Calcium-Activated Potassium Channel Inhibition in Autonomically Stimulated Human Atrial Myocytes.

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This example of Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide, but the efficacy of current anti-AF therapies is far from optimal. The autonomic nervous system has been reported to play a major role in the generation and maintenance of AF. Various investigations have suggested small-conductance calcium-activated potassium channels (SK) as potential targets for more effective pharmacological therapies. However, their contribution to atrial electrophysiology, particularly under autonomic stimulation, is not completely understood. In this study, we used in silico simulations to investigate the effects of SK channel inhibition on the action potential (AP) of autonomically stimulated human atrial cardiomyocytes.

The Grandi AP model was used to represent human atrial electrophysiology. A new formulation for the I_{KCa} current carried by SK channels was introduced into the model based on available experimental evidence. The impact of beta-adrenergic and cholinergic stimulation on AP was investigated at various concentrations of isoproterenol (Iso) and acetylcholine (ACh) respectively, with and without I_{KCa} inhibition.

Cholinergic stimulation hyperpolarized the AP and shortened the AP duration (APD) in a dose-dependent manner (up to 7 mV and >200 ms for 1 μM Ach), in agreement with previous experimental observations. Additional beta-adrenergic stimulation by 1 μM Iso partially attenuated the effects of cholinergic stimulation (17,5% APD prolongation under 0.01 μM ACh), in line with experimental evidence. I_{KCa} inhibition was able to reverse the effects of cholinergic activation, but only for moderate ACh doses and when combined with 1 μM Iso (22,5% APD prolongation under 0.01 μM ACh).

I_{KCa} inhibition in human atrial cardiomyocytes has moderate effects in antagonizing cholinergic stimulation, although only in combination with adrenergic stimulation and only for low ACh doses. Our computational results may serve as a basis to further ascertain the mechanisms underlying autonomic modulation and I_{KCa} inhibition and guide the development of novel anti-AF therapies.