Integration of energy metabolism

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14/09/2021
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.

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Literature references


Reactome database release: 77

This document contains 8 pathways and 1 reaction (see Table of Contents)
Many hormones that affect individual physiological processes including the regulation of appetite, absorption, transport, and oxidation of foodstuffs influence energy metabolism pathways. While insulin mediates the storage of excess nutrients, glucagon is involved in the mobilization of energy resources in response to low blood glucose levels, principally by stimulating hepatic glucose output. Small doses of glucagon are sufficient to induce significant glucose elevations. These hormone-driven regulatory pathways enable the body to sense and respond to changed amounts of nutrients in the blood and demands for energy.

Glucagon and Insulin act through various metabolites and enzymes that target specific steps in metabolic pathways for sugar and fatty acids. The processes responsible for the long-term control of fat synthesis and short term control of glycolysis by key metabolic products and enzymes are annotated in this module as six specific pathways:

**Pathway 1. Glucagon signalling in metabolic pathways:** In response to low blood glucose, pancreatic alpha-cells release glucagon. The binding of glucagon to its receptor results in increased cAMP synthesis, and Protein Kinase A (PKA) activation.

**Pathway 2. PKA mediated phosphorylation:** PKA phosphorylates key enzymes, e.g., 6-Phosphofructo-2-kinase /Fructose-2,6-bisphosphatase (PF2K-Pase) at serine 36, and regulatory proteins, e.g., Carbohydrate Response Element Binding Protein (ChREBP) at serine 196 and threonine 666.

In brief, the binding of insulin to its receptor leads to increased protein phosphatase activity and to hydrolysis of cAMP by cAMP phosphodiesterase. These events counteract the regulatory effects of glucagon.

**Pathway 3: Insulin stimulates increased synthesis of Xylulose-5-phosphate (Xy-5-P).** Activation of the insulin receptor results indirectly in increased Xy-5-P synthesis from Glyceraldehyde-3-phosphate and Fructose-6-phosphate. Xy-5-P, a metabolite of the pentose phosphate pathway, stimulates protein phos-
Pathway 4: AMP Kinase (AMPK) mediated response to high AMP:ATP ratio: In response to diet with high fat content or low energy levels, the cytosolic AMP:ATP ratio is increased. AMP triggers a complicated cascade of events. In this module we have annotated only the phosphorylation of ChREBP by AMPK at serine 568, which inactivates this transcription factor.

Pathway 5: Dephosphorylation of key metabolic factors by PP2A: Xy-5-P activated PP2A efficiently dephosphorylates phosphorylated PF2K-Pase resulting in the higher output of F-2,6-P2 that enhances PFK activity in the glycolytic pathway. PP2A also dephosphorylates (and thus activates) cytosolic and nuclear ChREBP.

Pathway 6: Transcriptional activation of metabolic genes by ChREBP: Dephosphorylated ChREBP activates the transcription of genes involved in glucose metabolism such as pyruvate kinase, and lipogenic genes such as acetyl-CoA carboxylase, fatty acid synthetase, acyl CoA synthase and glycerol phosphate acyl transferase.

The illustration below summarizes this network of events. Black lines are metabolic reactions, red lines are negative regulatory events, and green lines are positive regulatory events (figure reused with permission from Veech (2003) - Copyright (2003) National Academy of Sciences, U.S.A.).

Literature references


Editions

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Regulation of insulin secretion

**Location:** Integration of energy metabolism

**Stable identifier:** R-HSA-422356

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

Pancreatic beta cells integrate signals from several metabolites and hormones to control the secretion of insulin. In general, glucose triggers insulin secretion while other factors can amplify or inhibit the amount of insulin secreted in response to glucose. Factors which increase insulin secretion include the incretin hormones Glucose-dependent insulinotropic polypeptide (GIP and glucagon-like peptide-1 (GLP-1), acetylcholine, and fatty acids. Factors which inhibit insulin secretion include adrenaline and noradrenaline.

Increased blood glucose levels from dietary carbohydrate play a dominant role in insulin release from the beta cells of the pancreas. Glucose catabolism in the beta cell is the transducer that links increased glucose levels to insulin release. Glucose uptake and glycolysis generate cytosolic pyruvate; pyruvate is transported to mitochondria and converted both to oxaloacetate which increases levels of TCA cycle intermediates, and to acetyl-CoA which is oxidized to CO2 via the TCA cycle. The rates of ATP synthesis and transport to the cytosol increase, plasma membrane ATP-sensitive inward rectifying potassium channels (KATP channels) close, the membrane depolarizes, and voltage-gated calcium channels in the membrane open (Muoio and Newgard 2008; Wiederkehr and Wollheim 2006).

Elevated calcium concentrations near the plasma membrane cause insulin secretion in two phases: an initial high rate within minutes of glucose stimulation and a slow, sustained release lasting longer than 30 minutes. In the initial phase, 50-100 insulin granules already docked at the membrane are exocytosed. Exocytosis is rendered calcium-dependent by Synaptotagmin V/IX, a calcium-binding membrane protein located in the membrane of the docked granule, although the exact action of Synaptotagmin in response to calcium is unknown. Calcium also causes a translocation of reserve granules within the cell towards the plasma membrane for release in the second, sustained phase of secretion. Human cells con-
tain L-type (continually reopening), P/Q-type (long burst), R-type (long burst), and T-type (short burst) calcium channels and these partly account for differences between the two phases of secretion. Other factors that distinguish the two phases are not yet fully known (Bratanova-Tochkova et al. 2002; Henquin 2000; MacDonald et al. 2005).

**Literature references**


**Editions**

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Glucagon and insulin are peptide hormones released from the pancreas into the blood, that normally act in complementary fashion to stabilize blood glucose concentration. When blood glucose levels rise, insulin release stimulates glucose uptake from the blood, glucose breakdown (glycolysis), and glucose storage as glycogen. When blood glucose levels fall, glucagon release stimulates glycogen breakdown and de novo glucose synthesis (gluconeogenesis), while inhibiting glycolysis and glycogen synthesis.

At a molecular level, the binding of glucagon to the extracellular face of its receptor causes conformational changes in the receptor that allow the dissociation and activation of subunits Gs and Gq. The activation of Gq leads to the activation of phospholipase C, production of inositol 1,4,5-triphosphate, and subsequent release of intracellular calcium. The activation of Gs leads to activation of adenylate cyclase, an increase in intracellular cAMP levels, and activation of protein kinase A (PKA). Active PKA phosphorylates key enzymes of glycogenolysis, glycogenesis, gluconeogenesis, and glycolysis, modifying their activities. These signal transduction events, and some of their downstream consequences, are illustrated below (adapted from Jiang and Zhang, 2003).

**Literature references**


**Editions**

2005-04-28 Authored Gopinathrao, G.
PKA-mediated phosphorylation of key metabolic factors

Location: Integration of energy metabolism

Stable identifier: R-HSA-163358

Compartments: nucleoplasm, cytosol

Upon dissociation of protein kinase A (PKA) tetramers in the presence of cAMP, the released PKA catalytic monomers phosphorylate specific serine and threonine residues of several metabolic enzymes. These target enzymes include glycogen phosphorylase kinase, glycogen synthase and PF2K-Pase. PKA also phosphorylates ChREBP (Carbohydrate Response Element Binding Protein), preventing its movement into the nucleus and thus its function as a positive transcription factor for genes involved in glycolytic and lipogenic reactions.

Literature references


Editions

2005-05-13

Authored

Gopinathrao, G.
Insulin effects increased synthesis of Xylulose-5-Phosphate

Location: Integration of energy metabolism

Stable identifier: R-HSA-163754

Compartments: cytosol

One of the downstream effects of insulin, mediated via protein phosphatase 2A (PP2A), is increased synthesis of Fructose-2,6-bisphosphate, an allosteric activator of phosphofructokinase 1 (PFK1). PFK1 in turn catalyzes the committed step of glycolysis so the net effect of this whole sequence of events set off by insulin is to increase cytosolic concentrations of the small molecules formed in the course of glycolysis. This in turn drives the increased synthesis of Xylulose-5-phosphate, itself a positive regulator of PP2A.

Literature references


Editions

2005-05-13

Gopinathrao, G.
Activation of PP2A by Xylulose-5-phosphate

**Location:** Integration of energy metabolism

**Stable identifier:** R-HSA-163769

**Type:** transition

**Compartments:** cytosol

**Inferred from:** Activation of rPP2A by Xylulose-5-phosphate (Rattus norvegicus)

Xylulose-5-phosphate binds to Protein phosphatase 2A (PP2A), activating it. This regulatory step may be the crucial physiological link explaining the coordinately increased rates of glycolysis and lipogenesis generally observed in individuals consuming high-carbohydrate diets.

**Literature references**


**Editions**

2005-05-14 Authored Gopinathrao, G.
AMPK inhibits chREBP transcriptional activation activity

**Location:** Integration of energy metabolism

**Stable identifier:** R-HSA-163680

**Compartments:** nucleoplasm

AMP-activated protein kinase (AMPK) is a sensor of cellular energy levels. A high cellular ratio of AMP:ATP triggers the phosphorylation and activation of AMPK. Activated AMPK in turn phosphorylates a wide array of target proteins, as shown in the figure below (reproduced from Hardie et al. 2003, with the permission of D.G. Hardie). These targets include ChREBP (Carbohydrate Response Element Binding Protein), whose inactivation by phosphorylation reduces transcription of key enzymes of the glycolytic and lipogenic pathways.

**Literature references**


**Editions**

2005-05-13  Authored  Gopinathrao, G.
A member of the PP2A family of phosphatases dephosphorylates both cytosolic and nuclear forms of ChREBP (Carbohydrate Response Element Binding Protein). In the nucleus, dephosphorylated ChREBP complexes with MLX protein and binds to ChRE sequence elements in chromosomal DNA, activating transcription of genes involved in glycolysis and lipogenesis. The phosphatase is activated by Xylulose-5-phosphate, an intermediate of the pentose phosphate pathway (Kabashima et al. 2003). The rat enzyme has been purified to homogeneity and shown by partial amino acid sequence analysis to differ from previously described PP2A phosphatases (Nishimura and Uyeda 1995) - the human enzyme has not been characterized.

**Literature references**


**Editions**

2005-05-13  Authored  Gopinathrao, G.
ChREBP activates metabolic gene expression

Location: Integration of energy metabolism

Stable identifier: R-HSA-163765

Compartments: nucleoplasm, cytosol, endoplasmic reticulum membrane

ChREBP (Carbohydrate Response Element Binding Protein) is a large multidomain protein containing a nuclear localization signal near its amino terminus, polyproline domains, a basic helix-loop-helix-leucine zipper domain, and a leucine-zipper-like domain (Uyeda et al., 2002). Its dephosphorylation in response to molecular signals associated with the well-fed state allows it to enter the nucleus, interact with MLX protein, and bind to ChRE DNA sequence motifs near Acetyl-CoA carboxylase, Fatty acid synthase, and Pyruvate kinase (L isoform) genes (Ishi et al.2004). This sequence of events is outlined schematically in the picture below (adapted from Kawaguchi et al. (2001) - copyright (2001) National Academy of Sciences, U.S.A.).

Literature references


Editions

2005-05-13 Authored Gopinathrao, G.
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