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Illicit entry

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Botulinum neurotoxin A (BoNT/A), produced by the bacterium *Clostridium botulinum*, blocks neurotransmitter release in the presynaptic terminals of neurons. Although used clinically (under the name Botox) to treat a variety of conditions, the means by which BoNT/A recognizes and enters neurons has remained unknown. In a new study reported in *Science,* Dong *et al.* show that BoNT/A enters neurons by binding to the synaptic vesicle membrane protein SV2.

BoNT/A is one of seven neurotoxins produced by *Clostridium botulinum* — others include botulinum neurotoxin B (BoNT/B), which recognizes and enters neurons by binding the synaptic vesicle proteins synaptotagmin I and II, and also blocks neurotransmitter release. The authors showed that BoNT/A uptake into cultured hippocampal neurons was blocked by pretreatment of the neurons with BoNT/B, suggesting that the receptor for BoNT/A — no longer available following BoNT/B treatment — was also likely to be a synaptic vesicle protein.

Immunoprecipitation of a number of synaptic vesicle proteins revealed

an interaction between BoNT/A and SV2. This was confirmed by peptide interaction assays, which also enabled the authors to identify the largest luminal loop of SV2 as the BoNT/A-binding region. Recombinant SV2 fragments containing the BoNT/A-binding region reduced toxin binding and entry into neurons, providing evidence that SV2 acts as a receptor for uptake of BoNT/A.

To further probe the role of SV2 isoforms (SV2A, SV2B and SV2C) in BoNT/A binding and uptake, the authors created hippocampal neuronal cultures from mice that lacked SV2B and had wild-type, heterozygous or no SV2A expression. SV2C is not expressed in the hippocampus, and so was also absent from these cultures. Neurons expressing heterozygous levels of SV2A bound approximately half as much toxin as neurons expressing wild-type levels. SV2A null cultures showed no significant BoNT/A binding, but binding was restored by transient expression of any SV2 isoform. Whole-animal studies revealed that SV2B-knockout mice had reduced sensitivity to BoNT/A and a reduced toxin load: ~40% of that of wild-type mice.

The finding that at least two synaptic vesicle proteins are independently exploited by botulinum neurotoxins reveals the remarkable efficiency of these toxins at entering the nervous system.

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ORIGINAL RESEARCH PAPER Dong, M. *et al.* SV2 is the protein receptor for botulinum neurotoxin A. *Science* **312**, 592–596 (2006)