induction of nausea with these compounds appears to be short-lived and typically attenuates after 4–8 weeks of treatment (Defronzo et al., 2005). This finding indicates that the mechanisms underlying the induction of nausea and the prohibition of food intake are distinct from each other. Whether other putative actions of GLP-1, such as the preservation or regeneration of β cells, are also dependent on the pharmacokinetic properties of the GLP-1 receptor agonists is not known at present.

Albiglutide

Albiglutide is a fusion peptide consisting of two molecules of a GLP1 analogue covalently bound to human serum albumin (Heine et al., 2005). In this drug, resistance to cleavage by DPP4 has been caused by a single amino acid replacement. The half-life of the compound has been estimated at 6–8 days (Buse et al., 2011). Although HbA1c level reductions have been reported to be similar for weekly, biweekly and monthly administration regimens, fluctuations in patients' fasting plasma glucose levels were least pronounced when the drug was administered weekly (Ridge et al., 2012). Improvements in fasting blood glucose levels have been observed as early as 2 weeks after initiation of albiglutide treatment (Alan, 2011). Smaller reductions in HbA1c level (0.78% versus 0.99%) and body weight (−0.62 kg versus −2.21 kg) have been reported in patients treated with albiglutide than in those receiving liraglutide (Daniel et al., 2008). Even though evidence exists that native GLP-1 can reach the CNS through areas that lack a typical blood–brain barrier (Jason et al., 2006) the large size of the albiglutide molecule (which is mainly determined by the two molecules of human albumin) indicates that the drug might not affect the CNS to the same extent as GLP-1 receptor agonists of smaller molecular size. However, a modest reduction in body weight has been demonstrated in clinical studies of albiglutide treatment, which could still be due to central effects of the drug (Richard et al., 2010). Rates of nausea are lowest in patients administered albiglutide weekly (Loretta et al., 2004). Studies comparing different dosing regimens have shown an optimal ratio of efficacy and adverse effects (especially nausea) at a dose of 30 mg once per week (David et al., 2001). In a direct comparison with exenatide given twice per day, the incidence of nausea and vomiting was significantly lower with albiglutide. Local skin reactions at the injection site have been reported in 2.9–28.6% of patients during albiglutide administration, depending on the dose of the drug that was administered (Sirisha et al., 2008).

Dulaglutide

Dulaglutide is a GLP-1 peptide fused to IgG that exhibits extended biological activity due to its increased half-life (~90 h) compared with native GLP-1, supporting once-weekly administration of this drug (Thomas et al., 2008, Katherine et al., 2014). Doses of 0.05–8.0 mg per week have resulted in HbA1c level reductions of 0.2–1.2% after 5 weeks.93 Significant mean reductions in body weight, of 2.5 kg and 2.0 kg, were only observed in patients who received the two highest doses of 5 mg and 8 mg per week. Patients with T2DM who were overweight or had obesity and were failing to respond to treatment with oral antihyperglycaemic agents were enrolled in a 16-week placebo-controlled study. Patients were randomly assigned to receive dulaglutide, at a dose of 1 mg once per week for the first 4 weeks and 2 mg once per week for the subsequent 12 weeks, or a placebo. In comparison with patients taking the placebo, patients receiving dulaglutide demonstrated 1.35%

greater reductions in their HbA1c level and a weight reduction that was 2.43 kg greater (Fineman et al., 2003). Nausea occurred in 13.8% of those in the dulaglutide group compared with 7.6% in the placebo group. Heart rate increased by 1.3–4.6 bpm in the patients receiving dulaglutide, compared with a mean decrease in heart rate of 1.1 bpm in patients given the placebo. The formation of antibodies against dulaglutide has not been reported in the results of trials published to date.

Exenatide-LAR

The long-acting formulation exenatide-LAR was developed to maintain a constant plasma level of the drug with once-weekly administration. Exenatide-LAR consists of microspheres composed of a biodegradable poly (lactide-*co*-glycolide) polymeric matrix that contain the peptide exenatide. Following a once-weekly subcutaneous injection, exenatide is slowly released from the microspheres through diffusion and microsphere breakdown (Barnett et al., 2007) reaching a steady-state plasma concentration after ~6–8 weeks of treatment. In patients with type 2 diabetes mellitus, mean HbA1c reductions observed with exenatide- LAR treatment range between 1.3% and 1.9% (Tsunekawa et al., 2007, Viswanathan et al., 2007) In a head-to-head trial, the overall HbA1c reduction was significantly greater with exenatide-LAR treatment than with the twice-daily administration of exenatide (Li et al., 2008). This difference was primarily driven by a greater reduction in fasting blood glucose levels after treatment with the long-acting GLP-1 receptor agonist. However, in the same trial, postprandial glucose excursions after 14 weeks of treatment were reduced to a greater extent by exenatide than by exenatide-LAR (Virji et al., 2007, Minshall et al., 2008, Hayes et al., 2011, Scott et al., 2011). In another head-to-head comparison of GLP-1 receptor agonists in patients with type 2 diabetes mellitus, the HbA1c reduction in patients receiving 2 mg exenatide-LAR once per week was smaller than in patients receiving 1.8 mg liraglutide once per day (1.3% versus 1.5%) (Lawrence et al., 2014). However, the incidences of nausea (9% versus 20%) and vomiting (4% versus 11%) were both lower in patients treated with exenatide-LAR than in those receiving liraglutide (Julio et al., 2014). Nausea (25% versus 35%) and vomiting (11% versus 19%) were also less frequent in patients receiving exenatide-LAR than in those taking exenatide (Julio et al., 2014). Patients receiving exenatide-LAR seem to have a more pronounced increase in heart rate (~2–5 bpm) than do those being treated with short-acting exenatide. The reduction in body weight in patients receiving the long-acting and short-acting forms of exenatide is, however, comparable. Up to 74% of patients being treated with exenatide-LAR developed antibodies against this drug, compared with 43% of those treated with short-acting exenatide (HARMONY, 2014) In the majority of these patients, the efficacy of either drug did not seem to be diminished by the presence of antibodies (Lawrence et al., 2014). The necessity for using a larger-gauge needle might dissuade patients with fear of injections from using exenatide-LAR. Local injection site reactions might also lead to treatment discontinuation in patients receiving this drug. By contrast, in patients with predominant postprandial hyperglycaemia, the short-acting drugs might offer greater efficacy owing to their pronounced effects on gastric emptying (Jessica et al., 2008). However, findings from head-to-head studies in such patients have not yet been published. The individuals most likely to benefit from the short-acting drugs could, therefore, be those at early stages of type 2 diabetes mellitus whose postprandial glucose levels are often exaggerated, despite having between-meal glucose levels maintained within the normal range (Tomkin et al., 2009). In addition, patients who tend to consume the major proportion of their daily caloric intake in the morning might benefit from treatment with long-acting drugs because glucose excursions after lunch and dinner are poorly corrected by the short-acting drugs, as their efficacy wanes between injections. The increase in heart rate observed primarily with the long-acting compounds might also argue against the use of these drugs in patients with cardiac arrhythmia or heart failure, although no clinical data on the effects of either the short-acting or long-acting GLP-1 receptor agonists in such patients have yet become available. A final consideration is the feasibility of rapid discontinuation.

Should the patient develop acute pancreatitis, require abdominal surgery or experience other clinical events that necessitate the transient withholding of GLP-1 receptor agonist treatment, rapid withdrawal would not be possible if the patient is receiving the compounds that are administered once weekly. Another emerging use for GLP-1 receptor agonists is their administration in combination with insulin for the treatment of type 2 diabetes mellitus (Heather et al., 2014). To date, GLP-1 receptor agonists have been tested primarily in combination with basal insulin treatment strategies. Basal insulin therapy carries a lower risk of hypoglycaemia than short-acting insulin strategies. The major advantage of adding GLP-1 receptor agonists instead of short-acting insulin to basal insulin therapies is the reduced risk of hypoglycaemia and the additional weight loss benefit. Reductions in plasma HbA1c concentration have been described in patients receiving both short-acting and long-acting GLP-1 receptor agonists in combination with insulin (Zachary et al., 2012).

Liraglutide

Liraglutide was developed as a human GLP-1 analogue and shares ~97% sequence identity with the native hormone. The peptide differs from GLP-1 owing to a Lys34Arg amino acid substitution and the addition of glutamate and a 16-carbon free fatty acid to Lys26, modifications that induce noncovalent binding to plasma albumin (Terauchi et al., 2014). Consequently, ~99% of the liraglutide molecules are typically bound to plasma albumin, and the bound molecule has a half-life of 11–13 h (Umpierrez et al., 2014). This extended viability leads to a continuously high plasma level of liraglutide with once daily subcutaneous administration. The standard therapeutic dose of liraglutide is 1.2 mg once per day, but titration up to 1.8 mg once per day is recommended if the patient has an insufficient glycaemic response to the drug. In phase III clinical trials of liraglutide in patients with T2DM, HbA1c levels were reduced by 1.1–1.8%, with little apparent differences in HbA1c level reduction observed between patients taking the 1.2 mg and 1.8 mg doses. In the majority of patients, therefore, the 1.2 mg dose is sufficient. Blood glucose monitoring revealed a homogeneous reduction throughout the day, with no indication of a specific reduction in postprandial glucose excursions with either dose of liraglutide. Liraglutide also increases insulin levels and improves β-cell function in patients with type 2 diabetes mellitus and seems to have no major effect on gastric emptying. The reduction in body weight observed with liraglutide treatment ranges from 2 kg to 3 kg in various studies. Placebo-controlled trials involving individuals who have obesity, but who do not have diabetes mellitus have shown mean body weight reductions of up to 4.4 kg with liraglutide doses of 3.0 mg once per day. Thus, unlike its glucose-lowering effect, the reduction of body weight with liraglutide treatment seems to be clearly dose–dependent. The body weight reduction in patients administered 10 µg exenatide twice per day was similar to that seen in individuals receiving 1.8 mg liraglutide once per day (3.24 ± 0.33 kg versus 2.87 ± 0.33 kg; $P = 0.22$). In a study in which a dose of 1.8 mg once per day of liraglutide was compared with a 2 mg dose of exenatide once per week in patients with type 2 diabetes mellitus, the reduction in body weight was significantly greater with liraglutide (3.58 ± 0.18 kg versus 2.68 ± 0.18 kg; $P < 0.05$).(175)Liraglutide reduces systolic blood pressure by ~2–7 mmHg,19,50,100–102 but persistent increases in heart rate of ~2–4 bpm have also been reported. Whether the potentially detrimental effects of this increase in heart rate would outweigh the cardiovascular benefit of blood pressure reduction cannot yet be judged with certainty. As with all GLP-1 receptor agonists, gastrointestinal adverse effects have been reported during liraglutide treatment. The incidence of nausea is ~20–40%, but symptoms typically resolve after ~4–8 weeks of treatment (Efficacy and Safety, 2014, Dungan et al., 2014). Vomiting has been reported in ~5–10% of individuals receiving the drug (Scheen et al., 2014). Liraglutide improved the β-cell health, increase secretion of insulin and decrease glucagon production in diabetic patients (Aroda et al., 2011). The proportion of patients developing antibodies against the drug during treatment is low (3-10%) having no significant impairment in the antihyperglycemic efficacy of the compound (Aroda et al., 2011).

Liraglutide Improves Glycaemic Control in Patients Treated with Multiple Daily Insulin Injections, which is generally a final treatment option for patients with T2DM shows poor glycaemic control. However, they are often associated with weight gain and increased risk of hypoglycaemia. In addition, many individuals also have significantly reduced insulin production and do not reach glycaemic targets. Recently, Marcus Lind, MD, University of Gothenburg, Gothenburg, Sweden, and colleagues randomised patients with type 2 diabetes being treated with multiple daily insulin injections to receive liraglutide (n = 63) or placebo (n = 59) for 24 weeks. The primary endpoint was change in haemoglobin A1C (Hb A1C) from baseline to week 24 estimated by ANCOVA, adjusted for baseline Hb A1C. All patients could adjust their insulin doses as in clinical practice, and were advised to measure capillary glucose 3 to 4 times per day. In the intent-to-treat analysis, Hb A1C was reduced by 1.5% in the liraglutide group, compared with 0.4% in the placebo group (*P*< .0001). Compared with placebo (-0.4%), addition of liraglutide saw a greater change (-1.6%), which represented a significant treatment difference of -1.1% (*P*< .001). More patients in the liraglutide group achieved target Hb A1C levels of <53 mmol/mol compared with patients in the placebo group (42.9% vs 5.1%; *P*< .0001). Liraglutide treatment showed significant differences for body weight (-3.8 kg; *P*< .0001), total daily insulin dose (-15.8 U; *P*< .0001), fasting plasma glucose (-1.5 mmol/L; *P* = .0013), mean glucose estimated by masked continuous glucose monitoring (-1.9 mmol/L; *P*< .0001) and its standard deviations (-0.50 mmol/L; *P*< .0001), and mean postprandial glucose (-2.0; *P* = .0006). There were no severe hypoglycaemia events in either group. No significant difference existed in symptomatic or asymptomatic non-severe hypoglycaemias with values <4.0 or <3.0 mmol/l between the liraglutide and placebo groups. The most common type of hypoglycaemia was non-severe symptomatic hypoglycaemia (<4.0 mmol/l, mean number during follow-up 1.29 and 1.24 in the liraglutide and placebo groups, respectively; *P* = .96). This treatment is associated with low risk of hypoglycaemia when adding GLP-1 analogues to insulin may be of interest for use in clinical practice (Berrie, 2015).

CJC-1134 and CJC-1131

CJC-1134 and CJC-1131 are two long-acting GLP-1 receptor agonists under clinical investigation. These molecules consist of an exendin-4 backbone, which has been covalently linked to human serum albumin through a chemical linker. Early clinical studies have revealed a half-life of ~8 days for these drugs, meaning that once-weekly dosing would be possible with both of these compounds (Marre et al., 2009). Preclinical studies in mice have suggested that these compounds share the typical biological effects of other long-acting GLP-1 receptor agonists (Nauck et al., 2009). CJC1131 enhanced the synthesis and secretion of insulin, increase islet neogenesis and reduced the nutrient intake in type-2 diabetic mouse model (Russell-Jones et al., 2009). CJC1131 was found to inhibit fasting as well as postprandial glucose, body weight in diabetic patients (Russell-Jones et al., 2009). Although CJC1131 and exenatide-LAR are expected to make an extended pharmacokinetics profile which is suitable for once weekly dosing in the patients, small clinical data is available about the efficacy and safety of these albumin-based drugs in type-2 diabetic patients (Ji et al., 2014).

GLP-1 Receptor Agonist as a Drug

Comparative trials show that there are important differences between and among the glucagon-like peptide-1 (GLP-1) receptor agonists with respect to glycemic lowering, weight effects, and effects on systolic blood pressure and the lipid profile. From the clinical trial results provided by different research groups and therapeutic responses observed by different physicians, Exenatide appears to be a useful agent in the management of T2DM. Clinical trials on T2DM patients have been conducted both for short (about 30 d) as well as long (26 w or more) (Buse et al., 2009, Eduard Montanya, 2009) periods, employing the compound (at different doses) alone or in combination with

metformin/sulfonylureas. In all these trials Exenatide administered subcutaneously, has been found to possess significant beneficial effects on important antidiabetic parameters like reduction of $HbA(1)_c$ (Zhu et al., 2014, Wu et al., 2014), improved glycemic control including both fasting and pp plasma glucose level (Wu et al., 2014) and weight loss (Ando et al., 2014) along with mild to moderate persistent hypoglycemia (Katherine, 2009, Kuwata, 2014) nausea and vomiting (Yuya, 2012, Christensen, 2010) which disappeared in due course or persist, though mildly. Combination therapy produced better results] in comparison to monotherapy either with Exenatidee / metformin (Lund et al., 2011) / sulfonylurea (Julie et al., 2014) in addition to improved lipid profile. Some workers even showed that the addition of Exenatide is effective in T2DM patients when metformin/ sulfonylurea (alone failed. Ray *et al* compared the long-term benefits of Exenatide with that of insulin glargine and found the compound to be more effective than insulin glargine with respect to improvements in life-expectancy, quality-adjusted life-expectancy and lower cumulative incidence of CVD complications and CVD-related deaths (probably because of its ability to improve lipid profile). After the FDA approval for marketing, Exenatide was used for treatment of T2DM by Many physicians either alone or in combination with metformin/ sulfonylureas/ thiazolidinediones/ insulin, but its utility as a first line drug is yet to be defined(188). When used alone, the drug was found to reduce $HbA(1)_c$, fasting as well as pp blood glucose and body wt along with less hypoglycemia, nausea and vomiting (gastrointestinal symptoms)(189). Moreover, it was found to increase the insulin contents of pancreas along with retention of insulin-positive area. When EX was added to metformin/sulfonylureas/both in T2DM patients, better response was observed in relation to reduction of $HbA(1)_c$, plasma glucose (both fasting and pp) and wt. Moreover, improvement in health-related quality of life was observed (Tina et al., 2012). Hence, the drug can be considered as a good adjunct to metformin/sulfonylureas in T2DM patients. Several results of EX with insulin therapy in obese T2DM patients have been documented where the combination was found to reduce $HbA(1)_c$, body weight, systolic blood pressure, triglycerides and high-sensitivity CRP along with increased insulin sensitivity and protection against high-fat-induced insulin resistance. Though insulin is the best agent for controlling blood sugar level in diabetic patients, EX has been shown to possess some advantages over insulin glargine and biphasic insulin aspart in T2DM subjects. While reducing $HbA(1)_c$ and providing significant glycemic control like insulin, EX, in contrast to insulin, has been found to reduce wt, improve lipid profile and cause less hypoglycemia. In addition, EX administration is comparatively easier than insulin (though both of them used subcutaneously) because of the improved device for its s.c. administration and simple dosing schedule. *Minshall* et al found EX to produce sustained decrease in $HbA(1)_c$ in addition to improved lipid profile, decreased systolic blood pressure and body mass index; all of which positively contributed to the cost-effectiveness of the drug. Once-daily (q.d.) exendin-4 (0, 0.33, 1.5, and 3.0 μg/kg) and liraglutide (0, 50, 100, and 300 μg/kg, q.d.) both reduced the chow intake in nonobese rats in a dose-dependent fashion following either intraperitoneal (IP) or subcutaneous (SC) administration, whereas only liraglutide reduced 24 and 48 h body weight in nonobese, chow-maintained rats. Chow intake and body weight suppression by liraglutide were of greater magnitude and shorter latency following IP compared to SC delivery, whereas for exendin-4, the magnitude of intake-suppression was similar for IP and SC administration. In conclusion, administration of the GLP-1R ligands, exendin-4 (b.i.d.) and liraglutide (q.d.), lead to comparable and pronounced suppression of food intake and body weight in DIO rats, suggesting a potential role for these drugs as a clinical tool for obesity treatment. Food intake suppression after peripheral administration of exendin-4 and liraglutide is mediated by activation of GLP-1R expressed on vagal afferents as well as direct CNS GLP-1R activation. GLP-1R mediated neurotrophic and anti-apoptotic actions co-contribute to the neuroprotective property of GLP-1 in neuronal cell cultures, and reinforce the potential therapeutic value of GLP-1R agonists in neurodegenerative disorders involving oxidative stress.

Safety and Tolerability

Minor hypoglycemic events have been observed at a relatively low rate after the commencement of treatment with long acting GLP-1 receptor agonists, with between 0 and 14.5%of patients experiencing this side effect. As reported previously, the greatest proportion of patients reporting minor hypoglycemic events was when adding treatments to a sulfonylurea background. No major hypoglycemic events were reported. Gastrointestinal effects, including nausea and vomiting, appear to be the most frequently reported adverse effect seen with the long-acting GLP-1 receptor agonists (Table 2). These side effects occur early on in the treatment, but tend to be transient and rarely result in patient withdrawal. After taspoglutide treatment, for example, nausea and vomiting were usually resolved within 1 day,and subsequent taspoglutide administrations were less likely to induce nausea. Furthermore, a smaller proportion of patients reported nausea or vomiting after liraglutide treatment compared with patients treated with exenatide (25.5% of the study population vs. 28% with twice-daily exenatide; vomiting: 6.0% of the study population vs. 9.9%with twice-daily exenatide). Antibody formation was very low in patients treated with once-weekly GLP-1 receptor agonists. Antibodies to albiglutide, which has 95% amino acid identity with native GLP-1, were seen in 2.5% of albiglutide-treated patients Liraglutide shares 97% sequence identity with native GLP-1 and, across the LEAD trials, 8.6% of patients developed antiliraglutide antibodies; however, there were no indications from the clinical trial data that the formation of these antibodies affected efficacy ((27–32,42) Indeed, even after 78 weeks' treatment with liraglutide (26 weeks in the LEAD-6 trial plus a 52-week extension), only 2.6% of patients treated with liraglutide had low-titer liraglutide antibodies, and these antibodies did not affect reductions in A1C in these patients (193) During clinical development, and in the post marketing period, a small number of concerns arose regarding the clinical use of GLP-1 receptor agonists. Nausea is clearly the most frequent adverse effect of treatment with all GLP-1 receptor agonists developed so far. The incidence of nausea varies between 25% and 60% and its occurrence in a specific individual seems to be dependent upon various factors, such as meal size and frequency—and, potentially, BMI. Interestingly, the incidence of nausea and vomiting has been reported to be lower in Asian patients than in white patients. The incidence of vomiting in patients taking GLP-1 receptor agonists is ~5–15%. However, the long-acting GLP-1 receptor agonists seem to exhibit improved gastrointestinal tolerability, and the incidence of nausea declines over time, an effect that is likely to result from the development of tolerance. Typically, 5–10% of patients discontinue treatment owing to nausea and vomiting. Treatment with GLP-1 receptor agonists also causes diarrhoea in ~10–20% of patients, but the mechanisms underlying this adverse effect are unclear. Diarrhoea seems to occur more frequently with the long-acting than with the short-acting compounds. A side from these gastrointestinal adverse events, which were observed during the controlled clinical trials of GLP-1 receptor agonists as well as in clinical practice, a few cases of acute pancreatitis have been reported during treatment with exenatide and other GLP-1 receptor agonists. Importantly, the incidence of acute pancreatitis was not significantly increased during phase II and III clinical trials with any of the available GLP-1 receptor agonists, although these studies, by necessity, involved limited patient numbers and observation time. In any event, patients with type 2 diabetes mellitus seem to have a ~2–3-fold increased risk of acute pancreatitis compared with individuals who do not have diabetes mellitus.In addition, a plausible mechanistic explanation for a link between acute pancreatitis and GLP-1-based therapy has not thus far been proposed. A fair judgment of the postmarketing reports of acute pancreatitis, especially those listed in the FDA adverse events reporting system, is difficult because such reports are subject to various biases. In particular, systematic over-reporting of acute pancreatitis following the public discussion of such events in association with exenatide treatment might skew the results of any analysis. Large retrospective studies of medical records included in insurance company databases have not confirmed an increased risk of acute pancreatitis during GLP-1 receptor agonist therapy.

Nevertheless, an association between treatment with GLP-1-based drugs and an increased risk of pancreatitis cannot be ruled out. An analysis of data on patients with type 2 diabetes mellitus and obesity treated with liraglutide has revealed an increase in mean lipase concentrations of >10 IU, an effect that was reversible after treatment was discontinued. Cessation of treatment with GLP-1 receptor agonists in patients with clinical signs of acute pancreatitis is, therefore, advisable, and avoiding these drugs in patients with a history of pancreatitis would be prudent. However, routine blood monitoring of pancreatic enzymes in asymptomatic patients receiving GLP-1-based therapy does not seem to be necessary, given the current evidence. The presumed association between GLP-1-based therapy and pancreatic cancer seems to be even less substantiated by evidence from controlled trials. During the preclinical development of liraglutide, an increased incidence of C-cell hyperplasia and medullary thyroid cancer was reported in rats and mice. However, large-scale monitoring of patients' calcitonin levels during clinical trials of this drug did not reveal any indicators of cancer development, and no increased incidence of C-cell cancer was observed during clinical trials with other GLP-1 receptor agonists. However, these drugs should be avoided in patients with a history of thyroid cancer or multiple endocrine neoplasia. Although the associations between GLP-1 receptor agonist treatment and acute pancreatitis, pancreatic cancer or thyroid cancer still lacks verification in controlled trials, a trend towards an increase in heart rate is consistently observed during treatment with long-acting GLP-1 receptor agonists. The mean increase in heart rate observed in clinical trials of liraglutide or exenatide-LAR ranges between 2 bpm and 5 bpm. In a direct comparison of exenatide and liraglutide, the increase in heart rate was significantly greater in patients receiving liraglutide than in those receiving exenatide (3.28 bpm versus 0.69 bpm). In patients receiving exenatide-LAR, mean heart rate increases of 4.1 bpm and 4.0 bpm have been reported.By contrast, the findings of a trial in which short-acting exenatide was administered to patients twice daily did not show a significant increase in heart rate.48 In another direct comparison, long-acting liraglutide was associated with a mean heart rate increase of 5.3 bpm, whereas short-acting lixisenatide led to a mean heart rate reduction of 3.6 bpm. Thus, continuous activation of the GLP-1 receptor seems to result in a greater increase in heart rate than intermittent stimulation. The mechanism underlying this increase in heart rate has not yet been completely clarified. Reductions in body weight or a reflex mechanism triggered in response to the blood-pressure-lowering effect of GLP-1 receptor agonists do not seem to be plausible explanations, because both effects are similarly found with short-acting and long-acting GLP-1 receptor agonists. On the basis of data from studies in rodents, inhibition of vagus nerve signalling by GLP-1 might underlie the increase in heart rate. Whether the increase in heart rate induced by GLP-1 receptor agonists might result in an increased incidence of cardiovascular events, including heart failure or arrhythmia, cannot be judged at this point in time. Preliminary cardiovascular safety analyses of data on liraglutide and exenatide have even shown a trend towards a reduction in cardiovascular events. Studies undertaken to examine the effects of GLP-1 receptor agonists on the QT interval did not reveal a significant effect of either exenatide or liraglutide on this measure of heart function.Well-conducted, long-term studies will have to be undertaken to evaluate the clinical relevance of the positive chronotropic effects of GLP-1 receptor agonists.

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