Unveiling the sodium channel's open conformation

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Voltage-gated sodium (Na_v) channels are essential for electrical signaling in excitable cells, yet structural snapshots of the conductive state have remained elusive. In a recent study published in *Vita*[1], Nieng Yan and colleagues report the long-sought high-resolution cryo-electron microscopy structure of a eukaryotic Na_v channel in an open state, uncovering the molecular mechanisms of ion conduction and fast inactivation.

Na_v channels underpin the initiation and propagation of action potentials, with their activation and inactivation governing the spatiotemporal dynamics of electrical signals[2]. As voltage-gated ion channels, Na_v channels cycle through three main states: the resting state, characterized by hyperpolarized (down or resting) voltage-sensing domains (VSDs) and a non-conductive (closed) pore domain (PD); the activated state, featuring depolarized (up or activated) VSDs and a conductive (open) PD; and the inactivation state, where depolarized (up or activated) VSDs are coupled with a non-conductive (closed) PD. To fully elucidate the working mechanisms of Na_v channels, ideally, one should determine the structures of the same channel in all major states. However, structure determinations are typically carried out in aqueous solution at zero membrane potential, where the VSDs of Na_v channels adopt activated conformations. Meanwhile, to ensure the directional and repetitive firing of action potentials, activated Na_v channels usually undergo fast inactivation, wherein the Ile/Phe/Met (IFM) motif binds to the receptor site close to the intracellular gate, preventing continuous channel opening[3]. For these reasons, most available structures of eukaryotic Na_v channels — including human $Na_v1.1$ to $Na_v1.8$ — have been limited to inactivated states[4-7], leaving the resting state and the activated state poorly characterized. Using the analgesic target $Na_v1.7$ as a model, the Nieng Yan laboratory has been systematically elucidating molecular mechanisms of Na_v channels by capturing its structures in different conformations.

To trap $Na_v1.7$ in an open conformation, the authors incubated the protein sample with the neurotoxin veratridine (VTD). VTD exerts multiple effects on Na_v channels: it promotes channel opening at more negative potentials, delays inactivation, and reduces peak current amplitude[8,9]. Aligning with these electrophysiological observations, the authors determined two high-resolution cryo-electron microscopy structures of VTD-bound $Na_v1.7$ in different conformations. In one structure ($Na_v1.7V_I$), which resembles the apo inactivated-state structure ($Na_v1.7_I$), VTD binds close to the IFM motif (Site I). In the other structure ($Na_v1.7V_O$), VTD traverses the central cavity of the PD (Site C), dilating the intracellular gate to a constriction diameter of 8.2 Å — large enough for the permeation of hydrated Na^+ ions with a diameter of 7.2 Å. This open conformation was further validated by molecular dynamics simulations, which clearly showed that Na^+ ions can flow freely through the gate in $Na_v1.7V_O$, but not in other structures of Na_v channels[1]. By comparing the activated-state structure ($Na_v1.7V_O$) with the inactivated-state structure ($Na_v1.7_I$), the authors propose an updated "door wedge" model to decipher the fast inactivation of Na_v channels. When the IFM motif (the "wedge") docks into its receptor site between domains III and IV, it pushes the cytosolic half of $S6_{IV}$ towards the gate center by 4.5 Å via hydrophobic interactions, while simultaneously pulling the cytosolic half of $S6_{III}$ towards $S6_{IV}$ by 8.0 Å via both covalent and hydrophobic interactions. These motions of $S6_{IV}$ and $S6_{III}$ further induce concerted conformational changes of the cytosolic halves of $S6_I$ and $S6_{II}$: $S6_I$ undergoes an $\alpha \rightarrow \pi$ helical transition, and S6II moves towards the gate center by 4.3 Å. Meanwhile, an $\alpha \rightarrow \pi$ helical transition also occurs in $S6_{IV}$. These movements of the cytosolic halves of the four S6 segments collectively narrow the intracellular gate, trapping the channel in a non-conductive inactivated state.

The determination of the activated-state structure of $Na_v1.7$ represents a landmark advance, with profound implications in methodological, mechanistic, and therapeutic perspectives. First, it reinforces that ligands are powerful tools for trapping ion channels in rare but functionally relevant conformations, provided their effects are supported by rigorous electrophysiological data. Notably, the ligand-induced new conformations of ion channels remain difficult to predict using current AI models. Second, the high-resolution activated-state structure of $Na_v1.7$ provides a precise model for elucidating the ion conduction, activation, and inactivation of eukaryotic Na_v channels, a key step toward a comprehensive understanding of their working mechanisms. Third, this structure offers a template for the rational design of subtype-selective drugs specifically targeting the activated state of $Na_v1.7$, a long-sought goal for pain management with reduced off-target effects. Meanwhile, key questions regarding molecular mechanisms of eukaryotic Na_v channels, including voltage activation and slow inactivation, need to be addressed in the future. Specifically, capturing the resting-state structures of Na_v channels will likely require the introduction of mutations, ligands, cross-linking, or liposome-based reconstitution systems to mimic *in vivo* hyperpolarization conditions[10].

COMPETING INTERESTS

The author declares no competing interests.

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ADDITIONAL INFORMATION

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