“The Structure of the Potassium Channel: Molecular Basis of K⁺ Conduction and Selectivity”


Abdallah Bukari

BBSI 2008

Advisor: Dr. Madura, Duquesne University
Background

Cells coated in a membrane, typically a phospholipid bilayer, which protects intracellular components from extracellular environment.

Proteins embedded within the membrane allow for diffusion of select ions into the cell.

In *streptomyces lividans*, potassium ions diffuse through $K^+$ channels.

Potassium channels have diverse methods of gating (opening and closing of pore).

However, all known $K^+$ channels contain a critical signature sequence and have similar characteristics: $K^+$ is 10,000 times more permeant than $Na^+$ and evidence indicates a multi-ion conduction mechanism (multiple ions queuing single-file in long, narrow pore).

Figure from Engelman, DM (2005) Membranes are more mosaic than fluid. Nature 438, 578-580.
In all cases, the K⁺ channel protein is a tetramer, usually made up of four identical subunits. Each subunit has two transmembrane spanning α-helices. So-called “inverted tepee” architecture. Both intracellular and extracellular entryways are negatively charged. Entering selectivity filter requires dehydration of K⁺ ions. Internal pore and cavity wall primarily hydrophobic, while filter is lined by amino acids with polar side chains.
Essential Questions

“Two aspects of ion conduction by K⁺ channels have tantalized biophysicists for the past quarter century.

First, what is the chemical basis of the impressive fidelity with which the channel distinguishes between K⁺ and Na⁺ ions, which are featureless spheres of Pauling radius 1.33 Å and 0.95 Å, respectively?

Second, how can K⁺ channels be so highly selective and at the same time, apparently paradoxically, exhibit a throughput rate approaching the diffusion limit? The $10^4$ margin by which K⁺ is selected over Na⁺ implies strong energetic interactions between K⁺ ions and the pore. And yet strong energetic interactions seem incongruent with throughput rates up to $10^8$ ions per second.

*How can these two essential features of the K⁺ channel pore be reconciled?*”
A Closer Look: Surface

Surface representation of channel protein

Blue = positive charge
White = no charge
Red = negative charge
Yellow = hydrophobic
Green spheres represent K⁺ ions

The negative charge of both intracellular and extracellular entryways attracts cations and repels anions
A Closer Look: Cavity

Bottom 2/3 of tunnel is water-filled
A K⁺ ion that enters from the bottom can go 22 Å without shedding its waters
Thus, the hydrophobic residues at the bottom of the tunnel do not prevent water from entering the cavity, but keep the K⁺ ions from sticking to the walls of the pore
Location of cavity is significant - facilitates ions leaving selectivity filter by lowering electrostatic barrier
Amino to carboxyl orientation of helices also helps ions enter cavity from above
Ultimately the cavity facilitates a high throughput

Figure from Freeman, WH (2007) Biochemistry, Sixth Edition
Ions entering the selectivity filter (only 3 Å in diameter) must lose waters and interact with C=O groups, which function as “surrogate waters”

2 main features:

- main chain atoms form “a stack of sequential oxygen rings,” creating numerous closely spaced sites of appropriate dimensions for moving a dehydrated K⁺ ion
- Val, Trp and Tyr Side chains form a large sheet of aromatic amino acids that hold oxygen rings (O-rings) at their proper diameter

Red amino acid residues are absolutely required for K⁺ selectivity; the amino acid sequence that encodes the structure of the O-rings is well conserved among all potassium channels

[Diagram showing the structure of the selectivity filter with amino acids and chemical structures of Tryptophan and Tyrosine]
Why do K\(^+\) ions pass through easily?

The K\(^+\) ion fits precisely into the filter, producing a favorable loss of its waters.

In other words, the O-rings mimic the hydration shell of the potassium ion well.
Why do smaller Na\(^+\) ions have trouble passing through?

The O-rings do not mimic the hydration shell of the sodium ion well.

The selectivity filter’s structure (held open by the aromatic sheet) prevents the main chain carbonyl oxygens from interacting closely with Na\(^+\), resulting in an unfavorable process.

Counter intuitively, the smaller sodium atom can’t pass through the filter because it is too small.

Figure from Freeman, WH (2007) Biochemistry, Sixth Edition
Cross-section of the protein shows aromatic ring structure maintained by van der Waals forces and H-bonds (green)
Amino acid sequence that determines structure of O-rings is conserved among all known K⁺ channels
One last point: what about high conductivity through the filter?

A single $K^+$ ion would be held very tightly in the filter. When a second potassium ion enters, the repulsive force between the two allows conduction through the filter. Each new $K^+$ ion pushes the old one through.
Questions