Oral Contributions

[MS7 - 02] Sodium Binding Sites in Voltage-gated Sodium Channels B.A.Wallace

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In excitable cells, the initiation of an action potential results from the opening of voltage-gated sodium channels. In humans, mutations in different sodium channel isoforms have been shown to have causal relationships with a wide range of neurological and cardiovascular diseases, and they therefore represent key targets for development of pharmaceutical drugs. Sodium channels are also present in some prokaryotes, where they 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 (McCusker et al (2011)). 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 spectroscopic methods (SRCD and DEER-EPR) and a new crystal structure, the structure of the C-terminal extracellular domain (which is not visible in any of the previous crystal structures, but which we have shown to be critical for full functioning of the channel) has also been determined; it is compatible with an opening and closing mechanism that does not destabilise the tetrameric cytoplasmic domain coiled-coiled bundle.
A new crystal form enables us to view the positions of the sodium ions in the selectivity filger, and details of the fenestrations further suggest features important both for activity and for the design of new state-specific ligands/drugs

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