Table of Contents

Peptide inhibitors of botulinum neurotoxin serotype A: design, inhibition, cocrystal structures, structure-activity relationship and pharmacophore modeling

Gyanendra Kumar, Desigan Kumaran, S. Ashraf Ahmed and Subramanyam Swaminathan

Clostridium botulinum neurotoxins are classified as Category A bioterrorism agents by the Centers for Disease Control and Prevention (CDC). The seven serotypes (A–G) of the botulinum neurotoxin, the causative agent of the disease botulism, block neurotransmitter release by specifically cleaving one of the three SNARE (soluble *N*-ethylmaleimidesensitive factor attachment protein receptor) proteins and induce flaccid paralysis. Using a structure-based drug-design approach, a number of peptide inhibitors were designed and their inhibitory activity against botulinum serotype A (BoNT/A) protease was determined. The most potent peptide, RRGF, inhibited BoNT/A protease with an IC_{50} of 0.9 μ*M* and a K_i of 358 n*M*. High-resolution crystal structures of various peptide inhibitors in complex with the BoNT/A protease domain were also determined. Based on the inhibitory activities and the atomic interactions deduced from the cocrystal structures, the structure–activity relationship was analyzed and a pharmacophore model was developed. Unlike the currently available models, this pharmacophore model is based on a number of enzyme-inhibitor peptide cocrystal structures and improved the existing models significantly, incorporating new features.

Abstract of an article in *Acta Crystallogr. D Biol. Crystallogr*. **68**: 511-520 (2012).
Syed Ashraf Ahmed: Participant of the 6th UM, 1978-1979.

List of Publication for 2012: Syed Ashraf AHMED

1. Toth, S., Brueggmann, E. E., Oyler, G. A., Smith, L. A., Hines, H. B., and Ahmed, S. A. (2012). Tyrosine phosphorylation of botulinum neurotoxin protease domains. *Frontiers in pharmacology* **3**: 102.

2. Mizanur, R. M., Gorbet, J., Swaminathan, S., and Ahmed, S. A. (2012). Inhibition of catalytic activities of botulinum neurotoxin light chains of serotypes A, B and E by acetate, sulfate and calcium. *International journal of biochemistry and molecular biology* **3**: 313-321.

3. Kumar, G., Kumaran, D., Ahmed, S. A., and Swaminathan, S. (2012). Peptide inhibitors of botulinum neurotoxin serotype A: design, inhibition, cocrystal structures, strucuture-activity relationship and pharmacophore modeling. *Acta Crystallogr. D Biol. Crystallogr*. **68**: 511-520.