Trends in Endocrinology & Metabolism | Hormone of the Month

Liver-expressed antimicrobial peptide 2 (LEAP2)

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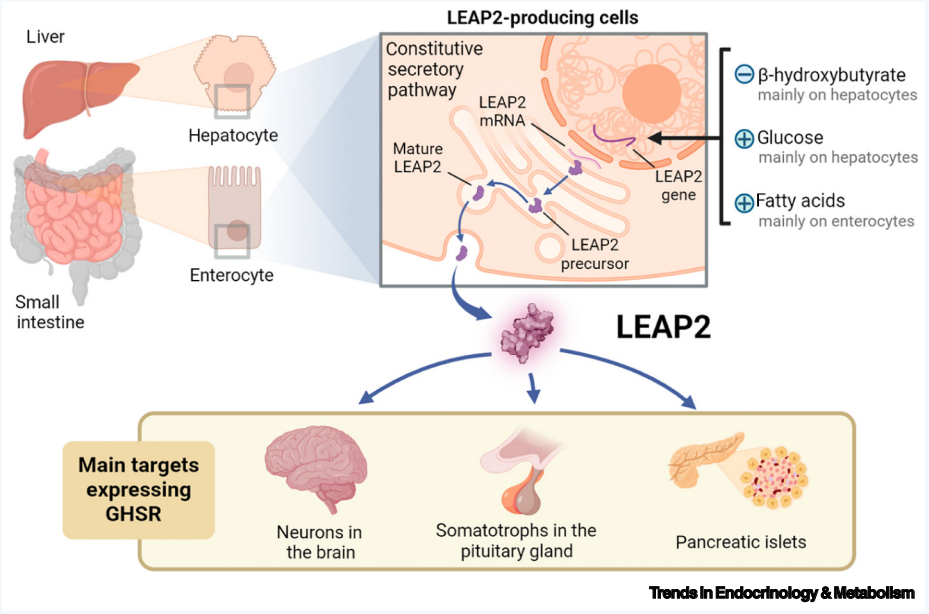
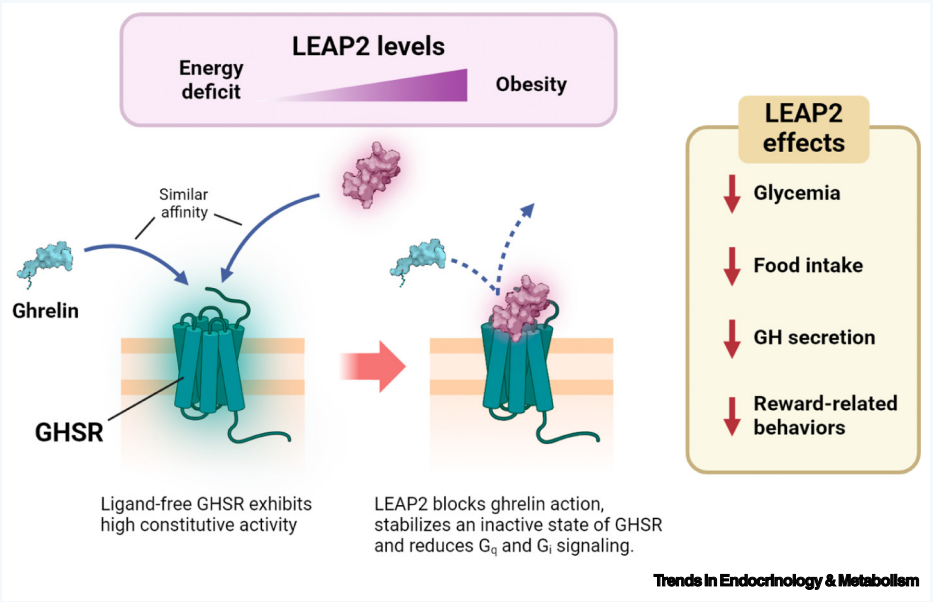


Liver-expressed antimicrobial peptide 2 (LEAP2) is a 40amino acid peptide secreted by hepatocytes and enterocytes. Since LEAP2-producing cells lack a regulated secretory pathway, LEAP2 secretion depends primarily on the rate of its biosynthesis. LEAP2 acts via the growth hormone secretagogue receptor (GHSR), previously known as the receptor for the stomach-derived hormone ghrelin. LEAP2 exerts its effects primarily in the central nervous system, the pituitary gland, and the pancreatic islets, where GHSR is predominantly expressed.



Plasma LEAP2 levels decrease under energy-deficit conditions and increase in obesity, acting as a physiologically relevant signal that modulates GHSR activity. LEAP2 binds to GHSR and functions as both an antagonist and an inverse agonist. The downregulation of GHSR's canonical and non-canonical modes of action influences key receptor functions and contributes to reducing glycemia, appetite, food intake, and other reward-related behaviors.

SIGNALING FACTS:

LEAP2 binds to GHSR with high affinity (~1.3 nM), similar to that of ghrelin.

LEAP2 is a competitive antagonist of GHSR, blocking ghrelin's actions.

LEAP2 also acts as an inverse agonist that reduces constitutive GHSR activity.

LEAP2 inhibits Gαq and Gαi/o signaling, reducing calcium and IP_3 levels while exhibiting slow dissociation and retaining GHSR on the plasma membrane.

The key targets of LEAP2 are the brain, pituitary gland, and pancreatic islets.

PHYSIOLOGICAL ROLE:

Plasma LEAP2 levels are ~2.3 nM, approximately tenfold higher than ghrelin levels, and higher in women than men.

Plasma LEAP2 levels are primarily determined by hepatocytes and regulated by various metabolites.

Postprandial changes in LEAP2 levels depend on sex, body weight, and macronutrients.

LEAP2 treatment reduces (i) spontaneous, ghrelin-induced, and high-fat-diet-induced food intake, (ii) glycemia, and (iii) ghrelin-induced and postprandial growth hormone (GH) secretion.

Plasma LEAP2 levels in humans are inversely associated with hunger and directly associated with glycemia, body weight, adiposity, and food-reward-related behaviors.

Plasma LEAP2 levels decrease during energy deficit conditions, when β-hydroxybutyrate levels increase and glycemia decreases.

Plasma LEAP2 levels increase in obesity, and are also higher in type 2 diabetes, positively correlated with glycosylated hemoglobin and plasma insulin, and inversely associated with insulin sensitivity.

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Acknowledgments

The figures were created with BioRender. In this article, LEAP2 stands for 'Liver-Expressed Antimicrobial Peptide 2', as this was the original meaning of the acronym in the first study that identified the peptide in human blood ultrafiltrates. The Ghrelin Nomenclature Consensus Group also recommends this expression (https://doi.org/10.1111/jne.13224). However, the HUGO Gene Nomenclature Committee refers to the human LEAP2 gene as 'liver-enriched antimicrobial peptide 2' (www.genenames.org).

Declaration of interests

No interests are declared.

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