Gating Mechanism of the AMPA-type Glutamate Receptors

Investigation of Gating and Ion Permeation in AMPA-type Glutamate Receptors

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In Short

- Simulation of ion permeation in AMPA receptor using molecular dynamics based computational electrophysiology.
- Determine different sub-conductive states of the AMPA receptor.
- Investigate how many glutamines need to be replaced by arginines in order to reduce calcium permeability at the physiological condition.

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) belong to the ionotropic glutamate receptor family and are among the most important neurotransmitter activated cation channels in the human brain. Since they are responsible for fast excitatory signal transmission, they are important for all higher brain functions. Dysfunctions in AMPAR lead to severe neurodevelopmental disorders [1]. Due to conformational changes induced by neurotransmitter binding in the extracellular ligand binding domain (LBD) of the receptor, the transmembrane domain part become open for a number of monovalent cations (K^+ and Na^+) as well as Ca^{2+} and functions as an ion channel. The AMPAR ion channel exhibits different conductive states depending on how many glutamates are bound to the LBD. Resolving the ion conductance and gating mechanism on an atomistic scale is of enormous interest. This includes the investigation of ion permeation of monovalent and divalent cations at physiological condition as well deciphering subconductive states with partially bound glutamate. Due to the limitations of wet lab experiments regarding the spatial resolution, atomistic molecular dynamics (MD) simulation became a widely employed theoretical approach to study ion conduction and gating at atomistic details.

The selectivity of the channel is influenced by a natural occurring post transcriptional editing in the selectivity filter region of the channel. Changing a glutamine to an arginine residue in a vital position of the selectivity filter (SF) alters the selectivity from entirely non-selective among cations into a channel that is only selective for monovalent ions. The tetrameric structure of the receptor allows for different compositions of glutamine and arginine residues at this position. The key question we want to answer is, is a single arginine enough to reduce calcium permeation?

In our previous study that was supported by the HLRN, we investigated non-selective cation permeation in an unedited form of AMPA-type glutamate receptor [2]. We revealed a single major ion binding site for Na^+ and K^+ in the pore, representing the simplest SF structure for any tetrameric cation channel of known structure. The minimal SF comprised only Q586 and Q587, and other residues on the cytoplasmic side formed a water-filled cavity with a cone shape that lacked major interactions with ions. We observed that Cl^- readily enters the upper pore, explaining anion permeation in the RNA-edited (Q586R) form of GluA2. A permissive architecture of the SF accommodated different alkali metals in distinct solvation states to allow rapid, nonselective cation permeation and copermeation by water.

Within this new project, we want to further enhance our understanding on gating and ion permeation of AMPA-type receptor at physiological condition. We have two main aims here: (I) From previous long time-scale MD simulations combined with Markov state modeling, together with our collaborators we identified an intermediate state of the channel pore that remained stable for several hundreds of nano-seconds equilibrium MD simulations. This intermediate state may explain previously identified sub-conductances of AMPA using electrophysiology. We will therefore simulate monovalent ion permeation of this intermediate state by means of computational electrophysiology method and compare the derived conductances with the open form of AMPA as well as with the experiments; (II) We want to address the question how many glutamines need to be replaced by arginines in order to reduce calcium permeability at the physiological condition. For that we will simulate ion permeation through the open-form of AMPAR with a mixture of Na^+ and Ca^{2+} at different Q/R editing forms (Figure 1).

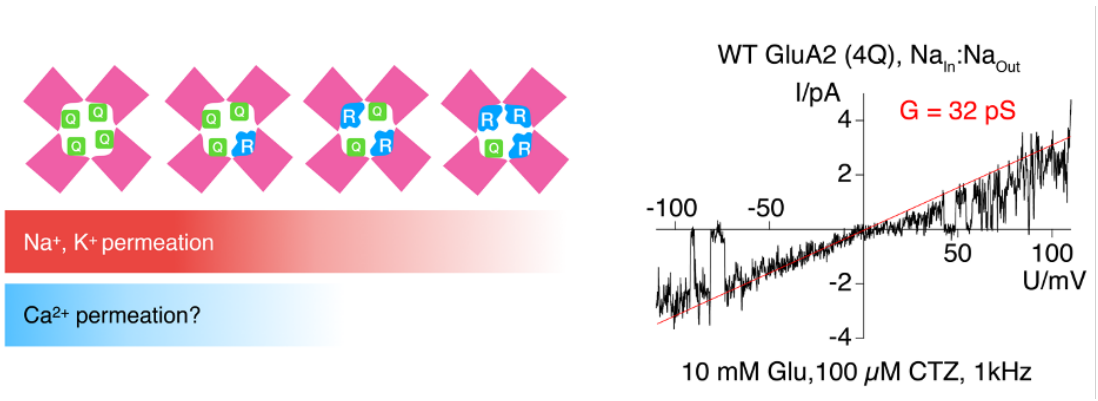

Figure 1: The Q/R switch in the pore loop and AMPA receptor ion current. *Left panel: We know that calcium permeation is reduced by incorporation of R-containing subunits. But is a single Arginine residue enough to stop calcium permeation? Right panel: Single channel of current-voltage relation for a 4-Q containing GluA2 channel.*

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https://www.leibniz-fmp.de/de/plested
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More Information

[1] Salpietro, V., Dixon, C.L., Guo, H. *et al.* AMPA receptor GluA2 subunit defects are a cause of neurodevelopmental disorders. *Nat Commun* **10,** 3094 (2019). doi:10.1038/s41467-019-10910-w

[2] Biedermann, J., Braunbeck, S., Plested, A. J. R., Sun, H. Nonselective cation permeation in an AMPA-type glutamate receptor. *PNAS* (2021) doi:10.1073/pnas.2012843118

Project Partners

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