**GLP-1 as a target for therapeutic intervention**

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Conflicts of interest:

JW has acted as a consultant, received institutional grants and given lectures on behalf of pharmaceutical companies developing or marketing medicines used for the treatment of diabetes, specifically AstraZeneca, Boehringer Ingelheim, Janssen Pharmaceuticals, Lilly, Novo Nordisk, Orexigen, Sanofi & Takeda. SPR has no conflicts of interest to declare.

**Abstract**

Glucagon-like peptide receptor agonists (GLP-1 RA) have multiple effects, including control of glycaemia via stimulation of insulin and suppression of glucagon secretion and reduction of adiposity by enhancing satiety, so are an attractive therapeutic option in type 2 diabetes management. Five GLP1-RA are used currently and more are in development. The HbA1c reduction obtained varies from 1-2%; they reduce body weight by about 2-3 kg when used to treat T2DM, while liraglutide results in greater weight loss at a higher dose and has recently been approved for the management of obesity. GLP-1 RA are usually used in combination with other glucose-lowering drugs, but dual combinations with basal insulin in a single injection have recently become available. The next decade is likely to see the development of more potent and longer lasting agents as well as hybrid molecules with dual or triple actions.

**Incretins and the incretin effect**

Type 2 Diabetes (T2DM) is a complex metabolic disorder and multiple pathophysiological processes contribute to its aetiology and progression, hence treatment modalities need to be targeted at various levels. The development of incretin based therapies stems from the observation that oral glucose ingestion results in an amplified insulin response compared to intravenous administration (the ‘incretin effect’), providing early evidence for the existence of an entero-insular axis(1). Gastric Inhibitory Peptide (GIP) was the first incretin to be isolated from the gut mucosa followed by the identification of glucagon-like peptide 1 (7-36) amide (GLP-1) (2) and together these are responsible for the incretin effect though the latter has a more preserved insulinotropic effect in T2DM. Nevertheless, incretin effects as well as GLP-1 levels are reduced in T2DM (3).

GLP-1 is a 30 amino acid peptide or a 31 residue peptide with C-terminal glycine and is a product of the proglucagon gene which undergoes tissue specific translational processing by the prohormone convertases. It exerts its effects by binding to the GLP-1 receptor (GLP-1R), a 463 amino acid G-protein-coupled receptor which is present abundantly in the pancreatic alpha and beta cells, gut and the central nervous system and moderately in the lung, heart, kidney, blood vessels and peripheral nervous system (4). GLP-1 (as well as GIP) is rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP4) (5).

**Biological actions of GLP-1**

The most well characterized physiological role of GLP-1 is its insulinotropic effect i.e., potentiation of insulin secretion from beta cells depending on the prevailing blood glucose, with minimal effects below about 3.5mmol/l, thereby reducing the risk of hypoglycaemia. It also inhibits glucagon release (6) due to its effects on alpha cells (receptor mediated or via stimulation of insulin or somatostatin release). These insulinotropic and glucagonostatic effects of GLP-1 contribute to its ability to lower glucose in T2DM (7). GLP-1 also delays gastric emptying (8) preventing the rapid entry of glucose into the circulation, an important factor for the control of postprandial glycaemic excursions. The role of GLP-1 in inducing satiety is through central (activation of GLP-1R in the brain) as well as peripheral mechanisms (dose-dependent decrease in gastrointestinal motility). The therapeutic potential of these effects makes these agents effective in treating T2DM and obesity. Apart from these well characterized effects, GLP-1 also decreases post prandial triglycerides and free fatty acid levels (9) and lowers blood pressure.

**GLP-1 receptor agonists (GLP-1 RA)**

These can be broadly classified into 1) native GLP-1 derivatives with amino acid modifications (conferring resistance to the action of DPP4) and addition of fatty acid (liraglutide), albumin (albiglutide) or immunoglobulin (dulaglutide) to prolong half-life,2) exendin-4 derivatives (exenatide, lixisenatide and exenatide-LR). Exendin-4 is a synthetic GLP-1 agonist originally isolated from the saliva of the Gila monster lizard which shares 53% sequence homology with human GLP-1 (10) and is resistant to the action of DPP4. The detailed molecular structures of available GLP-1 RA are illustrated in table 1.

 Another commonly used classification is short acting (exenatide, lixisenatide) and long acting GLP-1 RA (liraglutide, exenatide LR, dulaglutide, albiglutide). While the long acting agents primarily affect the glycaemic excursions via their insulinotropic and glucagonostatic properties, the short acting agents act partly via delay of gastric emptying making them effective agents for managing post-prandial hyperglycaemia.

Exenatide was the first GLP-1 RA and has been available for clinical use since 2005. It lowers glycated haemoglobin (HbA1c) when used alone, in combination with oral hypoglycaemic agents, and with insulin (11-14). The reduction in HbA1c is 0.8-1.5% and it is associated with weight loss of 2-3 kg. It is injected at dose of 10 mcg twice daily and controls post prandial blood glucose after breakfast and dinner to a greater extent than after lunch time. However, the reduction in fasting glycaemia is less compared to long acting GLP-1 RA (15; 16).

Lixisenatide is a C-terminally extended (with 6 lysine residues) 44 amino acid peptide derivative of exenatide. The half-life of this compound is 3-4 hrs, but as initial studies showed similar HbA1c reduction with once or twice daily dosage, a once daily dose was subsequently used. Lixisenatide has been compared with placebo in various combinations (with metformin, sulfonylurea, TZD and insulin) in the GetGoal trials (17-20) with HbA1c reductions of 0.7-1.0% and weight reduction of 1-3 kg. The incidence of nausea and hypoglycaemia was lower with lixisenatide than in patients on exenatide (21). Similar to exenatide, lixisenatide also results in reduction of postprandial hyperglycaemia which is associated with a reduction in insulin levels that is thought to be primarily due to a delay in gastric emptying (22). Its effects on fasting glycaemia are not marked compared with long acting agents.

The long-acting formulation of exenatide, exenatide LAR, is comprised of exenatide in a polymeric matrix of biodegradable microspheres and attains a steady-state plasma concentration after 6 weeks. It was studied in the DURATION series of trials (23-25) with reduction in HbA1c of 1.3-1.9%. When compared with exenatide twice daily, the HbA1c reduction was better for the once weekly preparation (mainly due to its effect on fasting glycaemia) with a better GI profile and similar reductions in body weight (15) .

Liraglutide shares 97% sequence identity with native GLP-1 and is non-covalently bound to plasma albumin extending its half-life to 11-13 hrs. It was studied extensively in the LEAD 1-6 series of trials (16; 26-30) resulting in HbA1c reductions of 1.1-1.8% and body weight of 2-3 kg. It causes a uniform reduction in glucose levels throughout the day with no significant effect on gastric emptying (31). It causes similar reduction in body weight when compared with exentaide bd and greater reductions than exenatide LAR (32). Liraglutide is less immunogenic when compared with exenatide due to its greater sequence homology with native GLP-1 (33). Most recently, liraglutide became the first GLP-1 RA to demonstrate a positive CV outcome in a cardiovascular outcome trial (CVOT).

Albiglutide consists of two molecules of GLP-1 covalently bound to human albumin with a half-life of 6-8 days and is administered weekly and was studied in HARMONY 1-8 (34-37) trials. When compared with liraglutide, albiglutide has demonstrated lower reductions in HbA1c (0.78% vs 0.99%) (38) as well as body weight (-0.62 kg vs -2.2 kg). This might be due to the large size of the molecule resulting in less penetration of blood-brain barrier and consequent reduction in central effects. However, it has better GI tolerability when compared against exenatide bd (39).

Dulaglutide is a GLP-1 peptide which is combined with immunoglobulin (IgG) thus extending its half-life to 90 hours and is administered in weekly doses. It has been studied in the AWARD series (40; 41) (42) resulting in HbA1c reductions of 0.2-1.2% and body weight reduction of 2-2.5 kg at the highest doses as well as in head-to-head trials demonstrating better HbA1c reductions against exenatide bd (43) and liraglutide (44).The availability of various GLP-1 RA opens a whole array of individualized treatment options for T2DM management. Long acting agents are more convenient due to less frequent and meal independent administration; they cause superior reductions in HbA1c primarily due to control of fasting hyperglycaemia; nausea and vomiting with these agents attenuate over time. Short acting agents on the other hand would be suitable for patients with fixed daily routines and those in whom control of post-prandial hyperglycaemia is required. There is also the feasibility of rapid discontinuation with short acting GLP-1 RA.

Rodent studies elucidated the role of GLP-1 in beta cell protection by increasing cell regeneration and inhibiting apoptosis (45). Preservation of beta cell function was also noted with exenatide in a study involving 69 patients over 3 years (46) and further long term studies are required to confirm the beta-cell protection theory.

**Emerging GLP-1 based therapies**

GLP-1 RA are available in combination with basal insulin. IdegLira, a combination of insulin degludec and liraglutide is now available and the glycaemic efficacy is superior to that of insulin degludec with the benefit of weight loss (47). Glargine-lixisenatide combination is submitted for regulatory approval. Semaglutide, a long acting GLP-1 RA has also been developed in oral formulation and is currently undergoing phase 3 trials(ClinicalTrials.gov : NCT02607865 )

 The development of single molecules which are multi-functional is another promising development in the therapeutic horizon for tackling obesity. Hybrid GLP-1/glucagon chimeric molecules which combine the anorectic, insulinotropic effects of GLP-1 and the thermogenic, lipolytic potential of glucagon have been demonstrated in rodent studies to cause more weight loss and increased energy expenditure when compared to GLP-1 on its own(48). This was with comparable glycaemic reductions possibly because of the potential of GLP-1 to offset glucagon induced hyperglycaemia. In humans, co-administration of GLP-1 and glucagon reduced food intake and increased energy expenditure (49) .

**Adverse effects and safety concerns**

GI intolerance is the most common adverse effect and includes nausea (25-60%), vomiting (5-15%) and diarrhoea (10-20%). However these are mostly mild, transient and dose-dependent and can be reduced to some extent with a gradual dose-escalation strategy (16) . Anti-exenatide antibodies are developed following treatment with exenatide (43%) and exenatide LAR (74%) and in the majority of patients not associated with a depreciation of therapeutic efficacy (32). However, patients with high titres of antibodies experienced less reduction in HbA1c levels (33). Concerns regarding pancreatitis and pancreatic carcinoma are not proven due to absence of a plausible mechanistic theory and lack of data from randomized controlled trials (50). Similarly, the increased incidence of C-cell hyperplasia and medullary thyroid carcinoma which was noticed in rodent studies (51) was not replicated in large scale human studies with monitoring of serum calcitonin levels (52). GLP-1 RAs are also associated with a fall in systolic blood pressure (2-3 mmHg) and a 2-3 beats per minute increase in heart rate (53).

The adverse effects depend on the pharmacokinetic profile of GLP-1 RA with higher incidence of GI events with short acting agents while long acting agents cause more chronotropic effects.

**CVOT on GLP-1 analogues**

The FDA now requires all glucose lowering agents to undergo CVOT to demonstrate their CV safety. The CV outcomes of lixisenatide were studied over a median follow-up period of 25 months in 6068 patients with T2DM who had a recent acute coronary event (54). Though the trial was designed to demonstrate superiority over placebo, there was no significant difference in CV events, thus only providing evidence of CV safety.

The most recent LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial on 9340 patients with T2DM and a high cardiovascular risk demonstrated superiority of liraglutide compared to placebo. The median follow-up period of the trial was 3.8 years. The primary composite outcome was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke.The magnitude and the time to benefit observed in this trial suggests that the effect could be driven by modification in atherosclerotic process. This study also demonstrated a reduction in the composite of renal and retinal microvascular events which was primarily driven by a lower rate of nephropathy progression (55).

**GLP-1 in the treatment of obesity**

Liraglutide became the first GLP-1 RA to be used in the management of obesity approved by FDA in December 2014 and EMA in January 2015 at a dose of 3 mg. The SCALE study investigated 3731 patients without T2DM with a BMI of more than 30 or more than 27 in the presence of hypertension and dyslipidemia and participants were randomized to liraglutide 3 mg or placebo as an adjunct to diet and exercise (56). The mean weight loss in liraglutide group was 8.4±7.3 kg and 2.8±6.5 kg in the placebo group (95% confidence interval, -6.0 to -5.1; P<0.001). 63% patients in the liraglutide group and 27% in the placebo group lost 5% of their body weight. Of particular note, the prevalence of pre-diabetes fell from 61.4% at baseline to 30.8% at 56 weeks while it increased from 60.9% to 68.3% over the same period in the placebo group. There was improvement in cardiometabolic parameters in the liraglutide group. The most common adverse events (AE) were GI events (mostly transient) with a withdrawal rate of 6% in the liraglutide group. Gall bladder disease and pancreatitis were also more common in the liraglutide group. The difference in body weight following cessation of liraglutide after a 12 week wash-out period was evaluated in 846 patients, weight regain was observed in both groups, more so in the placebo group (57). Another long-acting GLP-1 RA, semaglutide, is currently being investigated in the treatment of obesity (ClinicalTrials.gov Identifier: NCT02453711).

**Conclusion**

Manipulation of GLP-1 has become a valuable therapeutic tool in diabetes treatment with multiple advantages in addition to glucose-lowering, including appetite suppression resulting in weight loss, reduction of blood pressure, positive cardiovascular outcomes with liraglutide and possibly preservation of beta cell mass. The development of GLP-1 analogues is a welcome addition to the therapeutic armamentarium, in patients where insulin was deemed as the next step after failure of oral hypoglycaemic agents.GLP-1 analogues also result in weight loss with less propensity to cause hypoglycaemia and may have advantages when used earlier in the disease course. Future potential of GLP-1 RA in type 2 as well as type 1 diabetes & obesity are anticipated with further elucidation of the intriguing mechanisms of action of this class of drugs.

**Highlights**

* GLP-1 analogues are used in the management of type 2 diabetes and obesity.
* They improve glycaemic control, promote weight loss and have a low risk of hypoglycaemia.
* GLP-1 analogues are available for daily and weekly administration as injectables.
* Gastrointestinal intolerance is the most common adverse effect.

Table 1

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| GLP-1 RA | Molecular structure | T 1/2 | Dosing | Reduction in HbA1c in % | Reduction in body weight | Renal dosing | CVOT |
| Exenatide | 39 AA peptide | 2.4hrs | 5-10 mcg bd | 0.8-1.2 | 1-3 kg | avoid if eGFR <30ml/min/1.73m2eGFR 30-50ml/min/1.73m2(caution) | None |
| Lixisenatide | 44 AA derivative of exenatide | 4 hrs | 10-20 mcg od | 0.6-1 | 1.3-2.7 kg | avoid if eGFR<30 ml/min•1.73m2eGFR 30-50 ml/min•1.73m2(caution) | ELIXA |
| Exenatide-LAR | Polyglactin microspheres releasing exenatide | 96 hrs | 2 mg weekly | 1.3-1.9 | 2-3.7 kg | avoid if eGFR <50ml/min/1.73m2 | EXSCEL |
| Liraglutide | Lys34ArgAA, glutamate &16 C fatty acid to Lys26, non-covalent bond to albumin | 12 hrs | 1.2-1.8 mg od | 0.8-1.5 | 2-3 kg | avoid if eGFR <30ml/min/1.73m2 | LEADER |
| Albiglutde | 2GLP-1 analogues bound to albumin | 6-8 days | 30-50 mg weekly | 0.7-1 | 0.8-1.1 kg | No dose adjustmentsCaution during initiation and dose escalation | HARMONY |
| Dulaglutide | GLP-A peptide fused to Immunoglobulin G | 90 hrs | 0.75-1.5 mg weekly | 0.78-1.5 | 0.8-2.5 kg | avoid if eGFR <30ml/min/1.73m2 | REWIND |

AA-amino acid; Lys- Lysine; Arg-Arginine; C- Carbon; bd- twice daily; od- once daily; eGFR- estimated Glomerular Filtration Rate

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