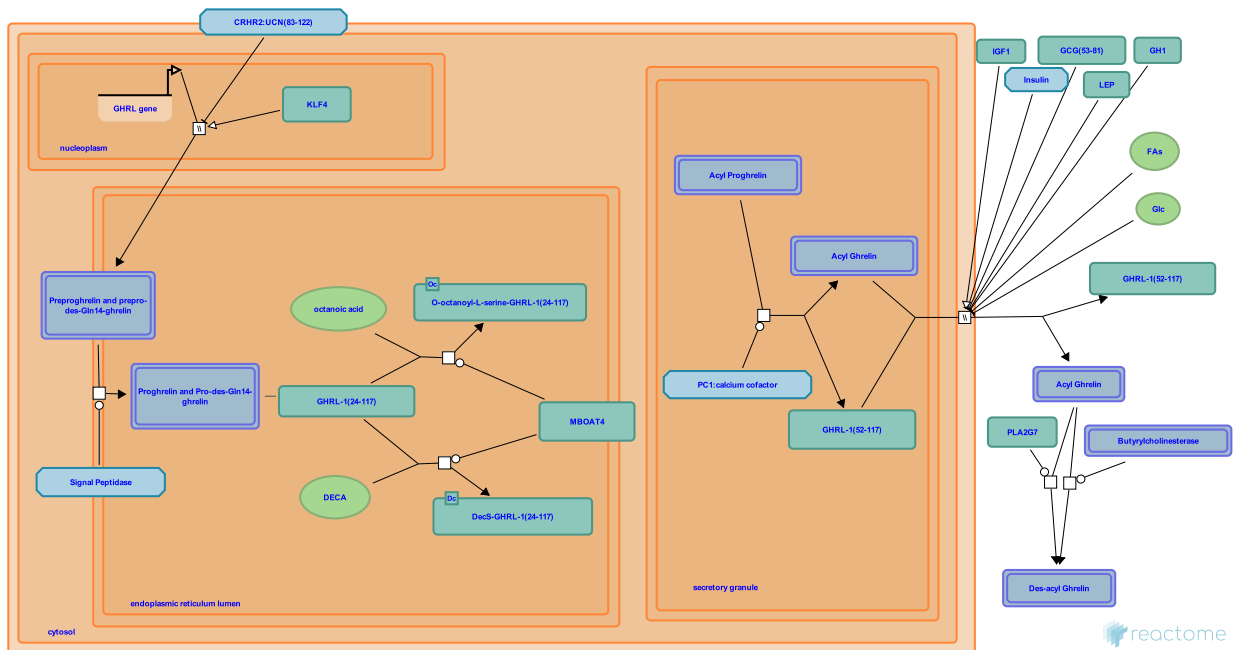


Synthesis, secretion, and deacylation of Ghrelin



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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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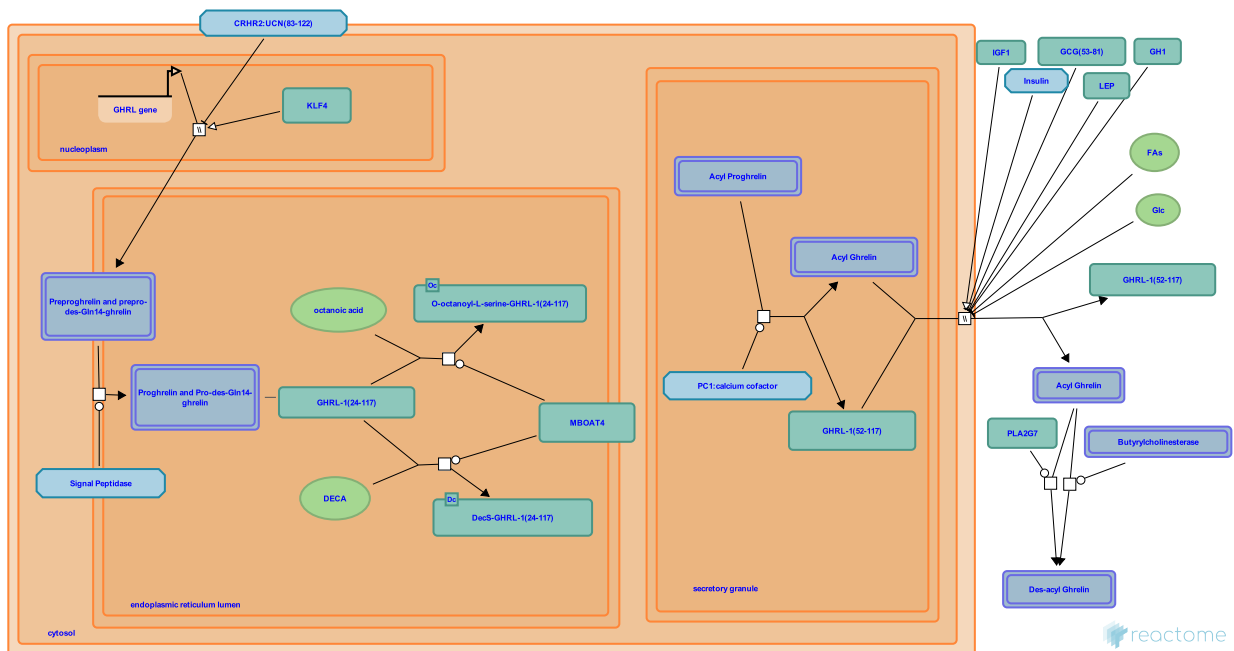
Reactome database release: 70

This document contains 1 pathway and 8 reactions ([see Table of Contents](#))

Synthesis, secretion, and deacylation of Ghrelin ↗

Stable identifier: R-HSA-422085

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



Ghrelin is a peptide hormone of 28 amino acid residues which is acylated at the serine-3 of the mature peptide. Ghrelin is synthesized in several tissues: X/A-like cells of the gastric mucosa (the major source of ghrelin), hypothalamus, pituitary, adrenal gland, thyroid, breast, ovary, placenta, fallopian tube, testis, prostate, liver, gall bladder, pancreas, fat tissue, human lymphocytes, spleen, kidney, lung, skeletal muscle, myocardium, vein and skin. Ghrelin binds the GHS-R1a receptor present in hypothalamus pituitary, and other tissues. Binding causes appetite stimulation and release of growth hormone. Levels of circulating ghrelin rise during fasting, peak before a meal, and fall according to the calories ingested.

Preproghrelin is cleaved to yield proghrelin which is then acylated by ghrelin O-acyltransferase to yield octanoyl ghrelin and decanoyl ghrelin. Only octanoyl ghrelin is able to bind and activate the GHS-R1a receptor. Unacylated ghrelin (des-acyl ghrelin) is also present in plasma but its function is controversial.

Acyl proghrelin is cleaved by prohormone convertase 1/3 to yield the mature acyl ghrelin and C-ghrelin. Secretion of ghrelin is inhibited by insulin, growth hormone (somatotropin), leptin, glucose, glucagon, and fatty acids. Secretion is stimulated by insulin-like growth factor-1 and muscarinic agonists.

In the bloodstream acyl ghrelin is deacylated by butyrylcholinesterase and platelet-activating factor acetylhydrolase. Other enzymes may also deacylate acyl ghrelin.

Literature references

- Yin, X., Li, Y., Xu, G., An, W., Zhang, W. (2009). Ghrelin fluctuation, what determines its production?. *Acta Biochim Biophys Sin (Shanghai)*, 41, 188-97. ↗
- Soares, JB., Leite-Moreira, AF. (2008). Ghrelin, des-acyl ghrelin and obestatin: three pieces of the same puzzle. *Peptides*, 29, 1255-70. ↗

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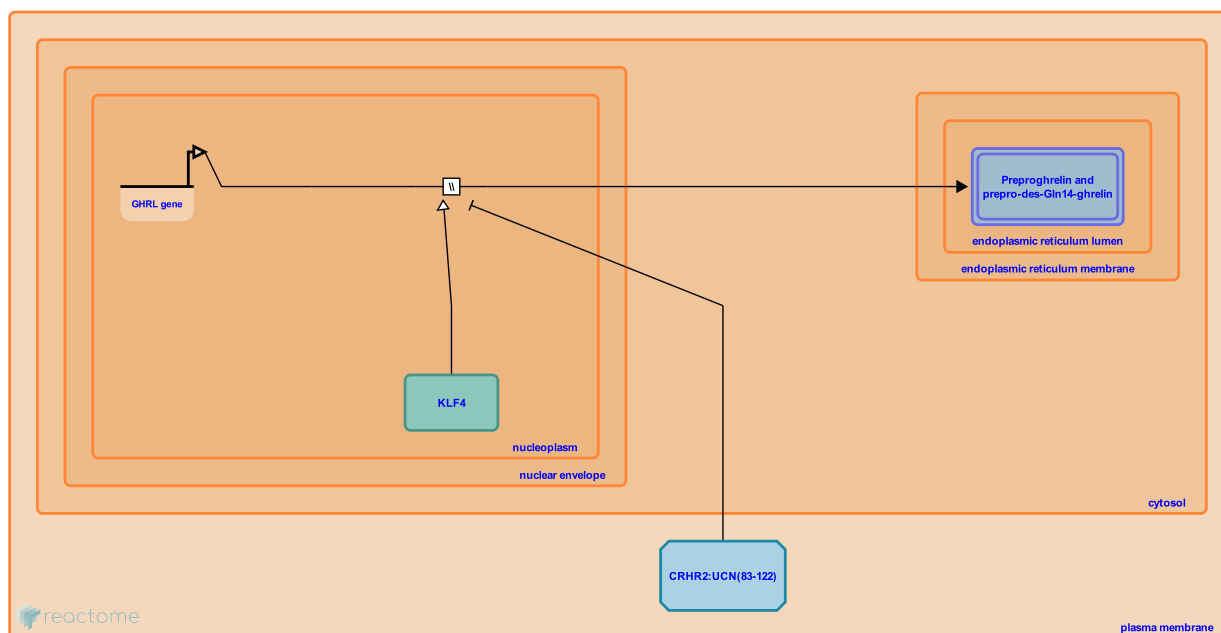
Expression of Preproghrelin ↗

Location: [Synthesis, secretion, and deacylation of Ghrelin](#)

Stable identifier: R-HSA-422088

Type: omitted

Compartments: nucleoplasm, endoplasmic reticulum lumen



The ghrelin gene is transcribed and spliced to yield two variants: isoform 1 encodes full-length preproghrelin and isoform 2 encodes des-acyl-Gln14 preproghrelin, which is missing glutamine at position 14 of the mature peptide. Des-acyl-Gln14 ghrelin is found in rodents but is present in negligible quantities in humans. Somatostatin and leptin inhibit ghrelin mRNA levels. Estrogen increases ghrelin mRNA levels. The KLF4 transcription factor binds the ghrelin promoter and activates transcription. Putative binding sites for other transcription factors have been identified but their functions have not been demonstrated.

Followed by: [Cleavage of the signal peptide of Preproghrelin](#)

Literature references

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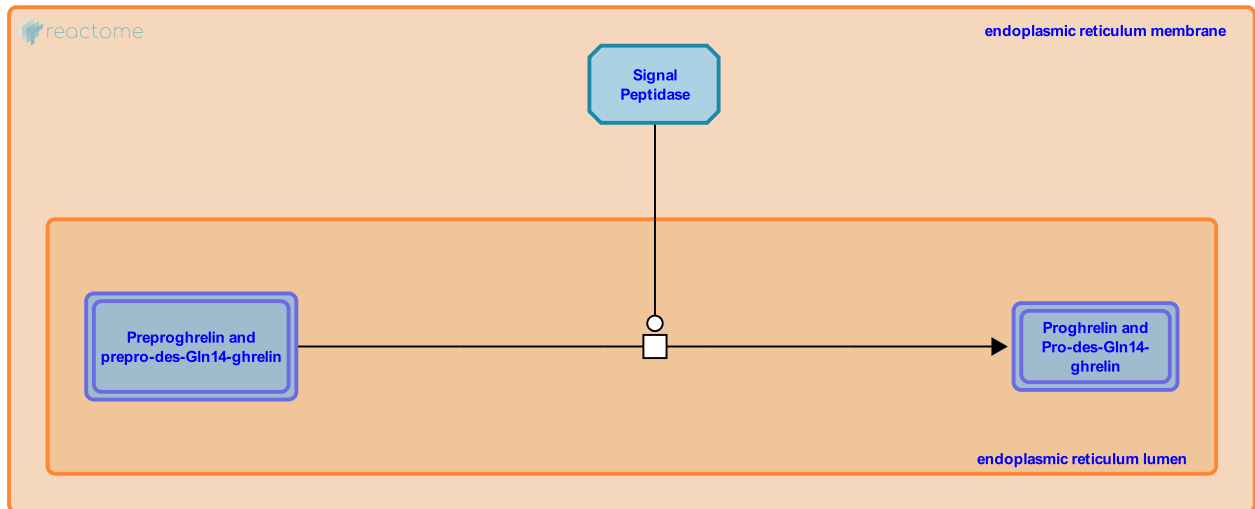
Cleavage of the signal peptide of Preproghrelin ↗

Location: [Synthesis, secretion, and deacylation of Ghrelin](#)

Stable identifier: R-HSA-422051

Type: transition

Compartments: endoplasmic reticulum lumen, endoplasmic reticulum membrane



The N-terminal 23 amino acid residues are cleaved from preproghrelin by the signal peptidase complex. The products are proghrelin (94 amino acid residues) or des-acyl-Gln14 proghrelin (93 amino acid residues), depending on the variant of the mRNA that was translated.

Preceded by: [Expression of Preproghrelin](#)

Followed by: [Ghrelin O-acyltransferase octanoylates Proghrelin](#), [Ghrelin O-acyltransferase decanoylates Proghrelin](#)

Literature references

Yin, X., Li, Y., Xu, G., An, W., Zhang, W. (2009). Ghrelin fluctuation, what determines its production?. *Acta Biochim Biophys Sin (Shanghai)*, 41, 188-97. ↗

Soares, JB., Leite-Moreira, AF. (2008). Ghrelin, des-acyl ghrelin and obestatin: three pieces of the same puzzle. *Peptides*, 29, 1255-70. ↗

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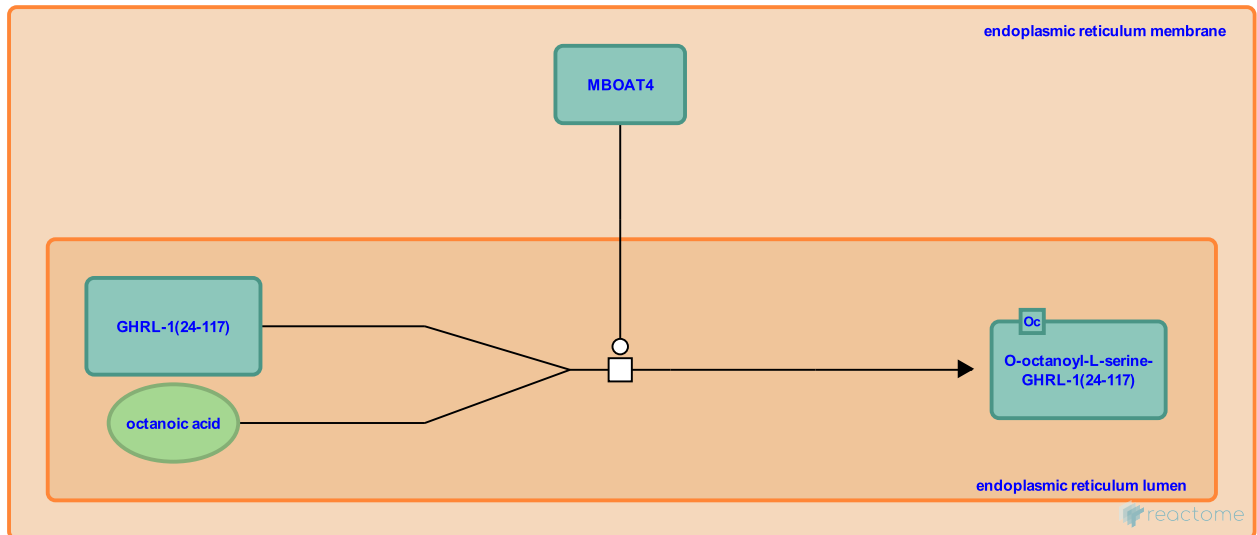
Ghrelin O-acyltransferase octanoylates Proghrelin ↗

Location: [Synthesis, secretion, and deacylation of Ghrelin](#)

Stable identifier: R-HSA-422104

Type: transition

Compartments: endoplasmic reticulum lumen, endoplasmic reticulum membrane



Proghrelin is octanoylated by ghrelin O-acyltransferase (GOAT/MBOAT4), an enzyme present in the endoplasmic reticulum membrane which both transports the octanoic acid substrate and condenses it on the hydroxyl group of serine-3 of the mature protein. The most common acylated form of ghrelin is octanoyl ghrelin but decanoyl ghrelin is also detected. Ghrelin is the only protein known to undergo such a modification.

Preceded by: [Cleavage of the signal peptide of Preproghrelin](#)

Followed by: [PCSK1 hydrolyzes acyl Proghrelin to acyl Ghrelin](#)

Literature references

- Gutierrez, JA., Solenberg, PJ., Perkins, DR., Willency, JA., Knierman, MD., Jin, Z. et al. (2008). Ghrelin octanoylation mediated by an orphan lipid transferase. *Proc Natl Acad Sci U S A*, 105, 6320-5. ↗
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- Hosoda, H., Kojima, M., Mizushima, T., Shimizu, S., Kangawa, K. (2003). Structural divergence of human ghrelin. Identification of multiple ghrelin-derived molecules produced by post-translational processing. *J Biol Chem*, 278, 64-70. ↗
- Yin, X., Li, Y., Xu, G., An, W., Zhang, W. (2009). Ghrelin fluctuation, what determines its production?. *Acta Biochim Biophys Sin (Shanghai)*, 41, 188-97. ↗
- Soares, JB., Leite-Moreira, AF. (2008). Ghrelin, des-acyl ghrelin and obestatin: three pieces of the same puzzle. *Pep-tides*, 29, 1255-70. ↗

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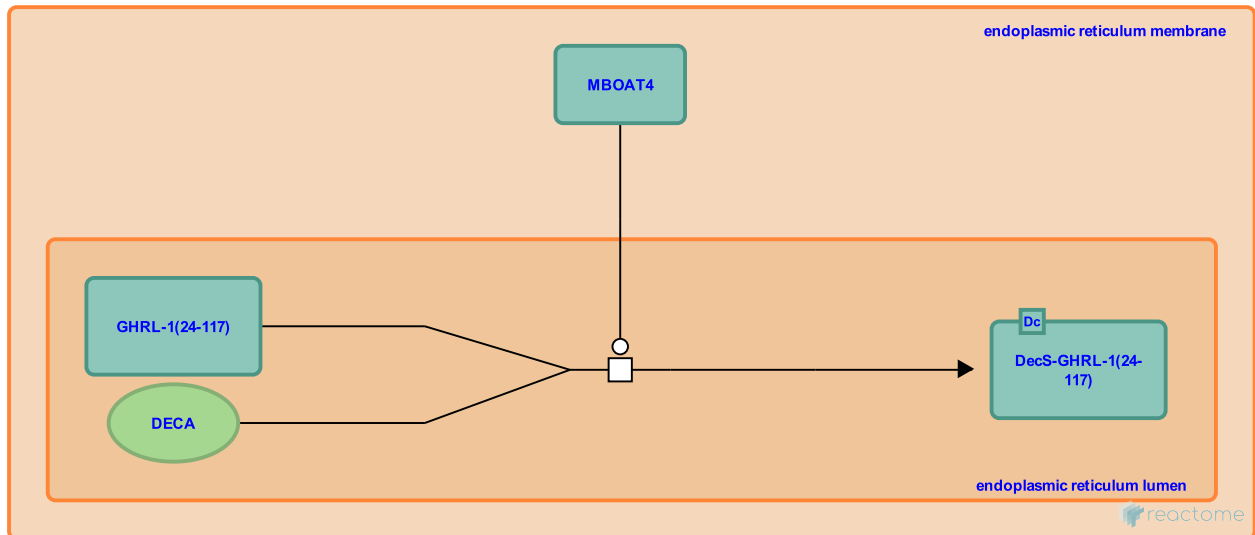
Ghrelin O-acyltransferase decanoylates Proghrelin ↗

Location: [Synthesis, secretion, and deacylation of Ghrelin](#)

Stable identifier: R-HSA-422017

Type: transition

Compartments: endoplasmic reticulum lumen, endoplasmic reticulum membrane



Proghrelin is decanoylated by ghrelin O-acyltransferase (GOAT/MBOAT4), an enzyme present in the endoplasmic reticulum membrane which both transports the decanoic acid substrate and condenses it on the hydroxyl group of serine-3 of the mature protein. The most common acylated form of ghrelin is octanoyl ghrelin but decanoyl ghrelin is also detected in plasma. GOAT is able to use substrates up to tetradecanoic acid. Ghrelin is the only protein known to undergo such a modification.

Preceded by: [Cleavage of the signal peptide of Preproghrelin](#)

Followed by: [PCSK1 hydrolyzes acyl Proghrelin to acyl Ghrelin](#)

Literature references

Gutierrez, JA., Solenberg, PJ., Perkins, DR., Willency, JA., Knierman, MD., Jin, Z. et al. (2008). Ghrelin octanoylation mediated by an orphan lipid transferase. *Proc Natl Acad Sci U S A*, 105, 6320-5. ↗

Takahashi, T., Ida, T., Sato, T., Nakashima, Y., Nakamura, Y., Tsuji, A. et al. (2009). Production of n-octanoyl-modified ghrelin in cultured cells requires prohormone processing protease and ghrelin O-acyltransferase, as well as n-octanoic acid. *J Biochem.* ↗

Hosoda, H., Kojima, M., Mizushima, T., Shimizu, S., Kangawa, K. (2003). Structural divergence of human ghrelin. Identification of multiple ghrelin-derived molecules produced by post-translational processing. *J Biol Chem*, 278, 64-70. ↗

Yin, X., Li, Y., Xu, G., An, W., Zhang, W. (2009). Ghrelin fluctuation, what determines its production?. *Acta Biochim Biophys Sin (Shanghai)*, 41, 188-97. ↗

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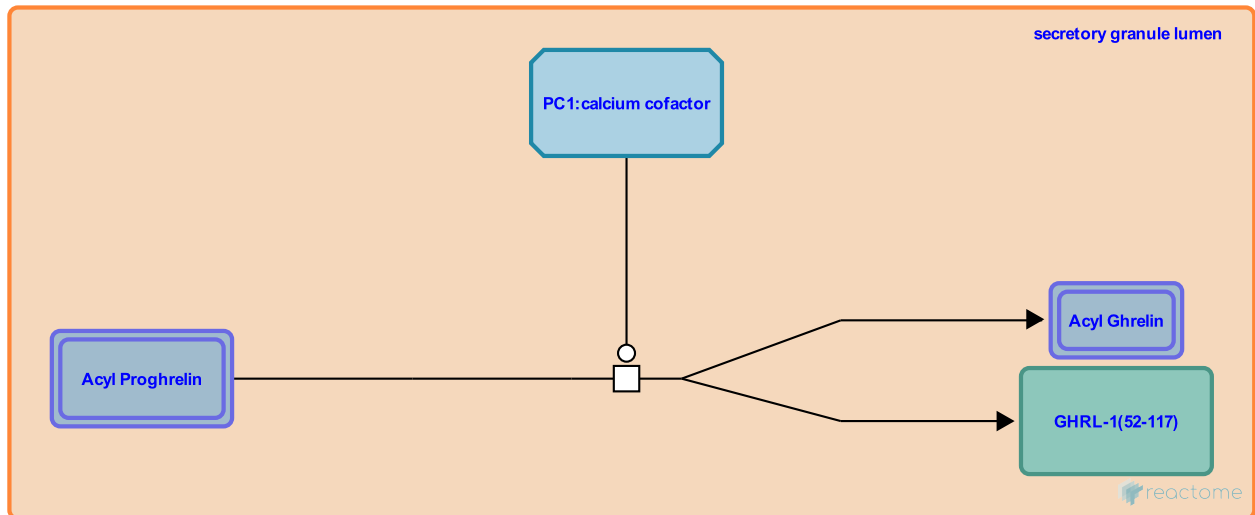
PCSK1 hydrolyzes acyl Proghrelin to acyl Ghrelin ↗

Location: [Synthesis, secretion, and deacylation of Ghrelin](#)

Stable identifier: R-HSA-422021

Type: transition

Compartments: secretory granule lumen



Acyl proghrelin is cleaved by prohormone convertase 1/3 (PC1/3) to yield acyl ghrelin (the N-terminal fragment) and C-ghrelin (the C-terminal fragment). Transfection experiments show that PC1/3 is sufficient to generate acyl ghrelin of 28 amino acid residues (acyl ghrelin-28). Acyl ghrelin of 27 amino acid residues (acyl ghrelin-27) can also be detected in plasma. How acyl ghrelin-27 is generated remains undetermined but it is speculated to derive from the cleavage of arginine-28 from the C-terminus of ghrelin by a carboxypeptidase B-like enzyme.

Preceded by: [Ghrelin O-acyltransferase decanoylates Proghrelin](#), [Ghrelin O-acyltransferase octanoylates Proghrelin](#)

Followed by: [Acyl Ghrelin and C-Ghrelin are secreted](#)

Literature references

- Takahashi, T., Ida, T., Sato, T., Nakashima, Y., Nakamura, Y., Tsuji, A. et al. (2009). Production of n-octanoyl-modified ghrelin in cultured cells requires prohormone processing protease and ghrelin O-acyltransferase, as well as n-octanoic acid. *J Biochem.* ↗
- Yin, X., Li, Y., Xu, G., An, W., Zhang, W. (2009). Ghrelin fluctuation, what determines its production?. *Acta Biochim Biophys Sin (Shanghai)*, 41, 188-97. ↗
- Soares, JB., Leite-Moreira, AF. (2008). Ghrelin, des-acyl ghrelin and obestatin: three pieces of the same puzzle. *Pep-tides*, 29, 1255-70. ↗

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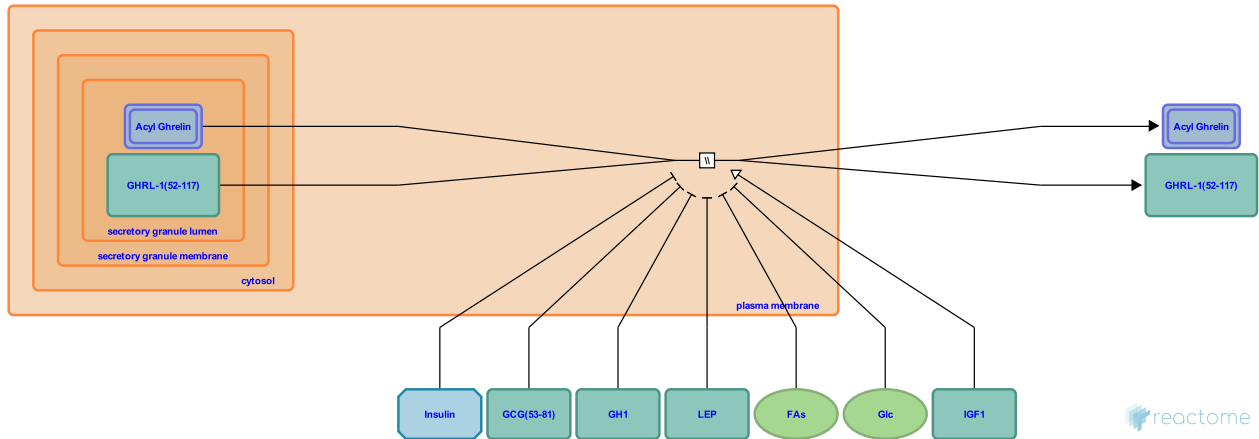
Acyl Ghrelin and C-Ghrelin are secreted ↗

Location: [Synthesis, secretion, and deacylation of Ghrelin](#)

Stable identifier: R-HSA-422048

Type: omitted

Compartments: plasma membrane



Acyl ghrelin and C-ghrelin are secreted from secretory granules into the bloodstream. Five forms of acyl ghrelin have been detected: octanoyl ghrelin-28, decanoyl ghrelin-28, octanoyl ghrelin-27, decanoyl ghrelin-27, and decenoyl ghrelin-28. Unacylated ghrelin (des-acyl ghrelin) occurs at higher levels than acyl ghrelin however its function and mechanism of generation are controversial. The function, if any, of C-ghrelin is also unknown.

Secretion of ghrelin is stimulated by insulin-like growth factor-1 and muscarinic agonists; Secretion is inhibited by insulin, somatotropin, leptin, glucose, glucagon, and fatty acids. Carbohydrates have more inhibitory effect than fat does. The mechanisms by which the regulation is effected are unknown.

Preceded by: [PCSK1 hydrolyzes acyl Proghrelin to acyl Ghrelin](#)

Followed by: [Platelet-activating factor acetylhydrolase \(PLA2G7\) hydrolyzes acyl Ghrelin](#), [Butyrylcholinesterase hydrolyzes acyl Ghrelin](#)

Literature references

- Wierup, N., Björkqvist, M., Weström, B., Pierzynowski, S., Sundler, F., Sjölund, K. (2007). Ghrelin and motilin are co-secreted from a prominent endocrine cell population in the small intestine. *J Clin Endocrinol Metab*, 92, 3573-81. ↗
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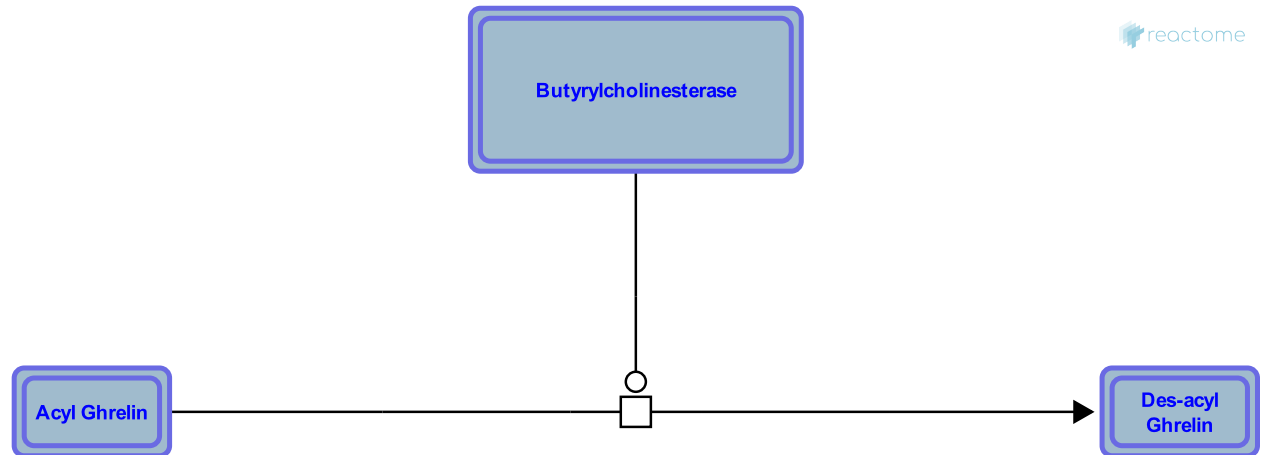
Butyrylcholinesterase hydrolyzes acyl Ghrelin ↗

Location: [Synthesis, secretion, and deacylation of Ghrelin](#)

Stable identifier: R-HSA-9023617

Type: transition

Compartments: extracellular region



The majority of circulating ghrelin is not acylated (des-acyl ghrelin). Acyl ghrelin can be deacylated in the bloodstream by butyrylcholinesterase and platelet-activating factor acetylhydrolase, which are associated with circulating lipids. Other enzymes may also have this capability. It is unknown if a portion of des-acyl ghrelin in the bloodstream is generated by direct synthesis and secretion.

Preceded by: [Acyl Ghrelin and C-Ghrelin are secreted](#)

Literature references

- De Vriese, C., Gregoire, F., Lema-Kisoka, R., Waelbroeck, M., Robberecht, P., Delporte, C. (2004). Ghrelin degradation by serum and tissue homogenates: identification of the cleavage sites. *Endocrinology*, 145, 4997-5005. ↗
- De Vriese, C., Hacquebard, M., Gregoire, F., Carpentier, Y., Delporte, C. (2007). Ghrelin interacts with human plasma lipoproteins. *Endocrinology*, 148, 2355-62. ↗
- Yin, X., Li, Y., Xu, G., An, W., Zhang, W. (2009). Ghrelin fluctuation, what determines its production?. *Acta Biochim Biophys Sin (Shanghai)*, 41, 188-97. ↗
- Soares, JB., Leite-Moreira, AF. (2008). Ghrelin, des-acyl ghrelin and obestatin: three pieces of the same puzzle. *Peptides*, 29, 1255-70. ↗

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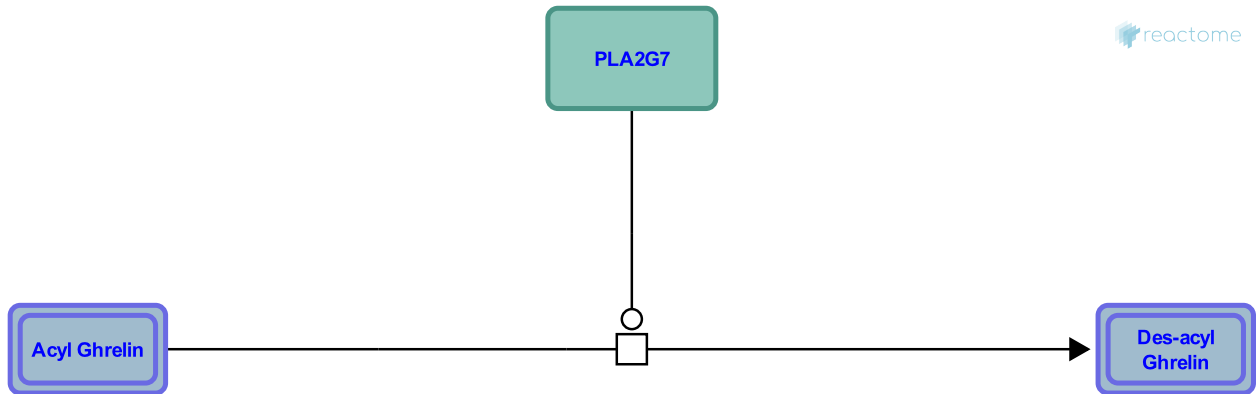
Platelet-activating factor acetylhydrolase (PLA2G7) hydrolyzes acyl Ghrelin ↗

Location: [Synthesis, secretion, and deacylation of Ghrelin](#)

Stable identifier: R-HSA-9023619

Type: transition

Compartments: extracellular region



The majority of circulating ghrelin is not acylated (des-acyl ghrelin). Acyl ghrelin can be deacylated in the bloodstream by butyrylcholinesterase and platelet-activating factor acetylhydrolase, which are associated with circulating lipids. Other enzymes may also have this capability. It is unknown if a portion of des-acyl ghrelin in the bloodstream is generated by direct synthesis and secretion.

Preceded by: [Acyl Ghrelin and C-Ghrelin are secreted](#)

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