Modulation of potassium channel conformation and function by permeating ions

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The Kv2.1 potassium channel is a very slowly inactivating delayed rectifier, with widespread distribution in brain, peripheral neurons and excitable cells such as heart and pancreas. In hippocampal neurons, where its function has been best studied, it appears to be profoundly important under conditions of high frequency firing or elevated extracellular [K^+]. For example, with physiologically relevant elevation of extracellular [K^+], action potential duration is increased ~10 fold in the absence of Kv2.1 function, yet is unaffected in the presence of normal Kv2.1 function (Du *et al.*, 2000). In contrast, Kv2.1 appears to have little importance to the integrity of single action potentials under physiological conditions. We have studied the molecular mechanism by which this seemingly standard delayed rectifier performs this very specific function. Kv2.1 channels open into one of two conformations. This conformational difference influences activation rate, inactivation rate, current magnitude and channel pharmacology. All of the functional effects of this difference in conformation are related to the orientation of a single outer vestibule lysine. In one conformation, currents are bigger and activate faster, whereas in the other, currents are smaller and activate more slowly. Which conformation the channel opens into appears to be determined by the occupancy of a particular K^+ binding site in the channel's selectivity filter. Thus, with elevation of [K^+], occupancy of this site is greater, and channels open into a conformation that produces a larger current. In addition, two outer vestibule lysines dramatically reduce current magnitude variation associated with changes in K^+ driving force that accompany changes in extracellular [K^+]. Together, these two mechanisms produce the unique phenotype of the Kv2.1 channel. Upon elevation of external [K^+], current density through Kv2.1 is increased at all membrane potentials, whereas in all other K^+ channels, it is reduced. We propose that this increase in outward current density acts to maintain action potential integrity in the face of elevated extracellular [K^+], which occurs during high frequency firing. From a biophysical perspective, the Kv2.1 channel displays another apparently unique mechanism. One of the fundamental mysteries in ion channel biophysics, which has potentially significant clinical importance, is how single channel conductance is controlled. Recent experimental and theoretical studies suggest that, in many K^+ channels, single channel conductance is determined by inner vestibule characteristics. In contrast, our data demonstrate that single channel conductance in Kv2.1 can be modulated by reorientation of the outer vestibule. Thus, it may be that targets of conductance modulation will be different in different K^+ channels.

Du, J., L.L. Haak, E. Phillips-Tansey, J.T. Russell & C.J. McBain (2000) *Journal of Physiology* 522: 19-31.