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The block of skeletal muscle nicotinic acetylcholine receptors caused by cyclic imine toxins can be antagonized by 3,4-diaminopyridine at isolated mouse neuromuscular preparation

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Résumé

Cyclic imine toxins (CiTXs) are a worldwide-distributed family of marine macrocyclic phycotoxins comprising different groups of lipophilic compounds: gymnodimines (GYMs), spirolides, pinnatoxins (PnTXs), pteriatoxins (PteTXs), portimines, prorocentrolides and spiroprorocentrimine. CiTXs and acyl derivative products of shellfish metabolism contaminate and bioaccumulate in filter-feeding bivalves, edible mollusks and other marine invertebrates and, thus, represent a risk for shellfish consumers and a menace for wildlife conservation. All CiTXs interact and block, with different affinities, mature ($\alpha 12\beta e\delta$) and embryonic ($\alpha 12\beta\gamma\delta$) nicotinic acetylcholine receptors (nAChRs) expressed in skeletal muscles. 3,4-Diaminopyridine (3,4-DAP) is a well-known K⁺-channel blocker that prolongs the presynaptic action potential and indirectly enhances Ca²⁺ entry into nerve terminals and, thereby, increases quantal ACh release from the neuromuscular junction. 3,4-DAP has been used effectively to treat muscular weakness in various human myasthenic syndromes. The aim of this work was to determine whether 3,4-DAP, which increases quantal ACh release, was able to reverse the action of CiTXs on skeletal muscle expressing $\alpha 12\beta e\delta$ nAChRs. The use of isolated mouse phrenic-nerve hemi-diaphragm muscle preparations allowed monitoring nerve-evoked isometric muscle contraction in the presence of GYM-A, PnTX-A, PnTX-G and PteTX-A and, afterwards, the action of 3,4-DAP (10-100 μ M) in the continuous presence of the respective CiTXs. The results show that 3,4-DAP improves neuromuscular function in a time- and concentration-dependent manner and completely reverses the neuromuscular block caused by the CiTX studied. These results support the view that GYM-A, PnTX-A, PnTX-G and PteTX-A are competitive and reversible inhibitors of muscle-type $\alpha 12\beta e\delta$ nAChRs. In fact, CiTXs can be characterized as competing with the binding of ACh (the natural ligand) to the nAChR. The ability of 3,4-DAP to antagonize the action of CiTXs is related to the increased release of ACh that is able to displace the CiTXs from their respective nAChR binding sites.

*Intervenant

Mots-Clés: Cyclic imine toxins, diaminopyridine, potassium channel block, muscle contraction, neuromuscular junction, nicotinic acetylcholine receptors, nerve terminals