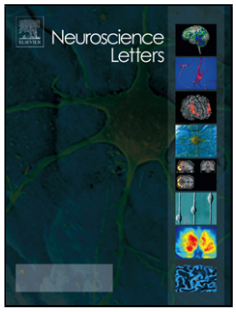

Title: A complicated complex: ion channels, voltage sensing, cell membranes and peptide inhibitors

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A complicated complex: ion channels, voltage sensing, cell membranes and peptide inhibitors

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Highlights:

- Definition of voltage sensing voltage-gated ion channels
- The structure and gating cycle of voltage-gated ion channels
- Venom peptides that inhibit $Na_V1.7$ by modulation of voltage sensing
- Channels that are likely off targets of $Na_V1.7$-inhibiting peptides
- Kinetic models accounting for peptide:membrane interactions in channel inhibition
- Impact of lipid composition in studies of channel:peptide interactions

Abstract

Voltage-gated ion channels (VGICs) are specialised ion channels that have a voltage dependent mode of action, where ion conduction, or gating, is controlled by a voltage-sensing mechanism. VGICs are critical for electrical signalling and are therefore important pharmacological targets. Among these, voltage-gated sodium channels (Na_Vs) have attracted particular attention as potential analgesic targets. Na_Vs, however, comprise several structurally similar subtypes with unique localisations and distinct functions, ranging from amplification of action potentials in nociception (e.g. $Na_V1.7$) to controlling electrical signalling in cardiac function ($Na_V1.5$). Understanding the structural basis of Na_V function is therefore of great significance, both to our knowledge of electrical signalling and in development of subtype and state selective drugs. An important tool in this pursuit has been the use of peptides from animal venoms as selective Na_V modulators. In this review, we look at peptides, particularly from spider venoms, that inhibit Na_Vs by binding to the voltage sensing domain (VSD) of this channel, known as gating modifier toxins (GMT). In the first part of the review, we look at the structural determinants of voltage sensing in VGICs, the gating cycle and the conformational changes that accompany VSD movement. Next, the modulation of the analgesic target $Na_V1.7$ by GMTs is reviewed to develop bioinformatic tools that, based on sequence information alone, can identify toxins that are likely to inhibit this channel. The same approach is also used to define VSD sequences, other than that from $Na_V1.7$, which are likely to be sensitive to this class of toxins. The final section of the review focuses on the important role of the cellular membrane in channel modulation and also how the lipid composition affects measurements of peptide-channel interactions both in binding kinetics measurements in solution and in cell-based functional assays.

Keywords: Voltage-gated ion channel, venom peptide, gating modifier toxins, receptor-ligand complex, lipid binding, cell membrane.