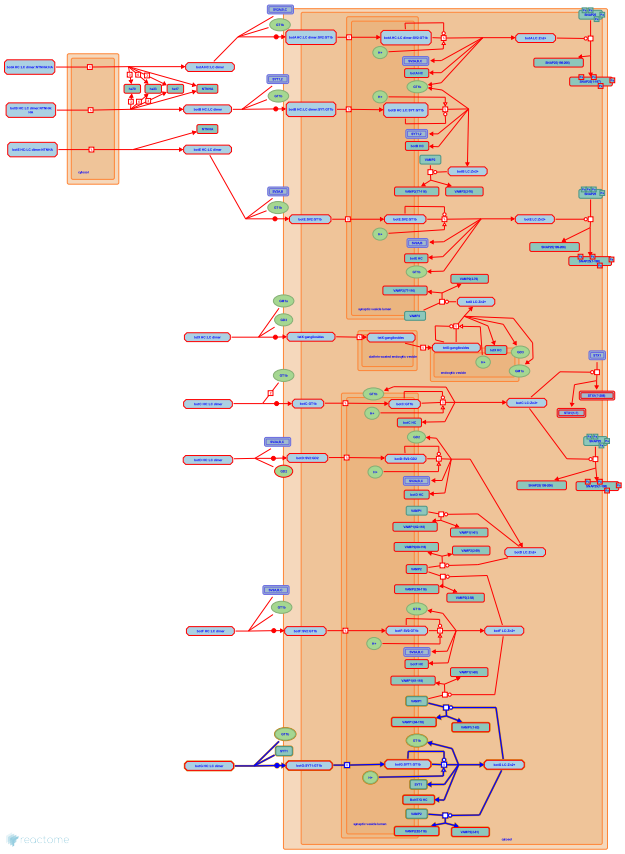
Toxicity of botulinum toxin type G (botG)



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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.
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. ↗

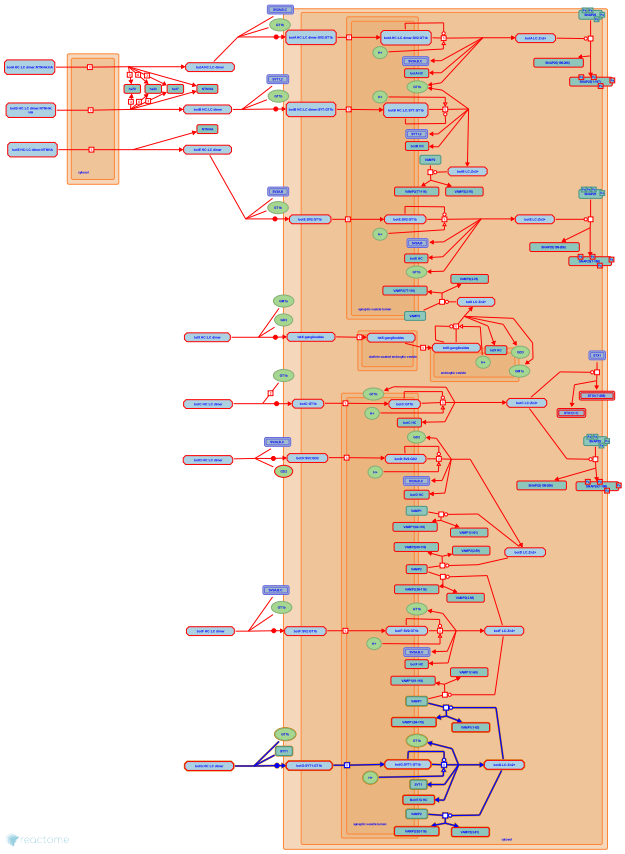
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Toxicity of botulinum toxin type G (botG)

Stable identifier: R-HSA-5250989

Diseases: botulism



Botulinum toxin type G (botG) is rarely if ever associated with human disease (Hatheway 1995) and a pathway by which it might enter the circulation from the human gut has not been described. Nevertheless, the toxin itself, a disulfide-bonded heavy chain (HC) - light chain (LC) heterodimer ("dichain"), is capable of binding to neurons by interactions with cell-surface ganglioside and syntagmin 1 (SYT1) (Peng et al. 2012; Willjes et al. 2013), the bound toxin can enter synaptic vesicles and release its LC moiety into the cytosol of targeted cells (Montal 2010), and the botG LC can cleave vesicle-associated membrane proteins 1 and 2 (VAMP1 and 2) on the cytosolic face of the synaptic vesicle membrane (Schiavo et al. 1994; Yamasaki et al. 1994). These four events are annotated here.

Literature references

Mahrhold, S., Strotmeier, J., Rummel, A., Eichner, T., Binz, T., Willjes, G. (2013). Botulinum neurotoxin G binds synaptotagmin-II in a mode similar to that of serotype B: tyrosine 1186 and lysine 1191 cause its lower affinity. *Biochemistry, 52*, 3930-8.

Hayashi, T., Yamasaki, S., Niemann, H., Eklund, M., Szabo, E., Binz, T. et al. (1994). Botulinum neurotoxin type G proteolyses the Ala81-Ala82 bond of rat synaptobrevin 2. *Biochem. Biophys. Res. Commun., 200*, 829-35.

Pitkin, RM., Tepp, WH., Berntsson, RP., Stenmark, P., Dong, M., Peng, L. et al. (2012). Botulinum neurotoxin D-C uses synaptotagmin I and II as receptors, and human synaptotagmin II is not an effective receptor for type B, D-C and G toxins. *J. Cell. Sci., 125*, 3233-42.

Montal, M. (2010). Botulinum neurotoxin: a marvel of protein design. *Annu. Rev. Biochem., 79*, 591-617.

Malizio, C., Polverino de Laureto, P., Trimble, WS., Schiavo, G., Milan, G., Montecucco, C. et al. (1994). Botulinum G neurotoxin cleaves VAMP/synaptobrevin at a single Ala-Ala peptide bond. *J. Biol. Chem., 269*, 20213-6.

Editions

2006-06-15	Authored	Gopinathrao, G., Krupa, S.
2007-08-03	Reviewed	Ichtchenko, K.
2014-02-11	Edited, Revised	D'Eustachio, P.
2014-11-18	Reviewed	Sharma, S., Thirunavukkarasu, N.

botG HC:LC binds SYT1 and GT1b on the target cell surface ↗

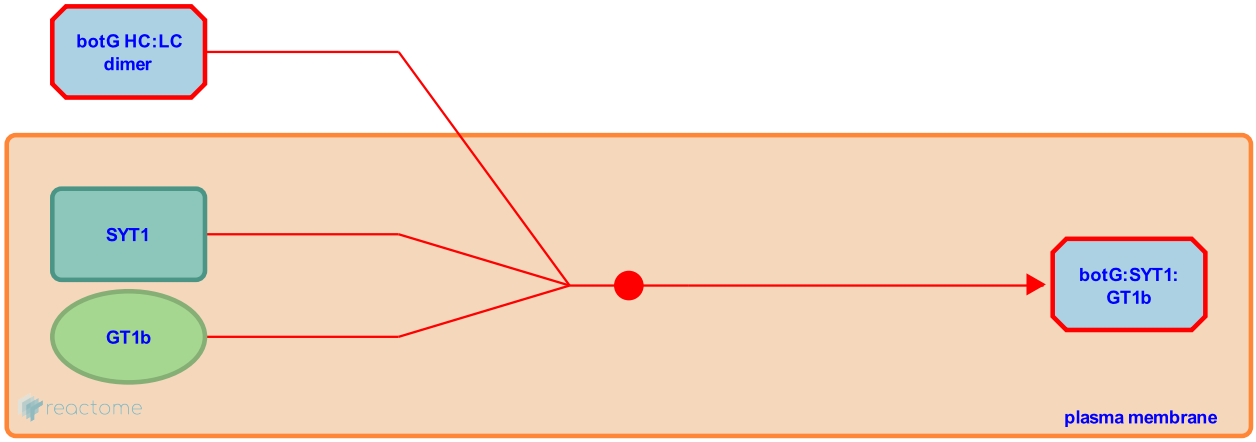
Location: Toxicity of botulinum toxin type G (botG)

Stable identifier: R-HSA-5250986

Type: binding

Compartments: plasma membrane, extracellular region

Diseases: botulism



The botulinum toxin type G disulfide-bonded heavy chain - light chain heterodimer ("dichain") (botG HC:LC) binds ganglioside GT1b and synaptotagmin-1 (SYT1) on the plasma membrane of a human target cell. In vivo, this process specifically targets synapses at neuromuscular junctions, where toxin association with ganglioside may position it to bind efficiently to SYT1 when that protein is exposed at the cell surface by exocytosis (Peng et al. 2012; Willjes et al. 2013).

Followed by: botG:SYT1:GT1b internalized from target cell plasma membrane to synaptic vesicle membrane

Literature references

Mahrhold, S., Strotmeier, J., Rummel, A., Eichner, T., Binz, T., Willjes, G. (2013). Botulinum neurotoxin G binds synaptotagmin-II in a mode similar to that of serotype B: tyrosine 1186 and lysine 1191 cause its lower affinity. *Biochemistry, 52*, 3930-8. ↗

Pitkin, RM., Tepp, WH., Berntsson, RP., Stenmark, P., Dong, M., Peng, L. et al. (2012). Botulinum neurotoxin D-C uses synaptotagmin I and II as receptors, and human synaptotagmin II is not an effective receptor for type B, D-C and G toxins. *J. Cell. Sci., 125*, 3233-42. ↗

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2006-06-15	Authored	Gopinathrao, G., Krupa, S.
2007-08-03	Reviewed	Ichtchenko, K.
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2014-11-18	Reviewed	Sharma, S., Thirunavukkarasu, N.

botG:SYT1:GT1b internalized from target cell plasma membrane to synaptic vesicle membrane ↗

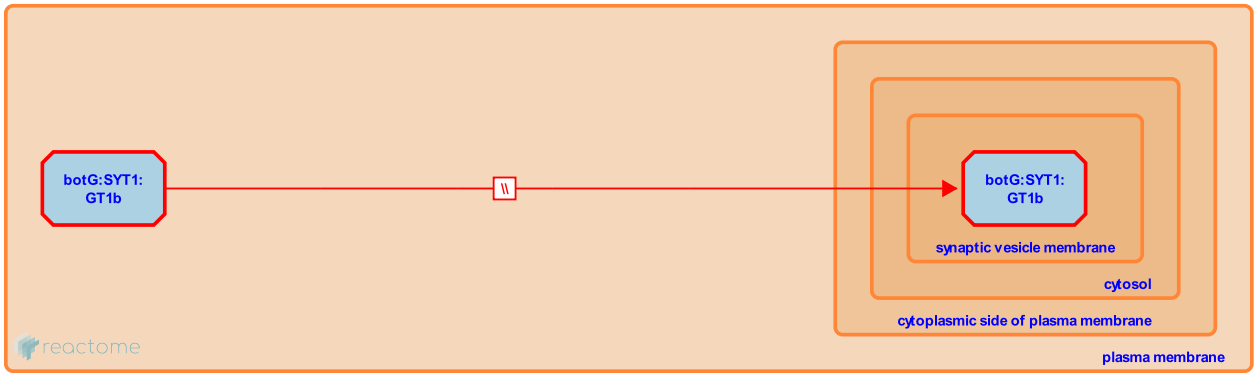
Location: Toxicity of botulinum toxin type G (botG)

Stable identifier: R-HSA-5250979

Type: omitted

Compartments: plasma membrane, synaptic vesicle membrane

Diseases: botulism



Synaptic vesicles re-form rapidly after exocytosis, carrying vesicle membrane proteins that had been exposed on the cell surface by exocytosis back into the cell (Sudhoff 2004). The botulinum toxin type G disulfide-bonded heavy chain - light chain heterodimer (botG HC:LC) bound to ganglioside GT1b and syntagmin 1 (SYT1) is inferred to be taken up as well, delivering it to the re-formed synaptic vesicle.

Preceded by: botG HC:LC binds SYT1 and GT1b on the target cell surface

Followed by: botG HC transports botG LC from target cell synaptic vesicle membrane into cytosol

Literature references

Südhof, TC. (2004). The synaptic vesicle cycle. *Annu Rev Neurosci, 27*, 509-47. ↗

Editions

2006-06-15	Authored	Gopinathrao, G., Krupa, S.
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botG HC transports botG LC from target cell synaptic vesicle membrane into cytosol

↗

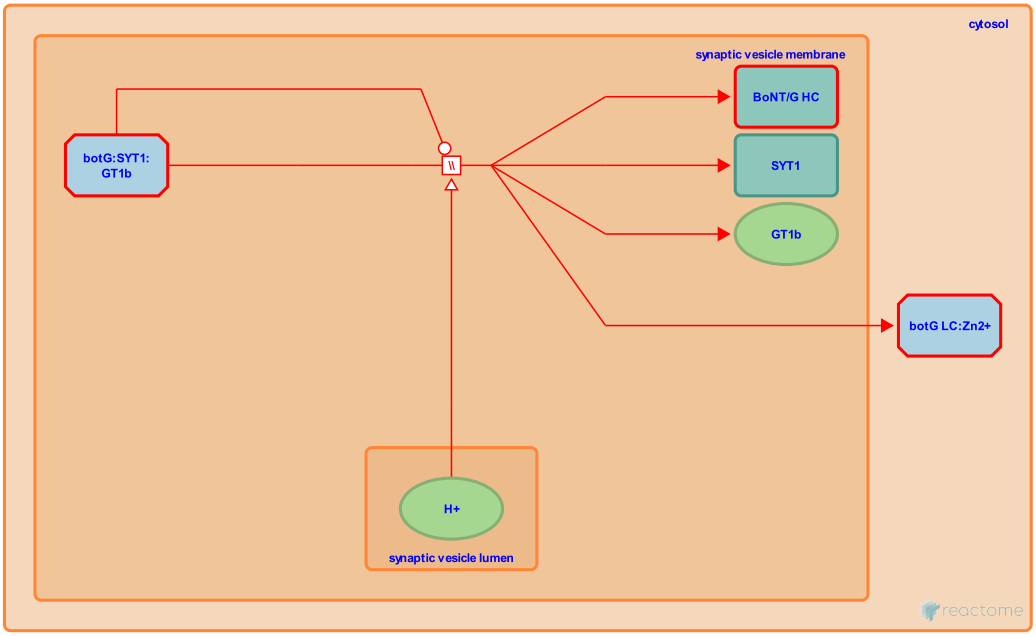
Location: Toxicity of botulinum toxin type G (botG)

Stable identifier: R-HSA-5250972

Type: omitted

Compartments: synaptic vesicle membrane, cytosol

Diseases: botulism



By analogy to the process described for botulinum toxin type A (Koriazova and Montal 2003; Montal 2010), acidification, a normal step in synaptic vesicle recycling, is inferred to cause a conformational change in the botulinum toxin type G disulfide-bonded heavy chain - light chain dimer (BoNT/G HC:LC) it contains, allowing the HC part of the toxin to function as a channel through which its LC part is extruded into the neuronal cytosol. The HC - LC disulfide bond is cleaved. Recent studies in vitro suggest that GT1b ganglioside associated with the toxin may play a role in this process (Sun et al. 2012).

Preceded by: botG:SYT1:GT1b internalized from target cell plasma membrane to synaptic vesicle membrane

Followed by: botG LC cleaves target cell VAMP2, botG LC cleaves target cell VAMP1

Literature references

Montal, M. (2010). Botulinum neurotoxin: a marvel of protein design. *Annu. Rev. Biochem., 79*, 591-617. ↗

Editions

2006-06-15	Authored	Gopinathrao, G., Krupa, S.
2007-08-03	Reviewed	Ichtchenko, K.
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botG LC cleaves target cell VAMP1 ↗

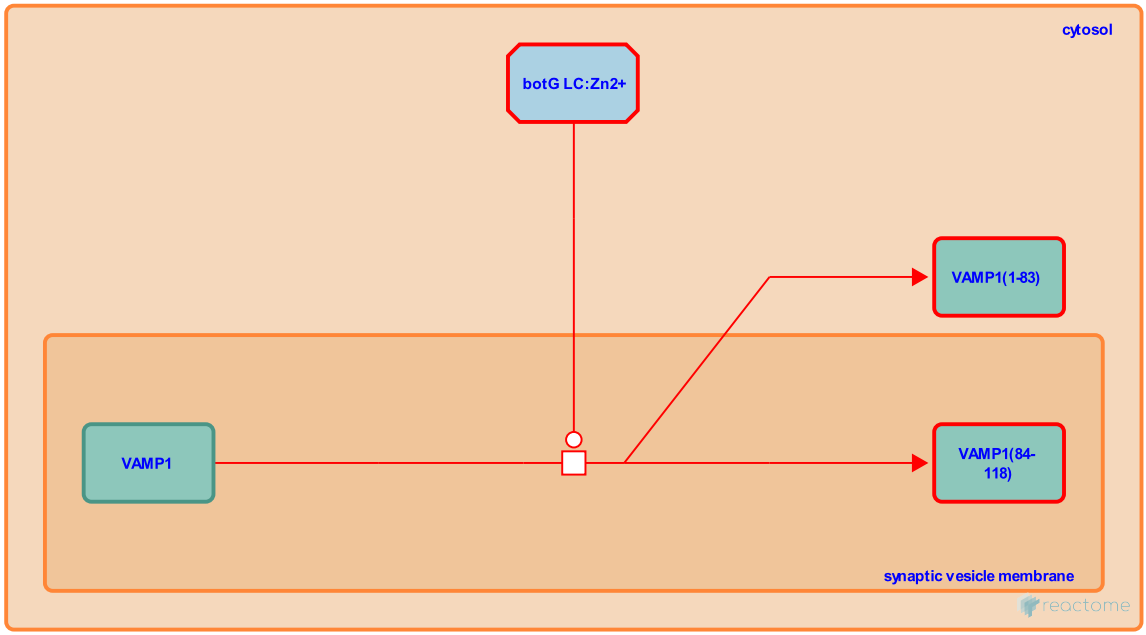
Location: Toxicity of botulinum toxin type G (botG)

Stable identifier: R-HSA-5250978

Type: transition

Compartments: synaptic vesicle membrane, cytosol

Diseases: botulism



Botulinum toxin type G light chain (botG LC), in the cytosol of a target cell, catalyzes the removal of an aminoterminal peptide from vesicle-associated membrane protein 1 (VAMP1). botG LC is a zinc metalloprotease (Schiavo et al. 1994; Yamasaki et al. 1994). VAMP1 is associated with the cytosolic face of the target cell synaptic vesicle and is required for vesicle docking and exocytosis.Its cleavage by botulinum toxin blocks synaptic vesicle fusion with the plasma membrane and neurotransmitter release (Sudhof et al, 1993; Sudhof 2004).

Preceded by: botG HC transports botG LC from target cell synaptic vesicle membrane into cytosol

Literature references

Schiavo, G., Montecucco, C. (1994). Mechanism of action of tetanus and botulinum neurotoxins. *Mol Microbiol, 13*, 1-8. ↗

Hayashi, T., Yamasaki, S., Niemann, H., Eklund, M., Szabo, E., Binz, T. et al. (1994). Botulinum neurotoxin type G proteolyses the Ala81-Ala82 bond of rat synaptobrevin 2. *Biochem. Biophys. Res. Commun., 200*, 829-35. ↗

Malizio, C., Polverino de Laureto, P., Trimble, WS., Schiavo, G., Milan, G., Montecucco, C. et al. (1994). Botulinum G neurotoxin cleaves VAMP/synaptobrevin at a single Ala-Ala peptide bond. *J. Biol. Chem., 269*, 20213-6. ↗

Südhof, TC. (2004). The synaptic vesicle cycle. *Annu Rev Neurosci, 27*, 509-47. ↗

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botG LC cleaves target cell VAMP2 ↗

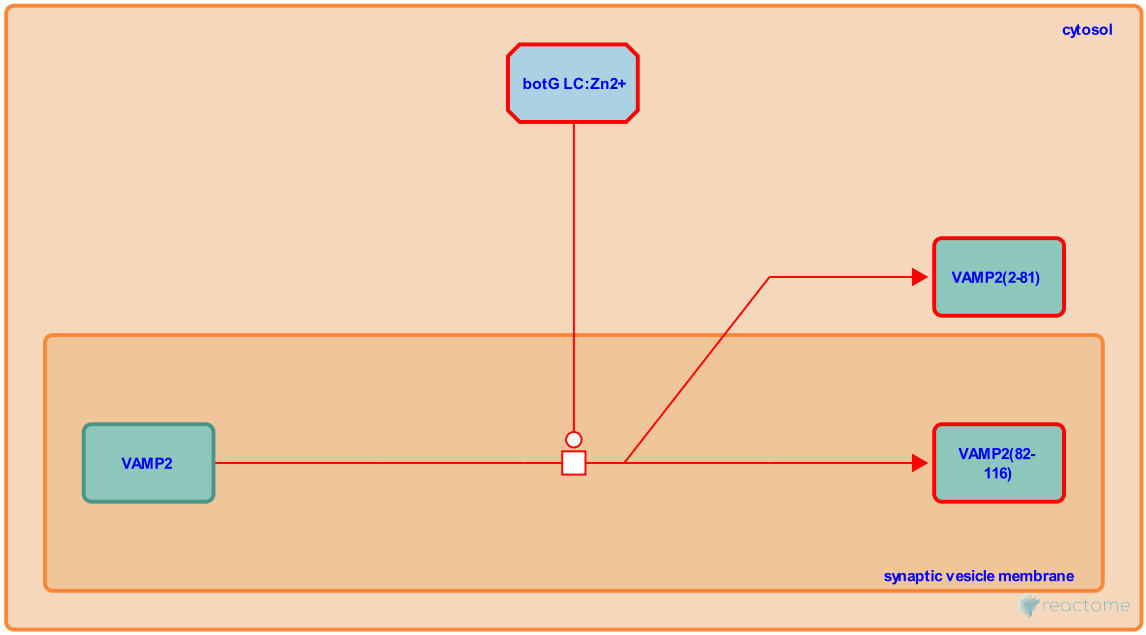
Location: Toxicity of botulinum toxin type G (botG)

Stable identifier: R-HSA-5250962

Type: transition

Compartments: synaptic vesicle membrane, cytosol

Diseases: botulism



Botulinum toxin type G light chain (botG LC), in the cytosol of a target cell, catalyzes the removal of an aminoterminal peptide from vesicle-associated membrane protein 2 (VAMP2). botG LC is a zinc metalloprotease (Schiavo et al. 1994; Yamasaki et al. 1994). VAMP2 is associated with the cytosolic face of the target cell synaptic vesicle and is required for vesicle docking and exocytosis. Its cleavage by botulinum toxin blocks synaptic vesicle fusion with the plasma membrane and neurotransmitter release (Sudhof et al, 1993; Sudhof 2004).

Preceded by: botG HC transports botG LC from target cell synaptic vesicle membrane into cytosol

Literature references

Hayashi, T., Yamasaki, S., Niemann, H., Eklund, M., Szabo, E., Binz, T. et al. (1994). Botulinum neurotoxin type G proteolyses the Ala81-Ala82 bond of rat synaptobrevin 2. *Biochem. Biophys. Res. Commun., 200*, 829-35. ↗

Südhof, TC., Niemann, H., Jahn, R., De Camilli, P. (1993). Membrane fusion machinery: insights from synaptic proteins. *Cell, 75*, 1-4. ↗

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