

The Science of GLP-1:

Exploring Functions and Mechanisms

1. The Science of GLP-1

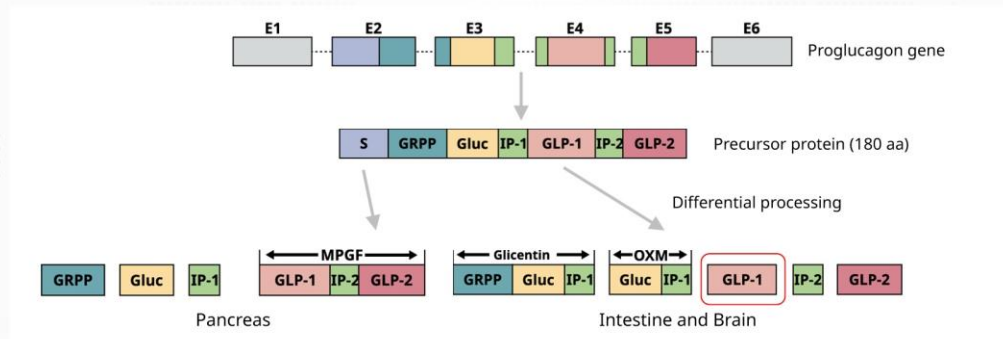
1.1 Module title



1.2 What is GLP-1?

What is GLP-1?

- o GLP-1 or 'glucagon-like peptide-1' is an incretin hormone.¹
- o It is a 31 amino acid long peptide encoded by the proglucagon gene.¹

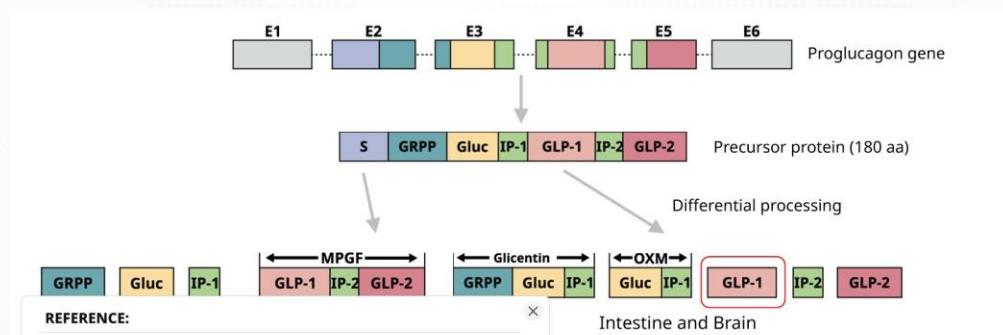


E1-E6 - Exon 1-Exon 6; GRPP - Glucagon-related polypeptide; Gluc - Glucagon; IP-1 and IP-2 - Intervening peptide-1 and 2; MPGF - Major proglucagon fragment; Glucagon; OXM - Oxyntomodulin; GLP-1 and 2 - Glucagon-like peptide 1 and 2

Reference (Slide Layer)

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1.3 What are Incretins?

What are Incretins?

Incretins are key protein hormones in glucose metabolism¹

1. Stimulate insulin release from pancreatic β cells
2. Inhibit glucagon release from pancreatic α cells
3. Regulate blood glucose levels

Diagram illustrating the effect of Incretins: The Pancreas releases Insulin (↑) and Glucagon (↓), which together regulate Blood glucose levels (↓).

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REFERENCE:

1. Farfan J. A., Moura C. S., Morato P. N., Lollo P. C. B., Chapter 17 - Dietary Whey Protein and Type 2 Diabetes: Molecular Aspects, Editor(s): Didac Mauricio, Molecular Nutrition and Diabetes, Academic Press, 2016, Pages 211-220,

1.4 How is GLP-1 produced?

How is GLP-1 produced?

GLP-1 is secreted by intestinal endocrine L-cells, primarily in the distal ileum and colon, in response to various nutrient, neural and endocrine factors.¹

Nutrients

Neural signals

Endocrine factors

GLP-1

GLP-1 - Glucagon-like peptide 1

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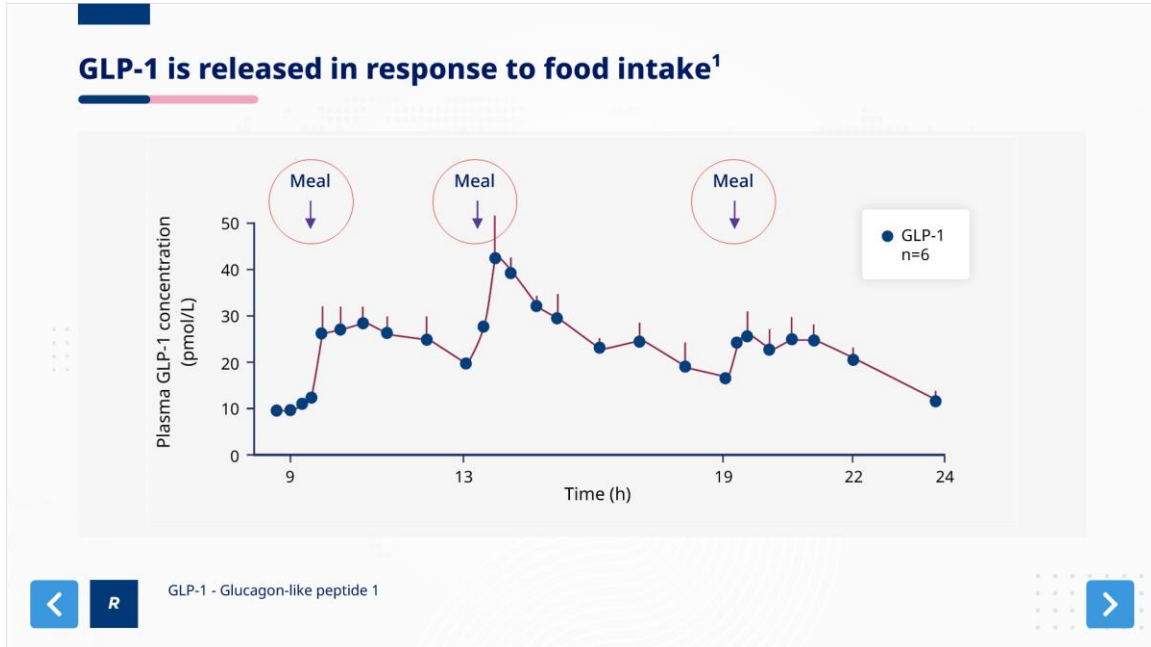
Endocrine factors

GLP-1

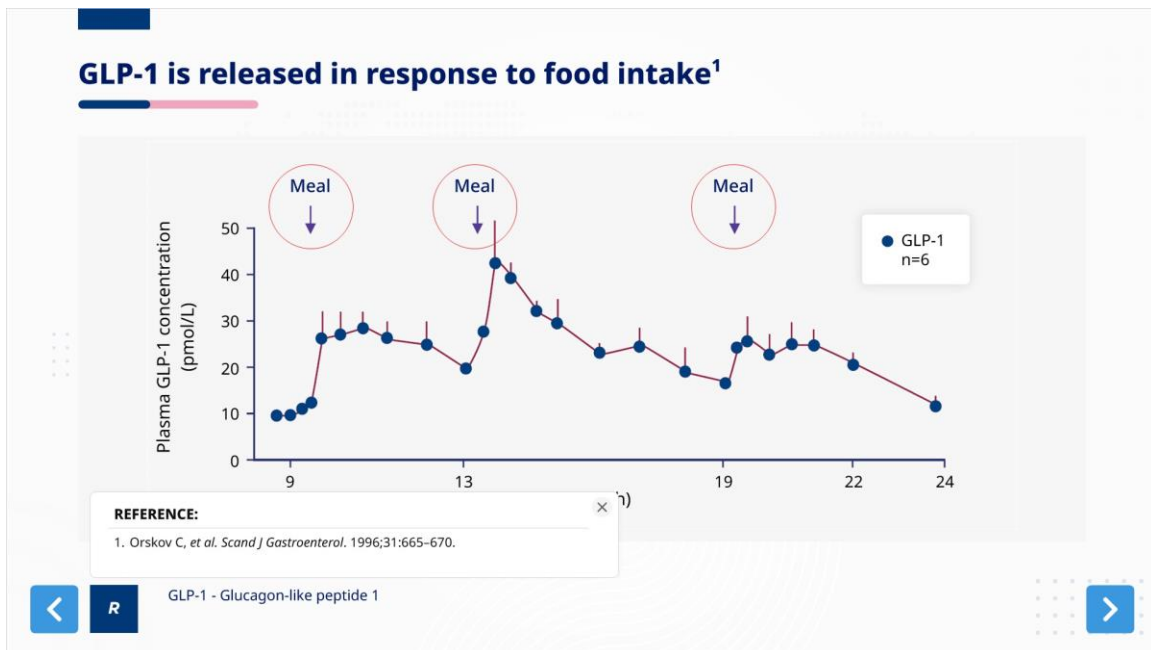
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GLP-1 - Glucagon-like peptide 1

1.5 GLP-1 is released in response to food intake¹



Reference (Slide Layer)

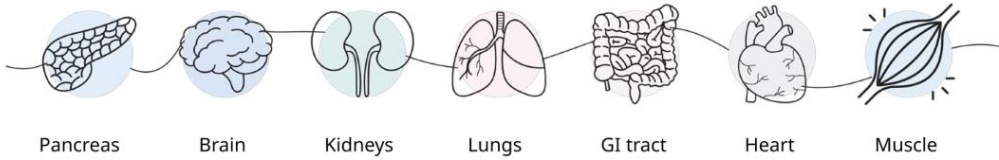


1.6 How does GLP-1 work?

How does GLP-1 work?

Most of the effects of GLP-1 are mediated by its direct interaction with GLP-1 receptors (GLP-1R) on specific tissues.²

GLP-1R expression pattern



Pancreas Brain Kidneys Lungs GI tract Heart Muscle

GLP-1 - Glucagon-like peptide 1; GLP-1R - GLP-1 receptor

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1. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006 Nov 11;368(9548):1696-705. PMID: 17098089.
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GLP-1 - Glucagon-like peptide 1; GLP-1R - GLP-1 receptor

1.7 GLP-1 and Insulin Secretion

GLP-1 and Insulin Secretion

The binding of GLP-1 to its cognate receptor GLP-1R on pancreatic β -cells leads to the stimulation of glucose-dependent insulin secretion.¹

The diagram illustrates the mechanism of action of GLP-1 on a pancreatic β -cell. An orange box labeled 'GLP-1' is shown binding to a blue, seven-transmembrane domain receptor labeled 'GLP-1R' on the cell membrane. A yellow box labeled 'Glucose' is shown entering the cell from the left. A green box labeled 'Insulin' is shown being secreted from the cell at the bottom. A vertical line with a downward arrow connects the GLP-1R to the Insulin box, indicating the signaling pathway.

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GLP-1 - Glucagon-like peptide 1; GLP-1R - GLP-1 receptor

1.8 How is GLP-1 activity regulated?

How is GLP-1 activity regulated?

Only 10-15% of bioactive GLP-1 enters the systemic circulation.¹⁻²

GLP-1 inactivation by DPP-4

Active GLP-1 (7-36)
(amidated form)

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg amide

7 10 15 20 25 30 35 36

DPP-4
(Dipeptidyl peptidase-4)

Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg amide

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Inactive GLP-1 (9-36)

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REFERENCES:

1. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Holst JJ. Both subcutaneously and intravenously administered glucagon-like peptide 1 are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects. *Diabetes* 1995;44:1126-1131.
2. Jens Juul Holst. The Physiology of Glucagon-like Peptide 1. *Physiol Rev* 87: 1409-1439, 2007

1.9 Key Takeaways

Key Takeaways

- GLP-1 is an incretin hormone.
- It is secreted by intestinal endocrine L-cells.
- GLP-1's actions are mediated through the GLP-1 receptor (GLP-1R).
- The bioactive form of GLP-1 is rapidly inactivated by DPP-4 enzyme.
- GLP-1, GLP-1R, and DPP-4 are important therapeutic targets.



1.10 Thank you

Thank you for your attention.

