Regulation of insulin secretion

D'Eustachio, P., Gillespie, ME., Gopinathrao, G., Jassal, B., Kebede, M., Le Novere, N., Madiraju, MS., May, B., Poitout, V.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.
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: 72

This document contains 5 pathways and 6 reactions (see Table of Contents)
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 contain 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**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-05-28</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2009-09-07</td>
<td>Reviewed</td>
<td>D'Eustachio, P.</td>
</tr>
</tbody>
</table>
The catecholamines adrenaline (epinephrine) and noradrenaline (norepinephrine) inhibit insulin secretion from pancreatic beta cells. Four effects are seen in the cells:

1. Inhibition of exocytosis of secretory granules, the major effect.
2. Opening of ATP-sensitive potassium channels (KATP channels) and repolarization of the cell.
3. Closing of L-type voltage-dependent calcium channels and inhibition of calcium influx.
4. Inhibition of adenylyl cyclase activity.

The first event in adrenaline/noradrenaline signaling in beta cells is the binding of adrenaline or noradrenaline to alpha-2 adrenergic receptors, which are G-protein coupled receptors. Binding activates the alpha subunits in heterotrimeric Gi and Go complexes to exchange GDP for GTP, forming the active G alpha:GTP complex. Experiments using specific antibodies against the alpha subunits in mice show that Gi alpha-1, Gi alpha-2, and Go alpha-2 are responsible for adrenergic effects. The exact beta and gamma subunits of the heterotrimeric G-proteins are unknown.

After activation by GTP, the heterotrimeric complex dissociates into the G alpha:GTP complex and the beta:gamma complex. The G alpha:GTP complex causes the inhibition of exocytosis by an unknown mechanism that involves protein acylation. This is responsible for most of the observed inhibition of insulin secretion. Additionally, the G alpha:GTP complex activates (opens) KATP channels, allowing the cell to repolarize. The beta:gamma complex inhibits (closes) voltage-dependent calcium channels, reducing the intracellular calcium concentration, and inhibits adenylyl cyclase, reducing the intracellular cAMP concentration.
Literature references

Zhao, Y., Fang, Q., Straub, SG., Sharp, GW. (2008). Both G\textsubscript{i} and G\textsubscript{o} heterotrimeric G proteins are required to exert the full effect of norepinephrine on the beta-cell K\textsubscript{ATP} channel. \textit{J Biol Chem}, 283, 5306-16.


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-05-27</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2009-06-02</td>
<td>Reviewed</td>
<td>D'Eustachio, P.</td>
</tr>
</tbody>
</table>
Acetylcholine regulates insulin secretion

**Location:** Regulation of insulin secretion

**Stable identifier:** R-HSA-399997

**Compartments:** plasma membrane, cytosol, endoplasmic reticulum membrane

Acetylcholine released by parasympathetic nerve endings in the pancreas causes a potentiation of insulin release when glucose is present at concentrations greater than about 7 mM. Acetylcholine binds the Muscarinic Acetylcholine Receptor M3 on pancreatic beta cells. The binding has two effects: an increase in permeability of the cell to Na+ ions through an unknown mechanism, and the activation of Phospholipase C beta-1 through a heterotrimeric G protein, G(q).

After acetylcholine binds the Muscarinic Acetylcholine Receptor M3, the receptor activates the G protein Gq by causing the alpha subunit of Gq to exchange GDP for GTP. Activation of Gq in turn activates Phospholipase C beta-1. Phospholipase C beta-1 hydrolyzes the phosphodiester bond at the third position of phosphoinositol 4,5-bisphosphate, producing diacylglycerols (DAG) and inositol 1,4,5-trisphosphate.

DAG remains in the cell membrane and causes Protein Kinase C alpha (PKC alpha) to translocate from the cytosol to the membrane. This results in the activation of PKC alpha which then phosphorylates target proteins on serine and threonine residues. One known target of PKC alpha is Myristoylated Alanine-rich C Kinase Substrate (MARCKS), which is believed to affect vesicle transport and may be responsible for the increased traffic of insulin granules seen in response to acetylcholine.

Inositol trisphosphate binds a receptor, the IP3 receptor, on calcium stores in the cell (probably the endoplasmic reticulum). The release of calcium into the cytosol stimulates the exocytosis of insulin granules.

**Literature references**


## Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Role</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-05-28</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2009-06-02</td>
<td>Reviewed</td>
<td>Gillespie, ME.</td>
</tr>
</tbody>
</table>
Free fatty acids regulate insulin secretion

**Location:** Regulation of insulin secretion

**Stable identifier:** R-HSA-400451

**Compartments:** cytosol, plasma membrane

Free fatty acids augment the glucose-triggered secretion of insulin. The augmentation is believed to be due to the additive effects of the activation of the free fatty acid receptor 1 (FFAR1 or GPR40) and the metabolism of free fatty acids within the pancreatic beta cell. This module describes each pathway.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-06-08</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2009-09-09</td>
<td>Reviewed</td>
<td>Poitout, V., Kebede, M.</td>
</tr>
<tr>
<td>2009-10-02</td>
<td>Reviewed</td>
<td>Madiraju, MS.</td>
</tr>
</tbody>
</table>
Glucagon-like Peptide-1 (GLP-1) regulates insulin secretion

Location: Regulation of insulin secretion

Stable identifier: R-HSA-381676

Compartments: cytosol, plasma membrane

Glucagon-like Peptide-1 (GLP-1) is secreted by L-cells in the intestine in response to glucose and fatty acids. GLP-1 circulates to the beta cells of the pancreas where it binds a G-protein coupled receptor, GLP-1R, on the plasma membrane. The binding activates the heterotrimeric G-protein G(s), causing the alpha subunit of G(s) to exchange GDP for GTP and dissociate from the beta and gamma subunits.

The activated G(s) alpha subunit interacts with Adenylyl Cyclase VIII (Adenylate Cyclase VIII, AC VIII) and activates AC VIII to produce cyclic AMP (cAMP). cAMP then has two effects: 1) cAMP activates Protein Kinase A (PKA), and 2) cAMP activates Epac1 and Epac2, two guanyl nucleotide exchange factors.

Binding of cAMP to PKA causes the catalytic subunits of PKA to dissociate from the regulatory subunits and become an active kinase. PKA is known to enhance insulin secretion by closing ATP-sensitive potassium channels, closing voltage-gated potassium channels, releasing calcium from the endoplasmic reticulum, and affecting insulin secretory granules. The exact mechanisms for PKA's action are not fully known. After prolonged increases in cAMP, PKA translocates to the nucleus where it regulates the PDX-1 and CREB transcription factors, activating transcription of the insulin gene.

cAMP produced by AC VIII also activates Epac1 and Epac2, which catalyze the exchange of GTP for GDP on G-proteins, notably Rap1A. Rap1A regulates insulin secretory granules and is believed to activate the Raf/MEK/ERK mitogenic pathway leading to proliferation of beta cells. The Epac proteins also interact with RYR calcium channels on the endoplasmic reticulum, the SUR1 subunits of ATP-sensitive potassium channels, and the Piccolo:Rim2 calcium sensor at the plasma membrane.

Literature references


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-05-28</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2009-06-02</td>
<td>Reviewed</td>
<td>Gillespie, ME.</td>
</tr>
</tbody>
</table>
Transport of Extracellular Glucose to the Cytosol by GLUT1 and GLUT2

Location: Regulation of insulin secretion

Stable identifier: R-HSA-499981