L-2

GATING MECHANISM AND VOLTAGE-DEPENDENT BLOCK BY EXTERNAL DIVALENT CATIONS OF THE DELAYED RECTIFIER K CHANNEL IN RABBIT SINO-ATRIAL NODE CELLS

Won-Kyung Ho, Suk Ho Lee & Yung E Earm
Department of Physiology, Seoul National University College of Medicine, Seoul 110-799

In sino-atrial node cells which act as the normal pacemaker of the heart, K conductance in resting state is minimal due to the absence of inward rectifier K channels. K conductance only increases when the membrane is depolarized by the activation of the delayed rectifier K current, I_K.
In the present study, we investigated the gating mechanism of I_K using the whole cell patch clamp technique in isolated single sinoatrial cells of the rabbit. Hyperpolarizing clamp pulses from 0 mV induced a time-dependent increase in inward current, resulting in an inwardly rectifying current-voltage relationship. Half maximal activation voltage was found at about -42 mV. When the pulse was more negative than -60 mV the current increase was followed by the current relaxation, indicating the presence of inactivation gate. Half maximal inactivation was at -59 mV. The rate of the relaxation was greatly affected by external divalent cation including Ca^{2+} and Mg^{2+} and by membrane potential. The effects of Ca^{2+} and Mg^{2+} are well explained by a time- and voltage-dependent blockade of the I_K channel by these ions. The fractional electrical distance of the binding site calculated from the voltage-dependence of the blocking rate constant is 0.69 for Ca^{2+} and 0.88 for Mg^{2+}. The blocking rate constant at 0 mV for Ca^{2+} is about 15 times faster than that for Mg^{2+}, indicating stronger effects of Ca^{2+}. Simulation model was made by using three independent mechanisms (an activation gate which opens on hyperpolarization, an inactivation gate which closes on hyperpolarization and a binding site for Ca^{2+} and Mg^{2+} inside the channel) and found that simulated currents correspond well with the experimental finding. We therefore conclude that the observed voltage dependence of I_K in physiological conditions results mainly from the voltage-dependent block of I_K channel by external Ca^{2+} and Mg^{2+}.