Control of Cardiac Rate by "Funny" Channels in Health and Disease

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ABSTRACT: Activation of the "funny" (pacemaker, I_f) current during the diastolic depolarization phase of an action potential is the main mechanism underlying spontaneous, rhythmic activity of cardiac pacemaker cells. In the past three decades, a wealth of evidence elucidating the function of the funny current in the generation and modulation of cardiac pacemaker activity has been gathered. The slope of early diastolic depolarization, and thus heart rate, are controlled precisely by the degree of I_f activation during diastole. I_f is also accurately and rapidly modulated by changes of the cytosolic concentration of the second messenger cAMP, operated by the autonomous nervous system through ß -adrenergic, mainly ß2, and in the opposite way by muscarinic receptor stimulation. Recently, novel *in vivo* data, both in animal models and humans, have been collected that confirm the key role of I_f in pacemaking. In particular, an inheritable point mutation in the cyclic nucleotide-binding domain of human HCN4, the hyper-polarization activated cyclic nucleotide (HCN) isoform forming native funny channels of the sinoatrial node, was shown to be associated with sinus bradycardia in a large family. Because of their properties, funny channels have long been a major target of classical pharmacological research, and are now stimulating innovative gene/cell-based therapeutic approaches aimed to exploit their function in cardiac rate control.

KEYWORDS: pacemaker; funny current; f- current; heart rate modulation; HCN channels

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