GOAL: GUIDANCE ORIENTED APPROACH TO LEARNING
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Unit No. 2

THE GLP-1RAS: FROM EVOLUTION TO REVOLUTION

Dr Nitish Mishra

ABSTRACT

Research on incretin hormones has advanced considerably over the past few decades. Although the initial molecule – glucose-dependent insulinotropic polypeptide – failed to stimulate insulin secretion in patients with type 2 diabetes, it led to the discovery of glucagon-like peptide 1 (GLP-1). As GLP-1 impacts on various tissues and cells throughout the body, it allows patients with type 2 diabetes to benefit in many ways, in addition to lowering blood glucose levels. In a bid to harness these benefits pharmacologically, analogues were evolved from GLP-1 to produce a class of peptides known as GLP-1 receptor agonists (GLP-1RAs). The mechanism of action by which GLP-1RAs achieve their effects on lowering glucose levels, body weight, systolic blood pressure as well as lipid profiles, and improving cardiovascular and renal outcomes will be further discussed. With the advancement in research and development, the advent of scientific research and development has greatly accelerated the global implementation and local approved use of the first oral GLP-1RA, allowing the abovementioned benefits to be easily accessed. Oral GLP-1RA is set to bring about a revolution in the management of type 2 diabetes in Singapore.

Keywords: Incretin, glucagon-like peptide 1, type 2 diabetes, semaglutide, SNAC

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INTRODUCTION

Researchers have been looking for insulin-stimulating factors for more than 100 years. In the 1960s, it was definitively proven that the gastrointestinal tract releases important insulinotropic factors upon oral glucose intake – the so-called "incretin hormones". The first significant factor identified was the duodenal glucose-dependent insulinotropic polypeptide (GIP), which did not stimulate insulin secretion in patients with type 2 diabetes (T2D). However, resection experiments clearly indicated the presence of an additional incretin. This molecule was identified to be glucagon-like peptide 1 (GLP-1), after an unexpected fragment – termed GLP-1^{7-36} amide – derived from proglucagon, a glucagon precursor, was isolated from the gut in 1986.

DR NITISH MISHRA
Endocrinologist & Endocrine Specialist
SMG Diabetes

GLP-1 was not only found to stimulate insulin secretion and inhibit glucagon secretion, it also inhibited appetite and food intake. Unlike GIP, this peptide maintained its effects in patients with T2D and it was soon documented to have powerful antidiabetic effects in clinical studies. GLP-1 has many effects on the different tissues and cells, enabling patients with T2D to benefit in many ways beyond lowering glucose levels.

THE ROLE OF GLP-1RA IN TREATMENT OF T2D

Upon discovery, the utility of GLP-1 was limited because of its extremely short half-life in humans. This issue was circumvented by two key pharmacological developments in T2D: (i) orally active inhibitors of the enzyme dipeptidylpeptidase 4 (DPP-4i), which prevented the rapid degradation of endogenous GLP-1 and unfolded its antidiabetic activity, and (ii) long-acting injectable GLP-1 analogues, which are resistant to DPP-4 degradation and given at pharmacologically effective levels (refer to Figure 1). In particular, the latter – referred to as GLP-1 receptor agonists (GLP-1RAs) – is so powerful that treatment with it alone or in combination with other antidiabetic agents allows more than two-thirds of T2D patients to achieve their glycaemic targets. In addition, these agents can potentially exceed more than 10 percent weight loss when co-administered with the most successful antidiabetic compounds. Recently, they have also been shown to be renoprotective and reduce cardiovascular risk and mortality. Due to the high specificity and good safety profile of peptide drugs, GLP-1RAs achieved approval for T2D in 2005.

GLP-1RA Mechanism Of Action

GLP-1RA reduces blood glucose levels by various mechanisms. These are detailed below and summarised in Figure 2.

GLP-1RA Effect on Glucose Levels

GLP-1RA promotes insulin production in a glucose-dependent manner by binding to GLP-1 receptors on pancreatic β cells. In presence of glucose, GLP-1 works synergistically to increase insulin gene transcription and mRNA stability, potentially replacing β cell insulin and preventing the depletion of the β cell.[1-3] GLP-1 also maintains β cell insulin stores and secretory capacity by augmenting glucose-induced insulin biosynthesis at the translational level.[4,5]

Figure 1. Comparison between GLP-1RAs and DPP-4is

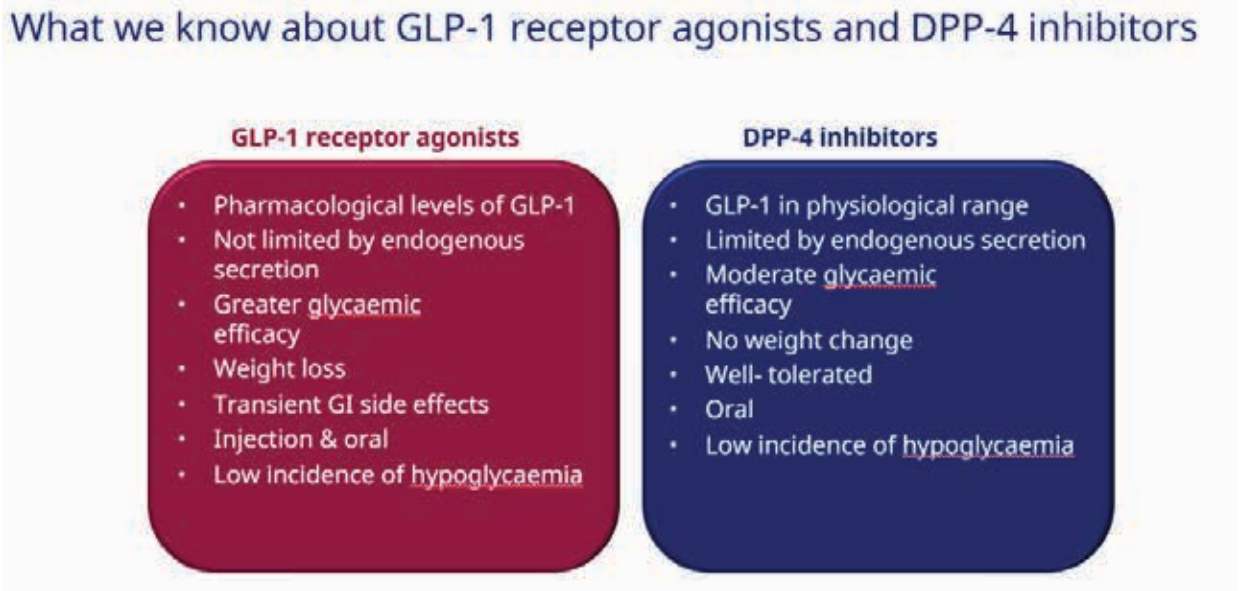
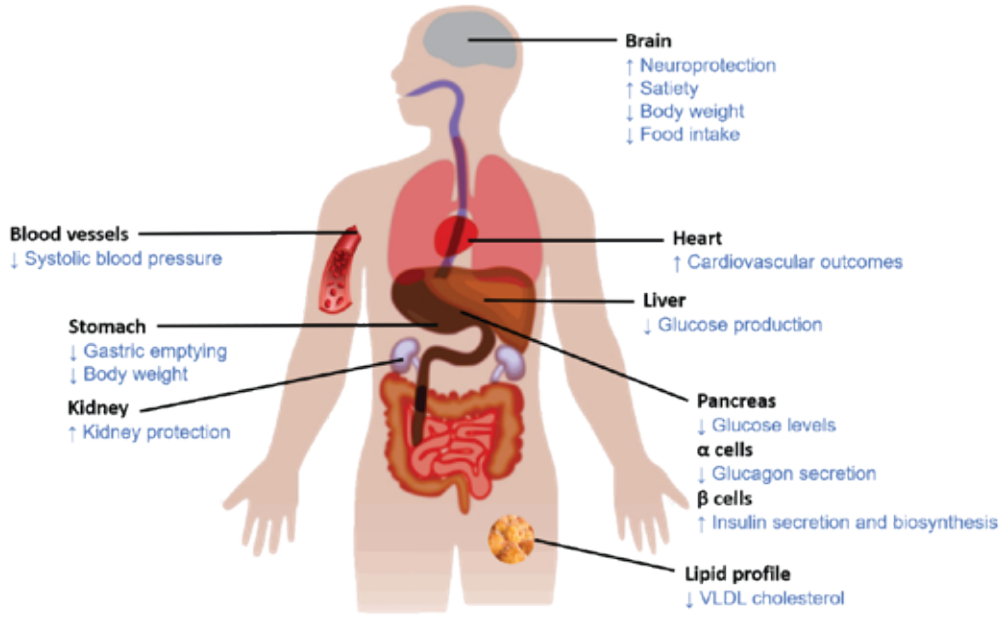


Figure 2. Mechanism of action of GLP-1RA on different organs



GLP-1RA Reduces Endogenous Glucose Synthesis

The direct binding of GLP-1RA to GLP-1 receptors on pancreatic α cells is one possible mechanism, in which α cells inhibit the secretion of glucagon. This reduces the quantity of glucose synthesised by the liver, which subsequently decreases the quantity of insulin required, allowing further improvement in glucose control.[4,6]

GLP-1RA Reduces Body Weight

Native GLP-1 is a biological modulator of food intake and energy intake in people, since it improves satiety, decreases hunger, and suppresses energy intake. The reduction in body weight is believed to be caused by GLP-1 RA action on receptors in the brain and stomach, where GLP-1 RA binds to GLP-1 receptors in the hypothalamic satiety regions of the brain that modulate hunger. GLP-1 RA also delays gastric emptying, resulting in slower absorption of glucose, greater feelings of fullness and decreased appetite.[4,7-11] Consequently, GLP-1RA administration lowers postprandial glucose.

GLP-1RA Improves Cardiovascular Outcomes

GLP-1 has several effects, other than glucose and body weight reduction, that may impact CV outcomes beneficially. The mechanism of action of GLP-1 RA cardiovascular effects has yet to be thoroughly elucidated.[12] The weight reduction and effective glycaemic management are possible contributors to the improved cardiovascular outcomes observed. Additionally, it may be due to the reduction of progression of atherosclerosis and improvement in systemic inflammation.[13-15]

GLP-1RA Decreases Systolic Blood Pressure

According to animal research, GLP-1RA regulates vascular, myocardial, renal, and central nervous system pathways, which may contribute to the decreased systolic blood pressure. However, these discoveries have yet to be demonstrated in humans, necessitating additional research.[16-18]

GLP-1RA Improves Lipid Profiles

Decreased absorption of ingested lipids, modulation of hepatic very-low-density lipoprotein synthesis, and improved hepatic fatty acid oxidation or autophagy may all have contributed to the improvement of lipid profiles.[12,19,20]

GLP-1RA Has Renoprotective Effects

The mechanism of action through which GLP-1RA protects the kidneys are unknown and it is also uncertain whether these results are related to a direct impact on renal function. The binding of GLP-1RA to GLP-1 receptors may protect the vascular endothelium from damage, lowering oxidative stress and local inflammation, according to animal studies. However, further research is required to define the mechanism of renal effects.[12,19,21,22]

PIONEERING THE FIRST ORAL GLP-1RA

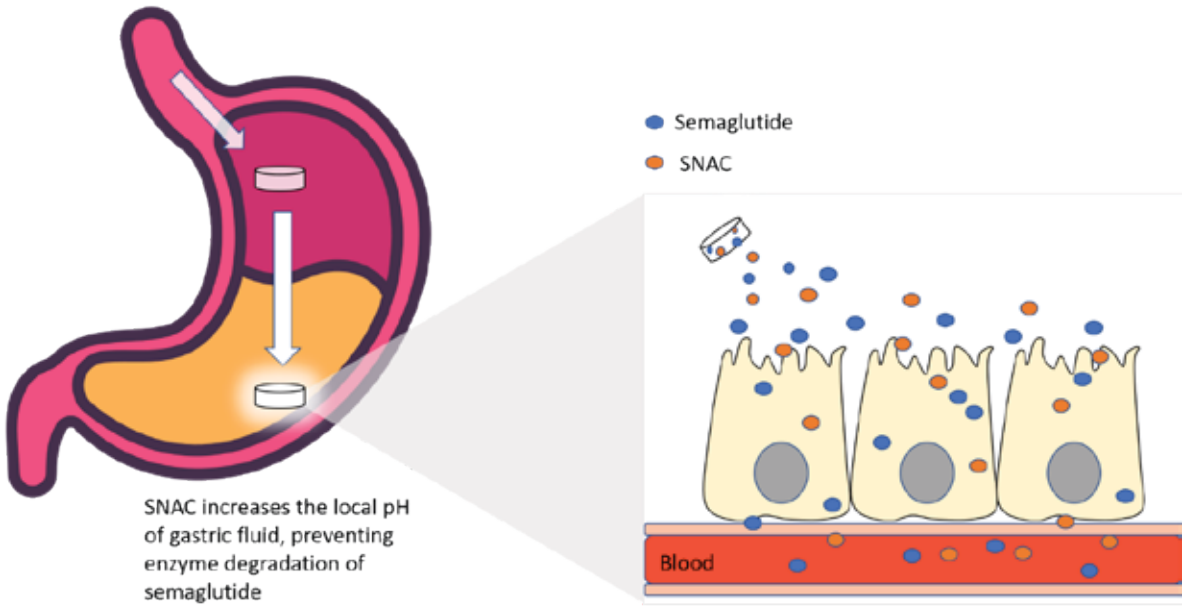
For a long time, only the injectable form had been available. Peptide drugs are usually unsuitable for oral administration as they exhibit low oral bioavailability, are enzymatically inactivated when they reach the gastrointestinal tract, and have low rates of diffusion into the cell. Recently, the first orally administered GLP-1 analogue was approved for the treatment of T2DM. The permeation enhancer sodium *N*-[8-(2-hydroxybenzoyl)amino] caprylate (SNAC) co-formulated with semaglutide elevates the local pH of gastric fluid, which prevents enzyme degradation and increases the absorption of semaglutide in the stomach. As a result, semaglutide achieves sufficient bioavailability for its pharmacological action (refer to Figure 3).

It is well known that patients with T2D generally prefer oral medications over subcutaneous injections. Oral drug delivery is easier to manage, quicker to use, and painless. Thus, oral semaglutide has an advantage over other comparable injectable GLP1-RAs.

CONCLUSION

In conclusion, incretin hormones have come a long way from GIP to GLP-1. GLP-1 has many effects on the different tissues and cells in the digestive system, circulatory system, and nervous system. This has enabled patients with T2D to benefit in many ways beyond lowering glucose levels. With the introduction of the first oral GLP-1 RA, semaglutide, the convenience and benefit that it brings about is a revolution for the management of T2D.

Figure 3. Mechanism of action of absorption of oral semaglutide using SNAC co-formulated tablet



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LEARNING POINTS

- **The discovery of glucagon-like peptide-1 (GLP-1), an incretin hormone with important effects on glycaemic control, led to efforts to extend its half-life and make it therapeutically effective in people with type 2 diabetes (T2D).**
- **GLP-1 analogues have made a vast contribution to the management of T2D in terms of improvements in not only glycaemic control but also body weight, blood pressure, lipids, beta-cell function, and CV outcomes.**
- **The GLP-1RAs add vital new tools to the physician's armoury in the fight against T2D. Furthermore, the development of an oral formulation for semaglutide may provide individuals with additional benefits in relation to treatment adherence.**