Incretin synthesis, secretion, and inactivation

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 71

This document contains 3 pathways (see Table of Contents)
Incretin synthesis, secretion, and inactivation

Stable identifier: R-HSA-400508

Compartments: nucleoplasm, cytosol, endoplasmic reticulum membrane, endoplasmic reticulum lumen, secretory granule lumen, extracellular region

Incretins are peptide hormones produced by the gut that enhance the ability of glucose to stimulate insulin secretion from beta cells in the pancreas. Two incretins have been identified: Glucagon-like Peptide-1 (GLP-1) and Glucose-dependent Insulotropic Polypeptide (GIP, initially named Gastric Inhibitory Peptide). Both are released by cells of the small intestine, GLP-1 from L cells and GIP from K cells.

The control of incretin secretion is complex. Fatty acids, phospholipids, glucose, acetylcholine, leptin, and Gastrin-releasing Peptide all stimulate secretion of GLP-1. Fatty acids and phospholipids are the primary stimulants of secretion of GIP in humans (carbohydrates have more effect in rodents).

Incretins secreted into the bloodstream are subject to rapid inactivation by Dipeptidyl Peptidase IV (DPP IV), which confers half-lives of only a few minutes onto GLP-1 and GIP. Inhibitors of DPP IV, for example sitagliptin, are now being used in the treatment of Type 2 diabetes.

Literature references


Editions

2009-05-19 Authored, Edited May, B.
2010-06-25 Reviewed Bloom, SR.
Synthesis, secretion, and inactivation of Glucagon-like Peptide-1 (GLP-1)

Location: Incretin synthesis, secretion, and inactivation

Stable identifier: R-HSA-381771

Compartments: nucleoplasm, cytosol, endoplasmic reticulum membrane, endoplasmic reticulum lumen, secretory granule lumen, plasma membrane, extracellular region

In L cells of the intestine the transcription factors TCF-4 (TCF7L2) and Beta-catenin form a heterodimer and bind the G2 enhancer of the Proglucagon gene GCG, activating its transcription to yield Proglucagon mRNA and, following translation, Proglucagon protein. The prohormone convertase PC1 present in the secretory granules of L cells cleaves Proglucagon at two sites to yield mostly Glucagon-like Peptide-1 (7-36) with a small amount of Glucagon-like Peptide-1 (7-37). Glucagon-like Peptide-1 (7-36 and 7-37) (GLP-1) is secreted into the bloodstream in response to glucose, fatty acids, insulin, leptin, gastrin-releasing peptide, cholinergic transmitters, beta-adrenergic transmitters, and peptidergic transmitters. The half-life of GLP-1 in the bloodstream is determined by Dipeptidyl Peptidase IV, which cleaves 2 amino acids at the amino terminus of GLP-1, rendering it biologically inactive.

Literature references


### Editions

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**Synthesis, secretion, and inactivation of Glucose-dependent Insulinotropic Polypeptide (GIP)**

**Location:** Incretin synthesis, secretion, and inactivation

**Stable identifier:** R-HSA-400511

**Compartments:** nucleoplasm, cytosol, endoplasmic reticulum membrane, endoplasmic reticulum lumen, secretory granule lumen, plasma membrane, extracellular region

In K cells of the intestine the transcription factors PAX6 and PDX-1 activate transcription of the gene encoding Glucose-dependent Insulinotropic Polypeptide (GIP, first called Gastric Inhibitory Peptide). Pro-GIP is cleaved in secretory granules by Prohormone Convertase 1 (PC1) at 2 sites to yield mature GIP. In response to fat the GIP is secreted into the bloodstream. The half-life of GIP in the bloodstream is determined by Dipeptidyl Peptidase IV, which cleaves 2 amino acids at the amino terminus of GIP, rendering it biologically inactive.

**Literature references**


**Editions**

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