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Effect of External Cations on the Voltage-dependent Inactivation of the Rapidly Activating Delayed Rectifier K^+ currents (I_{Kr}) and *HERG* Currents.

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It is well known that rapidly activating delayed rectifier K^+ channels (I_{Kr}) play a role in repolarisation in mammalian hearts. Recently, human *ether-a-go-go* related gene (HERG) channels was shown to be a molecular equivalent to I_{Kr}. We have investigated the permeation of various external cations on I_{Kr} in mammalian hearts and on HERG channels expressed in *Xenopus laevis oocytes*. The whole cell patch clamp technique and two microelectrode voltage clamp technique were used. I_{Kr} was identified as E-4031 (a methanesulfonanilide compound known as a class III antiarrhythmic agent) sensitive current. In isotonic K^+ solutions, I_{Kr} was only recorded as inward currents on hyperploarization, but outward currents were hardly identified due to rapid inactivation property. In isotonic Cs^+ solution, I_{Kr} was recorded in both direction: biphasic outward currents on depolarization and biphasic inward currents on repolarization. Voltage dependence of inactivation was compared in K^+ and in Cs^+, showing a positive shift by 28 mV in Cs^+. Voltage dependence of activation was unaffected by external cations. Cs^+ also showed a significant permeability and a modulatory effect on HERG channels. Replacement of external K^+ (2 mM) with Cs^+ in normal Ringer solutions shifted the voltage dependence of inactivation by 14.8 mV to the positive potential. The effect was concentration dependent, showing a greater shift (41 mV) by the replacement of 20 mM K^+ with Cs^+. The voltage dependence of activation was, however, unaltered. The permeability ratios, P_K/P_{Cs}, calculated using the constant field equation, were 1.4 for I_{Kr}, and 2.1 for HERG currents, respectively. In isotonic Na^+ solutions (K^+-free), both inward and outward components of I_{Kr} and HERG currents were abolished, indicating that external Na^+ neither showed permeability, nor affected gating parameters. From the above results, we concluded that the inactivation gates of I_{Kr} and HERG channels are interfered by external cations and Cs^+ is most powerful among them.