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인산화에 의한 사람심장 Voltage-gated K^+통로 (hKv1.5) 활성 조절기전에 대한 전기생리학적 및 분자생물학적 접근

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Voltage-gated K^+ channels represent the most complex group of ion channel genes expressed in cardiovascular system. The human Kv1.5 channel (hKv1.5) represents the I_{Kur} repolarizing current in atrial myocytes. The hKv1.5 channel is functionally modulated by the Kvβ1.3 subunit, which converts it from a delayed rectifier to a channel with rapid inactivation and enhanced voltage sensitivity. To explore the role of Kvβ1.3 subunit phosphorylation in modulation of hKv1.5, we examined the effects of activators and inhibitors of PKA and PKC following coexpression of hKv1.5 with the Kvβ1.3 subunit in HEK-293 cells. Activation of PKA by 8-bromo-cAMP increased the K^+ current in the cells cotransfected with hKv1.5 and Kvβ1.3 subunit without any significant effect in the cells transfected with hKv1.5 alone. Specifically, 8-bromo-cAMP slowed fast inactivation without any significant effect on other parameters. The increase in K^+ current induced by 8-bromo-cAMP was blocked by a PKA inhibitor, Rp-cAMP. Mutation of serine 24 to alanine in the Kvβ1.3 N-terminal removed the effect of PKA while mutation of other potential PKA phosphorylation sites in both Kvβ1.3 and hKv1.5 had no effect. Thus, serine-24 is the site responsible for PKA modulation

of Kvβ1.3-induced inactivation. In contrast to PKA, an activator of PKC, PMA, made no significant effect on Kvβ1.3-modified current. However, pretreatment with PKC inhibitor, calphostin C, removed fast inactivation and the hyperpolarizing shift of activation curve induced by the Kvβ1.3 subunit. This calphostin C-induced effect was partially blocked by a protein phosphatase inhibitor, okadaic acid, supporting the idea that the Kvβ1.3 effects require PKC phosphorylation. Calphostin C and okadaic acid had no effect on the function of hKv1.5 expressed in the absence of the Kvβ1.3 subunit. In summary, these results indicate that Kvβ1.3-induced modulation of hKv1.5 function is under control of PKA- and PKC-induced phosphorylation.