Iris-Like Mechanism of Pore Dilation in the CorA Magnesium Transport System

Nilmadhab Chakrabarti1, Chris Neale1,2, Ian Payandeh3, Emil F. Pai2,3, Regis Pomes1,2
1Hospital for Sick Children, Toronto, ON, Canada, 2University of Toronto, Toronto, ON, Canada, 3Ontario Cancer Institute, Toronto, ON, Canada.

Magnesium translocation across cell membranes is essential to numerous physiological processes. Three crystal structures of the CorA magnesium transport system have recently revealed a surprising architecture, with a bundle of giant α-helices forming a 60-A-long pore which extends beyond the membrane before widening into a funnel-shaped cytosolic domain. The presence of divergent cations in putative intracellular regulation sites suggests that these structures correspond to the closed conformation of CorA. To examine the nature of the conduction pathway, we performed 110-ns molecular dynamics simulations of two of these structures in a lipid bilayer with and without regulatory ions. Results show that a 15-A hydrophilic constriction straddling the membrane-cytosol interface constitutes a steric bottleneck whose location coincides with an electrostatic barrier opposing cation translocation. Structural relaxation induced by the removal of regulatory ions leads to concerted changes in the tilt angle and face shift was (26.2° to 42.0°, 48.0°) compared to the average of 105 CM structures for GPR35 TMH4 (18.04° ± 4.95°, −123.39° ± 58.1°, 1.63° ± 11.83°). The GPR35 one residue N-terminal TMH2 proline shift created a face shift of 53.04° ± 27.21° compared to 96.8° for the β2AR TMH2. The additional proline in GPR35 TMH5 resulted in a bend and face shift of (12.76° ± 4.74°, 47.43° ± 22.74°) vs. (6.0°, 80.1°) for the β2AR.

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Human Copper Transporter 1: Model-Structure, Function and Motion

Maya Schushan1, Yariv Barkan1, Turkan Hallioglu1, Nir Ben-Tal1
1Tel-Aviv University, Tel-Aviv, Israel, 2Bogazici University, Istanbul, Turkey.

Copper is an indispensable nutrient for functioning of various cell processes. Human CTR1 (hCTR1) is a member of the eukaryotic copper transporter family, essential for copper uptake in human cells and have been also implicated in cellular sensitivity to some chemotherapeutic drugs. We constructed a Cα-trace model of the transmembrane region of this trimeric transporter using cryo-electron microscopy and evolutionary data. The model-structure was supported by mutagenesis data, and provided a structural perspective of the roles of the evolutionary conserved and essential sequence motifs, MxxxM of TM2 and GxxxG of TM3. Specifically, Met150 and Met154 of the MxxxM motif, situated at the extracellular gate. To gain further insight into dynamics and cooperativity of hCTR1, we investigated the structural fluctuations of the model-structure using elastic network models. The analysis revealed that the most prominent hinges correspond to residues of the known sequence motifs, indicating their importance for protein functional motion. Moreover, we identified a role for TM2 in coupling between the three monomers of the TM region via rotational symmetry. Of the two main structural fluctuations modes, the slowest mode introduced structural changes mainly at the cytoplasmic, wide end of the pore, whereas another highly cooperative fluctuation manifested the activation of the extracellular pore entrance coupled to motion at the cytoplasmic ends.

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Concerted Motion and Hydration of the Beta-2-Adrenergic Receptor Revealed by Microsecond Time Scale Molecular Dynamics

Tod D. Romo1, Alan Grossfield1, Michael C. Pitman2
1University of Rochester Medical School, Rochester, NY, USA, 2IBM, Yorktown Heights, NY, USA.

The recent crystallographic structures of class A G protein-coupled receptors have shown important differences with their archetypal model, rhodopsin, such as the apparent breaking of the ionic lock that stabilizes the inactive structure. Here, we characterize a 1.02 microsecond all atom simulation of an apo beta-2-adrenergic receptor that is missing the 3rd intracellular loop in order to better understand the inactive structure. The lock rapidly reforms, although there is an activation-precursor-like event where the ionic lock opens for approximately 200ns, accompanied by movements in the transmembrane helices associated with activation. The lock is also found to exist in three states: closed, semi-open with a bridging water molecule, and open. The interconversion of the lock states involves concerted motion of the entire protein. We characterize these states and the concerted motions underlying their interconversion through principal component analysis. These motions are subtle, however, as the structure is found to be remarkably rigid throughout simulation. There is also a rapid influx of water into the protein core along with a slight expansion of the structure relative to the crystal model, leaving the core of the receptor persistently hydrated. We further characterize the structure and dynamics of the internal waters by applying pattern matching methods.

Activation Pathways of Agonists, Partial Agonists and Inverse Agonist in Beta1 and Beta2 Adrenergic Receptors

Supriyo Bhattacharya, Nagarajan Vaidehi
Beckman Research Institute of City of Hope, Duarte, CA, USA.

Modulation of cell signaling by ligands of different efficacies via G-protein coupled receptors (GPCRs), depends intrinsically on the effect of the ligand on the dynamics between the multiple conformational states of these proteins. Ligands with different efficacies can remodel the energy landscape of the receptors, thereby perturbing this conformational equilibrium in many ways depending on the nature of the ligand, and the G-proteins that the receptor couples to, thereby conferring functional specificity. Understanding activation dynamics and pathways is vital in designing functionally specific drugs for GPCRs.