CROTOXIN, THE PHOSPHOLIPASE A_2 NEUROTOXIN FROM THE VENOM OF *CROTALUS DURISSUS TERRIFICUS*

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Death following systemic crotoxin poisoning of experimental animals is due to respiratory paralysis of peripheral origin.[8] The primary defect lies in a failure of nerve impulses to release acetylcholine following arrival at motor nerve terminals but the molecular events are ill-understood. Crotoxin consists of two polypeptide subunits, a weakly toxic, basic phospholipase A_2 and a non-toxic acidic component devoid of enzymatic activity. Evidence suggests that the phospholipase A_2 subunit binds to specific sites at the motor nerve terminal and that the role of the acidic component is to reduce non-specific binding by chaperoning the phospholipase A_2 subunit to these sites.[1] Unlike botulinum toxin, crotoxin does not cross the axolemma by receptor-mediated endocytosis to act internally.[7]

Electrophysiological recordings from single endplates in frog and mouse nerve-muscle preparations show that crotoxin induces a series of changes in the amount of acetylcholine release per impulse viz. an initial fall, a secondary rise and a tertiary fall leading to complete inhibition of evoked release. The rate of spontaneous transmitter release initially falls in parallel but at intoxicated frog endplates, the secondary rise is slower and far more sustained.[4,5] The secondary increase in evoked transmitter release from intoxicated mouse motor nerve terminals is due, at least in part, to toxin blockade of a class of K^+ channels and so to a greater Ca^{2+} influx.[6] However, such a blockade has not been observed in the frog and another mechanism must be operative[6] as is also suggested by the increase in facilitation of endplate potential (e.p.p.) amplitude due to closely spaced twin impulses.[5] In the tertiary phase when transmitter release is declining towards zero, twin-impulse facilitation is reduced, delay time between stimulus and onset of the e.p.p. is increased and the rise-time of the e.p.p. is slowed.[5]

Phospholipase A_2 activity has been implicated in the secondary as well as tertiary phases of intoxication in the frog.[4] However, there is no evidence that prostaglandin synthesis is involved in any of the stages as pretreatment with inhi-

bitors of arachidonate metabolism such as aspirin and nordihydroguaiaretic acid failed to alter the characteristic changes in e.p.p. amplitude and miniature e.p.p. frequency induced by crotoxin.[2] Similarly there is no evidence that crotoxin initiates the activation of protein kinase C as pre-treatment with the blocker H-7 did not change the characteristic pattern of intoxication.[5]

It has been proposed that crotoxin's neurotoxicity is due to site-directed hydrolysis of the axolemma[4] affecting the release process *per se*.[5] This leads to a series of time-gated changes which include transient facilitation then uncoupling of phasic release and generalized acceleration of spontaneous release. Progressive hydrolysis leads to necrosis of the nerve terminal. Crotoxin binds to other sites less readily and focal lesions in the kidney,[3] skeletal muscle and lungs[4] have been reported following intoxication of experimental animals.

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