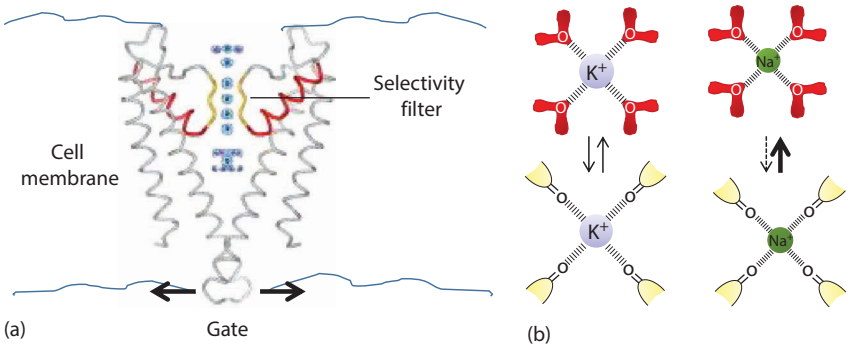

FIGURE 13.4 (a) Potassium channel structure with selectivity filter at the outer pore and gating mechanism at the inner pore. (b) Selectivity mechanism. The distance between the K^+ ions and the oxygen atoms is the same in water as in the selectivity filter enabling the K^+ ions to enter the pore at no energy cost. This is different for Na^+ ions, so they are excluded from the pore. (From MacKinnon, R., *FEBS Lett.*, 555, 62, 2003.)

made by concatenating four of the 6-TM subunits, making up a 24-TM subunit that forms the channel alone. This type is represented by the voltage-gated Na^+ and Ca^+ channels (Na_V and Ca_V). Within each of the four domains the six transmembrane segments are denoted S1–S6.

Three different parts of the channel are responsible for the functions: ion permeation, pore gating, and regulation. The narrow part of the pore is called the selectivity filter, and this has been studied by high-resolution X-ray in crystallized K^+ and Na^+ channels giving valuable insight into the selectivity mechanism (Figure 13.4). The residues in the pore loop line the K^+ channel selectivity filter and their peptide backbone carbonyl groups act as surrogate-water implying that the chemical energy of the dehydrated K^+ ions entering the pore is unchanged. By this means high selectivity and high permeability of the K^+ ions passing in single file are obtained. Although Na^+ ions are smaller than K^+ ions they will not enter the K^+ pore since it is energetically unfavorable. The Na^+ channel selectivity filter is larger and functions in a different way. At the extracellular end of the filter, the negatively charged side chains of four glutamate residues interact with Na^+ and partially remove its hydration. Following this two ion coordination sites formed by backbone carbonyls perfectly aligned to bind Na^+ with four planar waters of hydration are located. Thereby, Na^+ is conducted as a hydrated ion through the channel.

Crystal structure determination, molecular modeling, and crystal structures of voltage-gated Na^+ and K^+ channels explain how voltage sensing and gating occur. The membrane potential creates an electrical field across the membrane. Charged amino acids (usually arginine) are found in the fourth transmembrane segment (S4) of the channel, and move according to changes in the electrical field. Via the S4–S5 linker this movement bends the S6 segment (inner helix gate), and opens the pore.

13.2 PHYSIOLOGY AND PHARMACOLOGY OF VOLTAGE-GATED ION CHANNELS: POTASSIUM CHANNELS

The 2-TM K_{ir} channel family gives rise to six subtypes which play diverse roles in the body. Many K_{ir} channels are open at resting membrane potential and clamp the potential at −70 and −90 mV in nerve and heart cells, respectively (e.g., $K_{ir}4$ and $K_{ir}2$). The $K_{ir}3$ channels are gated by binding of the βγ subunit from the G_i protein. This mechanism is important in the atria of the heart, where stimulation of the para-sympathetic vagus nerve leads to release of acetylcholine, activating the G_i protein, and subsequently the $K_{ir}3$ channel to hyperpolarize the pacemaker cells. Crystal structures have revealed that K_{ir} channels have a longer ion permeation pathway as compared with other K^+ channels. It consists of both the transmembrane and a cytoplasmatic domain, that both