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Biophysical Characteristics of Mg^{2+} Blockades in Ion Channels and Their Physiological Roles

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Ionic currents through many different cation channels are specifically reduced by internal and/or external Mg^{2+} within a concentration range of physiological relevance. Although there are many ways for a divalent cation to reduce channel currents, the current blockade by directly binding to a conduction pore has been most well studied. Since the binding of Mg^{2+} to a site (or sites) within transmembrane voltage-drop affects the fundamental characteristics of an ion channel, biophysical mechanism and physiological significance of such a blockade have been under intensive investigation.

We have been studied the blockade of two different channels by Mg^{2+}. Ionic currents of cyclic nucleotide-gated (CNG) channels are reduced by sub-millimolar concentration of intra- and extracellular Mg^{2+}. In an earlier study, we identified a glutamte (Glu^{363}) residue within the pore-forming region of the channel as the high-affinity binding site of extracellular Mg^{2+}. We have further studied the electrophysiological and structural features of the site. In addition, we constructed several point-mutations of CNG channel at S6 region which is likely to compose of the internal vestibule of CNG channels to reveal the location of the second Mg^{2+}-binding site exposed to internal side of the membrane. In a recent study, we accidentally observed that the current-voltage (I-V) relationship of another channel, small conductance Ca^{2+}-activated K^+ channel (SK_{Ca} channel), got rectified as the concentration of internal $Mg^{2+}$was raised. The apparent affinity for Mg^{2+} varied as a function of membrane voltage and intracellular Ca^{2+} concentration, and extracellular K^+ altered the voltage-dependence as well as the apparent affinities of Mg^{2+} from

intracellular side. From the results, we tentatively concluded that the inwardly rectifying I-V relationship of SK_{Ca} channels are due to the voltage-dependent blockade of intracellular Mg^{2+} and that the Mg^{2+}-binding site is located within the ion-conducting pathway. We are currently localizing the Mg^{2+}-binding site within the putative pore-forming region of SK channels using site-directed mutagenesis and investigating the functional significance of the I-V rectification of SK_{Ca} channels.