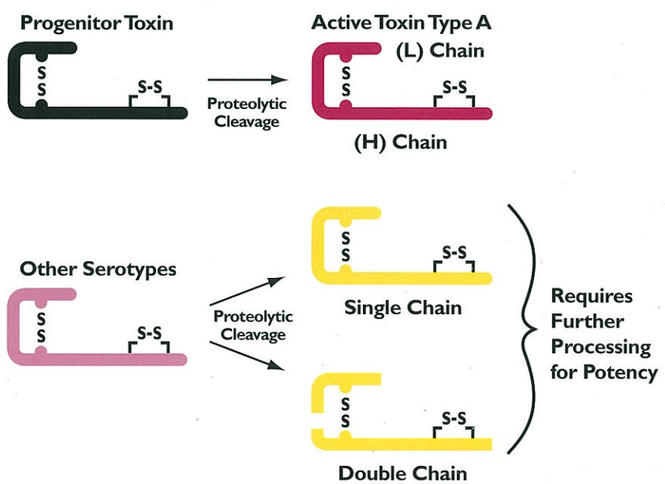
TOXIN STRUCTURE

BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex is a 900-kilodalton (900-kD) complex containing type A neurotoxin and associated proteins. There are general structural and functional similarities among all 7 botulinum neurotoxin types, A through G. All are synthesized as single-chain polypeptides with molecular weights of approximately 150 kD. These single-chain molecules are activated by proteolytic enzymes in a process referred to as nicking or cleaving.[1] In some cases, the bacteria are efficient at activating the toxin (as with type A). In other cases, activation requires a longer period of fermentation or exposure to exogenous enzymes (as with types B and E).

Once it is nicked or cleaved, the ~150-kD, single-chain molecule forms a dichain molecule consisting of an ~150-kD heavy chain linked by disulfide bonding to an ~50-kD light chain. The heavy chain is responsible for high-affinity docking of the neurotoxin to the presynaptic nerve terminal receptor, enabling the internalization of the bound toxin into the cell. The light chain is a zinc-dependent endopeptidase that cleaves membrane proteins responsible for docking acetylcholine vesicles on the inner side of the nerve terminal membrane.[5,6] The cleavage of these proteins precludes fusion of the vesicles with the nerve membrane, thereby preventing release of neurotransmitters into the neuromuscular junction.[7]



INTRACELLULAR TARGET

Although similar in structure and function, botulinum neurotoxin types have been shown to vary in potency and duration of action. A number of clinical studies illustrate these differences.

Mezaki et al evaluated 9 patients with blepharospasm in a double-blind, self-controlled study.[8] Each subject received the same dose of each toxin, one (toxin type A) in one eye and one (toxin type F) in the other eye. Onset of clinical effect, maximal benefit, and adverse reactions were similar between toxin types A and F. However, duration of clinical effect was significantly shorter in eyes injected with toxin type F.

In a study by Sloop et al, the maximal decrease in muscle activity, measured as the percent decline in M-wave amplitude, was measured 2 weeks postinjection in 17 healthy volunteers who received injections of toxin type B in the extensor digitorum brevis muscle.[9] Specifically, the maximal loss of effect was 50% to 75% using 320 to 480 mouse units (MU). Seven weeks postinjection, type B–induced effects had dissipated by 66%, with complete return of normal muscle activity after 11 weeks.

Botulinum toxin serotypes differ in light-chain intracellular targets. For example, toxin subtypes A and E cleave SNAP-25, while toxin subtypes B, D, F, and G cleave synaptobrevin (VAMP).* Type C cleaves SNAP-25 as well as syntaxin. It is possible that intracellular restoration of VAMP may occur at a more rapid rate than that of SNAP-25. Botulinum toxin type A is believed to be the most potent and long-lasting (as long as 12 to 24 weeks, in some cases) of the botulinum neurotoxin serotypes.

*SNAP-25 = synaptosome-associated protein of molecular weight 25 kD; VAMP = vesicle-associated membrane protein.