How is electrical signal generated? Structural and mechanistic investigations of Na_v channels

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The voltage-gated sodium (Na_v) channels are responsible for the initiation and propagation of action potentials. Being associated with a variety of channelopathies, they are targeted by multiple pharmaceutical drugs and natural toxins. We determined the crystal structure of a bacterial Na_v channel Na_vRh in a potentially inactivated state a few years ago, which is a homotetramer in primary sequence but exhibits structural asymmetry. Employing the modern methods of cryo-EM, we recently determined the near atomic resolution structures of a Na_v channel from American cockroach (designated Na_vPaS) and from electric eel (designated $EeNa_v1.4$). These structures reveal the folding principle and structural details of the single-chain eukaryotic Na_v channels that are distinct from homotetrameric voltage-gated ion channels. Unexpectedly, the two structures were captured in drastically different states. Whereas the structure of Na_vPaS has a closed pore and the four VSDs in distinct conformations, that of $EeNa_v1.4$ is open at the intracelluar gate with VSDs exhibiting similar "up"states. The most striking conformational differenc occurs to the III-IV linker, which is essential for fast inactivation. The III-IV undergoes a pronounced repositioning from Na_vPaS to $EeNa_v1.4$, resulting in the insertion of the IFM fast inactivation motif on the III-IV linker into the corner enclosed by the S4-S5 and S6 segments in repeats III and IV of $EeNa_v1.4$. Based on the structural features, we suggest an allosteric blocking mechanism for fast inactivation of Na_v channels by the IFM motif. Structural comparison of the conformationally distinct $EeNa_v1.4$ and Na_vPaS provides important insights into the electromechanical coupling mechanism of Na_v channels and offers the 3D template to map hundredes of disease mutations.