Regulation of insulin secretion

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18/04/2019
**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: 68

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

https://reactome.org
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).

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Adrenaline, noradrenaline inhibits insulin secretion

**Location:** Regulation of insulin secretion

**Stable identifier:** R-HSA-400042

**Compartments:** plasma membrane

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.
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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.

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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.

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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.

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Human pancreatic beta cells express glucose transporters 1 and (GLUT1, GLUT2), which are responsible for uptake of glucose from the extracellular medium into the cytosol. (Rodent pancreatic beta cells express only Glut2.)

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The beta-cell ATP-sensitive potassium channel (KATP channel) comprise the tetrameric ATP-sensitive inward rectifier potassium channel 11 (KCNJ11, Kir6.2) and the tetrameric channel regulator ATP-binding cassette sub-family C member 8 (ABCC8). When the ATP/ADP ratio is high, the KCNJ11 (Kir6.2) subunit binds ATP and the channel closes. Conversely, when the ADP:ATP ratio is high, the ABCC8 (SUR1) subunit binds magnesium-ADP and the channel is open.

The KATP channels in the beta cell are inwardly rectifying (allowing potassium ions to pass out of the cell) and are partially responsible for maintaining the resting potential of the cell, about -70 mV. Closure of the KATP channels causes a depolarization (a reduction in the voltage differential) across the plasma membrane.

The antidiabetic activity of sulfonylurea drugs such as acetohexamide, tolbutamide, glipzide, glibenclamide, and glimepiride is due to their binding ABCC8 (SUR1) subunits and inhibiting potassium efflux.

Followed by: Calcium Influx through Voltage-gated Calcium Channels

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Calcium Influx through Voltage-gated Calcium Channels

**Location:** Regulation of insulin secretion

**Stable identifier:** R-HSA-265645

**Type:** transition

**Compartments:** plasma membrane

Voltage-gated calcium channels respond to a change in voltage across the plasma membrane by opening and allowing free movement of calcium ions. In an unstimulated cell the concentration of calcium ions outside the cells is higher than inside due to calcium transporters so channel opening results in an influx of calcium into the cytosol. In the cytosol the calcium ions cause an immediate exocytosis of the readily releasable pool of docked insulin granules as well as a migration of reserve granules toward the plasma membrane where they will be released during the second, sustained phase of insulin secretion.

Mouse and human beta cells are known to contain L type channels Cav1.2 and Cav1.3, both of which have been shown to physically associate with docked insulin granules via Syntaxin1A. Cav1.2 and Cav1.3 predominate in the initial rapid release of insulin. Human beta cells also contain the P/Q type channel Cav2.1 and the R type channel Cav2.3. Cav2.3 is involved in regulating the second, sustained phase of insulin release but signaling and regulatory differences between the two phases of secretion are not fully characterized. Human cells also exhibit T-type (brief burst) calcium currents but the responsible channel has not been identified.

**Preceded by:** KCNJ11 tetramer:ABCC8 tetramer binds 4xATP, closing the channel

**Followed by:** Exocytosis of Insulin

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IP3 binds to the IP3 receptor, opening the endoplasmic reticulum Ca2+ channel

**Location:** Regulation of insulin secretion

**Stable identifier:** R-HSA-169680

**Type:** binding

**Compartments:** cytosol, endoplasmic reticulum membrane

**Inferred from:** IP3 binds to the IP3 receptor, opening the Ca2+ channel (Rattus norvegicus)

The IP3 receptor (IP3R) is an IP3-gated calcium channel. It is a large, homotetrameric protein, similar to other calcium channel proteins such as ryanodine. The four subunits form a 'four-leafed clover' structure arranged around the central calcium channel. Binding of ligands such as IP3 results in conformational changes in the receptor's structure that leads to channel opening.

**Followed by:** IP3R:I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol

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IP3R: I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol

**Location:** Regulation of insulin secretion

**Stable identifier:** R-HSA-169683

**Type:** transition

**Compartments:** endoplasmic reticulum membrane

**Inferred from:** Calcium release from intracellular stores by IP3 receptor activation (Rattus norvegicus)

IP3 promotes the release of intracellular calcium.

**Preceded by:** IP3 binds to the IP3 receptor, opening the endoplasmic reticulum Ca2+ channel

**Followed by:** Exocytosis of Insulin

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Exocytosis of Insulin

Location: Regulation of insulin secretion

Stable identifier: R-HSA-265166

Type: omitted

Compartments: plasma membrane, secretory granule membrane

Inferred from: Exocytosis of Insulin (Mus musculus)

Exocytosis of insulin-zinc granules occurs by the calcium-dependent fusion of the membrane of the secretory granule with the plasma membrane. In general, exocytosis proceeds by formation of a "SNARE pair", a complex between a SNARE-type protein on the granule and a SNARE-type protein on the plasma membrane. (The interaction is between coiled coil domains on each SNARE-type protein.)

In the particular case of insulin granules in beta cells, the SNARE protein on the granule is Synaptobrevin2/VAMP2 and the SNARE protein on the plasma membrane is Syntaxin1A in a complex with SNAP-25. Unc18-1 binds Syntaxin1A and thereby prevents association with Synaptobrevin2 until dissociation of Unc18-1. Syntaxin 4 is also involved and binds filamentous actin but its exact role is unknown.

Insulin exocytosis occurs in two phases: 1) a rapid release of about 100 of the 1000 docked granules within the first 5 minutes of glucose stimulation and 2) a subsequent slow release over 30 minutes or more due to migration of internal granules to the plasma membrane. Data from knockout mice show that Syntaxin 1A is involved in rapid release but not slow release, whereas Syntaxin 4 is involved in both types of release.

Calcium dependence of membrane fusion is conferred by Synaptotagmin V, which binds calcium ions and associates with the Syntaxin1A-Synaptobrevin2 pair. The exact mechanism of Synaptotagmin's action is unknown. The migration of internal granules to the plasma membrane during slow release is also calcium dependent.

Microscopically, exocytosis is seen to occur as a "kiss and run" process in which the membrane of the secretory granule fuses transiently with the plasma membrane to form a small pore of about 4 nm between the interior of the granule and the exterior of the cell. Only a portion of the insulin in a granule is secreted after which the pore closes and the vesicle is recaptured back into the cell. Dynamin-1 and
NSF may play a role in recapture but the mechanism is not fully known.

The major effect of adrenaline and noradrenaline on insulin secretion is the inhibition of exocytosis of pre-existing insulin secretory granules. The inhibition occurs at a "distal site", that is, the effect is most pronounced on granules already near the cytosolic face of the plasma membrane. The effect is caused by the Gi/o alpha:GTP complex but the exact mechanism by which Gi/o alpha:GTP inhibits exocytosis is unknown. On release, the higher pH in the extracellular region favours dissociation of Zn2+ from insulin. The insulin hexamer becomes unstable at this higher pH and it dissociates into the active insulin monomer.

**Preceded by:** Calcium Influx through Voltage-gated Calcium Channels, IP3R:I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol

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