HCN channels in the heart: lessons from mouse mutants.

Abstract:
Hyperpolarization-activated cation channels generate the I(f) current in the heart. In the sino-atrial node (SAN), I(f) is thought to play an essential role in setting the heart rate and mediating its autonomic control. This review focuses on the role of I(f) in pacemaking and non-pacemaking cardiomyocytes and the resulting therapeutic implications. HCN4 represents the principal isoform underlying sino-atrial I(f), but other isoforms may also be of importance. To examine the functional role of cardiac channels, several mouse mutants, most of them targeting HCN4, have been generated by different groups. Unexpectedly, these lines display greatly different and as yet unexplained phenotypes. We provide an overview about these HCN mutants and suggest an interpretation of the functional significance of I(f) in the SAN in light of these studies. HCN channels are also present in ventricular myocytes, and an up-regulation of I(f) in the hypertrophic and failing heart may contribute to arrhythmogenesis. Inhibition of I(f) by HCN channel blockers is a novel approach in the treatment of cardiac disorders, and ivabradine is approved for treatment of stable angina pectoris. Remarkably, a recent clinical trial assessing this substance in heart failure showed a significantly improved outcome. The mechanism underlying this beneficial effect is not yet clear and might lie beyond heart rate slowing. Thus, the growing knowledge about cardiac HCN channels will undoubtedly promote the development
of the promising class of HCN channel blockers.