## Tobias LINDER

Thesis Supervisor: Anna WEINZINGER

Department of Pharmacology and Toxicology, University of Vienna.

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# Title: Pore gating of potassium channels and its relevance for drug effects.

### Abstract in Englisch

K+ channels are involved in virtually all physiological processes and adopt critical roles in diverse events such as neuronal signaling, muscle contraction, cardiac action potential regulation, and hormone secretion. Thus, it is not surprising that malfunction of K+ channels can have a wide-spread disruptive impact on the homeostasis of the human body. With severe diseases such as cardiac arrhythmias, diabetes, and cancer linked to K+ channels, these membrane proteins are subject of extensive research to unravel their functional properties and develop future drugs.

While the function of K+ channels and their involvement in the ionic currents of cells are well studied by electrophysiological experiments, the atomistic details of transitions between conformations allowing and preventing ion flow, called gating, still lack important insights. Crystal structures of ion channels mark a major breakthrough in our understanding of channel architecture and have provided elementary information of the conformations that ion channels can adopt in different channel states. However, as ion channels are highly dynamical proteins, knowledge of the local and global conformational changes during gating on an atomistic level is of extraordinary interest. In particular, it was shown that a plethora of drugs targeting K+ channels are crucially dependent on channel gating to develop their blocking potency emphasizing the importance of detailed knowledge of channel dynamics. Comprehensive studies on three different K+ channels, the prototypical bacterial K+ channel KcsA, the bacterial inward rectifier K+ channel KirBac1.1, and the human Kv channel hERG, were performed to shed light on the gating dynamics of K+ channels and to identify channel specific structural rearrangements. Molecular dynamics simulations and two-electrode voltage clamp experiments revealed that aromatic amino acids adopt crucial roles in gating by unlocking channels from a specific state (F114 in KcsA), by forming the pore gate (F146 in KirBac1.1) and by shaping the drug binding site (Y652 and F656 in hERG). Specifically, studies on the hERG channel disclosed the important role of F656 for drug trapping which is characterized by the drug's retention in its binding site upon channel closure. While F656 is a key binding determinant of hERG blockers, it might also serve as physical barrier for drug dissociation. In case of KcsA and KirBac1.1, energy calculations allowed the investigation of the energy landscape of channel gating and correlations of structural rearrangements to energy changes. Gating studies on KirBac1.1 focused on the coupling between the transmembrane and the cytoplasmic domains and revealed that the communication between these two domains operates bidirectionally.

Summarizing, this thesis provides novel insights into channel specific movements during pore gating. Although the three investigated channels share similar global gating rearrangements in terms of transmembrane domain movements, they exhibit uniquely fine-tuned local gating changes at the amino acid level.