SODIUM CHANNELS: STRUCTURE, FUNCTION AND DISEASE

Wallace, B.A.

Institute of Structural and Molecular Biology, Birkbeck College, University of London, London, U.K.

The initiation of the action potential in excitable cells results from the opening of voltage-gated sodium channels. In humans, mutations in sodium channels produce a wide range of neurological and cardiovascular diseases; therefore these channels represent key targets for development of pharmaceutical drugs. Sodium channels are also present in some prokaryotes, where they appear to function in homeostasis, motility, and chemotaxis. All sodium channels undergo a series of conformational changes associated with their open, closed and inactivated functional states.

We have determined the crystal structure of the open conformation of the NavMs bacterial sodium channel pore. Comparisons between this structure and the structure of the closely-related NavAb channel in the closed state reveal the mechanism of channel gating. Using a combination of crystallography and spectroscopic methods (Synchrotron Radiation Circular Dichroism and DEER-EPR) and molecular dynamics calculations, the structure of the C-terminal domain (not visible in previous crystal structures, but critical for full functioning of the channel) has also been determined; its flexibility is compatible with an opening mechanism that does not destabilise the tetrameric cytoplasmic domain coiled-coiled bundle. The structural basis of ion selectivity and the locations of three sodium ions in the selectivity filter of the pore have also determined.

We have shown that drugs which block eukaryotic sodium channels also bind to and block the NavMs channel. Crystallographic, computational, spectroscopic and electrophysiology methods have demonstrated the structural and functional effects and locations of these blockers within the channel cavity. The binding sites identified were then validated by mutational studies. The affinities of the drugs are remarkably similar for the NavMs and human Nav1.1 channels; this is valuable information for the design of more specific and selective drugs and insecticides.

[This work was supported by grants from the U.K. Biotechnology and Biological Sciences Research Council]