Decoding Botulinum Neurotoxins: Harnessing Single Particle Cryo-EM for Molecular Insights

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Botulinum neurotoxins (BoNTs) include seven bacterial toxins (BoNT/A-G) that target the junction of motor neurons and muscles cleaving proteins involved in synaptic vesicle secretion. This blocks the release of the neurotransmitter acetylcholine, causing flaccid paralysis. BoNTs are produced as progenitor toxin complexes (PTCs), including the non-toxic non-hemagglutinin protein (NTNH) that shields the toxin from acidic and proteolytic degradation during host entry.[1,2] Although BoNT type D is primarily associated with animal botulism, recent evidence indicates that it can also block autonomic cholinergic synapses in humans[3], suggesting its potential as a therapeutic alternative – especially as immune reactivity and resistance to clinically used BoNT/A and /B continue to emerge.[4] To explore the therapeutic potential of BoNT/D, we aim to understand its precise mechanism of action. Here we present the assembly and high-resolution single particle cryo-EM structure of the BoNT/D-NTNH complex (M-PTC/D), revealing an interesting molecular architecture. Mass photometry analyses show that the complex remains intact at pH 5.5 and dissociates near pH 6.5. Solving the structures of M-PTCs with cryo-EM is crucial to fully understand their mechanism of action and to guide the development of next-generation botulinum neurotoxin therapeutics.

References:

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