Molecular structure and functional properties of cardiac pacemaker channels

Xiangang ZONG[1,2*], Andreas LUDWIG[1], Franz HOFMANN[1], Martin BIEL[2]

(1. *Institut für Pharmakologie und Toxikologie der Technischen Universität München, München, Deutschland*;
2. *Department Pharmazie-Zentrum für Pharmaforschung, Ludwig-Maximilians Universität München, München, Deutschland*)

Abstract: Cardiac pacemaking is controlled by an inward current called I_f, which is activated by membrane hyperpolarization of pacemaker cells in the sinoatrial node. Recently, a family of hyperpolarization-activated and cyclic nucleotide-gated cation (HCN) channels comprising at least four members (HCN1 – HCN4) has been cloned. Two of these channels, HCN2 and HCN4, are expressed in the heart. When expressed in heterologous cells, HCN2 and HCN4 reveal general features of native I_f. In the present review we describe the molecular diversity and functional expression of the HCN channels and discuss structural determinants of the channels.

Key words: heart; ion channels; hyperpolarization-activated current; pacemaker current; hyperpolarization-activated and cyclic nucleotide-gated cation channels

CLC number: R966
Document code: A
Article ID: 1000-3002(2001)02-0081-07

1 Introduction

The spontaneous and rhythmic activity of the heart is a prerequisite for life. Cardiac pacemaker activity is controlled by a mixed Na^+/K^+ inward current, named I_f (f for "funny"), which is activated during the diastolic depolarization phase of the action potential. This depolarizing current serves to drive the cell membrane potential back towards the threshold of its action potential, thereby maintaining rhythmic activity. I_f Was first identified in sinoatrial node cells of the heart in the late seventies and early eighties of the 20th Century[1,2]. A similar current was also found in cardiac Purkinje fibers[3], as well as in atrial[4,5] and ventricular muscle[6]. Likewise, I_f was discovered in neurons[7-10] where they were designated as I_h (h for hyperpolarization-activated; used in this review) or I_q (q for "queer").

The functional properties of I_h channels[11,12] are: ① activation by hyperpolarizing potential more negative than – 50 to – 70 mV; ② permeation of Na^+ and K^+; ③ upregulation by cyclic AMP; ④ inhibition by Cs^+.

Although pacemaker currents were identified some twenty years ago the molecular structure of these channels was elucidated only recently[13-17]. There are at least four genes encoding I_h channels. Expression of the respective cDNAs induces the formation of currents that reveal all common properties of native cardiac and neuronal pacemaker channels. The aim of this review is to summarize the recent data on the molecular structure, tissue distribution, functional expression, and relationship between structure and functional properties of hyperpolarization-activated and cyclic nucleotide-gated cation (HCN) channels.

2 Molecular structure and tissue distribution

A family of four I_h channel genes, designated as HCN1 – HCN4 for HCN channels[18,19] has been isolated from mouse, rabbit and human cDNA libraries (Tab 1). HCN channels belong to the superfamily of voltage-gated cation channels. Within the family the channels reveal the highest

Received date: 2000-11-06 **Accepted date**: 2000-12-26

Biography: Xiangang ZONG (1950 –), male, native of Wuhan, Hubei. Resides in Munich, Germany since 1989. Privatdozent, Dr. med. habil. Main research field is pharmacology of ion channels, to identify the hyperpolarization-activated and cyclic nucleotide-gated cation channels cloned from mouse brain and human heart.

* Corresponding author. Tel: 49-89-21807320, Fax: 49-89-21807326, E-mail: xzoph@cup.uni-muenchen.de

Tab 1. Classification and tissue distribution of hyperpolarization-activated and cyclic nucleotide-gated cation (HCN) channels

Nomenclature		Amino acid*	Tissue distribution**			Reference No.
New	Old		Brain	Heart	Other	
HCN1	HAC2/BCNG-1	910	+ + +	–	–	13,15,16,20
HCN2	HAC1/BCNG-2	863	+ + +	+ + +	–	13,15,16,20
HCN3	HAC3/BCNG-4	779	+ +	–	–	13,15,16,20
HCN4	HAC4/BCNG-3	1203	+ +	+ +	testis	14,16,22,23
spHCN	SPIH	767			sperm	17

* HCN1 – 3 from murine brain; HCN4 from human heart. ** Expression levels were classified as: +, low; + +, moderate; + + +, strong; –, no significant expression.

degree of sequence homology (about 25%) to the *eag* K^+ channel and the cyclic nucleotide-gated (CNG) channel α-subunits (Fig 1B). Like voltage-activated K^+ channels the HCN channels contain six transmembrane segments (S1 – S6), a pore region between S5 and S6, and cytosolic N- and C-termini. In addition, HCN channels contain a cyclic nucleotide binding domain (CNBD) in the cytosolic C-terminus (Fig 1A). Like other members of the superfamily, HCN channels are also to form tetrameric complexes. The four mammalian HCN subunits (HCN1 – HCN4) are closely related to each other revealing overall sequence identities of 50% – 60%. The homology is highest in the central core region (S1 through the CNBD) with a sequence identity of 80% – 90% at the amino acid level (Fig 1B). In contrast, the cytoplasmic N- and C-termini are not conserved between HCN1 – HCN4.

Tab 1 summarizes the classification and tissue distribution of HCN channels. The first HCN protein, HCN2 (old nomenclature: HAC1) was cloned from mouse brain[13]. HCN2 is abundantly expressed throughout the brain[20,21]. HCN2 is also present in the heart[13, 16]. By using reverse transcription-polymerase chain reaction analysis the mRNA of HCN2 was detected in atrial and ventricular myocytes of human heart[14]. Besides HCN2, HCN4 is the second channel that is expressed in both heart and brain. Within the heart HCN4 is highly enriched in sinoatrial pacemaker cells[22, Moosmang unpublished] but is also present, though at much lower density, in atrial and ventricular myocytes[14]. In brain HCN4 is most

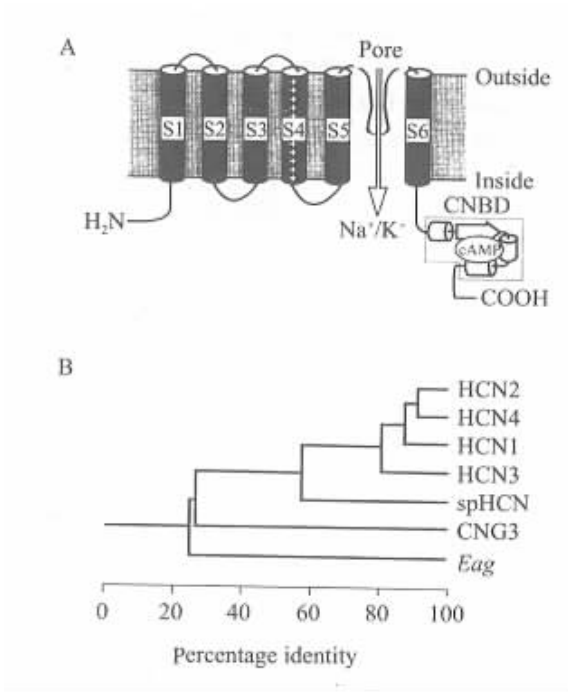

Fig 1. A: Structural model of HCN channels. The six membrane segments (S1 – S6) are indicated. The plus symbols represent the positive charged residues which are spaced regularly in the voltage-sensing S4 segment. As indicated by the arrow Na^+ and K^+ ions flux through the pore region. CNBD: cyclic nucleotide-binding domain. **B: Phylogenetic tree of HCN channel family, *eag* (*ether-à-gogo*) potassium channel and CNG3 (cyclic nucleotide-gated) channel.** The tree was calculated by comparison of the corresponding regions from segment S1 through the end of the CNBD. SpHCN was cloned in sea urchin testis[17].

abundant in neurons of the thalamus and olfactory bulb[20, 21, 23]. In contrast to HCN2 and HCN4, expression of HCN1 and HCN3 channel seems to be restricted to central and peripheral neurons.

3 Functional expression

Each member of the HCN channel family generates functional homomeric channels when heterologously expressed in HEK293 cells or *Xenopus* oocytes. HCN channels are activated by hyperpolarizing the plasma membrane to potentials more negative than − 60 mV. The inward I_h turns on with a typical delay and slowly relaxes to a steady state value, resulting in a characteristic sigmoidal shape of the current waveform (Fig 2). The membrane potential for a half-maximum activation ($V_{0.5}$) in HCN1 − HCN4 is about − 100 mV with a range from − 95 to − 110 mV (Tab 2). This value is consistant with the $V_{0.5}$ of native I_h channels. In sinoatrial nodal cells the $V_{0.5}$ was − 75 mV[24]. More negative values were obtained in Purkinje fibers (− 108 mV) and in ventricular myocytes (− 135 mV)[6]. In thalamic neurons $V_{0.5}$ value was − 78 mV[25]. Under physiological conditions the reversal potentials of HCN1, HCN2 and HCN4 currents are in the range between − 22 mV and − 30 mV indicating that the channels pass both Na^+ and K^+[14, 16, 22, 23]. The ratio of permeabilities to sodium and potassium (P_{Na}/P_K) is about 0.25 being in good agreement with the ion selectivity of native I_h channels[11,12].

The frequency of the heart beat is modulated by neurotransmitters through regulating the intracellular levels of cyclic nucleotides. DiFrancesco and Tortora[26] described a direct modulation of cardiac I_h channel by cAMP. The HCN2 and HCN4 channels are also clearly upregulated by cAMP and cGMP[13,14,22,23]. Cyclic AMP does not increase of the maximal open probability of I_h but shifts the activation curves of the channels towards more depolarizing potentials indicating that the upregulation by cAMP is due to an effect on the voltage-dependence of channel activation. The

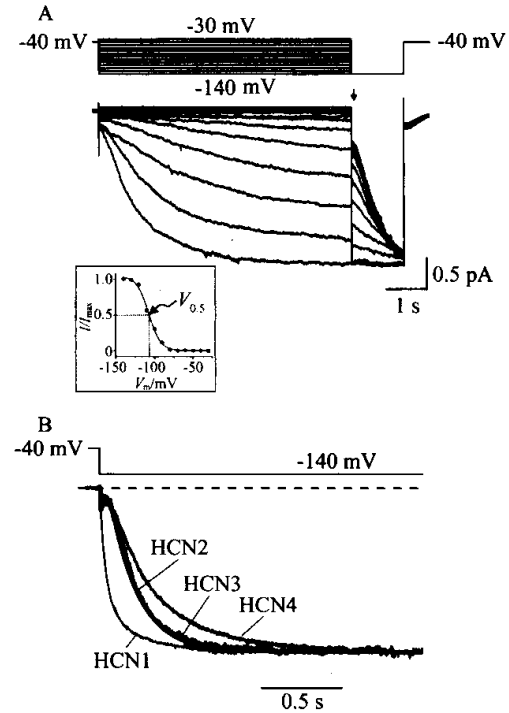

Fig 2. A: Representative whole-cell current traces recorded in a HEK 293 cell transfected with hHCN4. The cell was voltage-clamped from a holding potential of − 40 mV to various hyperpolarizing potentials with increments of 10 mV (see voltage protocol on top) followed by a step to − 140 mV. Tail currents measured immediately after the voltage step to − 140 mV (indicated by the arrow) were plotted as a function of the preceding potentials. The inset shows the activation curve and the measurement of the potential of half-maximum activation ($V_{0.5}$). **B: HCN1 − HCN4 channels differ from each other in their respective activation kinetics.** For clarity, current amplitudes of HCN2 − HCN4 were normalized to that of HCN1. Composition of intracellular solution (mmol·L^{-1}): KCl 130, NaCl 10, $MgCl_2$ 0.5, EGTA 1, HEPES 5, pH 7.4 with KOH. Composition of extracellular solution (mmol·L^{-1}): NaCl 110, KCl 30, $CaCl_2$ 1.8, $MgCl_2$ 0.5, HEPES 5, pH 7.4 with NaOH.

effect of cAMP is not restricted to the modulationof voltage-dependence of activation, and cAMP also accelerates the activation kinetics[13,14]. Cyclic GMP modulates both voltage-dependence and activation kinetics in a similar fashion as cAMP. However, the apparent affinity of the channel is about 10 fold higher for cAMP ($K_a = 0.5$ μmol·L^{-1})

Tab 2. Functional properties of HCN channels[13,14,17]

Channel	$V_{0.5}$ /mV	P_{Na}/P_K	Activation constant at −140 mV /ms τ_1	τ_2	Shift by cAMP /mV	K_a for cAMP /mmol·L^{-1}	Cs^+-sensitive
HCN1	−94	0.25	30	171	+1.8	n.d	yes
HCN2	−103	0.24	241		+13	0.5	yes
HCN3	−96*	n.d	n.d		n.d	n.d	n.d
HCN4	−109	0.22	660		+15	2.3*	yes
spHCN	−26.1	−	−		−24.7	0.74	yes

* Unpublished data from the author's laboratory. −, not given; n.d, not determined.

than for cGMP (K_a = 6 μmol·L^{-1}).

The basic electrophysiological properties are similar for all four HCN channels. The major difference between HCN channels refers to the speed of activation and the extent of modulation by cAMP. HCN1 reveals the fastest activation kinetics, whereas HCN4 activates with the slowest kinetics of all four HCN channels (Tab 2). On the other hand, HCN4 is very sensitive to cAMP, whereas HCN1 is almost insensitive to cAMP. The shifts of the activation curve by saturating cAMP are 17 to 23 mV, 12 mV and 2 mV for HCN4[14, 22], HCN2[13] and HCN1[16], respectively.

Like native I_h the expressed HCN channels are blocked by low-millimolar concentrations of extracellular Cs^+ but are insensitive to Ba^{2+} and tetraethylammonium. There are some blockers of native I_h such as ZD 7288, alinidine, and ivabradine (S16257)[27]. It will be interesting to investigate whether or not these compounds also block the cloned channels.

4 Structural determinants of channel function

4.1 Activation by hyperpolarization

HCN channels differ from other members of the superfamily of voltage-gated cation channels in that they are activated upon membrane hyperpolarization instead of depolarization. Having in mind that all channels of the family share the same transmembrane topology, the question arises which structural elements determine the unique gating mode of HCN channels.

The activation of the voltage-gated cation channels such as Na^+, K^+, or Ca^{2+} channels is controlled by a voltage-dependent translocation of the positively charged S4 helix (the voltage sensor) which is coupled by unknown conformational steps to the opening of the ion-conducting pore[28−30]. The S4 helix contains a series of regularly-spaced lysines or arginines separated from each other by two neutral amino acids. Suprisingly, HCN channels though activated by hyperpolarization also contain such a positively charged S4 sequence[13,15]. Even more surprisingly, the S4 of HCN channels contains a higher number of positive charges (ten) than depolarization-activated channels (five to eight). Why are HCN channels activated by hyperpolarization even though their S4 segments are also positively charged? Recent results from site-directed mutagenesis of K^+ channels[31−33] and HCN channels[34] suggest the following scheme to explain the different gating mode of depolarization- and hyperpolarization-actived cation channels[34,35].

In simple models of channel activation a channel protein can exist in three sequential states representing closed, open or inactivated state (closed ⇌ open ⇌ inactivated). At resting potential, depolarization-activated channels are in the closed state. Membrane depolarization drives the channels to the open state and later to the inactivated one. Activation of HCN channels by hyperpolarization could be explained by a profound shift of all three states to more hyperpolarizing volt-

ages. Thus, at resting potential most HCN channels will be in the inactivated state. Hyperpolarization opens the channels by driving the channels from the inactivated state to the open one. Thus, according to this model activation would be equivalent to the removal of inactivation.

4.2 Pore properties

The structural determinants of ion selectivity have been determined for Na^+, Ca^{2+} and K^+ channels. The Na^+ selectivity filter in sodium channels is formed by four amino acid residues DEKA (aspartate-glutamate-lysine-alanine) in the inner pore of domains Ⅰ－Ⅳ. Sodium channels can be rendered selective for Ca^{2+} if these residues (DEKA) are mutated to EEEE (glutamate-glutamate-glutamate-glutamate) that are responsible for the Ca^{2+} selectivity of Ca^{2+} channels[36]. Three amino acids, glycine-tyrosine-glycine (GYG), in the center of the pore loop form the electivity filter of almost all K^+ channels[37,38]. Notably, the GYG motif is also present in HCN channels although these channels pass both K^+ and Na^+. In K^+-selective channels the narrowest part of the pore is formed by the carbonyl backbones of the GYG motif which are constrained in an optimal geometry so that only a dehydrated K^+ fits with proper coordination. In HCN channels the carbonyl backbone may have lost some of its structural rigidity, thus allowing both K^+ and Na^+ to pass the pore.

4.3 Modulation by cyclic nucleotide

Cyclic AMP activates native I_f and expressed HCN channels by directly binding to the C-terminal CNBD of the channel proteins. The CNBD of HCN channels reveals a striking sequence similarity to that of other cyclic nucleotide-binding proteins such as the catabolite activator protein (CAP) of *E. coli*, cAMP- and cGMP-dependent protein kinase (PKA and PKG), and CNG channels[19]. The CNBD contains three α helices and eight β strands[39]. The amino acids which interact with the cAMP molecule are well conserved in HCN channels. Nevertheless, the HCN1 channel (+ 2 mV shift) is less modulated by cAMP as other members of the HCN channel family (shift of up to + 23 mV with HCN4). The molecular determinants of cyclic nucleotide efficacy have not been determined so far. However it is tempting to speculated, that like in CNG channels, the sequence that connects the S6 segment with the CNBD (the C-linker) is involved in coupling the ligand binding to the channel opening and thus may constitute a crucial determinant of cAMP-dependent channel modulation[40,41].

5 Conclusion

The cardiac pacemaker channel controls the rhythmic activity of heart. Two HCN channels (HCN2 and HCN4) are expressed in the heart. The identification of the structure of pacemaker channels enables us to characterize the molecular basis of channel regulation under physiological and pathological conditions. Furthermore, the molecular identification of HCN channel proteins will provide a new tool for the discovery of pharmacological agents that can be used for the therapy of cardiac diseases.

Acknowledgements The research conducted in the author's laboratory was supported by Fond der Chemischen Industrie, BMBF and Deutsche Forschungsgemeinschaft.

6 REFERENCES:

[1] Brown HF, Giles W, Noble SJ. Membrane currents underlying activity in frog sinus venosus[J]. *J Physiol* (Lond), 1977, **271**(3): 783－816.

[2] Yanagihara K, Irisawa H. Inward current activated during hyperpolarization in the rabbit sinoatrial node cell[J]. *Pflugers Arch*, 1980, **385**(1): 11－19.

[3] DiFrancesco D. A new interpretation of the pacemaker current in calf Purkinje fibres[J]. *J Physiol* (Lond), 1981, **314**: 359－376.

[4] Earm YE, Shimoni Y, Spindler AJ. A pacemaker-like current in the sheep atrium and its modulation by catecholamines[J]. *J Physiol* (Lond), 1983, **342**: 569－590.

[5] Zhou Z, Lipsius SL. Properties of the pacemaker current (I_f) in latent pacemaker cells isolated from cat right atrium[J]. *J Physiol* (Lond), 1992, **453**: 503－523.

[6] Yu H, Chang F, Cohen IS. Pacemaker current I_f in adult canine cardiac ventricular myocytes[J]. *J Physiol* (Lond), 1995, **485**(Pt 2): 469－483.

[7] Attwell D, Wilson M. Behaviour of the rod network in the tiger salamander retina mediated by membrane properties of

individual rods[J]. *J Physiol* (Lond), 1980, **309**:287 – 315.

[8] Halliwell JV, Adams PR. Voltage-clamp analysis of muscarinic excitation in hippocampal neurons[J]. *Brain Res*, 1982, **250**(1):71 – 92.

[9] Bader CR, Bertrand D. Effect of changes in intra- and extracellular sodium on the inward (anomalous) rectification in salamander photoreceptors[J]. *J Physiol* (Lond), 1984, **347**:611 – 631.

[10] Barnes S, Hille B. Ionic channels of the inner segment of tiger salamander cone photoreceptors[J]. *J Gen Physiol*, 1989, **94**(4):719 – 743.

[11] DiFrancesco D. Pacemaker mechanisms in cardiac tissue[J]. *Annu Rev Physiol*, 1993, **55**:455 – 472.

[12] Pape HC. Queer current and pacemaker: the hyperpolarization-activated cation current in neurons[J]. *Annu Rev Physiol*, 1996, **58**:299 – 327.

[13] Ludwig A, Zong X, Jeglitsch M, Hofmann F, Biel M. A family of hyperpolarization-activated mammalian cation channels[J]. *Nature*, 1998, **393**(6685):587 – 591.

[14] Ludwig A, Zong X, Stieber J, Hullin R, Hofmann F, Biel M. Two pacemaker channels from human heart with profoundly different activation kinetics[J]. *EMBO J*, 1999, **18**(9):2323 – 2329.

[15] Santoro B, Grant SG, Bartsch D, Kandel ER. Interactive cloning with the SH3 domain of N-src identifies a new brain specific ion channel protein, with homology to *eag* and cyclic nucleotide-gated channels[J]. *Proc Natl Acad Sci USA*, 1997, **94**(26):14815 – 14820.

[16] Santoro B, Liu DT, Yao H, Bartsch D, Kandel ER, Siegelbaum SA, *et al*. Identification of a gene encoding a hyperpolarization-activated pacemaker channel of brain[J]. *Cell*, 1998, **93**(5):717 – 729.

[17] Gauss R, Seifert R, Kaupp UB. Molecular identification of a hyperpolarization-activated channel in sea urchin sperm[J]. *Nature*, 1998, **393**(6685):583 – 587.

[18] Clapham DE. Not so funny anymore: pacing channels are cloned[J]. *Neuron*, 1998, **21**(1):5 – 7.

[19] Biel M, Ludwig A, Zong X, Hofmann F. Hyperpolarization-activated cation channels: a multi-gene family[J]. *Rev Physiol Biochem Pharmacol*, 1999, **136**:165 – 181.

[20] Moosmang S, Biel M, Hofmann F, Ludwig A. Differential distribution of four hyperpolarization-activated cation channels in mouse brain[J]. *Biol Chem*, 1999, **380**(7 – 8):975 – 980.

[21] Santoro B, Chen S, Lüthi A, Pavlidis P, Shumyatsky GP, Tibbs GR, *et al*. Molecular and functional heterogeneity of hyperpolarization-activated pacemaker channels in the mouse CNS[J]. *J Neurosci*, 2000, **20**(14):5264 – 5275.

[22] Ishii TM, Takano M, Xie LH, Noma A, Ohmori H. Molecular characterization of the hyperpolarization-activated cation channel in rabbit heart sinoatrial node[J]. *J Biol Chem*, 1999, **274**(18):12835 – 12839.

[23] Seifert R, Scholten A, Gauss R, Mincheva A, Lichter P, Kaupp UB. Molecular characterization of a slowly gating human hyperpolarization-activated channel predominantly expressed in thalamus, heart, and testis[J]. *Proc Natl Acad Sci USA*, 1999, **96**(16):9391 – 9396.

[24] Accili EA, Redaelli G, DiFrancesco D. Differential control of the hyperpolarization-activated current (I_f) by cAMP gating and phosphatase inhibition in rabbit sino-artial node myocytes[J]. *J Physiol* (Lond), 1997, **500**(Pt 3):643 – 651.

[25] Lüthi A, McCormick DA. Periodicity of thalamic synchronized oscillations: the role of Ca^{2+}-mediated upregulation of I_h[J]. *Neuron*, 1998, **20**(3):553 – 563.

[26] DiFrancesco D, Tortora P. Direct activation of cardiac pacemaker channels by intracellular cyclic AMP[J]. *Nature*, 1991, **351**(6322):145 – 147.

[27] Carmeliet E, Mubagwa K. Antiarrhythmic drugs and cardiac ion channels: mechanisms of action[J]. *Prog Biophys Mol Biol*, 1998, **70**(1):1 – 72.

[28] Bezanillla F. The voltage sensor in voltage-dependent ion channels[J]. *Physiol Rev*, 2000, **80**(2):555 – 592.

[29] Catterall WA. From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels[J]. *Neuron*, 2000, **26**(1):13 – 25.

[30] Horn R. A new twist in the saga of charge movement in voltage-dependent ion channels[J]. *Neuron*, 2000, **25**(3):511 – 514.

[31] Miller AG, Aldrich RW. Conversion of a delayed rectifier K^+ channel to a voltage-gated inward rectifier K^+ channel by three amino acid substitutions[J]. *Neuron*, 1996, **16**(4):853 – 858.

[32] Trudeau MC, Warmke JW, Ganetzky B, Robertson GA. HERG, a human inward rectifier in the voltage-gated potassium channel family[J]. *Science*, 1995, **269**(5220):92 – 95.

[33] Smith PL, Baukrowitz T, Yellen G. The inward rectification mechanism of the HERG cardiac potassium channel[J]. *Nature*, 1996, **379**(6568):833 – 836.

[34] Vaca L, Stieber J, Zong X, Ludwig A, Hofmann F, Biel M. Mutations in the S4 domain of a pacemaker channel alter its voltage dependence[J]. *FEBS Lett*, 2000, **479**(1 – 2):35 – 40.

[35] Santoro B, Tibbs GR. The HCN gene family: molecular basis of the hyperpolarization-activated pacemaker channels[J]. *Ann NY Acad Sci*, 1999, **868**:741 – 764.

[36] Heinemann SH, Terlau H, Stühmer W, Imoto K, Numa S. Calcium channel characteristics conferred on the sodium channel by single mutations[J]. *Nature*, 1992, **356**(6368):441 – 443.

[37] Heginbotham L, Lu Z, Abramson T, MacKinnon R. Mutations in the K^+ channel signature sequence[J]. *Biophys J*, 1994, **66**(4):1061 – 1067.

[38] Doyle DA, Morais-Cabral J, Pfuetzner RA, Kuo A, Gulbis JM, Cohen SL, *et al*. The structure of the potassium channel: molecular basis of K^+ conduction and selectivity[J]. *Science*, 1998, **280**(5360):69 – 77.

[39] Weber IT, Steitz TA. Structure of a complex of catabolite gene activator protein and cyclic AMP refined at 2.5Å resolution[J]. *J Mol Biol*, 1987, **198**:311 – 326.

[40] Zong X，Zucker H，Hofmann F，Biel M. Three amino acids in the C-linker are major determinants of gating in cyclic nucleotide-gated channels[J]. *EMBO J*，1998，**17**(2)：353 – 362.

[41] Paoletti P，Young EC，Siegelbaum SA. C-Linker of cyclic nucleotide-gated channels controls coupling of ligand binding to channel gating[J]. *J Gen Physiol*，1999，**113**(1)：17 – 34.

心脏起搏离子通道的分子结构和功能特性

宗贤刚[1,2]，Andreas LUDWIG[1]，Franz HOFMANN[1]，Martin BIEL[2]

(1. *Institut für Pharmakologie und Toxikologie der Technischen Universität München*，*München*，*Deutschland*；
2. *Department Pharmazie-Zentrum für Pharmaforschung*，*Ludwig-Maximilians Universität München*，*München*，*Deutschland*)

摘要：心脏的起搏受控于一类存在于心脏窦房结被称作 I_f 的离子通道，该通道是被细胞膜的超极化所激活. 新近，一类被命名为超极化激活及环化核苷酸调控的阳离子(HCN)通道被克隆. 该家族至少有 4 个成员，即 HCN1 ~ HCN4. 其中 2 个 HCN2 和 HCN4 在心脏有丰富表达. 用异体表达系统表达克隆的 HCN2 和 HCN4 通道蛋白，其通道特性类似心脏的天然 I_f 通道. 本综述讨论了 HCN 通道之间的分子结构差异，功能性表达特点以及与它们功能特性有关的分子结构.

关键词：心脏；离子通道；超极化激活电流；起搏电流；超极化激活及环化核苷酸调控的阳离子通道

（本文编辑　董立春）