Cation permeation in ion channels

Investigation of selectivity and conductance of AMPA-type glutamate receptors with computational electrophysiology

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In Short

- Deeper understanding the molecular mechanism of AMPAR cation permeation
- Simulation and analysis of the structural dynamics of cation permeation in AMPAR under different conditions
- Simulation and analysis of the structural dynamics of cation permeation in NaK mutated with AMPAR selectivity filter
- Observe conductance and selectivity under several conditions

1. Introduction and objectives

Ion transport across membranes is one of the most fundamental processes in biology. Ions like Na^+, K^+ and Ca^{2+} are not only mobile charges but have particular roles in specifying cellular functions. Particularly in the brain, ion channels selective for potassium or sodium have a key role in defining the shape and speed of action potentials, self-propagating waves of excitability that spread throughout cells and denotes excitability. At the synaptic junctions between cells, a further fundamental conduction occurs - the opening of glutamate receptor ion channels following the binding of their cognate neurotransmitter. Through this mechanism, a mix of cations (including Na^+, K^+ and Ca^{2+}) can permeate the synaptic membrane. In this way one cell can excite its neighbour and drive it to fire classical action potentials. In special cases, active membranes in cortical neurons incorporate a suite of calcium permeable ion channels to generate local calcium spikes in dendrites, that are involved in perception. But uncontrolled calcium permeability is dangerous for cells and is thought to underlie motor neurone disease and may contribute to other pathologies.

For these reasons, we are highly motivated to investigate the molecular details of cation permeation in the AMPAR-type glutamate receptor using molecular dynamics simulations. Until recently, the best understood channels in terms of ion permeation were bacterial channels selective for potassium, e.g. KcsA. These have been used as model systems to illustrate and clarify fundamental physical principles governing ion selectivity of pores [1,2].

These principles were expected to be conserved across other tetrameric channels. However, more recently, non-selective tetrameric channels that have properties similar to glutamate receptors ion channels, particularly the prokaryotic NaK channels, have emerged. These other channels have short selectivity filters with heterogeneous structures. Simulations using this channel allowed us to develop models of non-selective cation permeation [3]. With computational and structural experiments investigating non-selective permeation are well underway in bacterial channels, the situation in glutamate receptor ion channels from the mammalian central nervous system is much less clear and likely more complicated. Our model channel of interest is the AMPA-type glutamate receptor, for which several structural models are available. We want to examine basic permeation properties of ions including sodium and potassium, and then understand how the molecular composition of the channel can change permeation characteristics. For example, a key event in biogenesis of glutamate receptors is the RNA editing of a single residue in the pore loop from glutamine to arginine. This editing (which occurs only in the GluA2 subunit) stops calcium permeability, reduces the conductance of monovalent ions and makes receptors insensitive to polyamine block. Although we know that this edited residue is present in the pore, we do not know the copy number required for each property, and we do not know the copy number present in receptors in the central nervous system. Therefore, in silico studies with receptor pores with variable numbers and arrangement of arginine residues at the editing site are expected to give insight into these fundamental molecular mechanisms.

2. Results

We simulated AMPAR with the monovalent cations Na^+, K^+ and Cs^+. For all three we obtained a conductance that was similar to measured single channel recordings. We identified the narrow part of the pore with two adjacent glutamines (Q_{586} and Q_{587}) to be the single highest energy barrier in the channel. The remainder of the selectivity filter plays only a minor role in cation selectivity and permeation mechanism (see figure 2). Our results are available in a preprint on bioRxiv [5].

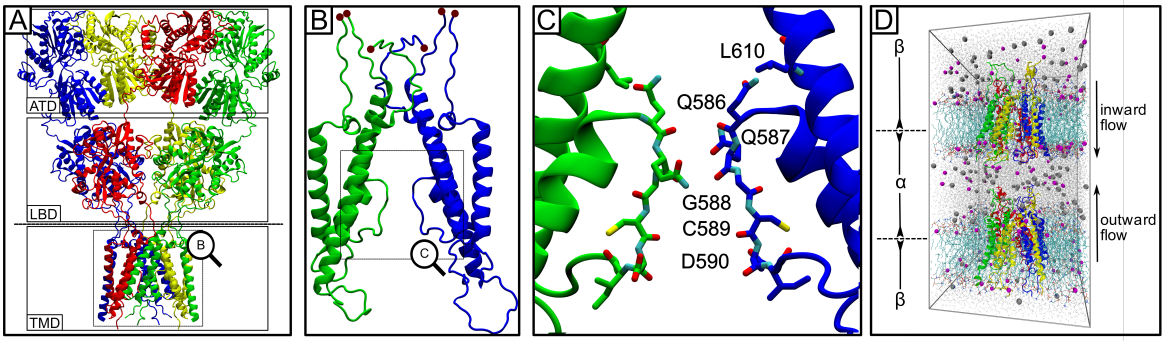

Figure 1: (A) The full AMPA receptor consists of four subunits. We are mainly interested in ion permeation through the transmembrane domain (TMD). (B) Only the TMD was simulated (two opposite subunits drawn for a better view). (C) The selectivity filter is responsible for selectivity and is subject of our investigations. (D) Our simulation system according to the computational electrophysiology setup [4]. Two separate compartments with different ion concentrations are separated by two channel containing lipid bilayers.

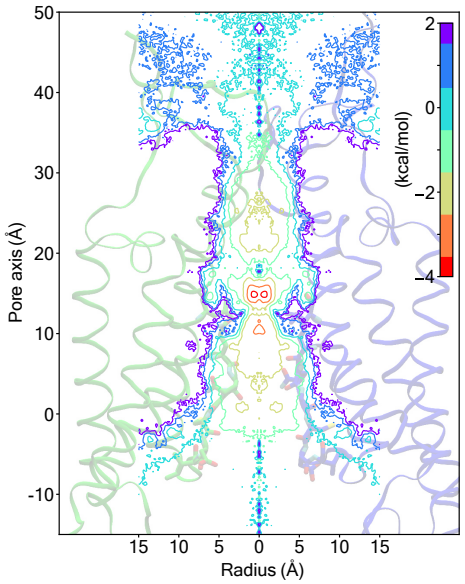

Figure 2: Ion occupancy of potassium ions in AMPAR observed over various permeation events. The central glutamines (around 15 Å pore axis) build up the narrowest point of the selectivity filter and the highest energy barrier.

3. Future investigations

AMPA receptors are non-selective also regarding the charge of cations: divalent Ca^{2+} permeates through AMPAR quite well. Since excessive calcium permeation harms cells all GluA2 type AMPARs are subject to a post-transcriptional mutation to prohibit calcium permeation. The upper glutamine is mutated to arginine ($Q_{586}R$). We want to investigate how many of those mutations are necessary to block calcium, the mechanism of calcium block and the influence on the conductance of monovalent cations by molecular dynamics.

WWW

https://www.leibniz-fmp.de/sun;https://www.leibniz-fmp.de/plested

More Information

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