

Glucagon Like Peptide-1 & Analogs

Tg Jayesh Trivedi¹, Virendra Kumar Goyal², Keyur Soni³, Atul Gupta³, Ayushya Pal Singh³, Shubham Balki³, Sudeep Deswal³, Abhishek Vijaywargiya^{4*}, Sohail⁵ and Priya Kunwar⁶

¹Professor Department of General Medicine Pacific Medical College & Hospital, Udaipur, India

²Professor & Head of Department of General Medicine Pacific Medical College & Hospital, Udaipur, India

³Post Graduate Residents, Department of General Medicine Pacific Medical College & Hospital, Udaipur, India

⁴Intern Doctor, MBBS Pacific Medical College & Hospital, Udaipur, India

⁵Assistant Professor, Department of General Medicine Pacific Medical College & Hospital, Udaipur, India

⁶Senior Resident, Department of General Medicine Pacific Medical College & Hospital, Udaipur, India

*Corresponding author

Abhishek Vijaywargiya, Intern Doctor, MBBS Pacific Medical College & Hospital, Udaipur, India.

Received: March 10, 2025; Accepted: March 21, 2025; Published: March 28, 2025

Glucagon-Like Peptide-1 (GLP-1) Is A Hormone That Helps Regulate Blood Sugar, Food Intake, And Appetite

Physiology & Mechanism of Action of GLP-1

Glucagon-like peptide 1 (GLP-1) is a 30-amino acid peptide hormone produced in the intestinal epithelial endocrine L-cells of distal small bowel and colon, by differential processing of proglucagon (Posttranslational processing of preproglucagon).

GLP-1 is released in response to meal intake. GLP-1 is extremely rapidly metabolized and inactivated by the enzyme dipeptidyl peptidase IV(DPP-4) even before the hormone has left the gut. Binding of GLP-1 to its receptors activates adenylate cyclase, hence, cAMP levels are elevated followed by activation of various intracellular 2nd messengers like PKA, cAMP-CEF2, IP3, calcium. All these pathways ultimately increase cytoplasmic Ca²⁺ that induce mitochondrial ATP synthesis and exocytotic release of insulin from insulin granules.

Functions of GLP-1

There are various actions of GLP-1 like:

- Stimulating insulin production in the pancreas and inhibits glucagon secretion.
- It slows gastric emptying, thus reducing food intake.
- It improves cardiovascular function.
- But the main actions of GLP-1 are to stimulate insulin secretion (i.e., to act as an incretin hormone).

GLP-1 Agonists/ Analogues

GLP-1 analogues/agonists are a class of medications that help lower blood sugar levels in people with Type 2 diabetes, and promote weight loss thus helping to treat obesity. GLP-1 agonists are most often injectable medications as subcutaneous injection (shots in fatty tissue under skin).

This class of medication is also known as:

- Glucagon-like peptide-1 agonists.
- GLP-1 receptor agonists.
- Incretin mimetics.
- GLP-1 analogs.

GLP-1 agonist medications currently available on the U.S. market include:

- Dulaglutide (Trulicity®).
- Exenatide (Byetta®).
- Exenatide extended-release (Bydureon®).
- Liraglutide (Victoza®).
- Lixisenatide (Adlyxin®).
- Semaglutide injection (Ozempic®).
- Semaglutide tablets (Rybelsus®).

But GLP-1 agonists alone can't treat Type 2 diabetes or obesity. Both conditions require other treatment strategies, like lifestyle and dietary changes.

4.Efpeglenatide

Efpeglenatide is a novel glp-1 analogue. Till date, there are only four clinical trials reported for this drug. 2nd trial being the longest trial. This drug can also use as an anti-obesity drug in addition to the anti-diabetic drug. The longer duration drug not only reduces side effects but has the probability to improve adherence and reduce injection site reactions.

5.Exenatide ER (Extended-Release)

Exenatide ER is formulated by encapsulation into Poly-(D, L-Lactide-Co-Glycolide) microspheres which provides a slow and steady increase in plasma concentration with long duration of action. Exenatide ER was superior over sitagliptin and pioglitazone regarding improvement in HbA1c and weight loss.

6.Albiglutide

It is a GLP-1 dimer fused to human albumin with DPP-4 resistance properties. Binding with albumin leads to increase in half-life (5-8 days) and makes it suitable for once per week dosing.

7.Dulaglutide

It is a GLP-1 analogue with 90% homology to native GLP-1. It binds covalently to Fc (Constant fragment) of human IgG4 hence remains protected against the hydrolytic action of DPP-4.

8.Lixisenatide

It is a 44-amino-acid peptide that is amidated at the C-terminal amino acid having structural similarity with exendin-4. Because kidneys are the major route of elimination for lixisenatide, it is contraindicated in severe renal impairment. No dosage adjustment is required in patients with mild to moderate renal impairment and in patients with hepatic impairment.

Conclusion

Diabetes is among the most common and prominent disease in various countries of the world with number expected to rise from 366 to 552 million by 2030. In this review we have focused on GLP-1 production, regulation, functions and mechanism of action by which GLP-1 increases insulin secretion from β -cells. Mostly discussed in this review are GLP-1 agonists, their pharmacology, and their current clinical trial status [1-4].

References

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