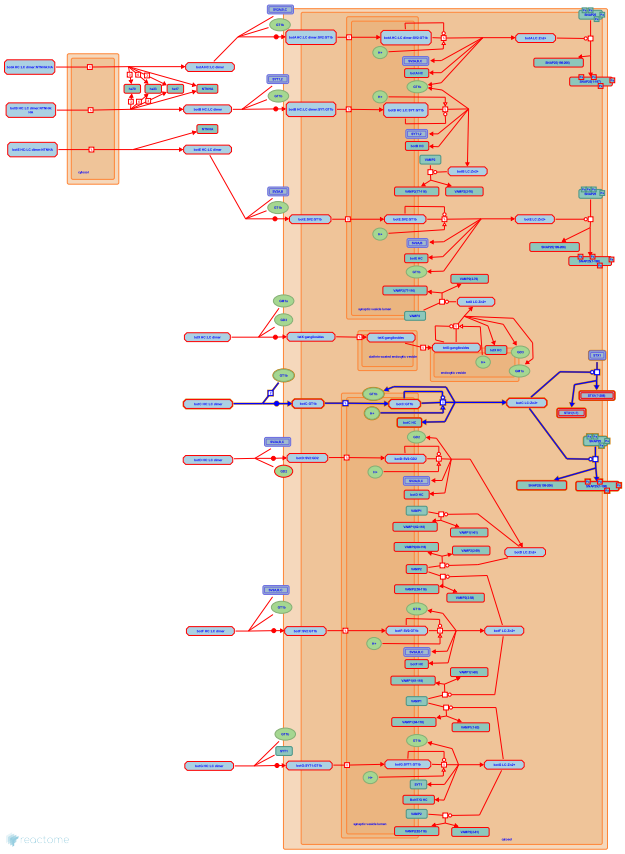
Toxicity of botulinum toxin type C (botC)



D'Eustachio, P., Gopinathrao, G., Ichtchenko, K., Krupa, S., Sharma, S., Thirunavukkarasu, N.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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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. ↗

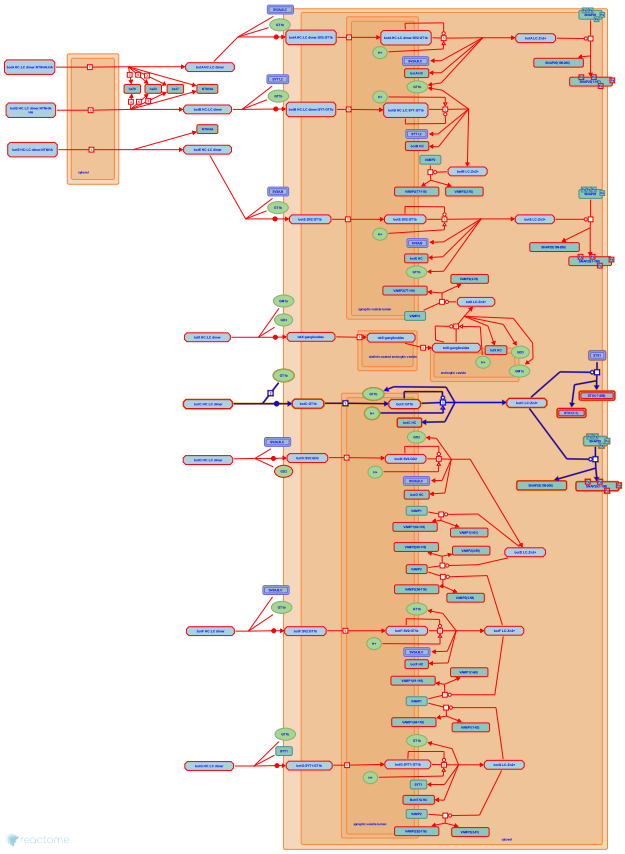
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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 C (botC)

Stable identifier: R-HSA-5250971

Diseases: botulism



Botulinum toxin type C (botC, also known as BoNT/C) 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 gangliosides (Karalewitz et al. 2012), the bound toxin can enter synaptic vesicles and release its LC moiety into the cytosol of targeted cells (Montal 2010), and the botC LC can cleave synaptosomal associated protein 25 (SNAP25) and syntaxin 1 (STX1) on the cytosolic face of the neuronal plasma membrane (Foran et al. 1996). These four events are annotated here.

Literature references

Baldwin, MR., Barbieri, JT., Kim, JJ., Fu, Z., Karalewitz, AP. (2012). Botulinum neurotoxin serotype C associates with dual ganglioside receptors to facilitate cell entry. *J. Biol. Chem., 287*, 40806-16.

Shone, CC., Lawrence, GW., Foster, KA., Foran, P., Dolly, JO. (1996). Botulinum neurotoxin C1 cleaves both syntaxin and SNAP-25 in intact and permeabilized chromaffin cells: correlation with its blockade of catecholamine release . *Biochemistry, 35*, 2630-6.

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

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

Editions

2006-06-15	Authored	Gopinathrao, G., Krupa, S.
2007-08-03	Reviewed	Ichtchenko, K.
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botC HC:LC binds GT1b on the target cell surface ↗

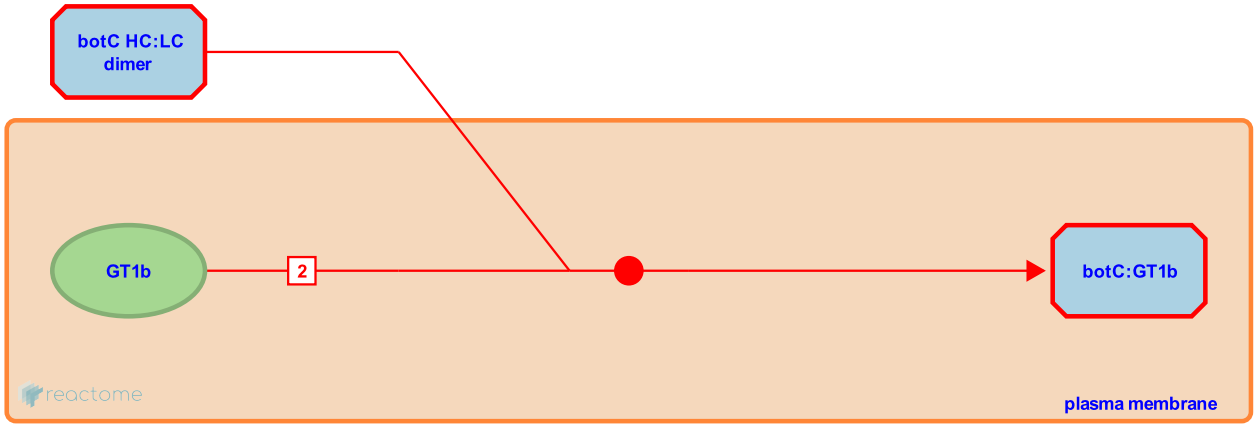
Location: Toxicity of botulinum toxin type C (botC)

Stable identifier: R-HSA-5246506

Type: binding

Compartments: plasma membrane, extracellular region

Diseases: botulism



The botulinum toxin type C disulfide-bonded heavy chain - light chain heterodimer (“dichain”) (botC HC:LC, encoded by the C. botulinum botC1 gene) binds two molecules of GT1b ganglioside on the plasma membrane of a human target cell (Karalewitz et al. 2012).

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

Literature references

Baldwin, MR., Barbieri, JT., Kim, JJ., Fu, Z., Karalewitz, AP. (2012). Botulinum neurotoxin serotype C associates with dual ganglioside receptors to facilitate cell entry. *J. Biol. Chem., 287*, 40806-16. ↗

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

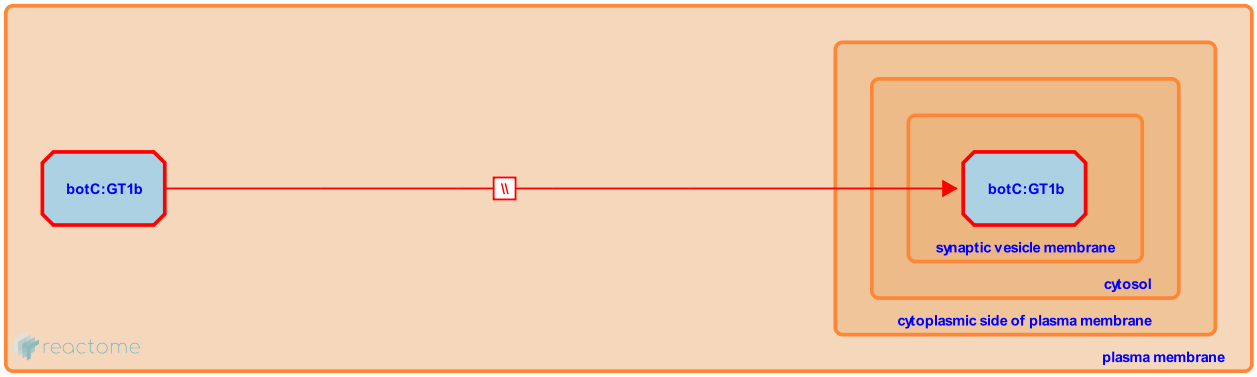
Location: Toxicity of botulinum toxin type C (botC)

Stable identifier: R-HSA-5246509

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 C disulfide-bonded heavy chain - light chain heterodimer (botC HC:LC) bound to ganglioside GT1b is inferred to be taken up as well, delivering it to the re-formed synaptic vesicle.

Preceded by: botC HC:LC binds GT1b on the target cell surface

Followed by: botC HC transports botC LC from target cell synaptic vesicle membrane to 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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botC HC transports botC LC from target cell synaptic vesicle membrane to cytosol ↗

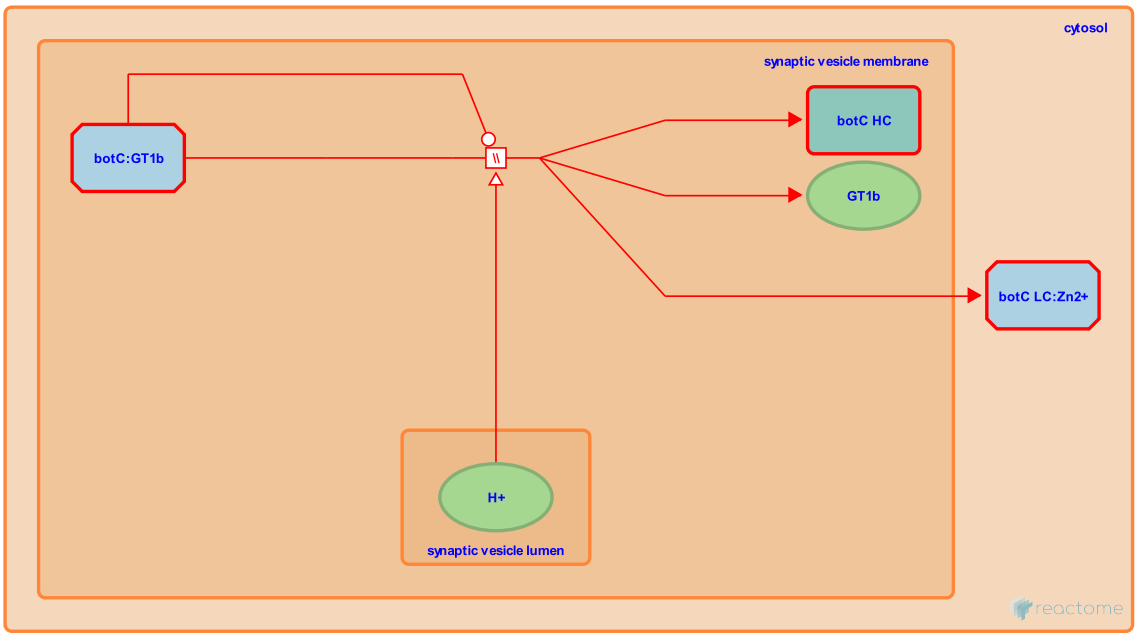
Location: Toxicity of botulinum toxin type C (botC)

Stable identifier: R-HSA-5246514

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 C disulfide-bonded heavy chain - light chain dimer (botC 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: botC:GT1b internalized from target cell plasma membrane to synaptic vesicle membrane

Followed by: botC LC cleaves target cell STX1, botC LC cleaves target cell SNAP25

Literature references

Tepp, WH., Chapman, ER., Sun, S., Johnson, EA. (2012). Botulinum neurotoxins B and E translocate at different rates and exhibit divergent responses to GT1b and low pH. *Biochemistry, 51*, 5655-62. ↗

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. ↗

Editions

2006-06-15	Authored	Gopinathrao, G., Krupa, S.
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botC LC cleaves target cell STX1 ↗

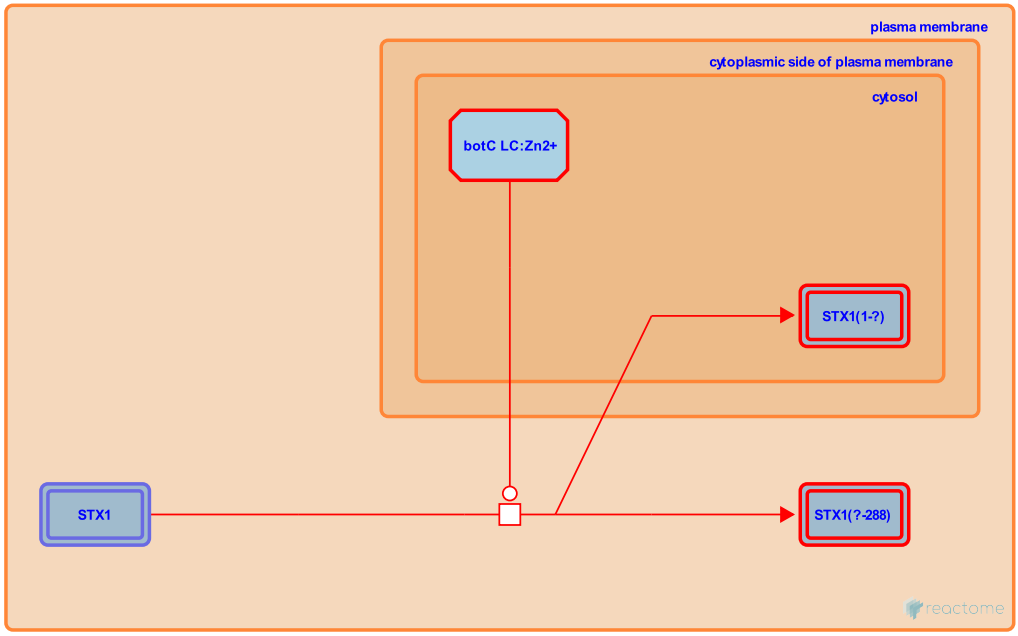
Location: Toxicity of botulinum toxin type C (botC)

Stable identifier: R-HSA-181567

Type: transition

Compartments: plasma membrane, cytosol

Diseases: botulism



Botulinum toxin type C light chain (botC LC), in the cytosol of a target cell, catalyzes the removal of an aminoterminal peptide from syntaxin 1 (STX1). botC LC is a zinc metalloprotease (Blasi et al. 1993; Foran et al. 1994). STX1 is associated with the cytosolic face of the target cell plasma membrane where it forms part of a complex required for synaptic 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: botC HC transports botC LC from target cell synaptic vesicle membrane to cytosol

Literature references

Shone, CC., Lawrence, GW., Foster, KA., Foran, P., Dolly, JO. (1996). Botulinum neurotoxin C1 cleaves both syntaxin and SNAP-25 in intact and permeabilized chromaffin cells: correlation with its blockade of catecholamine release . *Biochemistry, 35*, 2630-6. ↗

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

Chapman, ER., Yamasaki, S., Niemann, H., Binz, T., Jahn, R., Blasi, J. (1993). Botulinum neurotoxin C1 blocks neurotransmitter release by means of cleaving HPC-1/syntaxin. *EMBO J., 12*, 4821-8. ↗

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

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2006-06-15	Authored	Gopinathrao, G., Krupa, S.
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botC LC cleaves target cell SNAP25 ↗

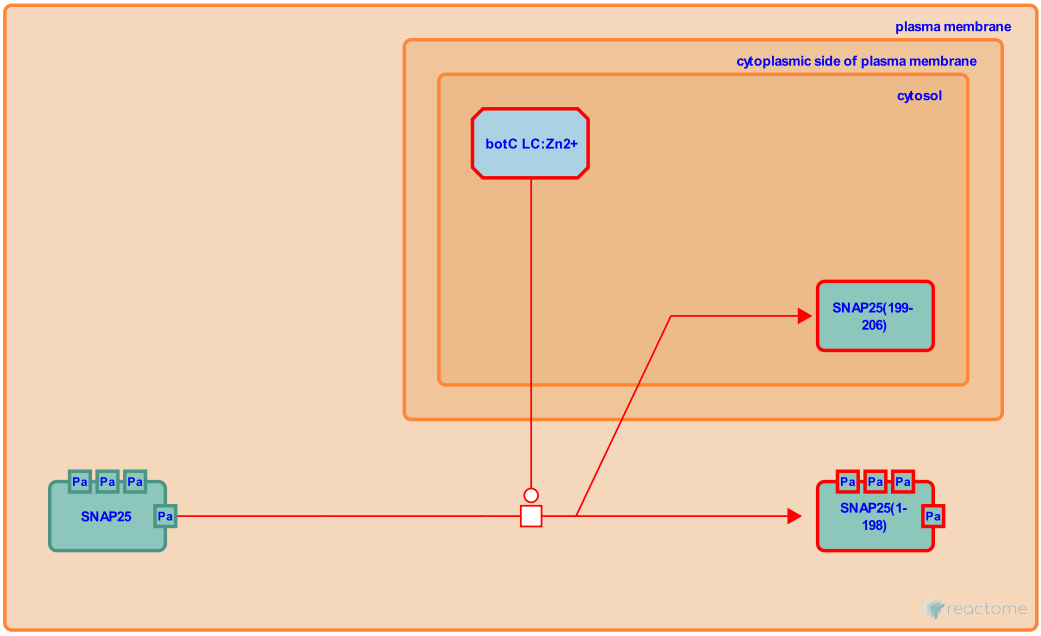
Location: Toxicity of botulinum toxin type C (botC)

Stable identifier: R-HSA-194793

Type: transition

Compartments: plasma membrane, cytosol

Diseases: botulism



Botulinum toxin type C light chain (botC LC), in the cytosol of a target cell, catalyzes the removal of a carboxyterminal peptide from synaptosomal associated protein 25 (SNAP25). botC LC is a zinc metalloprotease (Foran et al. 1994; Vaidyanathan et al. 1999). SNAP25 is associated with the cytosolic face of the target cell plasma membrane where it forms part of a complex required for synaptic 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: botC HC transports botC LC from target cell synaptic vesicle membrane to cytosol

Literature references

Shone, CC., Lawrence, GW., Foster, KA., Foran, P., Dolly, JO. (1996). Botulinum neurotoxin C1 cleaves both syntaxin and SNAP-25 in intact and permeabilized chromaffin cells: correlation with its blockade of catecholamine release . *Biochemistry, 35*, 2630-6. ↗

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

Niemann, H., Nauenburg, S., Dorries, C., Binz, T., Jahnz, M., Bade, S. et al. (1999). Proteolysis of SNAP-25 isoforms by botulinum neurotoxin types A, C, and E: domains and amino acid residues controlling the formation of enzyme-substrate complexes and cleavage. *J Neurochem, 72*, 327-37. ↗

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

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2014-02-11	Revised	D'Eustachio, P.
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