S2-1

Permeation and Gating of Inward Rectifer Potassium Channels

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The gating kinetics of an inward-rectifier K^+ channel, ROMK2 (Kir1.1b), were described by a model having one open state and two closed states. The long closed state was abolished by EDTA, suggesting that it was due to block by divalent cations. These closures exhibit a biphasic voltage-dependence, implying that the divalent blockers can permeate the channel. The short closures had a similar biphasic voltage dependence suggesting that they could be due to block by monovalent, permeating cations. The rate of entering the short closed state varied with the K^+ concentration and was proportional to current amplitude, suggesting that permeating K^+ ions may be related to the short closures. To explain the results, we propose a variable intrapore energy well model, in which a shallow well may change into a deep one, resulting in a normally permeant K^+ ion becoming a blocker of its own channel Another inward-rectifier K^+ channel, IRK1 (kir2.1), had slower gating than ROMK2 with single open state and 4 discrete closed states. Both the open and the 3 shortest closed-time constants of IRK1 decreased monotonically with membrane hyperpolarization. The open probability of IRK1 decreased sharply with hyperpolarization due to an increase in the frequency of long closed events which were attributable to divalent-cation blockade. Chelation of divalent cations with EDTA eliminated the slowest closed-time distribution of IRK1 and blunted the hyperpolarization-dependent fall in open probability. The property of multiple closed states was conferred by the second transmembrane domain of IRK. The long-lived open and closed states, including the higher sensitivity to extracellular divalent cations, correlated with the extracellular loop of IRK. Channel kinetics were essentially unaffected by the N- and C-termini. These data are consistent with the idea that the locus of gating is near the outer mouth of the pore.