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Invited review

Modelling the interactions between animal venom peptides and membrane proteins

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ABSTRACT

The active components of animal venoms are mostly peptide toxins, which typically target ion channels and receptors of both the central and peripheral nervous system, interfering with action potential conduction and/or synaptic transmission. The high degree of sequence conservation of their molecular targets makes a range of these toxins active at human receptors. The high selectivity and potency displayed by some of these toxins have prompted their use as pharmacological tools as well as drugs or drug leads. Molecular modelling has played an essential role in increasing our molecular-level understanding of the activity and specificity of animal toxins, as well as engineering them for biotechnological and pharmaceutical applications. This review focuses on the biological insights gained from computational and experimental studies of animal venom toxins interacting with membranes and ion channels. A host of recent X-ray crystallography and electron-microscopy structures of the toxin targets has contributed to a dramatic increase in the accuracy of the molecular models of toxin binding modes greatly advancing this exciting field of study.

This article is part of the Special Issue entitled 'Venom-derived Peptides as Pharmacological Tools.'

Contents

1. Introduction

Animal venoms are a rich source of peptide toxins mainly acting

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on the nervous system (Kalia et al., 2015). A number of peptides from this vast and complex pool of bioactive peptides have shown potential therapeutic applications, and the study of animal venoms attract considerable interest (Calvete, 2017; Kaas and Craik, 2015; Oldrati et al., 2016; Nasiripourdori et al., 2011). Venoms of snakes, spiders, cone snails, scorpions, anemones, bees and wasps have been the most investigated, resulting in the identification of several thousands of toxins (Jungo et al., 2012), but only a fraction of these toxins has been functionally characterised. For example, less than 200 out of the 2500 cone snail toxins currently identified have been pharmacologically characterised (Kaas et al., 2012); with the estimated total number of cone snail toxins being in the range of hundreds of thousand to millions (Akondi et al., 2014; Kaas and Craik, 2014). Animal peptide toxins typically target large membrane proteins, making the structural characterisation of these interactions by nuclear magnetic resonance (NMR), X-ray crystallography or electron microscopy (EM) challenging. To date, only four experimental structures of a complex between a toxin and its molecular target have been determined, two are shown in Fig. 1, and the other two are the scorpion charybdotoxin bound to the voltage-gated potassium channel $K_V1.2$ (Banerjee et al., 2013) and the spider toxin DkTx bound to the TRPV1 channel (Cao et al., 2013; Gao et al., 2016). The snake α-bungarotoxin was crystallised in complex with the ligand-binding domain of an isolated nicotinic acetylcholine receptor (nAChR) α1 subunit (nAChR) (Dellisanti et al., 2007) as well as with an isolated ligand-binding domain of a human α9 nAChR subunit (Zouridakis et al., 2014). The binding site in these crystal structures is largely incomplete because the binding site is located at the interface between two subunits. A number of experimental structures of complexes between toxin and structural homologues to the molecular target have also been determined, for example, the acetylcholine binding protein (AChBP), a structural surrogate for nAChRs, has been crystallised in complex with a range of toxins (Dutertre and Lewis, 2006). Molecular modelling therefore plays an essential role in building hypotheses on toxin binding modes and mode of action, and in guiding the engineering of toxin activity. This review will focus on recent findings resulting from the molecular modelling of interactions between animal toxins and their membrane targets.

Some toxins, such as the bee melittin, directly target cellular membranes (Section 1), but the vast majority of peptide toxins act on ion channels in the nervous systems. The most common classes of ion channels targeted by animal toxins are the voltage-gated ion channels (Section 2) and the nicotinic acetylcholine receptors (nAChRs) (Section 3). The high degree of sequence conservation of these channels across animal phyla explains the potent activity of these toxins in humans (Jegla et al., 2009; Liebeskind et al., 2015, 2011). Beyond voltage-gated ion channels and nAChRs, a diverse

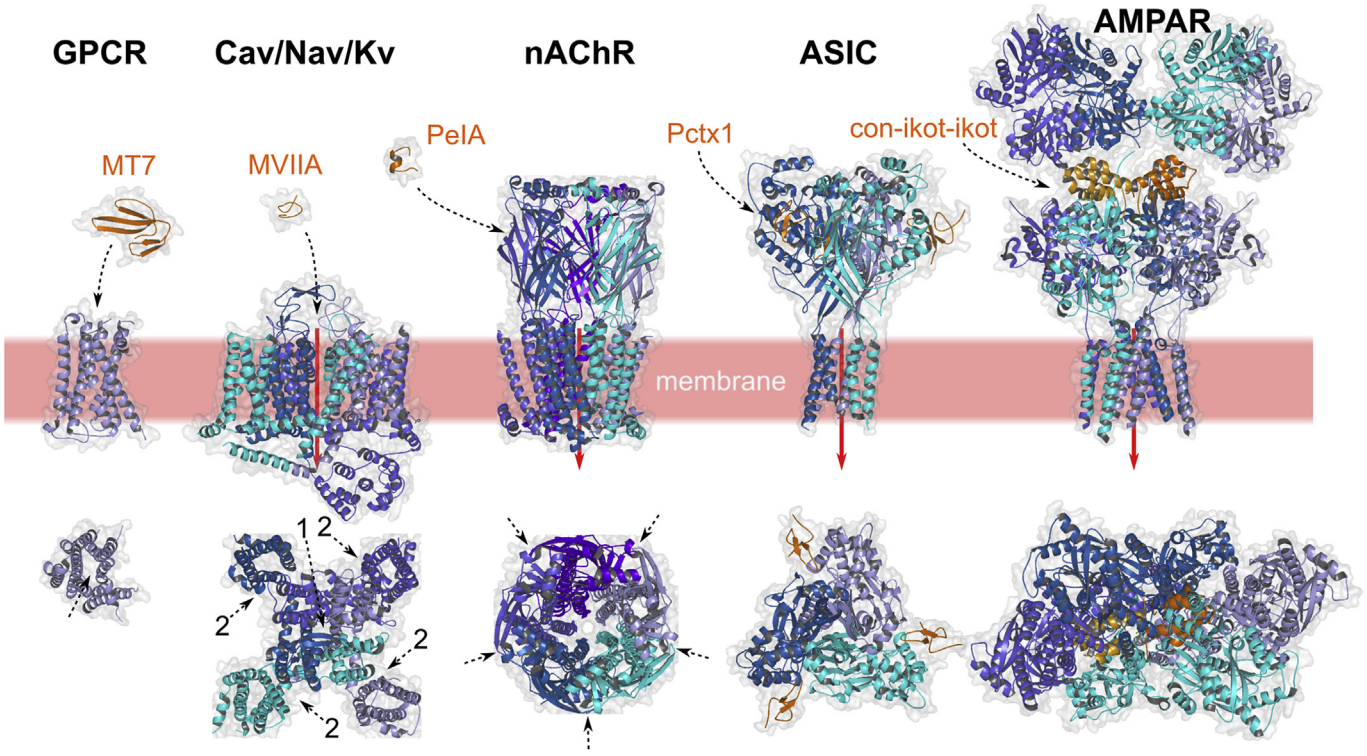

Fig. 1. Examples of membrane proteins targeted by venom toxins: the G-protein coupled receptors (GPCRs), the voltage-gated calcium/sodium/potassium ion channels (Ca_V/Na_V/K_V), the nicotinic acetylcholine receptors (nAChR), the acid-sensing ion channels (ASIC) and the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR). All these targets beside the GPCRs are ion channels. Representative toxins are shown in orange, and experimental structures of the targets are represented in blue colours. For each target, a view across the lipid membrane (pink) is at the top and a view from the extracellular side of the membrane is at the bottom. Red arrows indicate the flux of ions when the ion channels are open. The mamba snake toxin MT7 antagonises selectively the M1 muscarinic receptor, which is a GPCR. The crystal structure of the human M2 muscarinic receptor is here represented for illustration (Protein Data Bank PDB identifier: 4mqs) (Kruse et al., 2013). The marine cone snail toxin MVIIA specifically blocks the pore of human $Ca_V2.2$. The electron microscopy structure of the rabbit $Ca_V1.1$ is here represented for illustration (PDB: 5gjv) (Wu et al., 2016). Most toxins targeting voltage-gated channels act by blocking the pore (arrow numbered 1 on the bottom) or by blocking the voltage sensor domains in various states (arrows 2). The cone snail toxin PeIA inhibits the α9α10 nAChR by competing with acetylcholine in the orthosteric sites, which are located between subunits in the ligand binding domain (indicated by arrows on the bottom). The nAChRs are pentamers and there is consequently a maximum of five binding sites. The crystal structure of the human α4β2 nAChR is here represented for illustration (PDB: 5kxi) (Morales-Perez et al., 2016). The spider psalmotoxin-1, or PcTx1, binds at the interface between each subunit of ASIC 1a, stabilising the open state. The crystal structure of the complex between PcTx1 and chicken ASIC 1a is here represented (PDB: 4fz0) (Baconguis and Gouaux, 2012). The cone snail toxin con-ikot-ikot blocks the desensitisation of AMPAR by binding as a dimer on top of the ligand-binding domain, plying open the pore of the channel (Chen et al., 2014). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)