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## TOWARDS A STRUCTURAL VIEW OF GATING IN POTASSIUM CHANNELS

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### Abstract

**Voltage-activated cation channels have pores that are selective for K<sup>+</sup>, Na<sup>+</sup> or Ca<sup>2+</sup>. Neurons use these channels to generate and propagate action potentials, release neurotransmitters at synaptic terminals and integrate incoming signals in dendrites. Recent X-ray and electron microscopy studies of an archaebacterial voltage-activated K<sup>+</sup> (Kv) channel have provided the first atomic resolution images of the voltage-sensing domains in Kv channels. Although these structures are consistent with previous biophysical analyses of eukaryotic channels, they also contain surprises, which have provoked new ideas about the structure and movements of these proteins during gating. This review summarizes our current understanding of these intriguing membrane proteins and highlights the open questions.**

### Summary

- The gate region in K<sup>+</sup> channels controls whether ions can traverse the ion conduction pore. Studies using quaternary ammonium compounds and the X-ray structure of the KcsA K<sup>+</sup> channels are consistent with the presence of a gate at the intracellular side of the pore.
- There is substantial evidence that the structure of the gate region of Kv channels and the movements that occur during opening are different from that proposed for KcsA and MthK.
- The S4 transmembrane segment of the channels is rich in positively charged basic residues, and S4 is agreed to be important in voltage sensing, although the conceptual and structural basis for gating charge movement is the subject of intense controversy.
- There are two models for the movement of gating charges across the channels. The 'membrane translocation model' proposes that the gating charges completely translocate from one side of the hydrophobic phase of the membrane to the other, which corresponds to a movement of more than 20 Å. By contrast, the 'focused field model' proposes that charges move shorter distances between water-filled crevices in the protein, which serve to focus the electric field of the membrane.
- Most studies favoured the focused field model until 2003 when the X-ray structure of the KvAP channel was revealed. The X-ray structure of the intact KvAP protein was solved to 3.2 Å resolution, using Fab fragments of monoclonal antibodies bound to the voltage-sensors. This provided important evidence, which is in line with the translocation model but contradictory to the focused field model.

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table of contents

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issues

highlights

reviews

perspectives

this article



- Although MacKinnon and colleagues pointed out several reasons for suggesting that there could be distortions in the X-ray structure of KvAP, they concluded that the crystallized full-length channel is not far from a membrane-bound conformation.
- At present, the extent to which the structure of KvAP is distorted remains a central issue in the debate. This review argues that there are many indications that the distortions are extensive.
- The original paddle model for gating charge movement is a membrane translocation model that is supported by an intuitive interpretation of how and why the KvAP structure is distorted, and by functional experiments and electron microscopy reconstruction.
- Unlike the X-ray structure of KvAP, the electron microscopy reconstruction of KvAP is compatible with the focused field model because the S3 and S4 segments have transmembrane orientations. The focused field model is also supported by experiments demonstrating that S4 can form a proton conducting channel, and by experiments showing that the C terminus of S3 and the N terminus of S4 are positioned near the extracellular side of the membrane in the resting conformation.
- Although the membrane translocation and focused field models are useful for considering the mechanisms that underlie voltage-sensing, neither model has a solid structural framework. Future work should focus on the tertiary structure of the voltage sensing domain and the spatial proximity of specific residues within well-defined secondary structural elements of the voltage-sensors.

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