

## **HUMAN CARDIAC KV4.3 CHANNELS ARE REGULATED BY EGFR KINASE AND SRC-FAMILY KINASES**

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The transient outward potassium current I<sub>to</sub> (encoded by Kv4.3) plays an important role in the phase 1 rapid repolarization of cardiac action potentials in the heart. It further determines the duration of repolarization and the propensity to cardiac arrhythmias. Modulation of I<sub>to</sub> by intracellular signal transduction is not understood. The present study was designed to determine whether hKv4.3 channel (alpha-subunit of human cardiac I<sub>to</sub>) is regulated by protein tyrosine kinases (PTKs) in HEK 293 cells stably expressing human Kv4.3 gene using a whole-cell patch clamp technique, immunoprecipitation and western blot. It was found that human cardiac Kv4.3 current amplitude was remarkably inhibited by the broad-spectrum PTK inhibitor genistein (10 micromole), and the inhibition was partially antagonized by the protein tyrosine phosphatases (PTPs) inhibitor orthovanadate (1 millimole). It is interesting that the selective EGFR (epidermal growth factor receptor) kinase inhibitor AG556 (10 micromole) reversibly reduced Kv4.3 current, and the inhibitory effect was almost fully countered by orthovanadate. In addition, the Src-family kinase inhibitor PP2 (10 micromole) also decreased hKv4.3 current and the effect was partially antagonized by orthovanadate. Immunoprecipitation and Western blot analysis revealed that tyrosine phosphorylation level of hKv4.3 channel was reduced by genistein, AG556 or PP2. The reduction of hKv4.3 channel phosphorylation level was reversed by orthovanadate. These results demonstrate that hKv4.3 channel is regulated by both EGFR kinase and Src-family kinases. EGFR and Src-family kinases favor tyrosine phosphorylation of the channel, and therefore may modulate cardiac electrophysiology.