Selective Inhibition of Human Cardiac Kir2.2 Inward Rectifier Channels by Adrenergic Alpha-1a Receptors

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Background: Human Kir2.1 and Kir2.2 potassium channels predominantly contribute to the molecular basis of the cardiac inwardly rectifying potassium current (IK1). Reduction of IK1 (as seen in Andersen’s syndrome and in congestive heart failure) causes delayed afterdepolarizations which may result in premature ventricular beats and ventilant tachycardia. Inhibition of IK1 via activation of adrenergic alpha-1 receptors is a well-known phenomenon. However, its molecular basis has not been elucidated yet. Therefore, we investigated the interaction of alpha-1a receptors with Kir2.1 and Kir2.2 channels in the Xenopus oocyte expression system.

Methods: Cloned human adrenergic alpha-1a receptors and human Kir2.1 and Kir2.2 channels were co-expressed in Xenopus oocytes and pharmacological experiments were performed using the double electrode voltage clamp technique.

Results: Application of phenylephrin (10 µM) to Xenopus oocytes expressing only Kir2.1 or Kir2.2 channels was without any effect. However, phenylephrin (10 µM) caused a significant inhibition of Kir2.2 if the channels were co-expressed with adrenergic alpha-1a receptors. Steady state conditions were reached after 30 minutes and current amplitudes were reduced by 20 ± 5% compared to control measurements (p<0.05). In contrast, Kir2.1 currents were not affected by activation of the receptors. Surprisingly, in Kir2.2 mutant channels lacking all protein kinase C (PKC) consensus sites, the same effect as in the wild type could be observed.

Conclusion: Our study demonstrates that adrenergic alpha-1a receptors exert an inhibitory effect on human Kir2.2, but not Kir2.1 channels. The effect is independent of direct PKC mediated phosphorylation of the channel protein. These findings elucidate the molecular basis of a regulatory pathway which may contribute to the generation of ventricular arrhythmies in congestive heart failure.

Additional Gene Modifiers Reduce Effectiveness of β-Blockers in the Long QT Type 1 Syndrome

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Background: β-blockers are widely used to prevent the lethal cardiac events that associate long QT syndrome (LQTS) especially in KCNQ1-related LQTS (LQT1) patients. Some LQT1 patients, however, are refractory to this therapy.

Methods and Results: Eighteen symptomatic LQTS patients (12 families) were genetically diagnosed to have heterozygous KCNQ1 variants and received β-blocker therapy. Cardiac events occurred in 4 members (3 families) despite the continued therapy during the mean follow-up period of 70 months. Three of them (2 families) had the same mutation, A341V (KCNQ1), and the other had R243H (KCNQ1). The latter patient took aprindine that seemed to be responsible for the event. Because A341V (KCNQ1) has not been evaluated in heterologous mammalian expression system, we conducted functional analysis to investigate severe phenotype using COS7 cells. And we found that A341V (KCNQ1) is a loss-of-function type mutation (not dominant negative) as well as previous report in Xenopus oocytes. Further genetic screening revealed that one A341V (KCNQ1) family cosegregated with S706C (KCNH2) and another with G144S (KCNJ2). Produced functional outcome of S706C (KCNH2) mutation reduced current density with voltage shift of activation kinetics. Action potential simulation study was conducted based on the Kyoto model to estimate influences of additional gene modifiers. In both models mimicking LQT1 plus 2 and LQT1 plus 7, incidence of early afterdepolarization increased compared with LQT1 model under the setting of β-adrenergic stimulation.

Conclusion: Multiple mutations in different LQTS-related genes may modify the clinical characteristics. Expanded gene survey might be required in the LQT1 patients who are resistant to β-blocker therapy.