Newer Vistas in Glucagon-Like Peptide-1 Analog Therapy - Marvels of Peptide Engineering

Glucagon-like peptide–1 (GLP-1) is an intestinal incretin hormone released from the endocrine L-cells of the hind gut which augments glucose-mediated insulin release from the beta cells of the pancreas. Native human GLP-1 is a transcriptional product of the proglucagon gene. This gene is secreted in response to food intake and contains 30 amino acids.[1] The biologically active forms of GLP-1 are GLP-1 (7-37) and GLP-1 (7-36) both of which exert their action by binding to the GLP-1 receptor which is a G-protein coupled receptor. In addition, GLP-1 hormone also suppresses glucagon secretion from the pancreas which in turn reduces hepatic glucose production, and GLP-1 also slows down gastric emptying.[2] A second incretin called glucose-dependent insulinotropic polypeptide (GIP) is produced by the K cells in the duodenum and jejunum. Like GLP-1, GIP is released in response to nutrients and is quickly degraded by dipeptidyl peptidase-4 (DPP4) enzyme. The primary difference between GLP-1 and GIP is in its effect on the alfa cells in the production of glucagon. In the presence of hyperglycemia, GIP has a glucagonostatic affect like GLP-1 but in the presence of normoglycemia or hypoglycemia GIP has a glucagonotropic effect unlike GLP-1. The differential effects of both these incretins are given in Figure 1.

Native GLP-1 is considered unsuitable for clinical use because of its short half-life of <2 min. The half-life is extremely short because of two major reasons. First, both endogenous and exogenous GLP-1 are rapidly degraded and inactivated by the removal of a dipeptide at N-terminus by a circulating enzyme named DPP-4. Second because of the small size of the peptide, it is quickly eliminated by the process of filtration from the kidneys.[3] The development of clinically useful longer acting GLP-1 receptor agonists has been an area of intense and incremental successes in peptide engineering. The initial strategies used included the use of naturally occurring DPP-4 resistant GLP-1 agonists (e.g., Exendin-4), substitution of the second amino acid in native GLP-1 with another amino acid which is not recognized by DPP-4 enzyme (e.g., albiglutide containing glycine in the second position), conjugation of GLP-1 with larger molecules which shield them from DPP-4 cleavage (e.g., liraglutide containing a C16 fatty acid). A further increase in half-life was made possible when these DPP-4 resistant analogs are conjugated with larger moieties which prevented renal loss in the glomerular filtrate (e.g., liraglutide with C16 fatty acid, albiglutide with human albumin, and dulaglutide with modified Fc fraction of human immunoglobulin G). A third strategy has been to incorporate resistant GLP-1 analogs into polymers and other substances which enable sustained release (e.g., Exenatide LAR).[4]

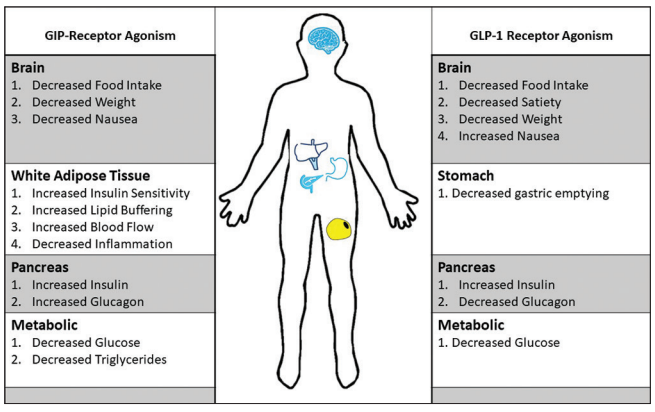

Figure 1: Cartoon showing the similarities and differences between the actions of glucagon like peptide-1 receptor agonism and glucose dependent insulinotropic polypeptide receptor agonism

In the last few years, we have seen two additional marvels of peptide engineering in the space of GLP-1 analog pharmacotherapy. First, it is the design of peptides capable of activating more than one target receptor. The most advanced of these agents is tirzepatide which is capable of being a GIP receptor (GIP-R) and a GLP-1 receptor (GLP-1-R) agonist at the same time. Combined activation of both these incretin receptors leads to synergy and additive benefits both in terms of glucose control and weight reduction. These added incremental benefits can be explained by three mechanisms. First, dual agonism of the incretin receptors in the brain leads to enhanced appetite suppression and greater degree of weight loss. Second, the dual agonism on the beta cells of the pancreas leads to greater glucose control because of an increase in glucose-dependent insulin secretion. Third, it is proposed that GIP-R agonism leads to improved white adipose tissue functions and increased lipid buffering capacity which in turn protects the vasculature and liver from "spillover" of postprandial lipids.[5]

In this issue of the journal, Dutta *et al*. bring out an early metanalysis of the therapeutic benefits of once weekly subcutaneous tirzepatide when compared with active controls. They included six randomized control trials (RCT) with 3484 patients to conclude better HbA1c lowering (0.7%) with better odds of getting to an Hba1c <6.5% (OR-4.3) and better weight reduction (8.6 kg) when compared to active controls which included potent active agents such as dulaglutide, weekly semaglutide, and basal insulins. There was no significant difference in adverse events or serious adverse events in these studies between tirzepatide and

active controls. Tirzepatide is an imbalanced dual agonist with more GIP-R activity compared to GLP-1-R activity. This may explain the exceptionally better glucose and weight control when compared to standard GLP-1-R agonists. In direct comparison with GLP-1 agonists, it is suggested than tirzepatide may have lower gastrointestinal side effects partly mediated by the anti-emetic effect of GIP-R agonism in the brain. The drug is awaiting approval. A large cardiovascular outcome trial, SURPASS-CVOT (NCT04255433) is currently recruiting over 12,000 patients and is expected to publish its results by 2024. Unlike usual CVOTs, tirzepatide in this trial is being compared to an active comparator dulaglutide and not a placebo.

However, all current GLP-1 analogs available in our country and tirzepatide are injectable agents limiting acceptability of these agents in some patients. The second marvel of peptide engineering in the GLP-1 analog armamentarium is the production of a therapeutically viable oral formulation of an existing GLP-1 analog. This was achieved by coformulation of semaglutide with an absorption enhancer called sodium N-(8-[2-hydroxybenzoyl] amino caprylate) (SNAC). SNAC has been previously demonstrated to be safe and appears to aid the absorption of semaglutide from the gastric mucosa by three mechanisms. First, SNAC increases the pH around the tablet protecting the peptide (semaglutide) from gastric enzymes such as pepsin and acid-mediated degradation. Second, SNAC induces fluidization and sloughing of a small area of the gastric mucosa directly in contact the tablet promoting absorption of the peptide. Finally, SNAC also promotes monomerization of the peptide making it easier for semaglutide to move across the fluidized mucosa and get absorbed into the portal circulation.[6]

As bioavailability of oral semaglutide is 1/100th of the subcutaneous version, the optimal drug dose is 14 mg once daily comparable to 1 mg once weekly for subcutaneous semaglutide. Lower doses can be used in patients who are unable to tolerate full doses of the product. At optimal dosing, a recent network metanalysis of 27 RCTs suggested that 14 mg of oral semaglutide is superior to most of the current GLP-1 analogs including once daily liraglutide (1.2 mg/day), once weekly exenatide (2 mg/once a week), and once a week dulaglutide (0.75 mg once weekly) in terms of glucose control and weight reductions. Glucose control and weight reductions were comparable with subcutaneous semaglutide. There was a similar frequency of gastrointestinal side effects among patients taking oral semaglutide as seen with subcutaneous GLP-1 agonists.[7] Cardiovascular safety for regulatory requirements was established for oral semaglutide in the PIONEER 6 study which involved 3183 patients followed up for a median of 15.9 months. The occurrence of the primary three-point major adverse cardiovascular outcome did not differ between the groups assigned to receive semaglutide or placebo (3.8 vs. 4.8%, respectively; hard ratio 0.79, 95% confidence interval 0.57–1.11, $P < 0.001$ for noninferiority).[8]

Oral semaglutide is currently approved in many countries including India. The drug should have commenced marketing in India by the time this issue comes online. Taken together both these innovations in GLP-1 peptide pharmacology should increase the number of prescriptions and the number of patients with type 2 diabetes mellitus who benefit from GLP-1 analogs in our country.

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