Ion channels and cardiac diseases: the pharmacologist's view

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During the last decade, the view of the interplay between ion channels/transporters and cardiomyopathies gradually evolved thanks to a more comprehensive view of cardiomyocyte function. From being considered the byproduct of a more general process of structural/molecular cardiac remodeling, ionic conductances are now viewed as key players of the progression toward cardiac diseases – severe hypertrophy, heart failure and, of course, the development of lethal arrhythmias. The basis of the arrhythmogenic propensity in the failing heart has been thoroughly investigated in the last decades, leading to the demonstration of disease-induced remodeling of ion-channel and ion-transport proteins, which are responsible of electrogenesis (action potential generation and conduction) and excitation-contraction coupling in the heart. Electrophysiological remodeling is a general phenomenon, initially adaptive, consisting of gain- or loss-of-function of channels/transporters and leading to maladaptive consequences such altered intracellular balance of calcium and sodium ions. A paradigmatic case is represented by the overexpression of Hyperpolarization-activated, Cyclic-Nucleotide- gated (HCN) channels, a common marker of functional remodeling induced by ventricular hypertrophy and failure. Notwithstanding its arrhythmogenic role at ventricular and atrial level (1), HCN represents a valuable pharmacological target to safely control heart rate in patients with ventricular dysfunction. The late sodium current (INaL) is a small, physiological component of sodium current due to persistent sodium ion influx following the fast-inactivation phase. In heart disease, the late component is abnormally enhanced thus contributing to prolonged action potential duration, i.e., a marker of electrophysiological remodeling. At variance with HCN, the gain- of-function of INaL is likely due to post-translational modification of the sodium channel, e.g., by CaMKII-mediated phosphorylation. Intracellular sodium and calcium loading is a major consequence, which is associated with the appearance of arrhythmogenic mechanisms. The pharmacological modulation of INaL by ranolazine not only abolished electrophysiological abnormalities in isolated human diseased cardiomyocytes (2) but also prevented, in vivo, the development of severe hypertrophy and contractile dysfunction in a transgenic model of hypertrophic cardiomyopathy (3). Altogether, pharmacological modulation of ion channels still represent a valuable and exploitable target in inherited and acquired cardiac diseases beyond antiarrhythmic strategy.

1. Sartiani L. et al. Curr Drug Targets, 16: 868-76, 2015

2. Coppini R. et al. Circulation 127: 575-84, 2013.

3. Coppini R. et al., Circulation-HF 10:e003565, 2017

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