PACEMAKER CHANNELS IN THE HEART: PHYSIOPATHOLOGY AND PHARMACOLOGY

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"Funny" (f) channels underlie the "pacemaker" I_f current, an inward current activated on hyperpolarization to voltages that are in the diastolic range of sino-atrial node cells. It is generally accepted that the pacemaker current I_f plays a major role in the spontaneous rhythmic activity of the sinoatrial node. The degree of current activation determines the slope of diastolic depolarization, and hence heart rate; I_f , being directly modulated by cAMP, underlies the regulation of cardiac rate by ß-adrenergic and muscarinic stimulation. I_f is also present in non automatic cardiac tissue. Electrophysiological and molecular data, demonstrated that f-channels are present in ventricular cardiomyocytes. Overexpression of f-channels in ventricular myocardium is a consequence of the process of electrophysiological remodelling, which mainly consists in the re-expression of fetal proteins. In cardiac hypertrophy and in heart failure, I_f current densitiy and/or mRNA levels of f-channels are increased compared with controls. Overexpression of f-channels in non-pacemaker cells may represent an arrhythmogenic mechanism in heart failure. Inhibition of the pacemaker I_f current to induce a direct and selective decrease in heart rate represents an attractive therapeutic approach for coronary artery disease. Substances acting as selective f-channel inhibitors, such as ivabradine, are useful in treating diseases such as chronic angina; experimental studies will contribute to clarify the role and relevance of I_f overexpressed in the working myocardium in heart failure, while ongoing clinical trials with ivabradine will assess the role of pure heart rate reduction in the treatment of congestive heart failure.