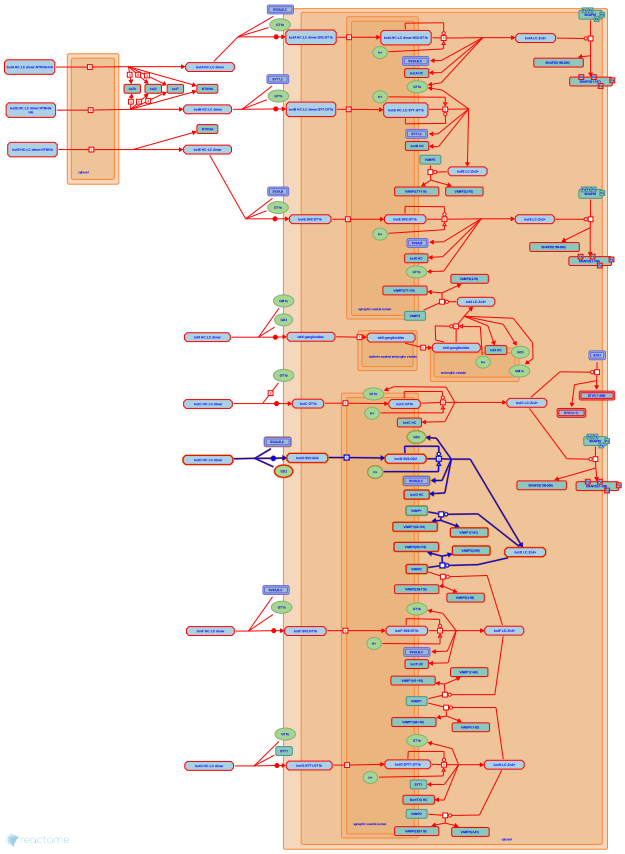
Toxicity of botulinum toxin type D (botD)



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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.
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. ↗

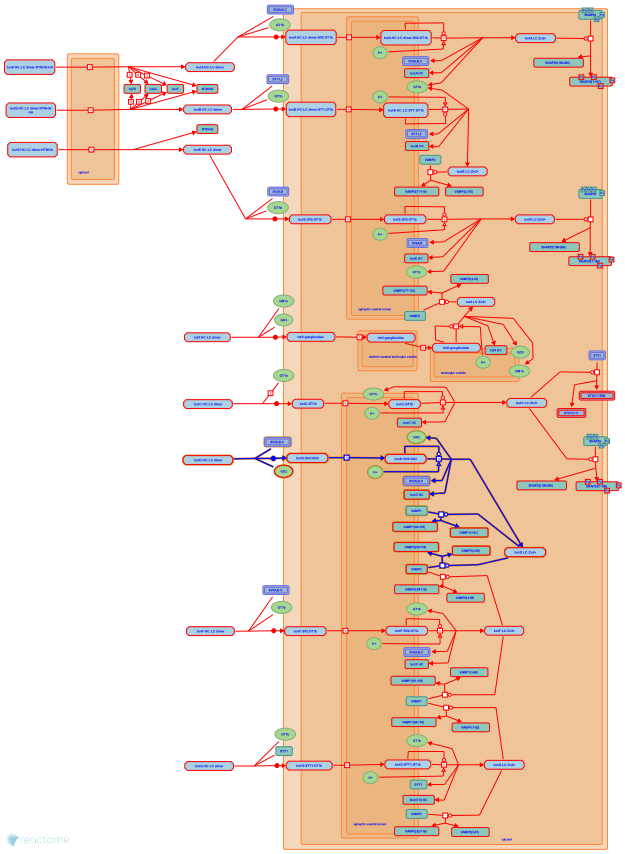
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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 D (botD)

Stable identifier: R-HSA-5250955

Diseases: botulism



Botulinum toxin type D (botD) is only very rarely 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 (Kroken et al. 2011) and synaptic vesicle protein 2 (SV2) (Peng et al. 2011), the bound toxin can enter synaptic vesicles and release its LC moiety into the cytosol of targeted cells (Montal 2010), and the botD 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. 1993; Yamasaki et al. 1994). These four events are annotated here.

Literature references

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

Polverino de Laureto, P., Schiavo, G., DasGupta, BR., Montecucco, C., Rossetto, O., Benfenati, F. et al. (1993). Identification of the nerve terminal targets of botulinum neurotoxin serotypes A, D, and E. *J. Biol. Chem., 268*, 23784-7.

Hatheway, CL. (1995). Botulism: the present status of the disease. *Curr. Top. Microbiol. Immunol., 195*, 55-75.

Barbieri, JT., Kroken, AR., Kim, JJ., Fu, Z., Karalewitz, AP. (2011). Novel ganglioside-mediated entry of botulinum neurotoxin serotype D into neurons. *J. Biol. Chem., 286*, 26828-37.

Tepp, WH., Dong, M., Peng, L., Johnson, EA. (2011). Botulinum neurotoxin D uses synaptic vesicle protein SV2 and gangliosides as receptors. *PLoS Pathog., 7*, e1002008.

Editions

2006-06-15	Authored	Gopinathrao, G., Krupa, S.
2007-08-03	Reviewed	Ichtchenko, K.
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botD HC:LC binds SV2A or B or C and GD2 on the target cell surface ↗

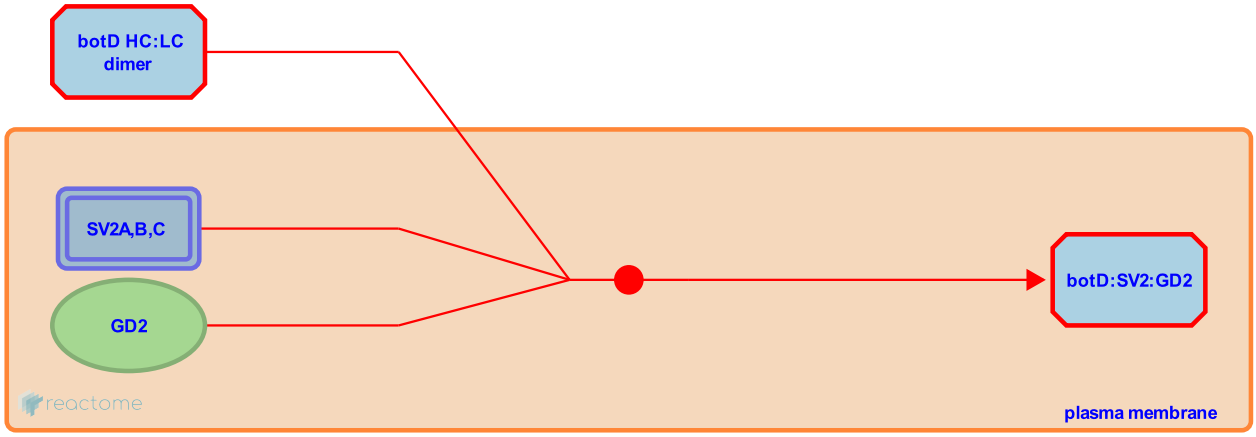
Location: Toxicity of botulinum toxin type D (botD)

Stable identifier: R-HSA-5250607

Type: binding

Compartments: plasma membrane, extracellular region

Diseases: botulism



The botulinum toxin type D disulfide-bonded heavy chain - light chain heterodimer ("dichain") (botD HC:LC, encoded by the C. botulinum botD gene) binds ganglioside GD2 and synaptic vesicle proteins 2A (SV2A), 2B (SV2B), or 2C (SV2C) 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 SV2A, SV2B, or SV2C when those proteins are exposed at the cell surface by exocytosis (Kroken et al. 2011; Peng et al. 2011).

Followed by: botD:SV2:GD2 internalized from target cell plasma membrane to synaptic vesicle membrane

Literature references

Barbieri, JT., Kroken, AR., Kim, JJ., Fu, Z., Karalewitz, AP. (2011). Novel ganglioside-mediated entry of botulinum neurotoxin serotype D into neurons. *J. Biol. Chem., 286*, 26828-37. ↗

Tepp, WH., Dong, M., Peng, L., Johnson, EA. (2011). Botulinum neurotoxin D uses synaptic vesicle protein SV2 and gangliosides as receptors. *PLoS Pathog., 7*, e1002008. ↗

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2006-06-15	Authored	Gopinathrao, G., Krupa, S.
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botD:SV2:GD2 internalized from target cell plasma membrane to synaptic vesicle membrane ↗

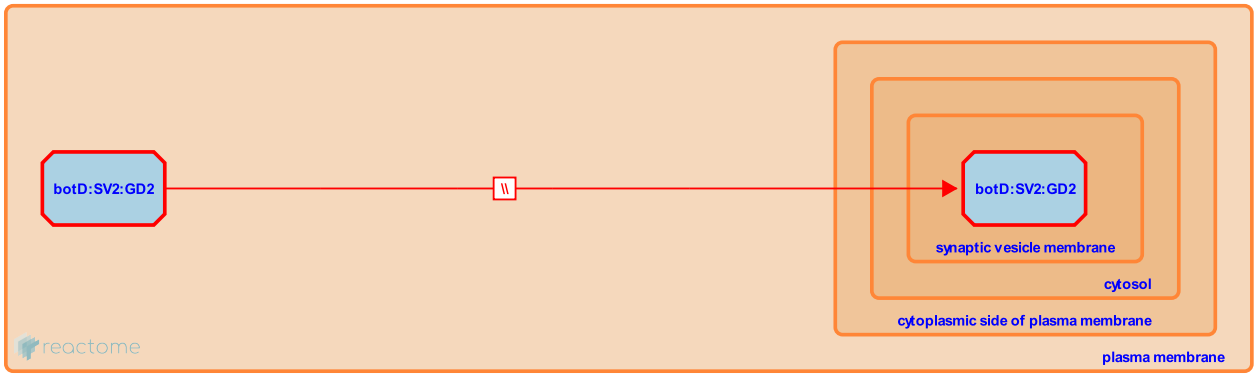
Location: Toxicity of botulinum toxin type D (botD)

Stable identifier: R-HSA-5250600

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 D disulfide-bonded heavy chain - light chain heterodimer (botD HC:LC) bound to ganglioside GD2 and synaptic vesicle protein 2A, 2B, or 2C (SV2A, B, or C) is inferred to be taken up as well, delivering it to the re-formed synaptic vesicle.

Preceded by: botD HC:LC binds SV2A or B or C and GD2 on the target cell surface

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

↗

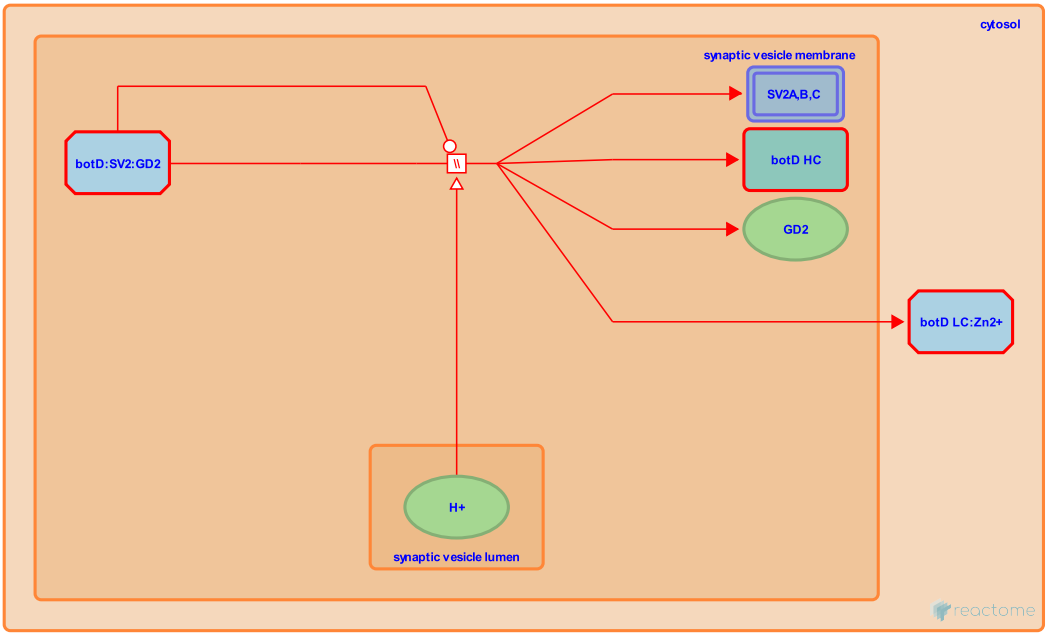
Location: Toxicity of botulinum toxin type D (botD)

Stable identifier: R-HSA-5250616

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 D disulfide-bonded heavy chain - light chain dimer (botD 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 where the HC - LC disulfide bond is cleaved.

Preceded by: botD:SV2:GD2 internalized from target cell plasma membrane to synaptic vesicle membrane

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

Literature references

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

Koriazova, LK., Montal, M. (2003). Translocation of botulinum neurotoxin light chain protease through the heavy chain channel. *Nat Struct Biol, 10*, 13-8. ↗

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2006-06-15	Authored	Gopinathrao, G., Krupa, S.
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botD LC cleaves target cell VAMP1 ↗

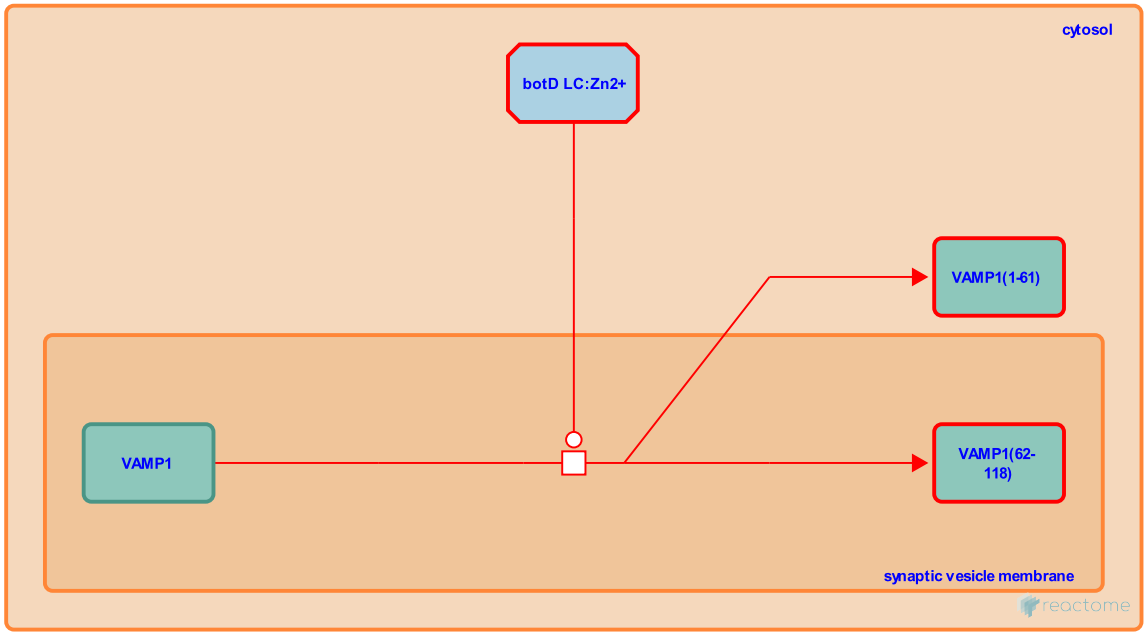
Location: Toxicity of botulinum toxin type D (botD)

Stable identifier: R-HSA-194809

Type: transition

Compartments: synaptic vesicle membrane, cytosol

Diseases: botulism



Botulinum toxin type D light chain (botD LC), in the cytosol of a target cell, catalyzes the removal of an aminoterminal peptide from vesicle-associated membrane protein 1 (VAMP1). botD LC is a zinc metalloprotease (Arndt et al. 2006; Schiavo et al. 1993; 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: botD HC transports botD LC from target cell synaptic vesicle membrane into cytosol

Literature references

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

Polverino de Laureto, P., Schiavo, G., DasGupta, BR., Montecucco, C., Rossetto, O., Benfenati, F. et al. (1993). Identification of the nerve terminal targets of botulinum neurotoxin serotypes A, D, and E. *J. Biol. Chem., 268*, 23784-7. ↗

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

Arndt, JW., Christian, T., Stevens, RC., Chai, Q. (2006). Structure of botulinum neurotoxin type D light chain at 1.65 A resolution: repercussions for VAMP-2 substrate specificity. *Biochemistry, 45*, 3255-62. ↗

Fykse, EM., Südhof, TC., Roques, B., Link, E., Yamasaki, S., Baumeister, A. et al. (1994). Cleavage of members of the synaptobrevin/VAMP family by types D and F botulinal neurotoxins and tetanus toxin. *J Biol Chem, 269*, 12764-72. ↗

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botD LC cleaves target cell VAMP2 ↗

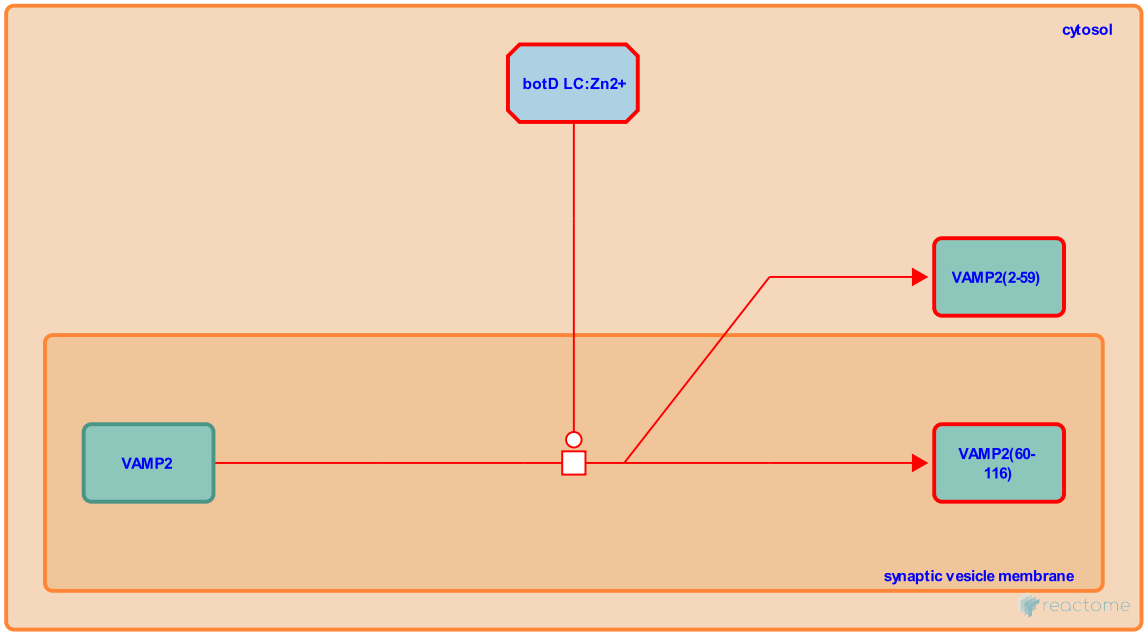
Location: Toxicity of botulinum toxin type D (botD)

Stable identifier: R-HSA-5250606

Type: transition

Compartments: synaptic vesicle membrane, cytosol

Diseases: botulism



Botulinum toxin type D light chain (botD LC), in the cytosol of a target cell, catalyzes the removal of an aminoterminal peptide from vesicle-associated membrane protein 2 (VAMP2). botD LC is a zinc metalloprotease (Arndt et al. 2006; Schiavo et al. 1993; 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: botD HC transports botD LC from target cell synaptic vesicle membrane into cytosol

Literature references

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

Polverino de Laureto, P., Schiavo, G., DasGupta, BR., Montecucco, C., Rossetto, O., Benfenati, F. et al. (1993). Identification of the nerve terminal targets of botulinum neurotoxin serotypes A, D, and E. *J. Biol. Chem., 268*, 23784-7. ↗

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