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Pitx2 decreases L-type Ca2+ current and increases the slow delayed rectifier K+ current in cardiac cells

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Purpose: Genome wide scan analyses demonstrated that single nucleotide polymorphisms in the human chromosome 4q25, proposed to regulate the activity of the adjacent transcription factor Pitx2, were associated with an increased risk in atrial fibrillation (AF). Recent evidence has shown that Pitx2 could play a role in AF-induced electrical remodelling. However, its putative role in the control of expression/function of the ion channels responsible for atrial action potential is currently unknown. This work was undertaken to determine the effects of Pitx2 on voltage-gated cardiac Ca2+ and K+ channels.

Methods: Currents were recorded in HL-1 cells transfected or not with the cardiac Pitx2 isoform (Pitx2c) by using whole-cell patch-clamp. L-type calcium current (ICa,L) was recorded by using Ba2+ as charge carrier (IBa).

Results: Under control conditions, peak IBa density was reached at +20 mV (-4.6±0.6 pA/pF). Pitx2c significantly reduced peak IBa density (-2.8±0.3 pA/pF at +20 mV, $P<0.05$) without modifying activation, inactivation, and reactivation kinetics or voltage- dependent activation and inactivation. Regarding voltage-gated K+ channels, under control conditions 2 groups of cells were identified based on the predominant voltage-gated K+ current exhibited. In most of the cells (≈80%), a rapid delayed rectifier current (IKr) sensitive to dofetilide could be recorded, which reached a mean density of 1.9±0.2 pA/pF at 0 mV. In the rest of the cells (≈20%), IKr was absent and the predominant current was a fast activating and slow inactivating outward current sensitive to 4-aminopyridine (2 mM), with biophysical properties compatible with the ultrarapid delayed rectifier K+ current (IKur) recorded in human atrial myocytes. In the presence of Pitx2c, only a small subset of the cells exhibited IKur (≈10%) sensitive to 4-aminopyridine. Importantly, most of the cells (≈90%) exhibited a voltage-gated, dofetilide-resistant, K+ current with a very slow activation kinetics (τact at +60 mV= 1.8±0.3 s) that reached 8.9±3.0 pA/pF after 5-s pulses to +60 mV. The mean midpoint of the activation curve was 20.0±3.9 mV. This current was completely abolished by HMR-1556 (1 μM). All the biophysical and pharmacological properties of the Pitx2c-induced current resembled those of the human cardiac IKs.

Conclusions: The results demonstrated that Pitx2c decreased ICa,L and increased IKs and suggested that this transcription factor could contribute to the reduction of ICa,L and the increase of IKs that characterise the AF-induced electrical remodelling.