Inhibition of a muscle chloride channel - structural and functional studies of ClC-1

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The chloride channel ClC-1 is expressed in human skeletal muscle where it modulates the action potential [1]. As a reduced activity of ClC-1 results in increased muscle activation, ClC-1 represents an attractive drug target for alleviating symptoms of a range of neuromuscular disorders that cause reduced muscle activity, such as myasthenia gravis, or for reversal of neuromuscular block [2]. To this end, development of compounds that inhibit ClC-1 is desirable, yet structural information on such complexes is lacking. Using cryo-EM and electrophysiological studies, we elucidate how inhibition of human ClC-1 occurs at the molecular level. We determine the first inhibitor-bound structures of ClC-1, covering two major classes of ligands that are known to interfere with the protein function. One structure in complex with the well-established inhibitor 9-anthracene carboxylic acid (9-AC), and the other with 2-(2-chlorophenoxy) butanoic acid (CPB). Both inhibitors block ClC-1 by binding in the channel pore, physically restricting access for permeating ions. Moreover, the ligands cause similar conformational shifts of three residues central for regulation of the chloride flux, including the crucial gating glutamate, E232. This is substantiated by electrophysiological studies, pinpointing key residues for interaction with each compound. This represents a considerable leap forward in basic science in the field, and opens new possibilities for rational drug design, information that will be invaluable also for a palette of ongoing clinical trials targeting ClC-1.

References

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