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Study reveals molecular basis of botulism toxin's deadly activity

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In the study, the scientists reveal the mysterious structural basis of the remarkably strong interaction that botulinum toxins form with nerve cells, a union so robust that a single toxin molecule can completely incapacitate a nerve cell. Because of this action, even in minute quantities these toxins are potentially deadly, leading to muscle weakness, paralysis, and sometimes respiratory failure.

"The structure finally helps to answer part of the mystery of how a very large protein can search through the body and locate the neuromuscular junction with such high affinity and specificity," says Scripps Research Professor Raymond Stevens, an author of the paper who has studied botulinum toxins for many years.

The toxins responsible for botulism are produced by the bacterium Clostridium botulinum. Humans can get the toxins from tainted food, certain wounds, and gastrointestinal tract colonization by the bacteria, the latter being particularly dangerous for infants. There is also growing concern that botulinum toxins might be used as weapons, with the Centers for Disease Control ranking them as one of the six highest-risk threats for bioterrorism.

Scientists had suspected for many years that botulinum toxins bind with nerve cells through a two-step process, but the details were unknown. Using x-ray crystallography on type B (there are seven structurally and functionally related botulinum neurotoxins, serotypes A through G) in action with receptors, the Scripps Research investigators took a

molecular snapshot of regions critical to the process. Analyzing the data along with colleagues at the University of Wisconsin, Madison, and the Howard Hughes Medical Institute led to the discovery of just how the binding proceeds.

Botulinum toxins first attach to a portion of a protein found on the surface of nerve cells that mates with two parallel, narrow grooves on the toxin. Because this protein receptor is only exposed on active cells, the toxins target those nerves that are most important to a victim, such as muscles needed for breathing that are constantly in use.

The team was also able to model the structure of the second step in the process, where a separate region of a botulinum toxin binds with a sugar known as a ganglioside that acts as a second receptor. The gangliosides are found on the nerve cell surface close to the protein receptor. This double binding to the nerve cell orients the toxin in such a way that it can penetrate the nerve cell and break apart proteins that are essential to proper transmission of nerve signals.

Solving the structures opens the possibility of developing new botulism treatments, including improved small molecule drugs, vaccines, and antibody therapies.

Currently, botulism treatment rests on a cocktail of antibodies derived from horses. Because the antibodies are not human, rejection is a pervasive problem with severe potential side effects, including anaphylactic shock. The development of new types of antibodies could be a boon for treatment, and this possibility is explored by Stevens and colleagues in a paper to be published in Nature Biotechnology later this week.

In addition, the structure will help the development of other types of therapeutics to treat botulism infection. "You could essentially design

smaller compounds that mimic those interactions," says Joseph Arndt, a Scripps Research postdoctoral fellow in the Stevens lab, who conducted the x-ray crystallography work for the study along with Qing Chai, another Scripps Research postdoctoral fellow. "If you block that step of recognition of the receptor, the toxin can't be internalized into the nerve cell, so it's basically shut down."

Another application for the new understanding of botulinum toxins is equally intriguing. Although botulinum toxins can have devastating effects, in very small concentrations injected directly into a specific muscle they can actually be a beneficial treatment for diseases such as cerebral palsy and multiple sclerosis that are caused by overactive nerve signaling, which the toxins can reduce. However, for reasons not completely clear, some patients do not respond to current treatments. This could be due to variations in their nerve cells that prevent the toxins from binding. If that is the case, researchers may be able to engineer toxins that bind to these variant receptors.

Source: Scripps Research Institute