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Botulinum Neurotoxins; Overview of Basic Science and Therapeutic Aspects

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Botulinum neurotoxin (BoNT), which has been considered the most poisonous substance to human, is produced by the Gram-positive, endospore-forming strict anaerobic bacteria, *Clostridium botulinum.* (1, 2). BoNT blocks acetylcholine release at peripheral cholinergic nerve endings (3). This unique characteristic enables BoNT to be a therapeutic muscle-relaxing agent for various movement-disorder diseases that occur at the end of the motor nerves.

BoNT is classified, serologically, into seven groups (A to G), and is synthesized as a 150 kDa of a single polypeptide. As shown in Fig. 1, it is subsequently activated by an endogenous, or exogenous, trypsin-like protease to generate the nicked form, which consists of C-terminal heavy chain (H chain; ~100 kDa) and N-terminal light chain (L chain; ~50 kDa) components, held together by a disulfide bond (3). The L chain, with pharmacological activity, cleaves one (or two) of the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complexes, which are key proteins in the docking/fusion process of neurotransmitter-containing synaptic vesicles. Conversely, the C-terminal domain of the H chain (HC) plays a role in neuronal target cell binding (4). The BoNT is internalized into the cell by a typical endocytosis mechanism. The N-terminal domain of the H chain (HN) is proposed to aid translocation of the L chain from the acidic part into the cytosol, from where it can

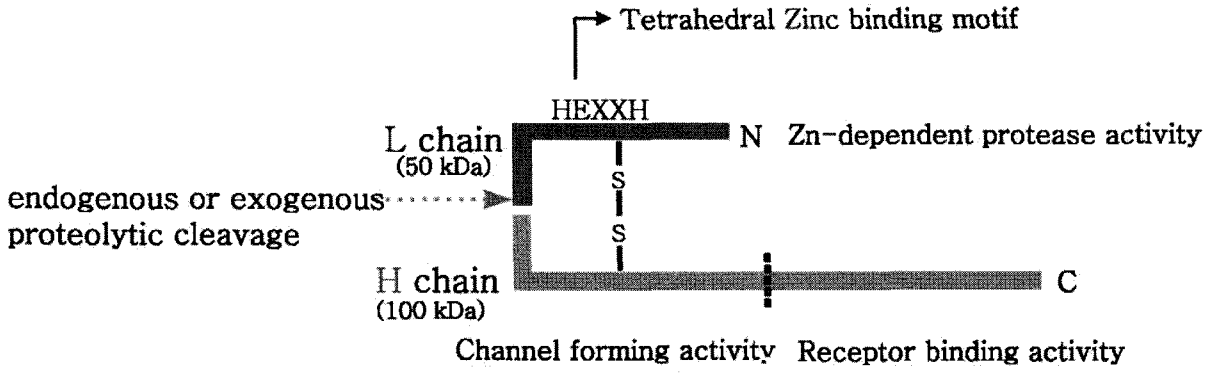

Fig. 1. Schematic representation of BoNT.

access its substrate (5,6). In culture, BoNT associates with non-toxic components, such as the non-toxic non-hemagglutinin component (NTNH; ~120 kDa) and hemagglutinin components (HA; ~33 kDa, ~15 kDa, ~19 kDa, and ~52 kDa), which are known to play roles in the protection of the toxin component from the acidity and proteases of the digestive track when orally ingested (7).

In 1946, Edward J. Schantz, Ph.D., and colleagues at the University of Wisconsin, succeeded in purifying botulinum toxin type A in a crystalline form that could be used for therapeutic purposes. In 1973, Alan B. Scott, M.D., of the Smith-Kettlewell Eye Research Foundation, found that by injecting a small amount of botulinum toxin in monkey hyperactive ocular muscles, the strabismic condition could be corrected without systemic toxicity. Later on, a collaboration of Dr. Schantz with Dr. Scott resulted in the development of botulinum toxin type A for human treatment. In 1989, Oculinum, Inc. founded by Dr. Scott in the late 1970s, received FDA approval to market Oculinum in the United States as an orphan drug to treat strabismus, and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and older. Shortly after the FDA approval, Oculinum Inc. was acquired by Allergan, Inc. which changed the product's name to Botox®. Botox® has also been approved for the treatment of glabella line and axillary hyperhidrosis by FDA in 2002 and 2004, respectively. In addition, two more botulinum neurotoxin type A preparations, named Dysport® (Ipsen Ltd., UK) and BTXA® (Lanzhou Institute, China), and a botulinum neurotoxin type B preparation, named Neurobloc (Solstice, Inc., US), have already been marketed.

In Korea, Medy-Tox, Inc. founded in 2000 by a group of scientists majoring in botulinum neurotoxins, has developed botulinum neurotoxin type A as a bio-pharmaceutical. Following process/analytical methods development and completion of two phase Ⅲ comparative clinical studies for the safety and efficacy of Neuronox® (the brand name of botulinum toxin type A developed in Medy-Tox Inc.) in hemifacial spasm and essential blepharospasm, Medy-Tox received KFDA approval on March 16, 2006.

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