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The Cyclic Imine family of dinoflagellate toxins targeting nicotinic acetylcholine receptors

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Keywords: marine dinoflagellates, phycotoxins, prorocentrolide A, pinnatoxins, spirolides, gymnodimines, nicotinic acetylcholine receptors. In this presentation, we summarize our current understanding of the lipophilic, fast-acting macrocyclic imine toxins. This worldwide distributed family of compounds is associated with dinoflagellate blooms and shellfish contamination, which are responsible for the closure of shellfish harvesting areas causing significant economic losses. Shellfish contamination episodes are spreading out, and the importance of these toxins for the shellfish food industry validates their detailed study. Well-defined dinoflagellates species are responsible for the production of cyclic imine toxins. *Prorocentrum lima* and *Karenia selliformis* species have been linked to the production of prorocentrolides and some gymnodimines, respectively. *Alexandrium ostenfeldii* /*Alexandrium peruvianum* are known to produce spirolides and 12-methy gymnodimine, and *Vulcanodinium rugosum* is the source of pinnatoxins, pteriatoxins, and portimine. Cyclic imine toxins are chemically typified by a macrocyclic skeleton comprising 14–27 carbon atoms, flanked by two preserved moieties, the cyclic imine and the spiroketal ring system. Using conventional competition-binding assays and voltage-clamp recordings we provided evidence that the toxicological profile of gymnodimines, spirolides, and pinnatoxins is associated to their specific interaction with nicotinic acetylcholine receptors (nAChRs). The cyclic imine component of these phycotoxins has been shown to be a significant pharmacophoric feature. In addition, we show for the first time that prorocentrolide-A, purified from cultured *P. lima* dinoflagellates collected in Japan, also blocks nAChRs. Structural factors responsible for activity are discussed based on molecular docking and modeling.

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