



Robert M Stroud

University of California San Francisco, USA

Engineering a 30-year-old intracellular channel: Twitching a voltage sensor with a taste of pharmacology

Proteins in plasma membranes are subject to large trans membrane potential of $\sim 200,000$ V/cm. This affects all such proteins. Some proteins harness voltage sensors to detect and respond to changes in potential. Such proteins are found also in internal organelles where they are often more intricately regulated. Hence by protein engineering it is possible to tune the responses to conducted ions and to voltage. I describe a channel in the TPC1 class^{1,2,3}. Because of its regulation by calcium ions, it can be restored to its closed resting state. A comparison between this and all other voltage sensors in full-length channels, which are generally activated at zero Volts, shows for the first time in a voltage sensitive channel how a voltage sensor responds, to effectively move charges across the membrane? A conformational transition indicates a mechanism that may be general. It accounts for the measured gating charge that defines how many charges must transition from one side to the other. Conformation changes lead to channel opening.

Biography

Robert M Stroud is Professor of Biochemistry and Biophysics, University of California in San Francisco. He focuses on the molecular basis for function of trans-membrane transporters and channels, and on structure-assisted drug discovery. He has contributed to fundamental mechanisms of receptor proteins, lipid-protein interactions, enzymes and protein-RNA recognition. He has obtained his BA and MA in Natural Sciences from the University of Cambridge (UK), his PhD is from University of London (JD Bernal). From a Post-doctoral and Professorship in Biological Chemistry at the California Institute of Technology, he came to UCSF. His research involves structural determination engineering and function of molecules and cells using X-ray crystallography, electron-cryo microscopy, computational simulations, spectroscopy, super-resolution optical microscopy. He is a Member of the National Academy of Sciences, a Fellow of the American Academy of Arts and Sciences, a Fellow of the Royal Society of Medicine (UK), Fellow and Former President of the US Biophysical Society.

stroud@msg.ucsf.com

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