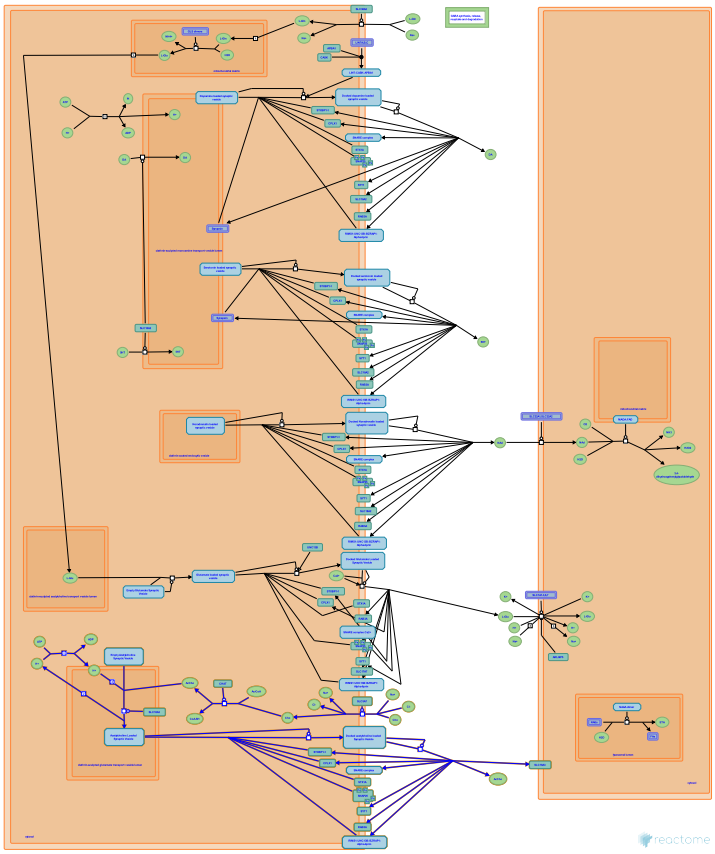
Acetylcholine Neurotransmitter Release Cycle



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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.

01/05/2024

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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

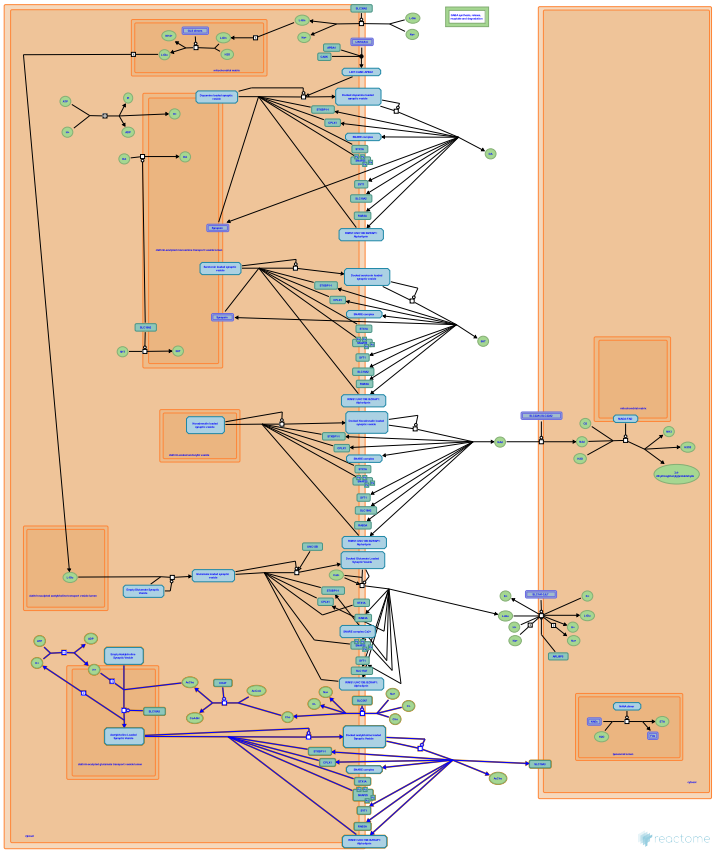
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Acetylcholine Neurotransmitter Release Cycle ↗

Stable identifier: R-HSA-264642



Acetylcholine neurotransmitter release cycle involves synthesis of acetylecholine, loading of synaptic vesicles, docking and priming of the acetyl choline loaded synaptic vesicles and then release of acetylcholine. This cycle occurs in neurons of central nervous system (CNS), peripheral, autonomic and somatic nervous system. In the CNS, the acetylcholine is released by the presynaptic neurons into the synaptic cleft where the released acetylcholine is accessible to acetylcholine receptors located on the postsynaptic neurons.

Literature references

Zimmermann, H. (2008). ATP and acetylcholine, equal brethren. *Neurochem Int, 52*, 634-48. ↗

Editions

2008-01-14	Authored	Mahajan, SS.
2008-04-24	Reviewed	Kavalali, E.
2008-11-18	Edited	Mahajan, SS.
2020-01-24	Reviewed	Wen, H.

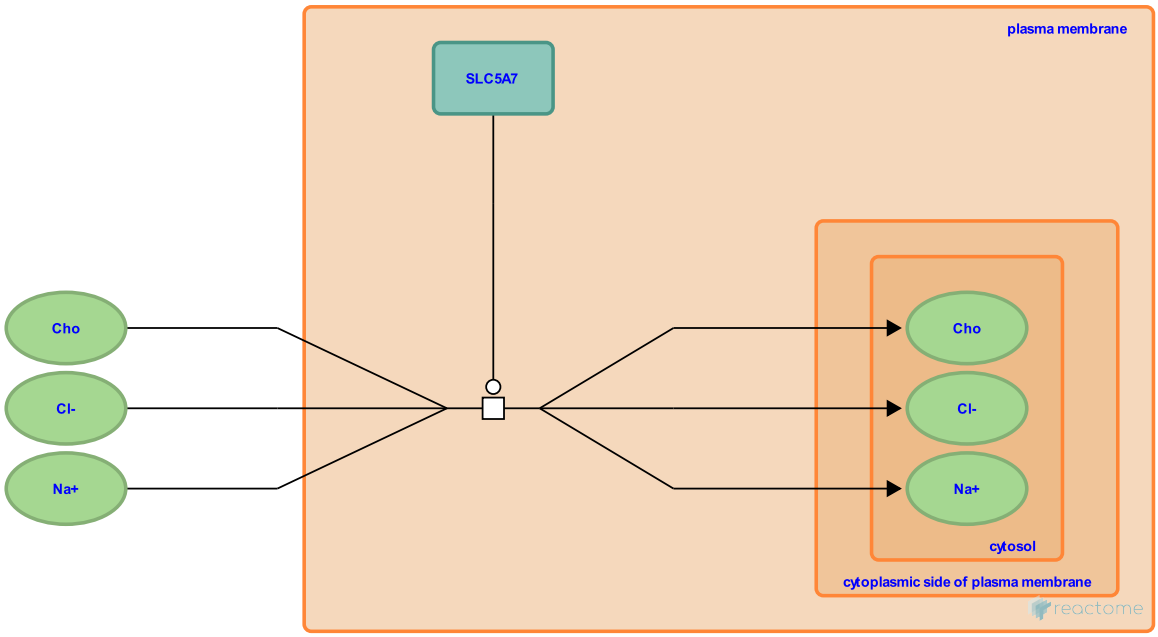
SLC5A7 cotransports Cho, Cl-, Na+ from extracellular region to cytosol

Location: Acetylcholine Neurotransmitter Release Cycle

Stable identifier: R-HSA-429594

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



The human SLC5A7 gene encodes a sodium- and chloride-dependent, high affinity choline transporter, CHT (Apparsundaram et al. 2000). CHT transports choline (Cho) from the extracellular space into neuronal cells and is dependent on Na+ and Cl- ions for transport (Okuda & Haga 2000). Choline uptake is the rate-limiting step in acetylcholine synthesis.

Followed by: Cho is acetylated to AcCho by CHAT

Literature references

Haga, T., Okuda, T. (2000). Functional characterization of the human high-affinity choline transporter. *FEBS Lett, 484*, 92-7.

Ferguson, SM., Blakely, RD., George AL, Jr., Apparsundaram, S. (2000). Molecular cloning of a human, hemicholinium-3-sensitive choline transporter. *Biochem Biophys Res Commun, 276*, 862-7.

Editions

2009-07-17	Authored, Edited	Jassal, B.
2009-08-24	Reviewed	He, L.

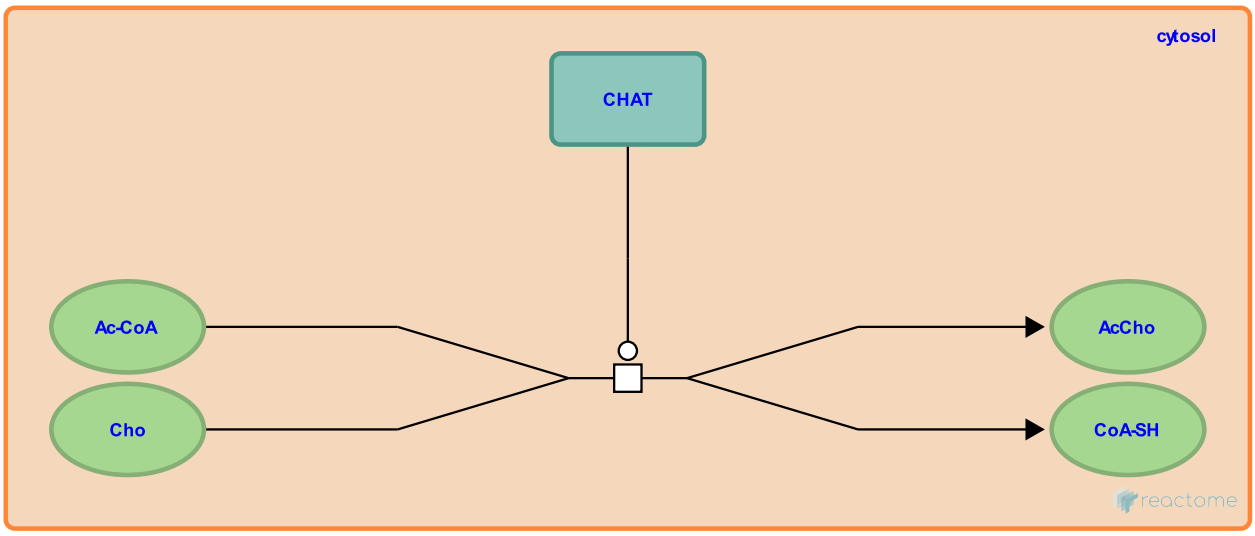
Cho is acetylated to AcCho by CHAT ↗

Location: Acetylcholine Neurotransmitter Release Cycle

Stable identifier: R-HSA-264622

Type: transition

Compartments: cytosol



In the cytosol, choline O-acetyltransferase (CHAT) acetylates choline (Cho) to produce acetylcholine (AcCho) (Toussaint 1992).

AcCho is synthesised in the cytoplasm of cholinergic neurons from acetyl-CoA and Cho by CHAT enzyme.

Preceded by: SLC5A7 cotransports Cho, Cl-, Na+ from extracellular region to cytosol

Followed by: Loading of acetylcholine in synaptic vesicles

Literature references

Toussaint, JL. (1992). Human choline acetyltransferase (CHAT): partial gene sequence and potential control regions. *Genomics, 12*, 412-6. ↗

Editions

2008-01-14	Authored	Mahajan, SS.

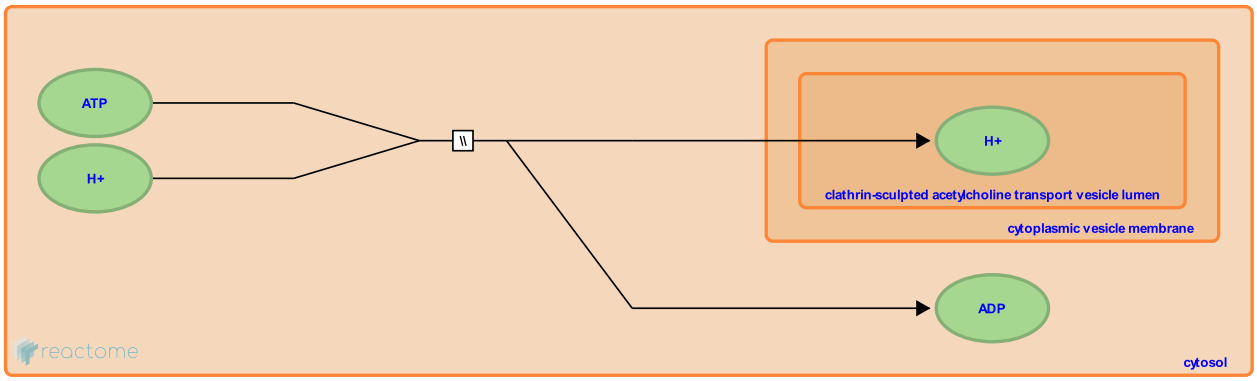
Re-acidification of acetylcholine transport vesicles ↗

Location: Acetylcholine Neurotransmitter Release Cycle

Stable identifier: R-HSA-349520

Type: omitted

Compartments: cytosol, clathrin-sculpted acetylcholine transport vesicle membrane



The proton gradient for the acetylcholine uptake is provided by vH+ type ATPase pump located in the synaptic vesicle membrane.

Followed by: Loading of acetylcholine in synaptic vesicles

Literature references

Michaelson, DM., Angel, I. (1980). Determination of delta pH in cholinergic synaptic vesicles: its effect on storage and release of acetylcholine. *Life Sci, 27*, 39-44. ↗

Editions

2008-01-14	Authored	Mahajan, SS.
2020-01-24	Reviewed	Wen, H.

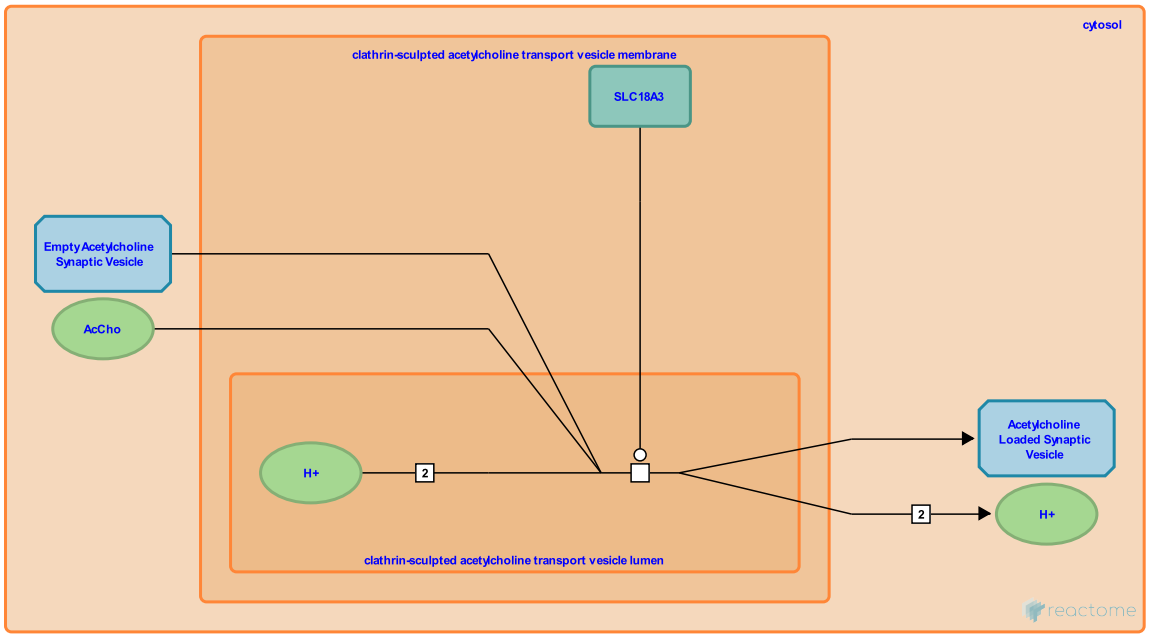
Loading of acetylcholine in synaptic vesicles ↗

Location: Acetylcholine Neurotransmitter Release Cycle

Stable identifier: R-HSA-264615

Type: transition

Compartments: clathrin-sculpted acetylcholine transport vesicle lumen, cytosol



Acetylcholine is actively transported from the cytosol to the lumen of the synaptic vesicle by vesicular acetylcholine transporter. Two protons are exchanged for 1 molecule of acetylcholine. The vesicular acetylcholine transporter is located in the membrane of the synaptic vesicle.

Preceded by: Cho is acetylated to AcCho by CHAT, Re-acidification of acetylcholine transport vesicles

Followed by: Acetylcholine synaptic vesicle docking and priming

Literature references

Eiden, LE., Diebler, MF., Varoqui, H., Weihe, E., Usdin, TB., Erickson, JD. et al. (1994). Functional identification of a vesicular acetylcholine transporter and its expression from a "cholinergic" gene locus. *J Biol Chem, 269*, 21929-32. ↗

Editions

2008-01-14	Authored	Mahajan, SS.

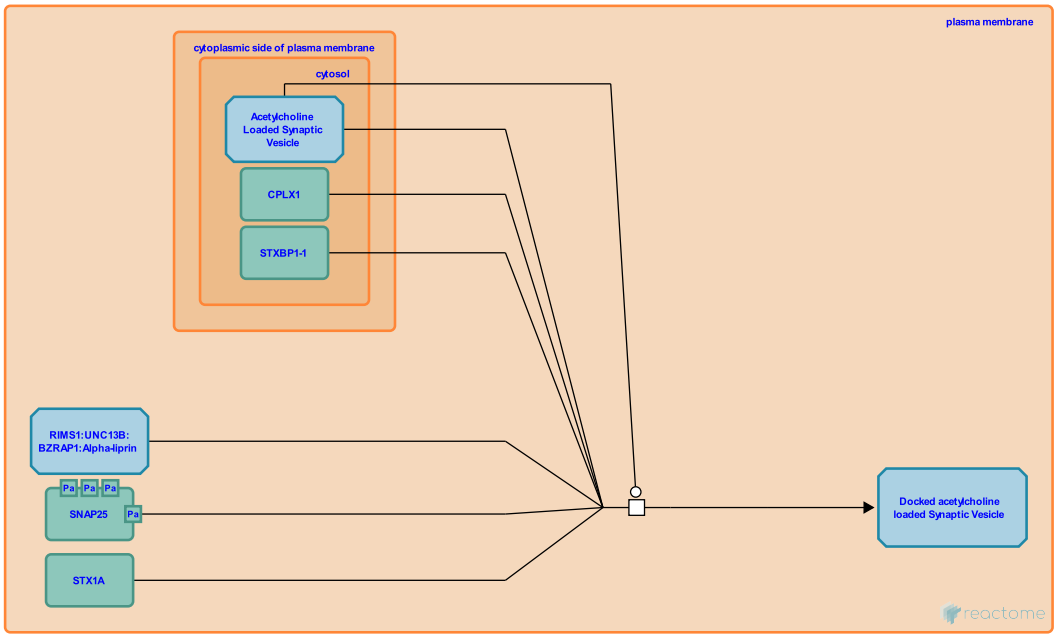
Acetylcholine synaptic vesicle docking and priming ↗

Location: Acetylcholine Neurotransmitter Release Cycle

Stable identifier: R-HSA-372505

Type: transition

Compartments: plasma membrane, cytosol



Docking and priming of acetylcholine loaded transport vesicle occurs once the synaptic vesicle has moved from the cytoplasm to a region apposed to the plasma membrane. The details of the docking and priming reaction have been worked out using synaptic vesicles loaded with glutamate and similar reactions may occur during the transport cycle of acetylcholine. The vesicle is held in close apposition to the plasma membrane by several proteins that bridge the synaptic vesicle to the plasma membrane. Some of these proteins are in the plasma membrane while others are in the synaptic vesicle. Vesicle fusion is preceded by a priming event where molecular interactions between the docked vesicle and the plasma membrane undergo changes. The molecules in the docking and the priming process are known, however, the exact sequence and the precise molecular changes involved in docking and priming are not well dissected. In this reaction the process of docking and priming has been condensed. It is known that Munc18 along with its interactors is critical for membrane docking and fusion events while Munc 13 along with its interacting proteins is central to priming. Munc 13 could act as a positive regulator for the priming recation. Finally the primed fusion complex is clamped in the pre-fusion form by a Complexin. Complexins are Ca2+ independent cytosolic proteins that bind to partly or fully assembled SNARE complexes. Complexins play both a positive and a negative role in the release process.

Preceded by: Loading of acetylcholine in synaptic vesicles

Followed by: Release of acetylcholine at the synapse

Literature references

de Vries, KJ., Zalm, R., Südhof, TC., Verhage, M., Toonen, RF. (2005). Munc18-1 stabilizes syntaxin 1, but is not essential for syntaxin 1 targeting and SNARE complex formation. *J Neurochem, 93*, 1393-400. ↗

Olkkonen, VM., Galli, T., Riento, K., Ehnholm, C., Lehtonen, E., Jansson, S. (1998). Interaction of Munc-18-2 with syntaxin 3 controls the association of apical SNAREs in epithelial cells. *J Cell Sci, 111*, 2681-8. ↗

Dai, H., Sun, J., Rizo, J., Südhof, TC., Dulubova, I., Khvotchev, M. (2007). Dual modes of Munc18-1/SNARE interactions are coupled by functionally critical binding to syntaxin-1 N terminus. *J Neurosci, 27*, 12147-55. ↗

Südhof, TC., Augustin, I., Rosenmund, C., Brose, N. (1999). Munc13-1 is essential for fusion competence of glutamatergic synaptic vesicles. *Nature, 400*, 457-61. ↗

Editions

2008-01-14	Authored	Mahajan, SS.
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2020-01-24	Reviewed	Wen, H.

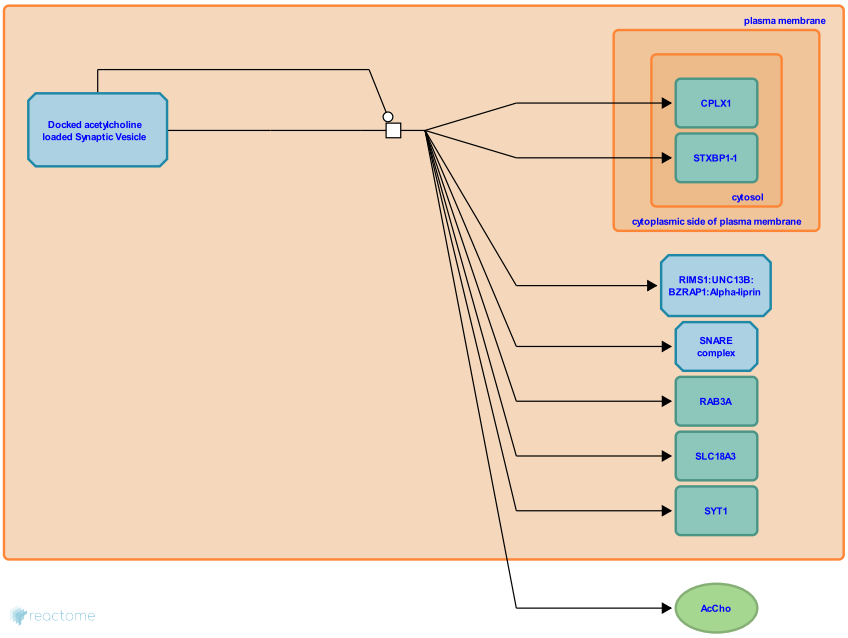
Release of acetylcholine at the synapse ↗

Location: Acetylcholine Neurotransmitter Release Cycle

Stable identifier: R-HSA-372529

Type: transition

Compartments: plasma membrane



Once vesicles are docked, primed and ready to be released fusion of the synaptic vesicle with the plasma membrane can be triggered by an influx of Ca2+ through the voltage gated Ca2+ channels (N, P/Q, R, and L type). Ca2+ influx initiates a cascade of events in which the Ca2+ sensing protein, synaptotagmin-1 (sty-1) is central. Sty-1 promotes the membrane fusion between the synaptic vesicle and the plasma membrane by Ca2+ dependant induction of membrane curvature. Synaptotagmin competes with SNARE complex binding in a Ca2+ dependent manner thereby displacing complexin-1 and causing membrane curvature and fusion of the synaptic vesicle with the plasma membrane. The fusion is characterized by the formation of a trans SNARE complex in which SNAP 25, syntaxin and synaptobrevin along with synaptotagmin, and Rab3a either become a part of the plasma membrane or membrane delimited in the vesicular membrane. Vesicle fusion ultimately results in the release of the acetylcholine into the synaptic cleft.

Preceded by: Acetylcholine synaptic vesicle docking and priming

Literature references

Fisher, RJ., Craig, TJ., Burgoyne, RD., Morgan, A., Evans, GJ., Ciufo, LF. et al. (2003). Phosphorylation of Munc18 by protein kinase C regulates the kinetics of exocytosis. *J Biol Chem, 278*, 10538-45. ↗

Martens, S., McMahon, HT., Kozlov, MM. (2007). How synaptotagmin promotes membrane fusion. *Science, 316*, 1205-8. ↗

Jahn, R., Radhakrishnan, A., Stein, A., Fasshauer, D., Riedel, D. (2007). Synaptotagmin activates membrane fusion through a Ca2+-dependent trans interaction with phospholipids. *Nat Struct Mol Biol, 14*, 904-11. ↗

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2008-01-14	Authored	Mahajan, SS.
2008-11-27	Reviewed	Restituito, S.
2009-11-19	Edited	Gillespie, ME.
2020-01-24	Authored	Wen, H.

Table of Contents