Ion Transport through Cellular Potassium Channels

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Ion channels are membrane proteins that mediate the rapid conduction of ions down the electrochemical potential.[1] Potassium channels transport K^+ ions from the intracellular to extracellular region with an almost diffusion limited conduction rate of $10^7 - 10^8$ K^+ per second with a high selectivity for K^+ (r = 1.33 Å) over Na^+ (r = 0.95 Å).[2,3]

Ion channels have been studied extensively since the early 1900's.[1,2] A major breakthrough in the study of ion channels came with the determination of the first high resolution structure of an ion channel, the K^+ channel from the bacteria *Streptomyces lividans* (the KcsA K^+ channel).[3]

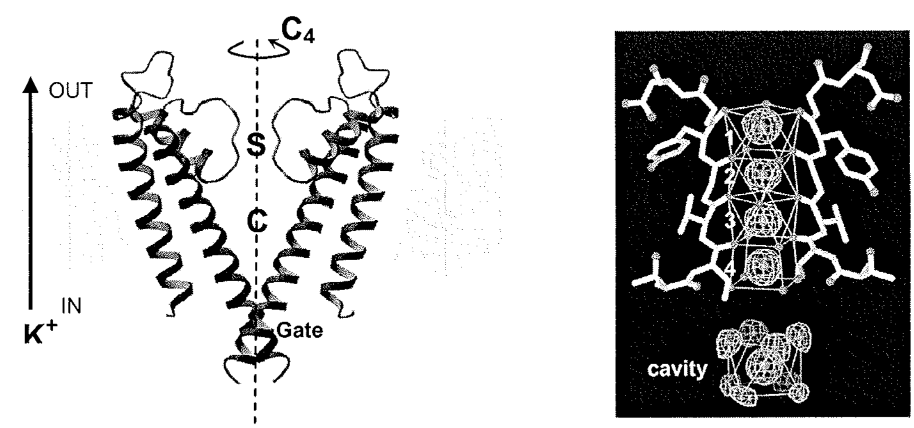

Figure 1: Structure of the KcsA K^+ channel with the front and back protein subunits omitted for clarity. a) Ribbon representation of two protein subunits surrounding the selectivity filter (S) and cavity (C).[4] C_4 denotes a four-fold rotation axis. b) Binding sites (1 - 4) for K^+ ions in the selectivity filter and a hydrated K^+ ion in the cavity. Red spheres: oxygen, green spheres: K^+ ion.[2,5]

The crystal structure of the KcsA K^+ channel shows that the pore region consists of four protein subunits of which only two are shown in figure 1.[3,5] The tetrameric K^+ channel has a four-fold rotational symmetry axis along its central ion pathway. There is a wide cavity (C) near the intracellular entryway and a narrow passageway, called the selectivity filter (S) on the extracellular side (Figure 1a). The cavity is lined by hydrophobic amino acids and a single K^+ ion lies at the center of the cavity in fully hydrated form surrounded by eight water molecules in square antiprismatic arrangement. The selectivity filter contains four ion binding sites. Sites 1 - 3 are formed by carbonyl oxygens of the protein backbone, with square antiprismatic coordination geometry around each K^+ ion. Site 4 is formed by carbonyl oxygens and oxygens of the threonine hydroxyl groups, and it has a cubic coordination geometry around the K^+ ion. (Figure 1b). It is believed that the smaller Na^+ ion is excluded as the oxygen atoms of the selectivity filter cannot come close enough to coordinate the Na^+ ion.[3,5]

Although the selectivity filter contains four ion binding sites, it is highly improbable that four K^+ ions could be present at the same time, since they would be separated by a distance of ~ 3.3 Å. Studies by Zhou *et. al* have shown that at a given time there is an average of two ions in the selectivity filter and therefore the electron density in positions 1 – 4 represents the superposition of K^+ ions in the 1,3 and 2,4 configurations which are considered to be equal in energy (Figure 2).[5,6] It is believed that ion conduction takes place when a queue of K^+ ions and water molecules move through the filter in a concerted manner and that an exchange between the two configurations occurs when a third ion enters from the intracellular side, pushing the outermost ion to exit.[6,7] The transition between 1,3 and 2,4 configuration possibly occurs via an intermediate in which each K^+ ion is coordinated in an octahedral manner with four coordination sites occupied by carbonyl oxygens and two sites occupied by water molecules.[6b]

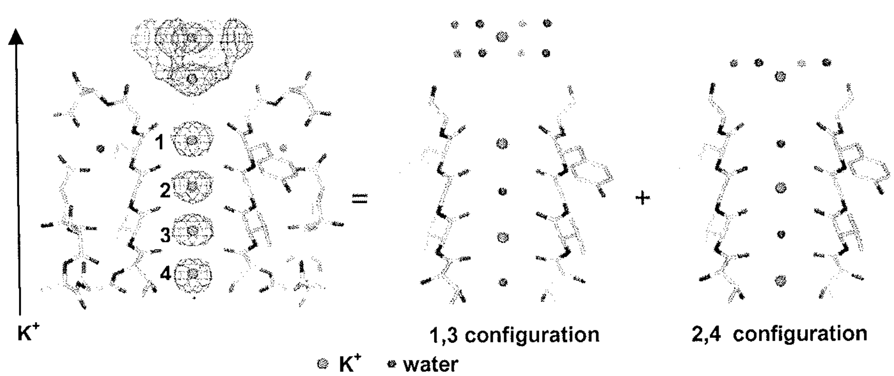

Figure 2: Configurations of the selectivity filter in the KcsA K^+ channel[2]

lectrophysiological studies of ion conduction show that the KscA K^+ channels are readily permeable to K^+ and its close analogs like Rb^+, NH_4^+ and Tl^+, whereas Na^+, Li^+ and Cs^+ are excluded.[8] It is believed that the larger Cs^+ ion can block the filter.

All potassium channels are gated, that is, ion conduction can be turned on and off in the presence of a stimulus such as voltage, pH, and ligand binding.[2,9] The gate is formed by the inner helices on the intracellular side (Figure 1a).[4] The mechanism of gating is a major area of current research on ion channels. Synthetic analogs of ion channels are being widely investigated and K^+ selective channels have been developed based on resorcin[4]arenes[10a-c] and cholic acid derivatives[10b,d] that can conduct ions across a lipid bilayer.

References

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