1. INTRODUCTION

Botulinum neurotoxin type A (BoNT/A) is a potent neurotoxin, causing muscle paralysis in the host by blocking the release of the neurotransmitter, acetylcholine, from motor neurons associated with skeletal muscle. Despite this toxicity, BoNT/A is used pharmaceutically as a treatment for numerous neurological diseases, such as migraines and dystonias, and as an anti-wrinkle agent in cosmetic surgery. BoNT/A is one of several serotypes of botulinum (A-G), which, along with tetanus toxin, are produced by several species of Clostridium. While the use of BoNT as a therapeutic agent is promising for treating various conditions, adverse side effects have prompted researchers to investigate the use of alternative serotypes, such as BoNT/B2, for clinical treatment. The Brookfield Academy SMART STUDENTS Model (A Research Topic) Team students modeled BoNT/A by using 3D printing technology, highlighting amino acid residues associated with protein activity in the catalytic domain, and observing GT1b and SV2 interactions within the synaptic vesicle (Figure 1). This model is meant to help understand and communicate structure/function relationships of BoNT/A and promote potentially therapeutic uses of the toxin.

2. MECHANISM OF BoNT TOXICITY IS A MULTI-STEP PROCESS

BoNT lethality is due to the toxin's ability to cleave and disable a SNAPRE. This SNAPRE protein is responsible for synaptic vesicle fusion, and in processes such as muscle contraction, fission allows essential neurotransmitters such as acetylcholine (ACh) to be released. Since ACh release is inhibited, resulting in flaccid muscle paralysis.

3. Binding: First, BoNT/A binds to presynaptic nerve endings through interactions of the receptor-binding domain with the ganglioside, GT1b, and the protein co-receptor, SV2. SV2 is a synaptic protein that binds to the neurotoxin, causing the exocytotic process to become inverted, creating an endosome-like vesicle, releasing neurotransmitter into the synaptic cleft. BoNT/A then enters the neuron by receptor-mediated endocytosis.

4. Translocation: Following endocytosis, the synaptic vesicles acidify, allowing for neurotransmitter uptake, which triggers the translocation domain to insert and transport the catalytic domain into the cytosol. Following reduction of the disulfide bridge connecting the two chains, the translocation domain is retained in the vesicle, while the catalytic domain travels to SNAPRE complex.

5. Cleavage of SNAPRE proteins: The catalytic domain is a Zn-dependent protease that cleaves SNAP-25, which is one of three major proteins present in the SNAPRE complex. The SNAPRE protein complex is required for the fusion of synaptic vesicles with the neuronal membrane. Cleavage of SNAP-25 inhibits fusion of synaptic vesicles to the plasma membrane to inhibit acetylcholine release and muscle contraction, leading to flaccid paralysis.

6. CONCLUSION

The two main commercial types of BoNT used are serotype A and serotype B. BoNT/A can also be used to treat a range of conditions including upper motor neuron syndrome, proboscis swelling, involuntary closing of the eyelid, poor eye muscle control and involuntary grinding of the teeth. For cosmetic applications, BoNT/A can be injected to paralyze facial muscles in order to prevent wrinkles. Some patients have experienced temporary muscle weakness in the areas treated, and some developed flu-like symptoms. In April 2009, the FDA announced that they were releasing a warning for two products involving the use of the BoNT/A. The warning stated that BoNT/A, when injected into the muscle, could lead to adverse side effects such as: difficulty with speaking, swallowing, and breathing, muscle weakness, loss of bladder control, drooping eyelids, and blurred vision.

REFERENCES AND ACKNOWLEDGEMENTS


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