INFECTIOUS DISEASE

Beating botulism with botulism

Miyashita, S. et al. *Sci. Transl. Med.* **13**, eaaz4197 (2021)
McNutt, P.M. et al. *Sci. Transl. Med.* **13**, eabd7789 (2021)

Botulism may be rare, but the paralytic disease can leave patients with considerable muscle weakness and in severe cases, difficulty breathing that can lead to death. Botulism can be caused by a handful of related neurotoxic bacteria, including the namesake *Clostridium botulinum*, that are usually picked up from eating improperly preserved or contaminated foods. Once consumed, botulinum neurotoxins (BoNTs) make their way into motor neurons, where they disrupt the neurotransmission that controls muscle activity.

There are antitoxins available, but these antibody treatments are only effective if they are administered *before* BoNTs have gained entry into the nervous system – the neuron's cell membranes have a pesky habit of blocking the entry of such biologic therapies. Once a BoNT gets inside a patient's motor neurons, the only option is supportive care until the toxins wear off. Two independent groups studying ways to treat botulism *after* BoNTs have invaded the nervous system recently came to similar solutions: to use the neurotoxins against themselves.

BoNTs don't have the cellular entry problem that biologics by themselves do – the bacteria manage to slip right in to neurons via receptor-mediated endocytosis. The two labs behind the papers, both published in *Science Translational Medicine*, decided to use that detail to their advantage.

The delivery platforms they developed differ slightly – Min Dong and his lab at Harvard Medical School attached antibodies to an inactivated BoNT while NYU Grossman School of Medicine's Konstantin Ichtchenko and his collaborators made use of an atoxic derivative – but both approaches managed to ferry antibodies against the toxins through the cell membrane and into neurons, where the cargo could be released to fight off the infection. The Dong lab's platform reversed paralysis and rescued mice injected with lethal doses of BoNTs, while Ichtchenko and his collaborators successfully tested their treatment in infected mice, guinea pigs, and rhesus macaques.

There still needs to be longer-term studies to fully assess the safety of these biologic delivery vehicles, but both groups suggested that such 'Trojan Horse' approaches could potentially be adapted to target other pathogens that can reside in previously inaccessible neurons.

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