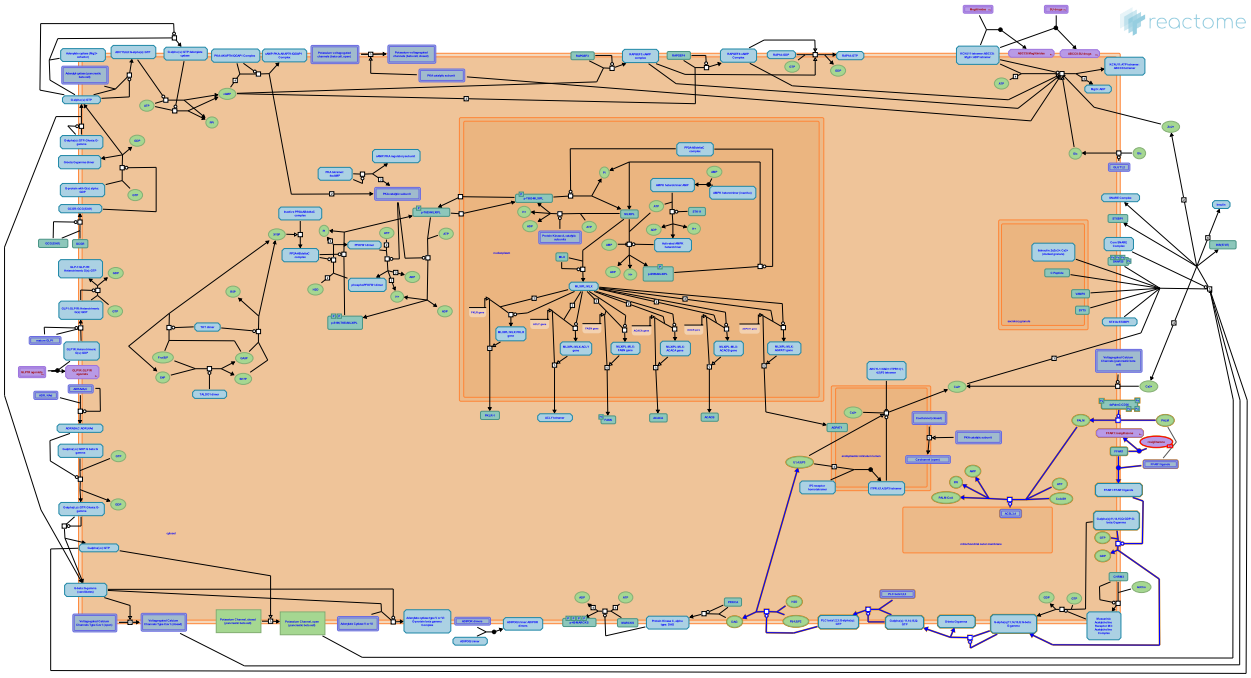
Free fatty acids regulate insulin secretion



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

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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.
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Literature references

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Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

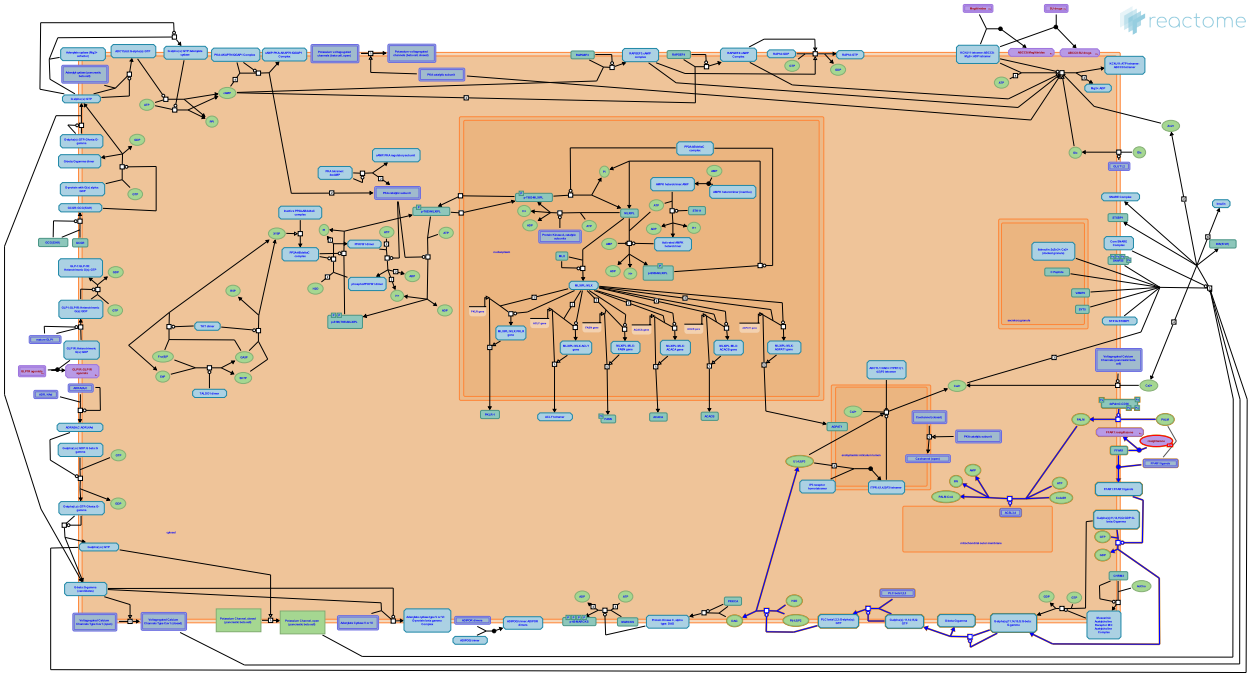
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Free fatty acids regulate 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

Lin, DC., Tremblay, C., Alquier, T., Poitout, V., Oseid, E., Jetton, TL. et al. (2007). GPR40 is necessary but not sufficient for fatty acid stimulation of insulin secretion in vivo. *Diabetes, 56*, 1087-94. ↗

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Massie, B., Delghingaro-Augusto, V., Prentki, M., Ruderman, N., Moore, P., Massé, F. et al. (2004). A role for the malonyl-CoA/long-chain acyl-CoA pathway of lipid signaling in the regulation of insulin secretion in response to both fuel and nonfuel stimuli. *Diabetes, 53*, 1007-19. ↗

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Editions

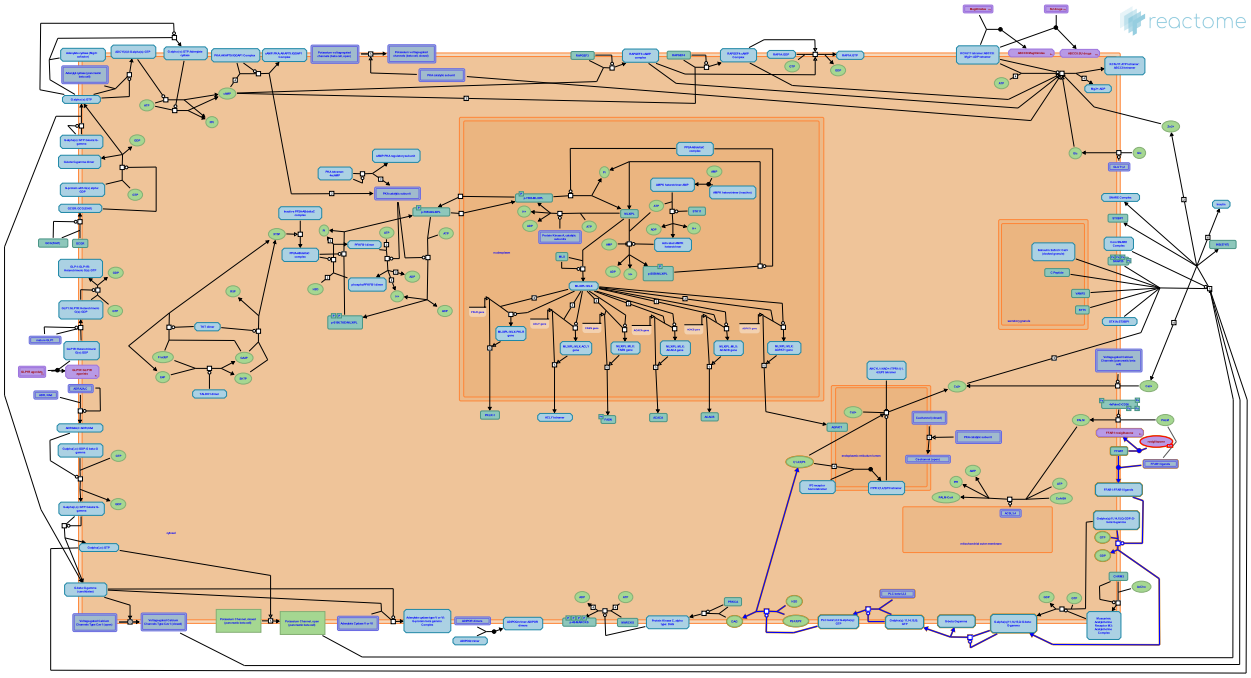
2009-06-08	Authored, Edited	May, B.
2009-09-09	Reviewed	Poitout, V., Kebede, M.
2009-10-02	Reviewed	Madiraju, MS.

Fatty Acids bound to GPR40 (FFAR1) regulate insulin secretion ↗

Location: Free fatty acids regulate insulin secretion

Stable identifier: R-HSA-434316

Compartments: plasma membrane, cytosol



Fatty acids augment the glucose triggered secretion of insulin through two mechanisms: intracellular metabolism and activation of FFAR1 (GPR40), a G-protein coupled receptor. Based on studies with inhibitors of G proteins such as pertussis toxin FFAR1 is believed to signal through Gq/11. Binding of free fatty acids by FFAR1 activates the heterotrimeric Gq complex which then activates Phospholipase C, producing inositol 1,4,5-trisphosphate and eventually causing the release of intracellular calcium into the cytosol. From experiments in knockout mice it is estimated that signaling through FFAR1 is responsible for about 50% of the augmentation of insulin secretion produced by free fatty acids.

Literature references

Shimada, Y., Masuzaki, H., Nakao, K., Kawamura, J., Tanaka, T., Fujikura, J. et al. (2005). GPR40 gene expression in human pancreas and insulinoma. *Biochem Biophys Res Commun, 338*, 1788-90. ↗

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Olde, B., Flodgren, E., Owman, C., Kotarsky, K., Nilsson, NE. (2003). A human cell surface receptor activated by free fatty acids and thiazolidinedione drugs. *Biochem Biophys Res Commun, 301*, 406-10. ↗

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Editions

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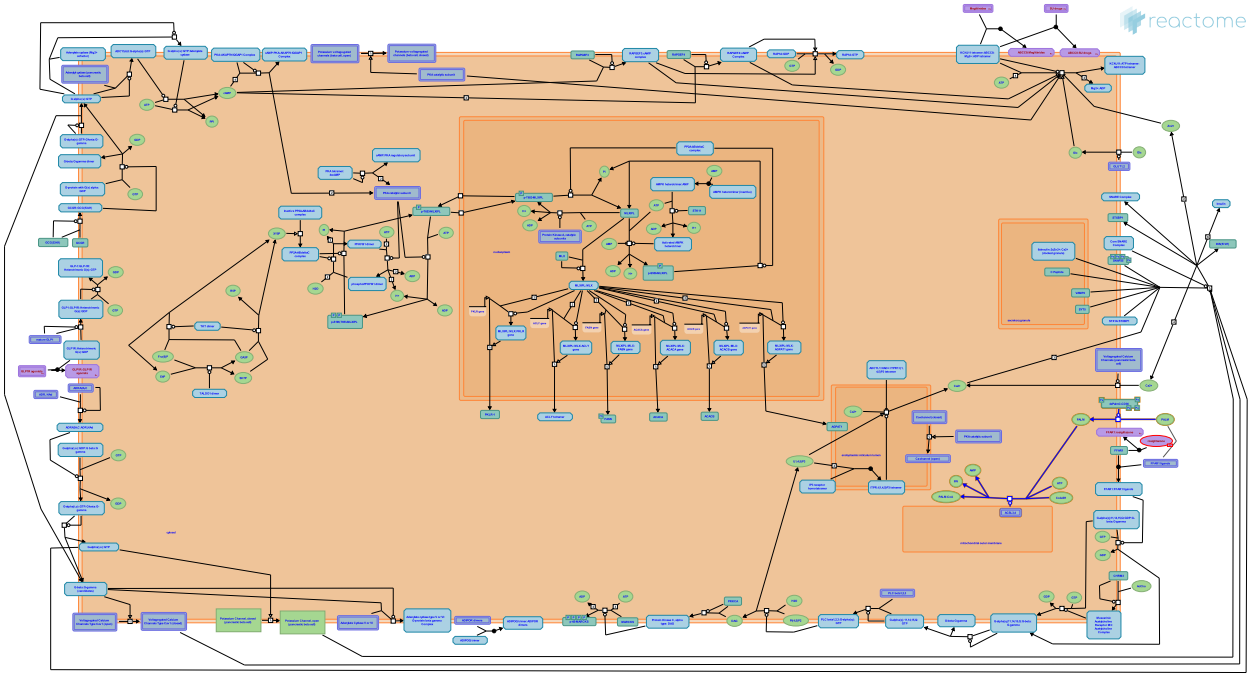
2009-10-02	Reviewed	Madiraju, MS.

Intracellular metabolism of fatty acids regulates insulin secretion ↗

Location: Free fatty acids regulate insulin secretion

Stable identifier: R-HSA-434313



Fatty acids augment the glucose triggered secretion of insulin through two mechanisms: activation of FFAR1 (GPR40) and intracellular metabolism of fatty acids. Fatty acids are transported into the cell by CD36 (FAT) (Noushmehr et al. 2005) and metabolized by ligation to coenzyme A (Ansari et al. 2017), transport into mitochondria, and beta oxidation which generates ATP. The ATP increases the intracellular ratio of ATP:ADP and thereby closes potassium channels (K(ATP) channels) at the plasma membrane (reviewed in Acosta-Montano and Garcia-Gonzalez 2018). The enzymes that metabolize fatty acids in beta cells also metabolize fatty acids in other tissues however their combinations and subcellular locations may differ.

Literature references

Doria, A., Noushmehr, H., Wawrowsky, KA., Farilla, L., Mlynarski, W., D'Amico, E. et al. (2005). Fatty acid translocase (FAT/CD36) is localized on insulin-containing granules in human pancreatic beta-cells and mediates fatty acid effects on insulin secretion. *Diabetes, 54*, 472-81. ↗

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Editions

2009-08-28	Authored, Edited	May, B.
2018-12-22	Reviewed	D'Eustachio, P.

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