An electrostatic basis for valence selectivity in cationic channels

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It is well known that the charge distribution surrounding the pore is responsible for ion selectivity in cation channels. Negative charges lining the pore region present an energy well for cations and a barrier of a similar magnitude for anions, thereby selecting one species and excluding the other. Less well known is how these channels select between cations with differing magnitudes of charge. Here we have constructed models of the KcsA, sodium and calcium channels and compared the permeation of monovalent and divalent ions to understand the basis of this valence selectivity.

For both the KcsA and sodium channels, monovalent ions readily pass through the channel. However, as soon as a divalent ion enters the selectivity filter it binds strongly, rarely leaving and thereby almost completely preventing the permeation of monovalent ions. This effect is equally important for inward and outward currents in the KcsA channel, but more pronounced for the inward current in the sodium channel. In contrast, calcium channels conduct monovalent ions in the absence of any divalent ions, but when a mixture of monovalent and divalent ions is present, they allow only the divalent ions to pass.

This phenomenon of selectivity between monovalent and divalent ions can be attributed to electrostatics. We have used simulations of Brownian dynamics and electrostatic calculations to show that in all three channel types, the distribution of charges in the protein creates an energy well that attracts many ions into the channel, making conduction a three ion process for sodium and calcium channels and a four ion process for the KcsA channel. But for the case of divalent ions, the energy well in the KcsA and sodium channels is very deep. Once a divalent ion has entered it finds it difficult to leave, even with the aid of a repulsive kick from other ions in the channel. Thus divalent ion block of the channel causes the currents to plummet. On the other hand, for the calcium channel a second divalent ion entering the channel presents enough repulsion to push a resident divalent ion out of the channel, but a monovalent ion does not. Thus, the calcium channel is able to select divalent ions in a divalent-monovalent ion mixture.