No. 202403

Creation of Novel Ion Channels with Lithium Selectivity

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Summary

Selective permeation of Na^+ is crucial for neural activity since voltage-gated sodium channels (Navs) contribute to a rapid increase in action potentials in neuronal signaling. Li^+ is known to permeate Navs with about 70% efficiency of Na^+, and Li^+ has been used for a long time as a treatment for bipolar disorder. However, the difference between the permeation mechanism of Na^+ and Li^+ in Navs remained unclear.

To elucidate the mechanism of Li^+ permeation, we searched for a mutant that increases Li^+ selectivity in NavAb, a prokaryotic Nav whose structure is most analyzed. NavAb forms a tetramer, with an ion pathway at the center of the tetramer. The five most important residues (TLESW) are named the selectivity filter (SF). We found that Li^+ selectivity increases when the serine residue in the SF is mutated to several small side chain residues by electrophysiological measurement. We determined the crystal structure of these mutants. The mutated SF residue is located at the outer entrance of the ion pathway. In smaller-side-chain mutants, this entrance was found to be widened. In the glycine mutant, additional water molecules are located in the space created by the mutation. The position of this water molecule corresponds to that of the hydroxyl group of the serine residue in the wild-type channel. Considering the glycine mutant's increased Li^+ selectivity, the hydroxyl group of the entrance of the ion pathway disturbs Li^+ permeation. Because Li^+ has a smaller ionic radius than Na^+, it exchanges hydrated waters more slowly than Na^+. Due to this property, in the wild-type channel, Li^+ takes a longer time to pass through the hydroxyl group of serine residue compared to Na^+. The lack of hydroxy group in the glycine mutant may facilitate Li^+ passage, enhancing Li^+ selectivity.

These results provide the first insight into the molecular mechanism increasing Li^+ selectivity and may aid in the development of novel ion channels with enhanced Li^+ permeability