Gating of the ClC-1 Chloride Channel

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Abstract

The ClC-1 chloride channel, a dimeric channel with two ion conducting pores, has two unique gating processes. The 'fast' gating processes open and close each pore independently, whereas the 'common' gate acts on both pores simultaneously. Although the crystal structure of two prokaryotic ClC channels has recently been solved there is still little knowledge of the parts of the channel involved in channel gating. The research in this thesis has used mutagenesis and electrophysiological techniques to provide significant further insight into the structure and function of the ClC-1 common gate.

ClC-1 mutations known to cause the dominant form of the muscle hyperexcitability disorder myotonia, and which are therefore likely to affect the common gating process, cluster in the H, I, P, and Q helices, which are at the interface of the ClC-1 dimer, as well as the G helix, which is situated immediately behind the H and I helices. Introduction of mutations into the G, H, and I helices of ClC-1 causes changes in channel gating, in most cases affecting the common gating process. Mutations in the P and Q helices also affect channel gating, again primarily through affects on ClC-1 common gating, although mutations in P and Q generally have less affect on ClC-1 gating than those in G, H and I. This research has also looked at the interaction of zinc with the ClC-1 channel, showing that zinc is able to attenuate currents through ClC-1 by stabilising the closed state of the channel, rather than through mechanisms such as occlusion of the channel pore. Furthermore, the interaction of zinc with mutant channels exhibiting altered common gating suggests that zinc can stabilise the closed state of the channel common gate.