Toxicity of botulinum toxin type E

(BoNT/E)

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


Reactome database release: 70

This document contains 1 pathway and 5 reactions (see Table of Contents)
Toxicity of botulinum toxin type E (BoNT/E)

Stable identifier: R-HSA-5250992

Diseases: botulism

Botulinum toxin type E (BoNT/E), a disulfide-bonded heavy chain (HC) - light chain (LC) heterodimer (“-dichain”), enters the gut typically as a result of consuming contaminated food (Hatheway 1995), as a complex with nontoxic nonhemagglutinin protein (NTNHA, encoded by the C. botulinum ntnha gene) (Benefield et al. 2013). The complex protects the toxin from degradation in the gut and mediates its association with the gut epithelium and transcytosis to enter the circulation (Fujinaga et al. 2013). Circulating toxin molecules associate with gangliosides and synaptic vesicle protein 2 (SV2) exposed by exocytosis at a synapse of a target neuron (Dong et al. 2008; Yowler & Schengrund 2004). Vesicle recycling brings the toxin into the neuron where the vesicle is acidified (Sudhoff 2004). The lowered pH induces a conformational change in the toxin: its HC forms a passage in the vesicle membrane through which its LC is extruded into the neuronal cytosol and released by reduction of the HC - LC disulfide bond (Montal 2010). The LC then catalyzes the cleavage of synaptosome-associated protein 25 (SNAP25) on the cytosolic face of the neuronal plasma membrane (Binz et al. 1994; Schiavo et al. 1993), thereby inhibiting synaptic vesicle fusion with the plasma membrane and exocytosis.

Literature references


**Editions**

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Transcytosis and dissociation of BoNT/E:NTNHA

**Location:** Toxicity of botulinum toxin type E (BoNT/E)

**Stable identifier:** R-HSA-5228941

**Type:** omitted

**Compartments:** extracellular region

**Diseases:** botulism

The bacterial BoNT/E:NTNHA complex, consisting of a Botulinum toxin type E (BoNT/E) disulfide bonded heavy chain (HC) - light chain (LC) heterodimer (“dichain”) associated with nontoxic nonhemagglutinin protein (NTNHA) (Benefield et al. 2013), associates with the plasma membrane of a human cell (in vivo, the apical surface of a gut epithelial cell) and undergoes transcytosis. While the molecular details of transcytosis remain to be established definitively, the process enables the toxin heterodimer to cross the epithelial cell layer and enter the circulation (Fujinaga et al. 2013; Simpson 2004).

**Followed by:** BoNT/E HC:LC binds SV2A or B and GT1b on the target cell surface

**Literature references**


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BoNT/E HC:LC binds SV2A or B and GT1b on the target cell surface

**Location:** Toxicity of botulinum toxin type E (BoNT/E)

**Stable identifier:** R-HSA-5244503

**Type:** binding

**Compartments:** extracellular region, plasma membrane

**Diseases:** botulism

The Botulinum toxin type E disulfide bonded heavy chain - light chain heterodimer (BoNT/E HC:LC, encoded by the C. botulinum botE gene) (Kumaran et al. 2009) binds ganglioside GT1b and synaptic vesicle protein 2A (SV2A) or 2B (SV2B) 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 or B when those proteins are exposed at the cell surface by exocytosis (Dong et al. 2008; Rummel et al. 2009).

**Preceded by:** Transcytosis and dissociation of BoNT/E:NTNHA

**Followed by:** BoNT/E:SV2:GT1b internalized from target cell plasma membrane to synaptic vesicle membrane

**Literature references**


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BoNT/E:SV2:GT1b internalized from target cell plasma membrane to synaptic vesicle membrane

**Location:** Toxicity of botulinum toxin type E (BoNT/E)

**Stable identifier:** R-HSA-5244500

**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 E disulfide bonded heavy chain - light chain heterodimer (BoNT/E HC:LC) bound to ganglioside GT1b and synaptic vesicle protein 2A (SV2A) or 2B (SV2B) is inferred to be taken up as well, delivering it to the re-formed synaptic vesicle.

**Preceded by:** BoNT/E HC:LC binds SV2A or B and GT1b on the target cell surface

**Followed by:** BoNT/E HC transports BoNT/E LC from target cell synaptic vesicle membrane into cytosol

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BoNT/E HC transports BoNT/E LC from target cell synaptic vesicle membrane into cytosol

**Location:** Toxicity of botulinum toxin type E (BoNT/E)

**Stable identifier:** R-HSA-5244506

**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 E disulfide bonded heavy chain - light chain dimer (BoNT/E 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:** BoNT/E:SV2:GT1b internalized from target cell plasma membrane to synaptic vesicle membrane

**Followed by:** BoNT/E LC cleaves target cell SNAP25

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BoNT/E LC cleaves target cell SNAP25

**Location:** Toxicity of botulinum toxin type E (BoNT/E)

**Stable identifier:** R-HSA-194800

**Type:** transition

**Compartments:** cytosol, plasma membrane

**Diseases:** botulism

Botulinum toxin type E light chain (BoNT/E LC), in the cytosol of a target cell, catalyzes the removal of a carboxyterminal peptide from synaptosomal-associated protein 25 (SNAP25). BoNT/E LC is a zinc metalloprotease (Binz et al. 1994; Schiavo et al. 1993; 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 and in vivo leads to a long lasting flaccid paralysis (Sudhof et al, 1993; Sudhof 2004).

**Preceded by:** BoNT/E HC transports BoNT/E LC from target cell synaptic vesicle membrane into cytosol

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