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Glucagon-Like Peptide-1 Receptor Agonist (GLP-1R): An Important Therapy to Treat Type 2 Diabetes

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Abstract

The glucagon-like peptide-1 (GLP-1) is a multifaceted hormone, and it has the ability to decrease blood sugar levels in a glucose-dependent nature to increase the secretion of insulin, and consequently, it reduces hyperglycaemia in T2D. GLP-1 has a half-life of about 1.5 minutes and is rapidly proteolytic degraded by dipeptidyl peptidase-4 (DPP-4). But GLP-1 receptor agonist (GLP-1R) works like GLP-1 but last much longer. GLP-1R control glycemia via glucose-dependent mechanisms of action and promote weight loss in obese and diabetic individuals. It also suppresses inappropriately elevated glucagon levels, both in fasting and postprandial states, slows gastric emptying, and decreases appetite. It reduces glycosylated hemoglobin (HbA1c) and fasting plasma glucose levels. It is associated with weight loss, and reductions in blood pressure with a low risk of hypoglycaemia. It is generally recommended as second- and third-line therapy for T2D. In this study an attempt has been taken to discuss aspects of GLP-1R in briefly.

Keywords: GLP-1R, DPP-4, incretin, T2D

1. Introduction

The glucagon-like peptide-1 (GLP-1) is a gut-derived peptide secreted from intestinal L-cells after a meal. It is 30 amino acids in length and is synthesized from the posttranslational modification of proglucagon. It is an effective insulinotropic agent that effects on potentiation of glucose-stimulated insulin secretion. It has a very short half-life depending on the species about 1-2 minutes and results from two causes; i) the action of the enzyme dipeptidyl peptidase-4 (DPP-4), and ii) renal elimination (Hui et al., 2002). GLP-1R has some enormous physiological actions, such as enhancement of β-cell growth and survival, and inhibition of glucagon release, gastric emptying, and food intake (Lim & Brubaker, 2006). This type of increase in insulin is called the “incretin effect” that maintains glucose concentrations at low levels irrespective of the amount of glucose ingested (Holst et al., 2008). The GLP-1R responses within 15 minutes after food ingestion, and it reaches its maximum point after about 30 minutes (Wang et al., 2015).

GLP-1 receptor (GLP-1R) agonists control glycemia via glucose-dependent mechanisms of action and promote weight loss in obese and diabetic individuals (Baggio & Drucker, 2014). It improves glycaemic control through multiple mechanisms, with a low risk of hypoglycaemia and the additional benefit of clinically relevant weight loss. This class is recognized as an important therapy in the management of T2D due to better efficacy, tolerability, and safety (Kalra et al., 2016).

GLP-1R agonist drugs are based therapies that reduce hyperglycaemia among T2D patients. These exert their action by binding receptor at the cell surface. At present these are available in mimetics, such as Dulaglutide,

Exenatide, Liraglutide, Lixisenatide, and Semaglutide. These GLP-1R analogues are resistant to degradation by DPP-4, and thus have a longer half-life than endogenous GLP-1 (Kreymann et al., 1987).

2. Literature Review

The literature is an introductory unit of research, which exhibits the works of previous researchers in the same field within the existing knowledge (Polit & Hungler, 2013). It is a hard-working search, scholarly inquiry, and investigation that aim for the discovery of new facts and findings (Adams et al., 2007). Timo D. Müller and his coauthors have provided a detailed overview on the multifaceted nature of GLP-1R and its pharmacology and discuss its therapeutic implications on various diseases (Müller et al., 2019). Josh Reed and his coworkers have highlighted recent findings from long-term human GLP-1 therapy studies and summarize postulated mechanisms as to how GLP-1R agonism may alleviate cardiovascular disease (Reed et al., 2018).

Sanjay Kalra and his coauthors have shown that the GLP1R improves glycemic control through multiple mechanisms with a low risk of hypoglycaemia and facilitates clinically relevant weight loss (Kalra et al., 2016). Gareth E. Lim and Patricia L. Brubaker have wanted to summarize the known signaling mechanisms of GLP-1 secretagogues based on the underlying GLP-1 secretion that may lead to novel approaches by which the levels of this important insulinotropic hormone can be enhanced in patients with T2D (Lim & Brubaker, 2006). Estela Lajthia and her coworkers have shown that concomitant use of once-weekly GLP-1R and DPP-4 inhibitors provides only modest improvement in glycemic control with minimal weight loss benefits that is similar to monotherapy with either agent. Therefore, the combination is unlikely to provide synergistic effects and is not cost effective (Lajthia et al., 2019).

Alexandra M. Bodnaruc and her coworkers have discussed GLP-1 physiology and the nutritional modulation of its secretion in the context of obesity and type 2 diabetes management (Bodnaruc, et al., 2016). Devajit Mohajan and Haradhan Kumar Mohajan have studied diabetes mellitus, eating disorders, and various anthropometric indices. They have also studied on insulin and various oral medications for the treatment of T2D. They have stressed that overweight and obesity are the roots of many non-communicable diseases (Mohajan & Mohajan, 2023a-z).

3. Research Methodology

Research is the procedures of systematic investigations that requires collection, interpretation and refinement of data, and ultimately prepares an acceptable article, working paper, book chapter or a thesis by the appropriate use of human knowledge (Pandey & Pandey, 2015). It serves as an indicator of the subject that has been carried out previously (Creswell, 2007). Methodology is a guideline of any research, which is considered as an organized procedure that follows scientific methods efficiently (Kothari, 2008). It provides the research design and analysis procedures to perform a good research (Hallberg, 2006). Research methodology provides the principles to the researchers for organizing, planning, designing and conducting a good research (Legesse, 2014). To prepare this article we have dependent on the secondary data sources. We have used books of famous authors, research articles, handbooks, and theses related to our research area. We have also collected valuable information from websites and internets to enrich the paper (Mohajan & Mohajan, 2023A; Mohajan, 2017, 2018, 2020).

4. Objective of the Study

The main objective of this study is to discuss Glucagon-like peptide-1 (GLP-1) and its usefulness for the treatment of type 2 diabetes (T2D) patients. The positive influences of GLP-1 on blood glucose homeostasis, appetite sensations, and food intake provide a strong rationale for its therapeutic potential in the nutritional management of obesity and T2D. Other some minor objectives of this study are as follows:

- to provide an idea of GLP-1,
- to highlight on the historical background of GLP-1, and
- to create awareness on side-effects of GLP-1.

5. GLP-1R Incretins

Incretins are gastrointestinal hormones that act to postprandial insulin release. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are two major incretins. The GIP gene is mainly expressed in K-cells and enterochromaffin cells of the proximal small intestine (Nauck et al., 2011). GLP-1R is a multifaceted incretin hormone with broad pharmacological potential. It enhances glucose-dependent stimulation of insulin secretion, decreases gastric emptying, inhibits food intake, increases natriuretic and diuresis, and modulates of rodent β-cell proliferation. It also has cardio- and neuro- protective effects, decreases inflammation and apoptosis, and has implications for learning and memory, reward behavior, and palatability (Müller et al., 2019). Many different GLP-1 secretagogues have been described in the literature over the past few decades, such as nutrients, neurotransmitters, neuropeptides, and peripheral hormones (Dube & Brubaker, 2004).

6. Historical Background

Glucagon-like peptide-1 (GLP-1) is a 30-amide long peptide hormone that derives from the tissue-specific posttranslational processing of the proglucagon peptide (Baggio & Drucker, 2007). In 1902, W. M. Bayliss and E. H. Starling proposed that intestinal mucosa produced a chemical that stimulated the pancreas to produce secretions (Bayliss & Starling, 1902). Interestingly, this chemical did not earn its name until 30 years later when, in 1932, J. La Barre called it “incretin” to refer to an extract from upper gut mucosa that produces hypoglycemia (La Barre, 1932). Glucose-dependent insulinotropic polypeptide (GIP) is discovered in 1975 that is the first incretin hormone. This is produced by K-cells of the small intestine. GIP concentrations after food intake are either normal or slightly elevated among T2D patients (Creutzfeldt, 2005). In 1981, the antibodies against GIP did not abolish the incretin effect that led to the discovery of glucagon-like peptide-1 (GLP-1) in the translational products of mRNAs isolated from pancreatic islets of anglerfish (Graaf et al. 2016).

In 1985, a glucagonlike peptide1 (GLP1), GLP1 (7–36 amide) was characterized and shown to have insulinotropic properties (Kim & Egan, 2008). In 1993, Michaei Nauck and his coworkers have demonstrated that in patients with poorly controlled T2D, a single exogenous infusion of GLP1R increased insulin levels in a glucose dependent manner normalizing fasting hyperglycaemia (Nauck et al., 1993). GLP1R was introduced in the USA in 2005, in Europe in 2006, and to the Indian market in 2007 (Kalra et al., 2016).

7. Activities of GLP-1R

The actions of GLP-1 primarily mediate through its receptor GLP-1R that is a G-protein coupled receptor (GPCR) (Thompson & Kanamarlapudi, 2013). It has two important actions: i) it stimulates insulin secretion and inhibits glucagon secretion and thereby inhibits hepatic glucose production and lowers blood glucose levels, and ii) it potently inhibits gastrointestinal secretion and motility (Holst, 1994). GLP-1R is expressed in the pancreas, cardiovascular system, gastrointestinal tract (GIT), lung, kidney, and in the peripheral and central nervous system (Graaf et al., 2016). GLP-1R reduces blood glucose levels by indirectly inhibiting glucagon secretion from islet α-cells. It also decreases gastric motility and inhibits postprandial gastric acid secretion. It improves glucose homeostasis through multifaceted action (Dailey & Moran. 2013). It has multiple cardiovascular benefits, such as it reduces arrhythmias, improves left ventricular function, and improves endothelial function, and with cardiovascular conditions, such as coronary artery disease. It enhances kidney function and has a protective effect on the kidney (Graaf et al., 2016).

8. Side-Effects of GLP-1R

The plasma half-life of native GLP-1 is very short, owing to its rapid inactivation by DPP-4, continuous infusion or multiple injections of GLP-1 are required to attain adequate glycaemic control (Müller et al., 2019). Gastrointestinal side-effects of GLP-1R are nausea, vomiting, and diarrhea. GLP-1 infusion has increased heart rate, blood pressure, and glucose uptake (Graaf et al., 2016). Some patients face irritation, redness, swelling, pain, fever, chills, sore throat, cough, runny nose or body aches, itching, terrible stomach pain, constipation, back pain, and burning or a lump at the injection site. Some more side-effects are weakness, trouble in breathing, tight feeling in the chest, headache, and swelling in the face, eyes, lips, hands, mouth or throat. The side-effects decrease over time with ongoing treatment because of tolerance and tachyphylaxis (Meier, 2012).

9. Conclusions

The prevalence of diabetes and obesity rising worldwide, therapeutic strategies that facilitate weight loss, improve glycemic control, and reduce cardiovascular risk are emphasized by the T2D patents. From this study we have observed that GLP-1R improves glycemic control through multiple mechanisms with a low risk of hypoglycaemia and enables clinically relevant weight loss. Therefore, the specific intracellular proteins are crucial for GLP-1R secretion to enhance GLP-1 levels for the management of T2D. We have observed that GLP-1R is safe and does not increase the long-term risk of major cardiovascular adverse events. Since the GLP-1R lowers postprandial hyperglycaemia by increasing insulin secretion and inhibiting glucose secretion, it becomes an ideal candidate for the treatment of T2D.

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