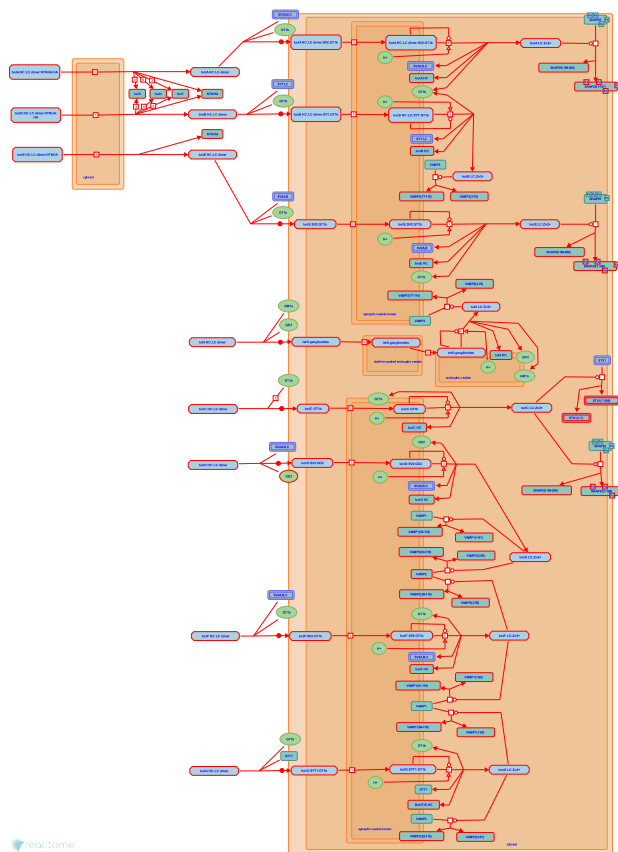


# Neurotoxicity of clostridium toxins



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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](https://reactome.org/page/about-us).

25/10/2024

## 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.

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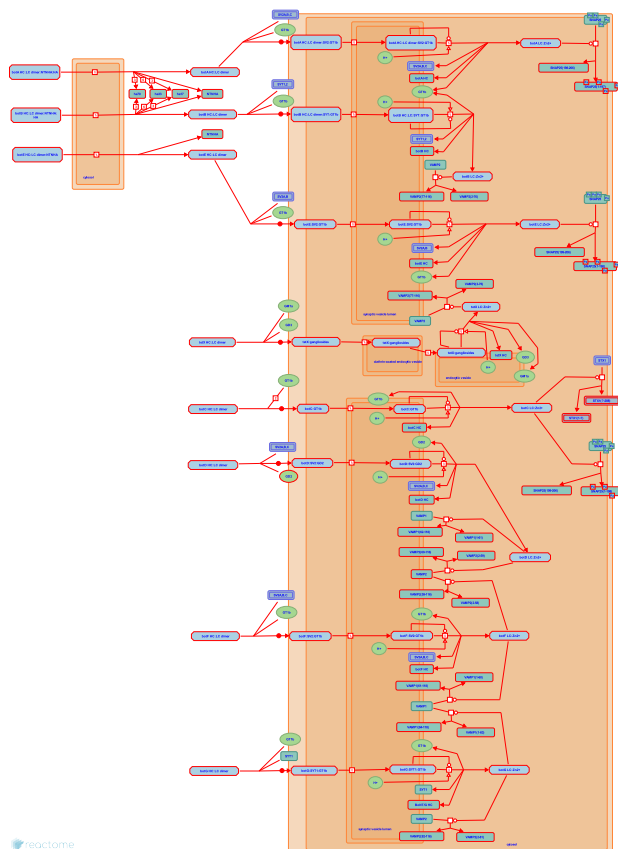
Reactome database release: 90

This document contains 9 pathways ([see Table of Contents](#))

## Neurotoxicity of clostridium toxins ↗

**Stable identifier:** R-HSA-168799

**Diseases:** tetanus, botulism



Clostridial neurotoxins, when taken up by human neurons, block synaptic transmission by cleaving proteins required for the fusion of synaptic vesicles with the plasma membrane. They are remarkably efficient so that very small doses cause paralysis of an affected person (Lalli et al. 2003; Turton et al. 2002). All characterized clostridial neurotoxins are synthesized as products of chromosomal, plasmid or prophage-borne bacterial genes. The nascent toxin may be cleaved into light (LC) and heavy (HC) chain moieties that remain attached by noncovalent interactions and a disulfide bond (Turton et al. 2002).

Strains of *Clostridium botulinum* produce seven serologically distinct toxins, BoNT/A, B, C, D, E, F, and G. An eighth toxin, BoNT/H has recently been identified (Barash & Arnon 2014) but its molecular properties have not yet been described. Human poisoning most commonly result from ingestion of toxin contaminated food. More rarely, it is due to wound infection or clostridial colonization of the gut of an infant whose own gut flora have not yet developed or of an older individual whose flora have been suppressed. While all seven characterized toxins can cleave human target proteins, three, BoNT/A, B, and E, are most commonly associated with human disease (Hatheway 1995; Sakaguchi 1982). BoNT/F is also able to cause human botulism.

Once ingested, the botulinum toxin must be taken up from the gut lumen into the circulation, a process mediated by four accessory proteins. These proteins form a complex that mediates transcytosis of the toxin molecule across the gut epithelium, allowing its entry into the circulation. The accessory proteins produced by different *C. botulinum* strains differ in their affinities for polarized epithelia of different species (e.g., human versus canine), and may thus be a key factor in human susceptibility to the toxins of strains A, B, and E and resistance to the others (Simpson 2004).

*Clostridium tetani* produces TeNT toxin. Human poisoning is the result of toxin secretion by bacteria growing in an infected wound and the toxin is released directly into the circulation.

Circulating clostridial toxins are taken up by neurons at neuromuscular junctions. They bind to specific gangliosides (BoNT/C, TeNT) or to both gangliosides and synaptic vesicle proteins (BoNT/A, B, D G) exposed on the neuronal plasma membrane during vesicle exocytosis (Montal 2010). All seven characterized forms of BoNT are thought to be taken up into synaptic vesicles as these re-form at the neuromuscular junction. These vesicles remain close to the site of uptake and are rapidly re-loaded with neurotransmitter and acidified (Sudhoff 2004). TeNT, in contrast, is

taken up into clathrin coated vesicles that reach the neuron cell body by retrograde transport and then possibly other neurons before undergoing acidification. Vesicle acidification causes a conformational change in the toxin, allowing its HC part to function as a channel through which its LC part is extruded into the neuronal cytosol. The HC - LC disulfide bond is cleaved and the cytosolic LC functions as a zinc metalloprotease to cleave specific bonds in proteins on the cytosolic faces of synaptic vesicles and plasma membranes that normally mediate exocytosis (Lalli et al. 2003; Montal 2010).

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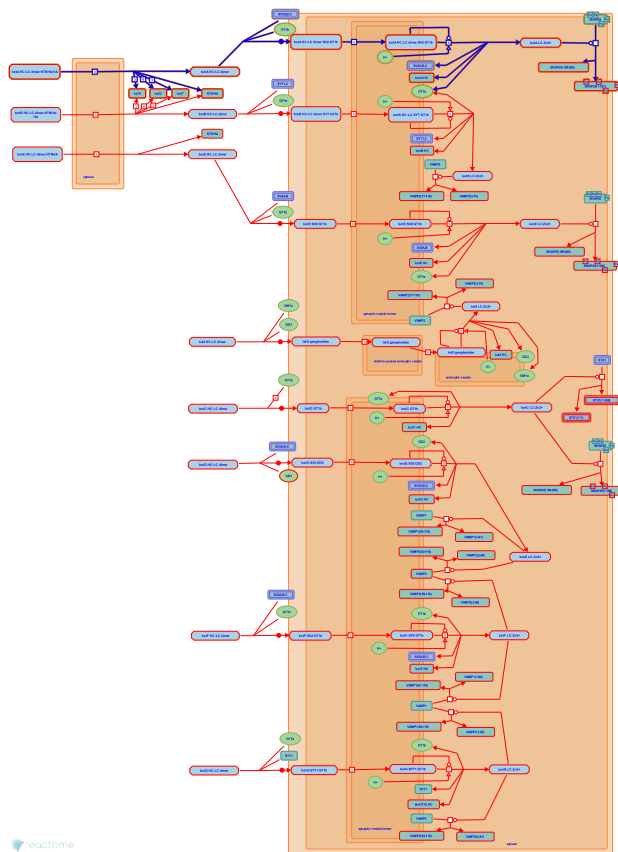
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## Toxicity of botulinum toxin type A (botA) ↗

**Location:** [Neurotoxicity of clostridium toxins](#)

**Stable identifier:** R-HSA-5250968

**Diseases:** botulism



Botulinum toxin type A (botA, also known as BoNT/A), 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) and multiple copies of three hemagglutinin proteins (HA, encoded by the *C. botulinum ha17*, *ha34*, and *ha70* genes) (Lee 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. Recent studies in vitro raise the possibility that the toxin may also directly disrupt the basolateral membrane of the gut epithelium (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 in the neuromuscular junction (Yowler & Schengrund 2004; Dong et al. 2006). 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 cytosolic LC then catalyzes the cleavage of synaptosomal 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.

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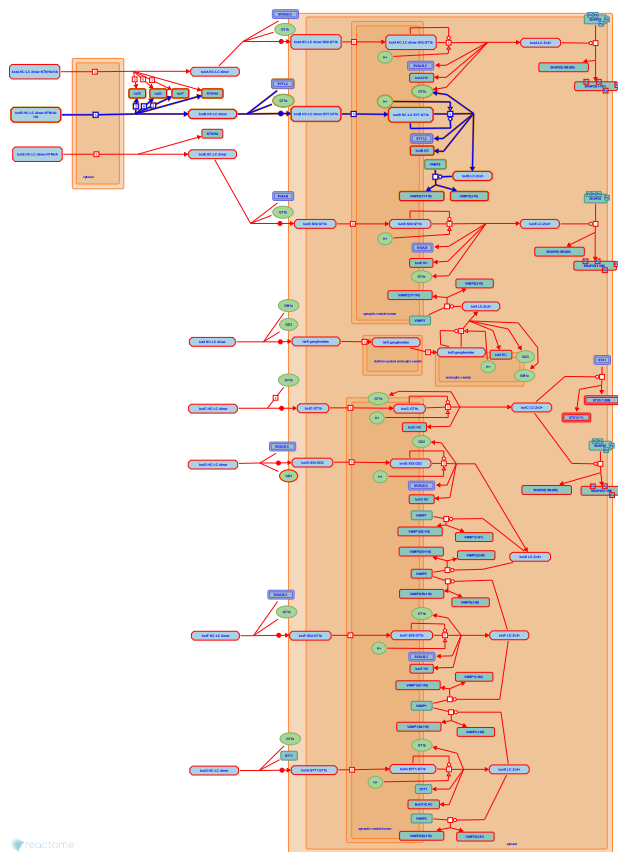
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## Toxicity of botulinum toxin type B (botB) ↗

**Location:** [Neurotoxicity of clostridium toxins](#)

**Stable identifier:** R-HSA-5250958

**Diseases:** botulism



Botulinum toxin type B (botB, also known as BoNT/B), a disulfide-bonded heavy chain (HC) - light chain (LC) heterodimer, 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) and multiple copies of three hemagglutinin proteins (HA, encoded by the *C. botulinum* *ha17*, *ha34*, and *ha70* genes) (Amatsu 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 synaptotagmin (SYT) proteins exposed by exocytosis at a synapse of a target neuron (Dong et al. 2003; 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. The HC - LC disulfide bond is reduced (Montal 2010). The LC then catalyzes the cleavage of vesicle-associated membrane protein 2 (VAMP2) on the cytosolic face of synaptic vesicle membranes (Foran et al. 1994; Schiavo et al. 1992), thereby inhibiting synaptic vesicle fusion with the plasma membrane and exocytosis.

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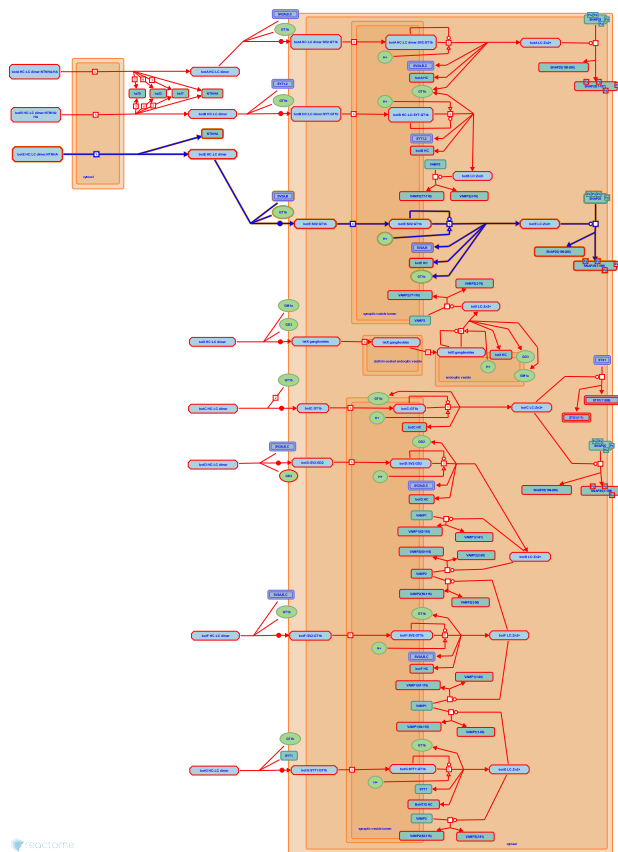
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## Toxicity of botulinum toxin type E (botE) ↗

**Location:** [Neurotoxicity of clostridium toxins](#)

**Stable identifier:** R-HSA-5250992

**Diseases:** botulism



Botulinum toxin type E (botE, also known as 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.

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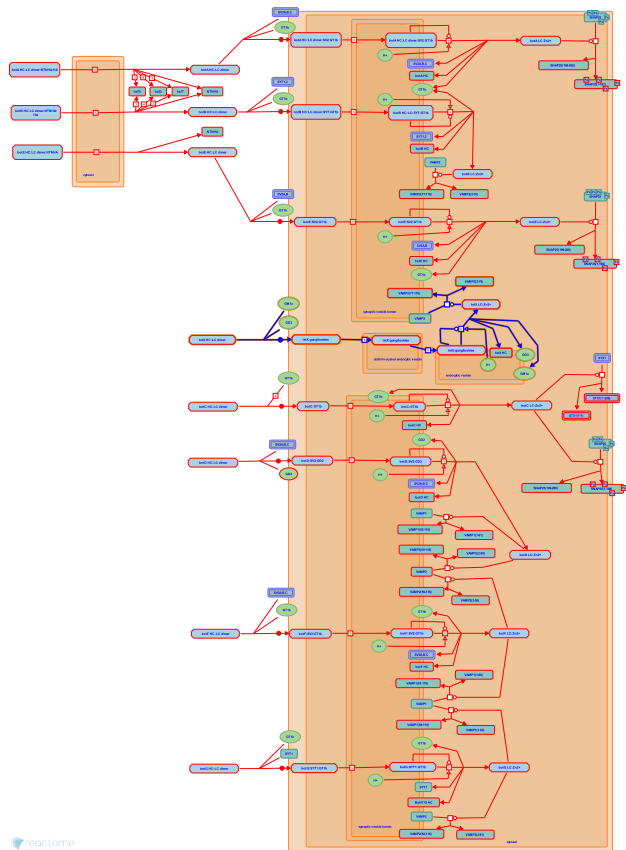
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**Toxicity of tetanus toxin (tetX)**

**Location:** [Neurotoxicity of clostridium toxins](#)

**Stable identifier:** R-HSA-5250982

**Diseases:** tetanus



Tetanus toxin (tetX, also known as TeNT), a disulfide-bonded heavy chain (HC) - light chain (LC) dimer, is secreted from bacteria growing in an infected wound directly into the circulation. Circulating toxin molecules associate with gangliosides at a synapse of a target neuron. The toxin is taken up into clathrin-coated vesicles that reach the neuron cell body by retrograde transport and then possibly other neurons before undergoing acidification. Vesicle acidification causes a conformational change in the toxin, allowing its HC part to function as a channel through which its LC part is extruded into the neuronal cytosol. Cleavage of the HC - LC disulfide bond releases the LC into the cytosol, where it functions as a zinc metalloprotease to cleave vesicle-associated membrane protein 2 (VAMP2), thereby blocking synaptic vesicle exocytosis (Lalli et al. 2003).

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Verastegui, C., Schiavo, G., Lalli, G., Deinhardt, K., Bohnert, S. (2003). The journey of tetanus and botulinum neurotoxins in neurons. *Trends Microbiol*, 11, 431-7. [↗](#)

**Editions**

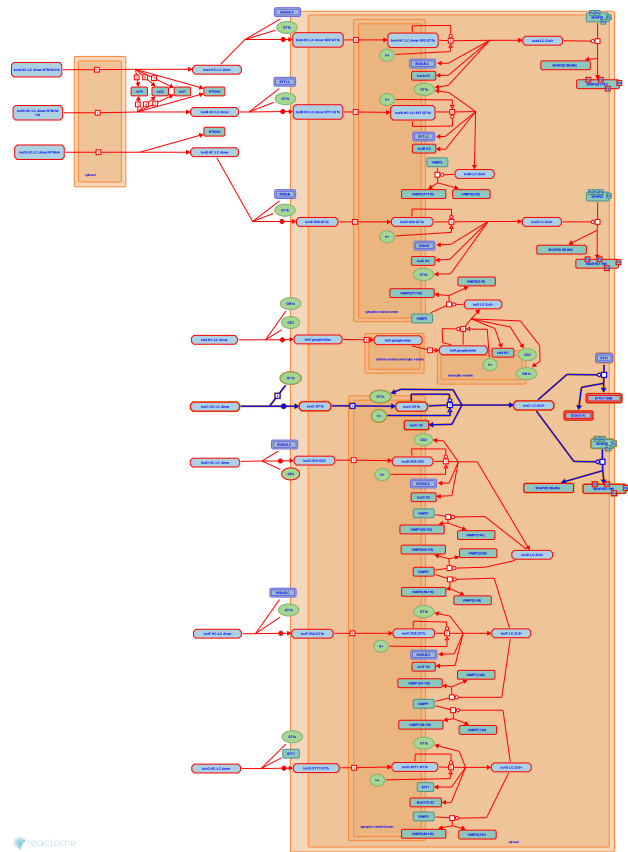
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**Toxicity of botulinum toxin type C (botC)**

**Location:** [Neurotoxicity of clostridium toxins](#)

**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.

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**Editions**

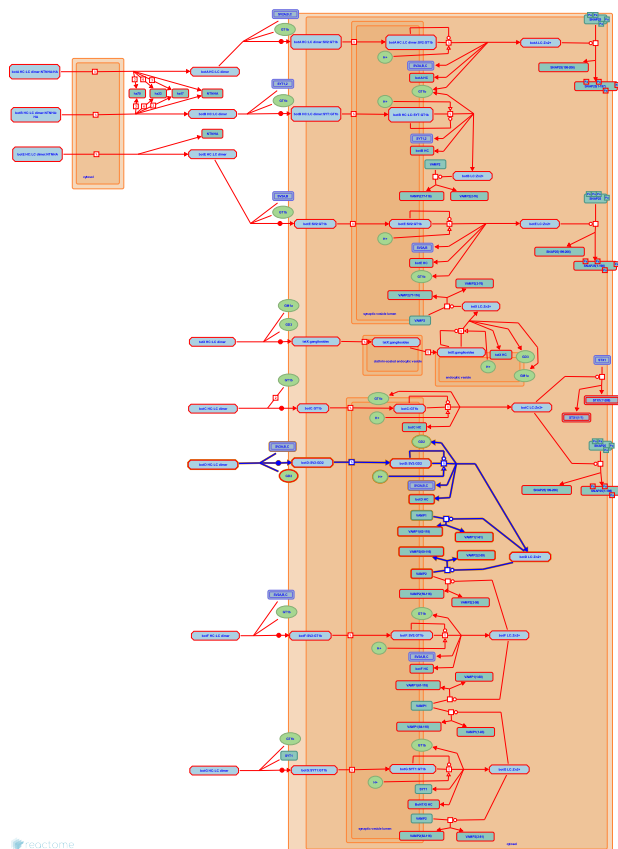
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## Toxicity of botulinum toxin type D (botD) ↗

**Location:** [Neurotoxicity of clostridium toxins](#)

**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.

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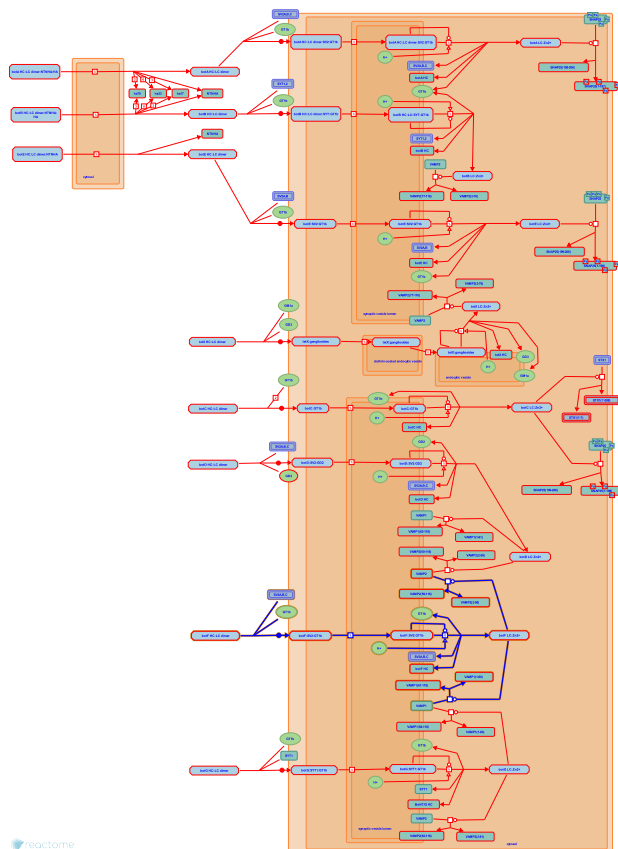
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## Toxicity of botulinum toxin type F (botF) ↗

**Location:** [Neurotoxicity of clostridium toxins](#)

**Stable identifier:** R-HSA-5250981

**Diseases:** botulism



Botulinum toxin type F (botF) 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 and synaptic vesicle protein 2 (SV2) (Fu et al. 2009; Rummel et al. 2009), the bound toxin can enter synaptic vesicles and release its LC moiety into the cytosol of targeted cells (Montal 2010), and the botF LC can cleave vesicle-associated membrane proteins 1 and 2 (VAMP1 and 2) on the cytosolic face of the synaptic vesicle membrane (Yamasaki et al. 1994). These four events are annotated here.

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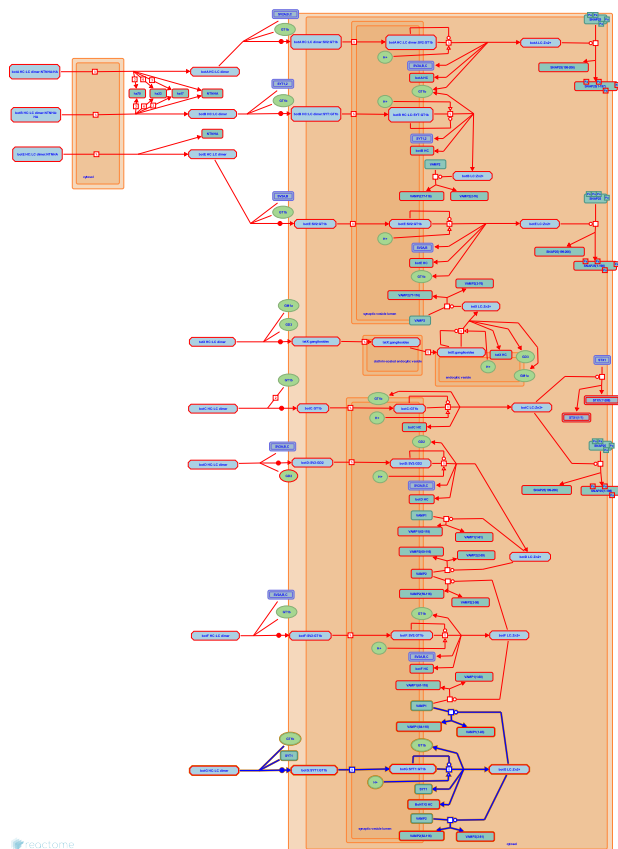
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## Toxicity of botulinum toxin type G (botG) ↗

**Location:** [Neurotoxicity of clostridium toxins](#)

**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.

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