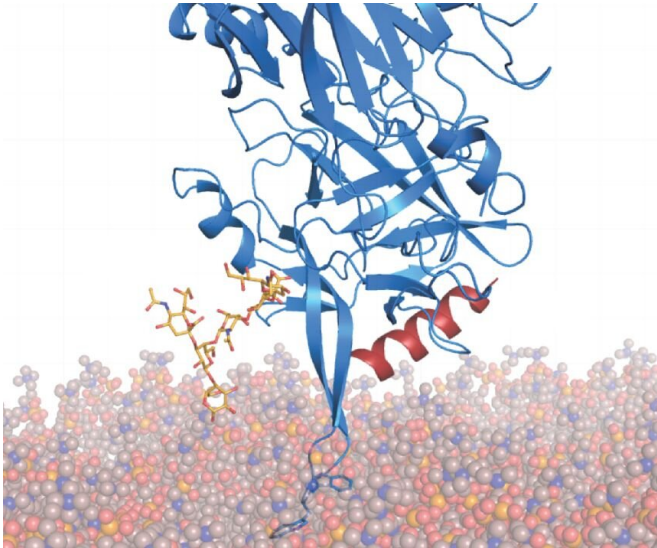


# Engineered botox is more potent and safer in mice

17 March 2020



Modified BoNT/B (blue) is modeled onto membranes through anchoring with its two receptors (yellow and red), showing that the two tryptophan residues interact with membranes. Credit: From Fig 6D, Yin et al, 2020

Botulinum toxin (BoNT) is used for a range of applications from treating chronic pain to reducing the appearance of wrinkles, but when injected it can diffuse into the surrounding tissue and give rise to adverse effects. A new study publishing March 17 in the open-access journal *PLoS Biology* by Linxiang Yin and Min Dong of Boston Children's Hospital, USA and colleagues shows that a subtle modification of an FDA-approved form of BoNT enhances binding to the nerve cells and improves the drug's potency and safety.

Botulinum toxin (BoNT) is produced by the *Clostridium botulinum* bacterium in seven serotypes, BoNT/A through G. All work in a similar way: after attaching to nerves near their junction with muscles (the neuromuscular junction), a portion of the toxin crosses the nerve's membrane to prevent release of neurotransmitter and thereby

paralyze the muscle. A commercial form of BoNT/A is approved for clinical treatment of various forms of muscle overactivity as well as cosmetic reduction of wrinkles, while a commercial form of BoNT/B is approved for a movement disorder called cervical dystonia.

BoNTs have two sites that recognise two separate receptors at the nerve terminal. Previous work has shown that several BoNTs including BoNT/B have an extended loop along the [amino acid chain](#) between the two receptor binding sites. Structural modeling suggested that if this loop contains hydrophobic (oily) [amino acids](#) it could interact with lipids in the nerve cell membrane, providing a third point of attachment and so increasing binding efficiency. These hydrophobic amino acids are present in the loop of several BoNTs, but not in BoNT/B.

Because potency is increased and adverse effects decreased by stronger binding, the authors investigated whether adding hydrophobic amino acids to this lipid-binding loop in BoNT/B might improve binding of the toxin to the [nerve](#) terminal. They showed that replacing just two amino acids in the loop with hydrophobic tryptophans did in fact enhance binding in vitro. They then produced a new BoNT/B containing this mutation plus a pair of mutations that had been previously shown to enhance binding to one of the two BoNT/B receptors, and demonstrated that this engineered toxin was more potent than the approved form of BoNT/B in a standard mouse paralysis assay. In addition, the new toxin caused less reduction in body weight, an effect consistent with a reduction in diffusion of the toxin away from the injection site.

"Our study shows that the changes introduced into BoNT/B can increase the therapeutic potential of the [toxin](#) and reduce adverse effects," Dong said. "Engineering the botulinum toxins in this way may provide a new avenue for improving safety and clinical benefit from these drugs."

**More information:** Yin L, Masuyer G, Zhang S, Zhang J, Miyashita S-I, Burgin D, et al. (2020) Characterization of a membrane binding loop leads to engineering botulinum neurotoxin B with improved therapeutic efficacy. *PLoS Biol* 18(3): e3000618. [doi.org/10.1371/journal.pbio.3000618](https://doi.org/10.1371/journal.pbio.3000618)

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