Ion Conduction in Cyclic Nucleotide-gated Ion Channel

Deciphering Ion Permeation, Selectivity and Gating Mechanism in CNGA1 Channel

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In Short

- Simulate ion permeation of different monovalent cations in CNGA1 channels.
- Identify conformational changes in the selectivity filter between open and closed states.
- Investigate the effect of Ca^{2+} binding in ion permeation and gating of CNGA1 channel

Mammalian cyclic nucleotide-gated (CNG) channels are crucial components of numerous signal transduction pathways, most classically in the visual and olfactory sensory systems [1]. Although classified as members of the voltage-gated ion channels, CNG channels are mostly gated by ligands rather than voltage. Structurally, they share similarity with voltage-gated K^+ channels, assembling as tetramers with each subunit composed of six membrane-spanning segments and a C-terminal cytoplasmic cyclic nucleotide binding domain (CNBD) that modulates channel opening (Figure 1A) [2]. The transmembrane domain part of the CNG channels function as non-selective cation channels, conducting a number of monovalent cations. Previous single-channel patch-clamp electrophysiology measurements revealed a following conductance relationship for alkali metals in the CNGA1 channel: $Na^+ > K^+ > Rb^+$ [3].

In 2017, the first putative open structure of the TAX-4 CNG channel became available by cryo electron microscopy (cryo-EM) [4]. Earlier this year, high-resolution structures of human CNGA1 channel have been determined for both ligand-bound open and apo closed states, revealing the structural mechanism of cGMP-dependent gating in CNGA1 (Figure 1B) [5]. This study revealed also the ion binding profile of different monovalent ions as well as Ca^{2+} in the selectivity filter (SF). Interestingly, although the ion binding profiles of open and closed CNGA1 in presence of K^+/Ca^{2+} are clearly different from the electron density map, cryo-EM data did not reveal significant conformational change in the SF.

Within this project, we have overall three aims: (i) We will determine whether the new cryo-EM structures of the CNGA1 [4] represent the conductive state. To this end, we will simulate ion permeation of different alkali metals in the CNGA1 channels and compare them with the experimental single-channel recording data collected by our collaborators in Jena. (ii) Cryo-EM structures revealed no significant conformational changes in the SF between the open and closed CNGA1 channels. We will simulate both open- and closed-state of CNGA1 and investigate whether conformational change of the SF can be observed in the MD simulations. This result will be especially interesting, because previous experimental studies suggested that the SF functions as a gate in the CNG channels [6], which contradicts the finding of Cryo-EM. (iii) We will use the newly developed multi-site Ca^{2+} parameter [7] to simulate Ca^{2+} binding profile in CNG channels to investigate the effect of Ca^{2+} binding in ion permeation and gating of CNGA1 channel.

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More Information

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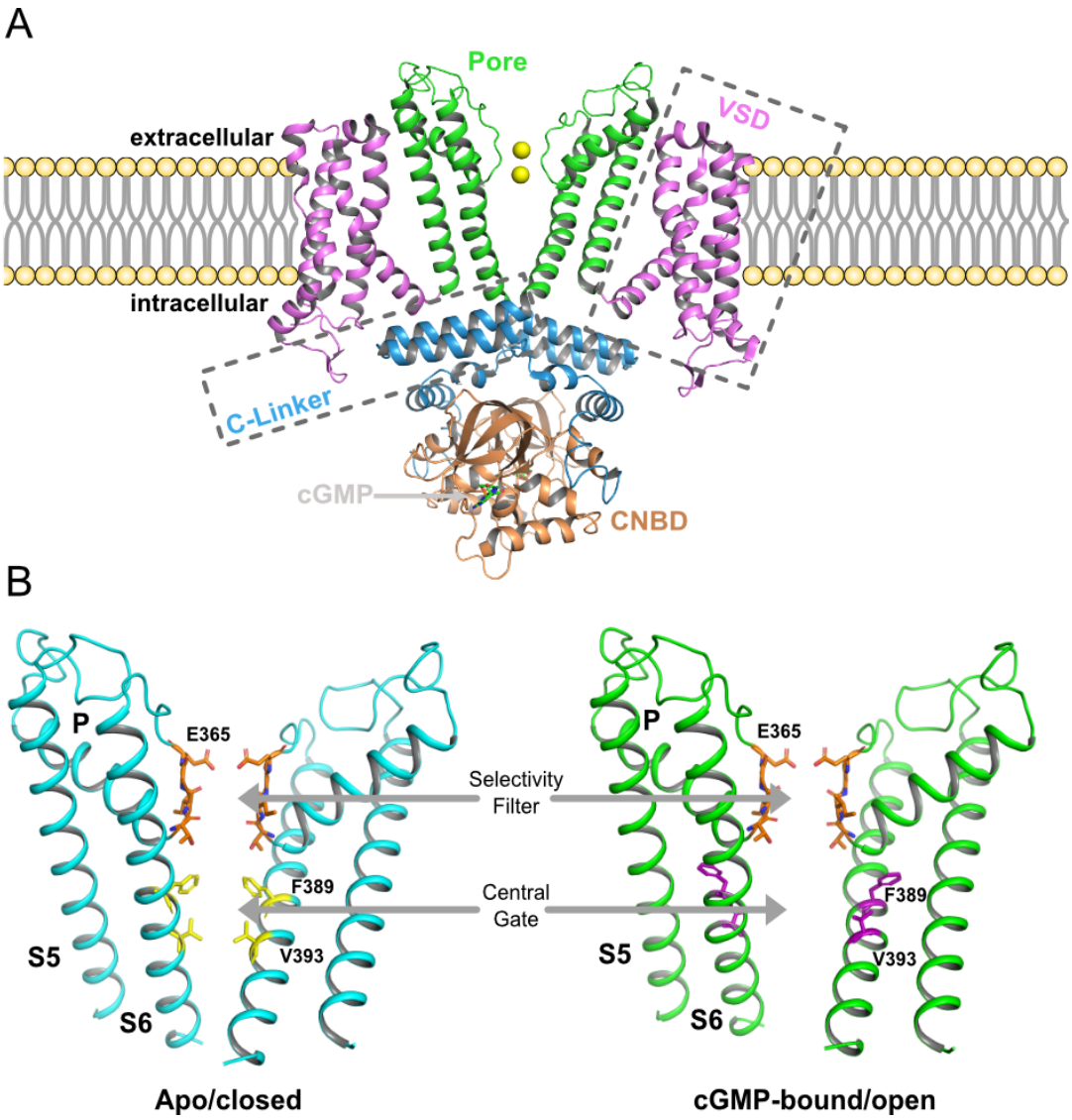

Figure 1: Structures of human CNGA1 channel. ***(A)*** *Structure of cGMP-bound CNGA1 within membrane.* ***(B)*** *The ion conduction pore of the apo/closed (left, PDB ID: 7LFT) and cGMP-bound/open (right, PDB ID: 7LFW) CNGA1. The front and rear subunits are removed for clarity. Key gating and filter residues are shown as sticks.*

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Project Partners

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