RATE-DEPENDENT BLOCK OF HKV1.5 CHANNELS AND THE MOLECULAR DETERMINANT BY THE NATURAL FLAVONE ACACETIN

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We have recently demonstrated that the natural flavone acacetin is an atrial-selective compound that inhibits ultra-rapid delayed rectifier potassium current (IKur) and transient outward potassium current (Ito) in human atrial myocytes, and also acetylcholine-activated potassium current (IK.ACh). It increased atrial effective refractory period and effectively prevented atrial fibrillation (AF) in anesthetized dogs without prolonging QT interval of ECG. The present study was designed to determine whether the IKur block of acacetin is rate- and/or use-dependent, and the molecular determinant of the channel block in HEK 293 cells expressing hKv1.5 channels (coding IKur in human atrial myocytes). It was found acacetin was an open channel blocker of hKv1.5 channels and inhibited hKv1.5 current in use- and frequency- dependent manner. The IC50 of acacetin for inhibiting hKv1.5 was reduced from 3.7 microM at 0.2 Hz to 3.1 microM at 0.5Hz, 2.9 microM at 1Hz, 2.1 microM at 3 Hz, and 1.7 microM at 4 Hz. The mutagenesis study showed that the hKv1.5 mutant I508A in the S6-segment exhibited a significant reduction of the channel block by acacetin (IC50, 19.4 microM, 5.2- fold of WT). These results demonstrate that acacetin is an open channel blocker by binding to the S6 domain of hKv1.5 channels. The use- and rate-dependent blocking property of hKv1.5 by acacetin indicates that this natural compound could exert a strong suppressive effect on atrial fibrillation in man.