Toxins mamba venoms that facilitate neuTromuscular transmission

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Abstract:

Two toxins that are potent inhibitors of acetylcholinesterase have been isolated from the venom of the green mamba, Dendroaspis angusticeps. The toxins have been called fasciculins since after injection into mice (i.p. 0.5-3 micrograms/g body weight) they cause severe, generalized and long-lasting (5-7 h) fasciculations. Homogenates of diaphragm, tibialis anterior and gastrocnemius muscles from mice injected with fasciculins showed a decrease in acetylcholinesterase activity by 45-60% compared to muscles from control animals. Histochemical staining revealed a greatly reduced acetylcholinesterase activity at neuromuscular junctions. Fasciculins have 61 amino acid residues and four disulfides. The molecular weights are 6765 (fasciculin 1) and 6735 (fasciculin 2). The sequences of the two toxins differ probably only at one position by a replacement of Tyr with Asp/Asn. 1 g of venom contained about 40 mg of fasciculins, 2/3 of which was fasciculin 2. A similar inhibitor has also been isolated from D. polylepis (black mamba) venom. The sequence of fasciculin 2 is known. Most of the positive charges are concentrated in a small section of the central part of the molecule, and most of the negative charges are in the C-terminal region. Fasciculins appear to have a pronounced dipole character. Fasciculin binds to the peripheral anionic site, since it can displace propidium, a probe for that site, from acetylcholinesterase. In vitro, in Krebs-Henseleit solution containing 2 mM NaH2PO4 (pH 7.4), fasciculin 2 inhibits acetylcholinesterase from human erythrocytes (Ki = 1.1 X 10(-10) M, 37 degrees C), rat muscle (Ki = $1.2 \times 10(-10) \text{ M}$, 37 degrees C) and Electrophorus electricus (Ki = 3.0 X 10(-10) M, 22 degrees C).(ABSTRACT TRUNCATED AT 250 WORDS)