TOXIN MEDICAL COUNTERMEASURES - DEVELOPMENT OF NOVEL, BROAD-SPECTRUM COUNTERMEASURES FOR TOXIN EXPOSURE

Investigating A Possible Disulfide Shuffling Mechanism Of Alpha-conotoxins Using Qm/mm Molecular Dynamics Simulation.

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Conotoxins are potent neurotoxic peptides, rich in disulfide bonds, that derive from cone snail venom and can pose a significant risk to human health with potential for human fatality. There currently exist no FDA approved treatments to mitigate conotoxin exposure, representing a clear unmet need toward biological hazard countermeasures. This family of conotoxins exhibit the capability to selectively target a wide ensemble of critical receptors of the nervous system.

Currently, our research focuses on the α-GI conotoxin, which selectively targets the nicotinic acetylcholine receptor (nAchR). Recent solving of the Torpedo californica nAchR structure with a bound αGI conotoxin strongly implicated a possible interaction between the conotoxin disulfide bond and two receptor cysteine thiol groups in close proximity. However, due to non-native redox conditions required to facilitate crystallisation, the true state of disulfide interactions for conotoxins remains unclear. It has already been shown that one of the two α-GI disulfides is critical for inhibitory function, yet the mechanistic process of this function is unknown.

We have pursued a hybrid computational approach to elucidate the role of cysteine interaction networks in the conotoxin mechanism of action. By combining slow quantum mechanical (QM) simulations, capable of modelling covalent bond breaking and formation, with fast molecular mechanical (MM) simulations that can capture overall protein dynamics, we hope to be able to visualise the mechanism of disulfide interactions that mediate the conotoxins inhibitory functions. From this insight, we seek to identify whether these disulfide interactions facilitate conformational changes to electrostatic interactions to mediate function, or whether the conotoxin is capable of disulfide shuffling to covalently link to the target receptors.

Validation of disulfide shuffling in the α-GI mechanism of action through both experimental and computational approaches could drive the development of medicinal countermeasures to focusing on a disulfide-exchange covalent binding approach to sequester and degrade the toxin. The consistency of disulfide-rich internal structure between conotoxins may further suggest a conserved mechanism of disulfide-facilitated binding that can be used to derive a broad-spectrum countermeasure to this class of hazardous agents.