Abstract

Important physiological functions like the beating of the heart, breathing, the release of hormones and the cycle of sleep and wakefulness are controlled by rhythmic activities of single cells or cellular networks. The generation of cellular rhythmic activity relies on a complex interplay between several distinct ion channels. One particular family of ion channels, often referred to as “pacemaker” channels, plays a crucial role in the generation of rhythmic activity in the heart and in the brain. These channels are activated by hyperpolarization of the membrane potential and their activity is modulated by binding of cyclic nucleotides. Therefore, they have been designated as HCN channels. Recently, four mammalian HCN channel genes have been cloned (HCN1-4). The specific contribution of each HCN isoform to the different physiological functions is not known.

In the present study, the physiological role of the HCN4 channel has been analyzed in mice. Via a gene-targeting approach, a mutation has been introduced in the murine HCN4 gene which leads to a single amino acid exchange in the cyclic nucleotide-binding domain of the HCN4 channel. The mutation disables the binding of cAMP to HCN4. Homozygous mice carrying the mutation die before birth. Most likely, a dysfunction of the heart is responsible for the death of the embryos *in utero*. My results indicate that HCN4 can only act as a pacemaker in the embryonic heart when cAMP is bound to the channel. In addition, I could demonstrate that during embryonic development the main target for cAMP-dependent acceleration of the heart beat is HCN4.