Cryo-EM structure of a gating modifier–sodium channel complex reveals the complex molecular basis of allosteric modulation of channel gating

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Over a period of more than 300 million years, spiders evolved pharmacologically complex venoms that are dominated by disulfide-rich insecticidal toxins. Insect voltage-gated sodium channels are one of the primary targets of these spider toxins. In contrast with chemical insecticides such as DDT and pyrethroids, these toxins do not target the pore of the channel but rather allosterically modulate channel gating by interfering with movement of the channel's voltage sensor domains. There has been much speculation, based on indirect experimental evidence, about the molecular mechanism of gating modifier toxins, but no structural data has been available. In collaboration with Nieng Yan's lab at Princeton, we recently solved the first ever structure of a gating modifier toxin complexed with a voltage-gated sodium channel. The 2.8 Å resolution cryo-EM structure reveals that the toxin-channel interaction is much more complex than envisaged by any previous model of the interaction, with the peptide toxin (Dc1a) making key contacts with both the voltage sensor and pore domains. This structure provides a template for rational engineering of therapeutics and insecticides that target voltage-gated sodium channels with enhanced potency and selectivity. In addition, we took advantage of the Dc1a-stabilised channel to solve the structure of the channel complexed with tetrodotoxin (TTX), the lethal pore blocking toxin found in Japanese pufferfish and the deadly blue-ringed octopus. The 2.6 Å resolution cryo-EM structure of the TTX-channel complex provides intimate details of how this small 300-Da toxin prevents access of sodium ions to the channel pore, and it demonstrates that cryo-EM is now approaching resolutions suitable for structure-aided development of ion channel drugs.