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Block of HERG Channels Expressed in *Xenopus* Oocytes by External H⁺

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We reported previously that HERG current, molecular equivalent of I_{Kr}, expressed in *Xenopus* oocytes is blocked by external Ca²⁺ and Mg²⁺. In the present study, we have investigated the effect of external H⁺ on HERG current (I_{HERG}) using the two microelectrode voltage clamp. When [H⁺]_o was increased, the amplitude of outward I_{HERG} activated by depolarization decreased and the rate of current onset slowed. The threshold and fully activated potential of I_{HERG} shifted to a more positive potential. The time course of deactivation produced by repolarization was accelerated. These effects of external H⁺ were similar to those of external Ca²⁺ and Mg²⁺. To test whether external Ca²⁺ affects the effect of external H⁺ on I_{HERG}, the activation curve of I_{HERG} in 0.5 mM [Ca²⁺]_o was compared with that in 5 mM [Ca²⁺]_o. The shift of activation by external H⁺ in 0.5 mM [Ca²⁺]_o was larger than that in 5 mM [Ca²⁺]_o and the competitive interaction between H⁺ and Ca²⁺ was expected using double reciprocal plot. These results suggest that external H⁺ and Ca²⁺ are competing at the same binding site. From these results, we conclude that HERG channels are blocked not only by divalent cations such as Ca²⁺ and Mg²⁺ but also by a monovalent cation, H⁺ and that H⁺ and Ca²⁺ compete at the same binding site in HERG channel.