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# International Union of Pharmacology. LI. Nomenclature and Structure-Function Relationships of Cyclic Nucleotide-Regulated Channels

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## Introduction

The family of cyclic nucleotide-regulated channels comprises two groups: the cyclic nucleotide-gated (CNG[1]) channels and the hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels.

## Cyclic Nucleotide-Gated Channels

CNG cation channels are ion channels whose activation is mediated by the direct binding of cGMP or cAMP to the channel protein (Biel et al., 1999b; Kaupp and Seifert, 2002; Matulef and Zagotta, 2003). CNG channels are expressed in the cilia of olfactory neurones and in outer segments of rod and cone photoreceptor neurones, where they play key roles in sensory transduction. Low levels of CNG channel transcripts have also been found in a variety of other tissues, including brain, testis, kidney, and heart. CNG channels are heterotetramers composed of homologous A subunits (CNGA1–CNGA4) and B subunits (CNGB1 and CNGB3) (Bradley et al., 2001). Both types of subunits are members of the six-transmembrane segment channel superfamily. In the cytosolic C terminus, CNG channel subunits carry a cyclic nucleotide-binding domain (CNBD) that serves as activation domain. The CNBD of CNG channels reveals significant sequence similarity to the CNBDs of other cyclic nucleotide receptors (Kaupp et al., 1989). The subunit stoichiometries have been determined for the channels expressed in rod photoreceptors (3 CNGA1: 1 CNGB1a) (Weitz et al., 2002; Zheng et al., 2002; Zhong et al., 2002), cone photoreceptors (2 CNGA3: 2 CNGB3) (Peng et al., 2004), and olfactory neurons (2 CNGA2: 1 CNGA4: 1 CNGB1b) (Zheng and Zagotta, 2004). The physiological relevance of CNGA2–4 and CNGB1 subunits has been elucidated by gene deletion in mice (Brunet et al., 1996; Biel et al., 1999a; Munger et al., 2001; Huttl et al., 2005).

CNG channels pass monovalent cations, such as $Na^+$ and $K^+$, but do not discriminate between them. Calcium is also permeable but at the same time acts as a voltage-dependent blocker of monovalent cation permeability (Frings et al., 1995; Dzeja et al., 1999). Moreover, $Ca^{2+}$ provides feedback inhibition of CNG channel activity by binding to calmodulin (Kaupp and Seifert, 2002; Matulef and Zagotta, 2003). CNG channels reveal a higher sensitivity for cGMP than for cAMP. The extent of ligand discrimination varies significantly between the individual CNG channel types. Photoreceptor channels strongly discriminate between cGMP and cAMP, whereas the olfactory channel is almost equally sensitive to both ligands.

## Drugs That Act on CNG Channels

Several drugs have been reported to block CNG channels, although not with very high affinity. L-*cis*-diltiazem has been studied most extensively. It blocks CNG channels in a voltage-dependent manner at micromolar concentration (Haynes, 1992). The D-*cis*-enantiomer of diltiazem that is used therapeutically as a blocker of the L-type calcium channel is much less effective than the L-*cis*-enantiomer in blocking CNG channels. High-affinity binding of L-*cis*-diltiazem is only seen in heteromeric CNG channels containing the CNGB1 subunit (Chen et al., 1993). CNG channels are also moderately sensitive to block by some other inhibitors of the L-type calcium channel (e.g., nifedipine), the local anesthetic tetracaine, and calmodulin antagonists (Kaupp and Seifert, 2002). Interestingly, LY83583 blocks both the soluble guanylate cyclase and some CNG channels at similar concentrations (Leinders-Zufall and Zufall, 1995). H-8, which has been widely used as a nonspecific cyclic nucleotide-

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[1] Abbreviations: CNG, cyclic nucleotide-gated; HCN, hyperpolarization-activated, cyclic nucleotide-gated; CNBD, cyclic nucleotide-binding domain; LY83583, 6-(phenyl-amino)-5,8-quinolinedione; H-8, *N*-2-(methyl-amino)ethyl-5-isoquinolinesulfonamide; SA, sinoatrial; ZD7288, 4-(*N*-ethyl-*N*-phenylamino-1,2-dimethyl-6-(methylamino) pyrimidinum chloride.

dependent protein kinase inhibitor, blocks CNG channels, although at significantly higher concentrations than needed to inhibit protein kinases (Wei et al., 1997).

## Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels

Like CNG channels, the HCN cation channels are members of the six-transmembrane superfamily (Kaupp and Seifert, 2001; Biel et al., 2002; Robinson and Siegelbaum, 2003). In contrast to most other voltage-gated channels, HCN channels open upon hyperpolarization and close at positive potential. The cyclic nucleotides cAMP and cGMP enhance HCN channel activity by shifting the activation curve of the channels to more positive voltages. The stimulatory effect of cyclic nucleotides does not depend on protein phosphorylation but is caused by direct interaction with the HCN channel protein. The current produced by HCN channels, termed $I_h$, $I_f$, or $I_q$, is found in a variety of excitable cells, including neurones, cardiac pacemaker cells, and photoreceptors (Pape, 1996; Robinson and Siegelbaum, 2003). The best-understood function of $I_h$ is to control heart rate and rhythm by acting as "pacemaker current" in the sinoatrial (SA) node (Stieber et al., 2004). $I_h$ is activated during the membrane hyperpolarization following the termination of an action potential and provides an inward $Na^+$ current that slowly depolarizes the plasma membrane. Sympathetic stimulation of SA node cells raises cAMP levels and increases $I_h$, thus accelerating diastolic depolarization and heart rate. Stimulation of muscarinic acetylcholine receptors slows down heart rate by the opposite action. In neurons, $I_h$ fulfills diverse functions, including generation of pacemaker potentials ("neuronal pacemaking"), determination of resting potential, transduction of sour taste, dendritic integration, control of synaptic transmission, and plasticity (Pape, 1996; Kaupp and Seifert, 2001; Robinson and Siegelbaum, 2003).

In mammals, the HCN channel family comprises four members (HCN1–HCN4) that share approximately 60% sequence identity to each other (Gauss et al., 1998; Ludwig et al., 1998; Santoro et al., 1998; Ludwig et al., 1999). HCN channels contain six-transmembrane helices (S1–S6) and assemble in tetramers (Zagotta et al., 2003). There is evidence that HCN subunits can coassemble to form heteromers (Much et al., 2003; Robinson and Siegelbaum, 2003). The S4 segment of the channels is positively charged and serves as voltage sensor (Mannikko et al., 2002). The C terminus of HCN channels contains a CNBD that confers regulation by cyclic nucleotides (Wainger et al., 2001; Zagotta et al., 2003). When expressed in heterologous systems, all four HCN channels generate currents displaying the typical features of native $I_h$: 1) activation by membrane hyperpolarisation; 2) permeation of $Na^+$ and $K^+$ with a permeability ratio $P_{Na}/P_K$ of approximately 0.2; 3) positive shift of voltage dependence of channel activation by direct binding of cAMP; and 4) channel block by extracellular $Cs^+$. The HCN1–HCN4 channels mainly differ from each other with regard to their speed of activation and the extent by which they are modulated by cAMP. HCN1 is the fastest channel, followed by HCN2, HCN3, and HCN4. Unlike HCN2 and HCN4, whose activation curves are profoundly shifted by cAMP, HCN1 is only weakly affected by cAMP (Kaupp and Seifert, 2001; Biel et al., 2002; Robinson and Siegelbaum, 2003).

HCN channels are found in neurons and heart cells. In SA node cells, HCN4 represents the predominantly expressed HCN channel isoform (Ishii et al., 1999; Moosmang et al., 2001; Stieber et al., 2003). In brain, all four HCN subunits have been detected (Notomi and Shigemoto, 2004). The expression levels and regional distribution of the HCN channel mRNAs vary profoundly between the respective channel types. HCN2 is the most abundant neuronal channel and is found almost ubiquitously in the brain. By contrast, HCN1 and HCN4 are enriched in specific regions of the brain such as thalamus (HCN4) or hippocampus (HCN1). HCN3 is expressed at low density in most parts of the brain but is enriched in olfactory bulb and some hypothalamic nuclei (Notomi and Shigemoto, 2004). HCN channels have also been detected in the retina (Muller et al., 2003) and some peripheral neurones such as dorsal root ganglion neurones (Moosmang et al., 2001). The specific roles of individual HCN channel types have been defined by analysis of mouse lines deficient for HCN1 (Nolan et al., 2003), HCN2 (Ludwig et al., 2003), and HCN4 (Stieber et al., 2003).

## Drugs That Act on HCN Channels

Given the key role of HCN channels in cardiac pacemaking, these channels are promising pharmacological targets for the development of drugs used in the treatment of cardiac arrhythmias and ischemic heart disease. Several blockers of native $I_h$ channels are known. The most extensively studied blocker is ZD7288 (BoSmith et al., 1993). Low micromolar concentrations of this agent specifically block both native $I_h$ and cloned HCN channels in a voltage-dependent manner. Three other use-dependent blockers of $I_h$ are ivabradine (Bois et al., 1996), zatebradine (Raes et al., 1998), and cilobradine (Stieber et al., 2004). Structurally, these substances are related to verapamil, a classic L-type calcium channel blocker. These agents block $I_h$ at concentrations comparable to ZD7288. Ivabradine is considered as a heart rate-lowering agent in the therapy of angina pectoris.

The molecular, physiological, and pharmacological properties of these channels are presented in Tables 1 through 10.

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TABLE 1
*CNGA1 channels*

| | |
|---|---|
| Channel name | CNGA1[1–3] |
| Description | Cyclic nucleotide-gated cation channel A subunit |
| Other names | CNG1, CNGa1, RCNC1 |
| Molecular information | Human: 690aa, NM_000087, NP_000087, chr. 4p12-cen<br>Rat: 683aa, NM_053497, NP_445949, chr. 14p11<br>Mouse: 683aa, NM_007723, NP_031749, chr. 4 C5 |
| Associated subunits | CNGB1a (rod photoreceptor channel: 3 CNGA1:1 CNGB1a) |
| Functional assays | Patch-clamp, calcium imaging |
| Current | Cyclic nucleotide-activated current |
| Conductance | 25–30pS (in calcium-free solution) |
| Ion selectivity | $Ca^{2+} > K^{+} \sim Na^{+}$ |
| Activation | Not established |
| Inactivation | Not established |
| Activators | cGMP $\gg$ cAMP (partial agonist) |
| Gating modifiers | None |
| Blockers | L-*cis*-diltiazem (in the presence of CNGB1a) |
| Radioligands | None |
| Channel distribution | Outer segment of rod photoreceptors, pinealocytes, some neurones |
| Physiological functions | Light transduction (low light intensities) |
| Mutations and pathophysiology | Missense mutations in CNGA1 cause autosomal recessive retinitis pigmentosa |
| Pharmacological significance | Not established |

aa, amino acids; chr., chromosome.

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TABLE 2
*CNGA2 channels*

| | |
|---|---|
| Channel name | CNGA2[1–3] |
| Description | Cyclic nucleotide-gated cation channel A subunit |
| Other names | CNG2, CNGa3, OCNC1 |
| Molecular information | Human: 664aa, NM_005140, NP_005131, chr. Xq27<br>Rat: 664aa, NM_012928, NP_037060, chr. Xq37<br>Mouse: 664aa, NM_007724, NP_031750, chr. X A6 |
| Associated subunits | CNGB1b, CNGA4 (olfactory CNG channel: 2 CNGA2: 1 CNGA4:1 CNGB1b) |
| Functional assays | Patch-clamp, calcium imaging |
| Current | Cyclic nucleotide-activated current |
| Conductance | 35pS (in calcium-free solution) |
| Ion selectivity | $Ca^{2+} > K^{+} \sim Na^{+}$ |
| Activation | Not established |
| Inactivation | Not established |
| Activators | cGMP > cAMP |
| Gating modifiers | $Ca^{2+}$-calmodulin |
| Blockers | Pseudechetoxin |
| Radioligands | None |
| Channel distribution | Olfactory neurones, hippocampus, some other neurones |
| Physiological functions | Olfactory transduction |
| Mutations and pathophysiology | Not established in humans |
| Pharmacological significance | Not established |

aa, amino acids; chr., chromosome.

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TABLE 3
*CNGA3 channels*

| | |
|---|---|
| Channel name | CNGA3[1–5] |
| Description | Cyclic nucleotide-gated cation channel A subunit |
| Other names | CNG3, CNGa2, CCNC1 |
| Molecular information | Human: 694aa, NM_001298, NP_001298, chr. 2q11.2<br>Rat: 611aa, NM_053495, NP_445947, chr. 9q21<br>Mouse: 631aa, NM_009918, NP_034048, chr. 1 B |
| Associated subunits | CNGB3 (cone photoreceptor channel: 2 CNGA3:2 CNGB3) |
| Functional assays | Patch-clamp, calcium imaging |
| Current | Cyclic nucleotide-activated current |
| Conductance | 40pS |
| Ion selectivity | $Ca^{2+} > K^+ \sim Na^+$ |
| Activation | Not established |
| Inactivation | Not established |
| Activators | cGMP $\gg$ cAMP (partial agonist) |
| Gating modifiers | None |
| Blockers | L-*cis*-diltiazem (in the presence of CNGB3) |
| Radioligands | None |
| Channel distribution | Cone photoreceptor, subpopulation of olfactory neurones, some central neurones, pinealocytes, sperm |
| Physiological functions | Light transduction (daylight, color vision) |
| Mutations and pathophysiology | Missense mutations in CNGA3 cause achromatopsia (rod monochromacy) and retinal degeneration |
| Pharmacological significance | Not established |

aa, amino acids; chr., chromosome.

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TABLE 4
*CNG4A channels*

| | |
|---|---|
| Channel name | CNGA4[1,2] |
| Description | Cyclic nucleotide-gated cation channel A subunit |
| Other names | CNG5, CNGa4, OCNC2, CNGB2 |
| Molecular information | Human: 575aa, XM_290552, XP_290552, chr. 11p15.4<br>Rat: 575aa, NM_053496, NP_445948, chr. 1q32<br>Mouse: 575aa, XM_145875, XP_145875, chr. 7 E3 |
| Associated subunits | CNGA2, CNGB1b |
| Functional assays | When assembled with CNGA2 and CNGB1b subunits: patch-clamp, calcium imaging |
| Current | Not functional on its own |
| Conductance | Not established |
| Ion selectivity | Not established |
| Activation | Not established |
| Inactivation | Not established |
| Activators | None |
| Gating modifiers | $Ca^{2+}$-calmodulin (in native olfactory channel) |
| Blockers | None |
| Radioligands | None |
| Channel distribution | Olfactory neurons, some central neurons |
| Physiological functions | Modulatory subunit of native olfactory CNG channel: increases cAMP sensitivity and accelerates $Ca^{2+}$-calmodulin-dependent odor adaptation |
| Mutations and pathophysiology | Not established in humans |
| Pharmacological significance | Not established |

aa, amino acids; chr., chromosome.

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TABLE 5
*CNGB1 channels*

| | |
|---|---|
| Channel name | CNGB1[1,2] |
| Description | Cyclic nucleotide-gated cation channel B subunit |
| Other names | CNG4, CNGb1, RCNC2 |
| Molecular information | Human CNGB1a: 1245aa, NM_001297, NP_001288, chr: 16q13<br>Rat CNGB1a: 1339aa, NM_031809, NP_113997, chr. 19p12<br>Rat CNGB1b: 858aa, CAA04152, AAC19120<br>Mouse CNGB1b: 966aa, XM_286113, XP_286113, chr. 8 C5 |
| Associated subunits | CNGB1a assembles with CNGA1 in rod photoreceptors; CNGB1b assembles with CNGA2 and CNGA4 in olfactory neurones |
| Functional assays | When assembled with CNGA1 or CNGA2/CNGA4: patch-clamp, calcium imaging |
| Current | Not functional on its own |
| Conductance | Not established |
| Ion selectivity | Not established |
| Activation | Not established |
| Inactivation | Not established |
| Activators | None |
| Gating inhibitors | $Ca^{2+}$-calmodulin (in native rod and olfactory channel) |
| Blockers | L-*cis*-diltiazem binds to this subunit and inhibits the current flowing through the CNGA1/CNGB1a channel |
| Radioligands | None |
| Channel distribution | Rod photoreceptors, olfactory neurones, sperm |
| Physiological functions | $Ca^{2+}$-calmodulin-dependent desensitization of rod and olfactory CNG channel; required for cell surface expression of rod channel |
| Mutations and pathophysiology | Recessive retinitis pigmentosa is caused by the G993V mutation |
| Pharmacological significance | Not established |
| Comments | Splice variants have been identified in various mammals; CNGB1a, the "long" isoform, contains a glutamic acid-rich protein domain (GARP); CNGB1b, the "short" isoform (858aa in rat), does not have this domain; GAR1 (315aa in rat) corresponds to the N terminus of CNGB1a; the GARP domain is involved in association with other proteins |

aa, amino acids; chr., chromosome.

1. Ardell MD, Bedsole DL, Schoborg RV, and Pittler SJ (2000) Genomic organization of the human rod photoreceptor cGMP-gated cation channel beta-subunit gene. *Gene* **245:**311–318.
2. Chen TY, Peng YW, Dhallan RS, Ahamed B, Reed RR, and Yau KW (1993) A new subunit of the cyclic nucleotide-gated cation channel in retinal rods. *Nature (Lond)* **362:**764–767.

TABLE 6
*CNGB3 channels*

| | |
|---|---|
| Channel name | CNGB3[1,2] |
| Description | Cyclic nucleotide-gated cation channel B subunit |
| Other names | CNG6, CNGb2, CCNC2 |
| Molecular information | Human: 809aa, NM_019098, NP_061971, chr. 8q21–q22<br>Rat: not cloned<br>Mouse: 694aa, NM_013927, NP_038955, chr. 4 A3 |
| Associated subunits | CNGB3 assembles with CNGA3 in cone photoreceptors |
| Functional assays | When assembled with CNGA3: patch-clamp, calcium imaging |
| Current | Not functional on its own |
| Conductance | Not established |
| Ion selectivity | Not established |
| Activation | Not established |
| Inactivation | Not established |
| Activators | None |
| Gating modifiers | None |
| Blockers | L-*cis*-diltiazem binds to this subunit and inhibits the current flowing through the CNGA3/CNGB3 channel |
| Radioligands | None |
| Channel distribution | Cone photoreceptors, testis |
| Physiological functions | Modulatory subunit of CNGA3, color vision |
| Mutations and pathophysiology | Missense mutations in CNGB3 causes achromatopsia (Pingelapese blindness) |
| Pharmacological significance | Not established |

aa, amino acids; chr., chromosome.

1. Gerstner A, Zong X, Hofmann F, and Biel M (2000) Molecular cloning and functional characterization of a new modulatory cyclic nucleotide-gated channel subunit from mouse retina. *J Neurosci* **20:**1324–1332.
2. Sundin OH, Yang JM, Li Y, Zhu D, Hurd JN, Mitchell TN, Silva ED, and Maumenee IH (2000) Genetic basis of total colour blindness among the Pingelapese islanders. *Nat Genet* **25:**289–293.

TABLE 7
*HCN1 channels*

| | |
|---|---|
| Channel name | HCN1[1–3] |
| Description | Hyperpolarization-activated cyclic nucleotide-gated cation channel |
| Other names | HAC2, BCNG1 |
| Molecular information | Human: 890aa, NM_021072, NP_066550, chr. 5p12<br>Rat: 910aa, NM_053375, NP_445827, chr. 2q15<br>Mouse: 910aa, NM_010408, NP_034538, chr. 13 D2.3 |
| Associated subunits | Not established |
| Functional assays | Voltage-clamp |
| Current | $I_h$, $I_f$, or $I_q$ |
| Conductance | Not established |
| Ion selectivity | $K^+$, $Na^+$ ($P_{Na}/P_K \sim 0.2$); divalents do not permeate |
| Activation | $V_{0.5}$ = −70 mV to −90 mV; $t_a$ = 30–300 ms at −140 mV to −95 mV (values are strongly influenced by experimental parameters such as temperature, pH, and pulse protocol) |
| Inactivation | No voltage-dependent inactivation |
| Activators | cAMP > cGMP (both induce a positive shift of $V_{0.5}$ in the range of +2 to +7 mV) |
| Gating inhibitors | ZD7288 |
| Blockers | $Cs^+$, ZD7288, ivabradine, zatebradine, cilobradine |
| Radioligands | None |
| Channel distribution | Central and peripheral neurones (hippocampus, cerebellum, neocortex, dorsal root ganglion, taste cells, photoreceptors), sinoatrial node cells |
| Physiological functions | Motor learning, spatial memory and plasticity, modulation of retinal light response, sour taste transduction |
| Mutations and pathophysiology | Not established in humans |
| Pharmacological significance | Not established |

aa, amino acids; chr., chromosome.

1. Ludwig A, Zong X, Jeglitsch M, Hofmann F, and Biel M (1998) A family of hyperpolarization-activated mammalian cation channels. *Nature (Lond)* **393:**587–591.
2. Monteggia LM, Eisch AJ, Tang MD, Kaczmarek LK, and Nestler EJ (2000) Cloning and localization of the hyperpolarization-activated cyclic nucleotide-gated channel family in rat brain. *Brain Res Mol Brain Res* **81:**129–139.
3. Santoro B, Liu DT, Yao H, Bartsch D, Kandel ER, Siegelbaum SA, and Tibbs GR (1998) Identification of a gene encoding a hyperpolarization-activated pacemaker channel of brain. *Cell* **93:**717–729.

TABLE 8
*HCN2 channel*

| | |
|---|---|
| Channel name | HCN2[1–3] |
| Description | Hyperpolarization-activated cyclic nucleotide-gated cation channel |
| Other names | HAC1, BCNG2 |
| Molecular information | Human: 889aa, NM_001194, NP_00185, chr. 19p13.3<br>Rat: 834aa, NM_053684, NP_446136, chr. 7q11<br>Mouse: 863aa, NM_008226, NP_032252, chr. 10 C1 |
| Associated subunits | Not established |
| Functional assays | Voltage-clamp |
| Current | $I_h$, $I_f$, or $I_q$ |
| Conductance | Not established |
| Ion selectivity | $K^+$, $Na^+$ ($P_{Na}/P_K \sim 0.2$); divalents do not permeate |
| Activation | $V_{0.5}$ = −75 mV to −100 mV; $t_a$ = 180–600 ms at −140 mV to −100 mV (values are strongly influenced by experimental parameters such as temperature, pH, and pulse protocol) |
| Inactivation | No inactivation |
| Activators | cAMP > cGMP (both induce a positive shift of $V_{0.5}$ by ~ +15mV) |
| Gating modifiers | ZD7288 |
| Blockers | $Cs^+$, ZD7288, ivabradine, zatebradine, cilobradine |
| Radioligands | None |
| Channel distribution | Central and peripheral neurones, retina, heart cells |
| Physiological functions | Resting membrane potential of neurons and cardiac pacemaker cells, modulation of firing mode of thalamic neurons |
| Mutations and pathophysiology | Not established in humans |
| Pharmacological significance | Not established |

aa, amino acids; chr., chromosome.

1. Ludwig A, Zong X, Jeglitsch M, Hofmann F, and Biel M (1998) A family of hyperpolarization-activated mammalian cation channels. *Nature (Lond)* **393:**587–591.
2. Ludwig A, Zong X, Stieber J, Hullin R, Hofmann F, and Biel M (1999) Two pacemaker channels from human heart with profoundly different activation kinetics. *EMBO J* **18:**2323–2329.
3. Monteggia LM, Eisch AJ, Tang MD, Kaczmarek LK, and Nestler EJ (2000) Cloning and localization of the hyperpolarization-activated cyclic nucleotide-gated channel family in rat brain. *Brain Res Mol Brain Res* **81:**129–139.

TABLE 9
*HCN3 channels*

| | |
|---|---|
| Channel name | HCN3[1,2] |
| Description | Hyperpolarization-activated, cyclic nucleotide-gated cation channel |
| Other names | HAC3, BCNG4 |
| Molecular information | Human: 774aa, NM_020897, NP_065948, chr. 1q22<br>Rat: 780aa, NM_053685, NP_446137, chr. 2q34<br>Mouse: 779aa, NM_008227, NP_032253, chr. 3 F2 |
| Associated subunits | Not established |
| Functional assays | Voltage-clamp |
| Current | $I_h$, $I_f$, or $I_q$ |
| Conductance | Not established |
| Ion selectivity | Not established |
| Activation | $V_{0.5}$ = −95 mV; $t_a$ = 260 ms at −140 mV (values are strongly influenced by experimental parameters such as temperature, pH, and pulse protocol) |
| Inactivation | No inactivation |
| Activators | None |
| Gating modifiers | None |
| Blockers | None |
| Radioligands | None |
| Channel distribution | Brain, retina, heart |
| Physiological functions | Not established |
| Mutations and pathophysiology | Not established |
| Pharmacological significance | Not established |

aa, amino acids; chr., chromosome.

1. Ludwig A, Zong X, Jeglitsch M, Hofmann F, and Biel M (1998) A family of hyperpolarization-activated mammalian cation channels. *Nature (Lond)* **393:**587–591.
2. Monteggia LM, Eisch AJ, Tang MD, Kaczmarek LK, and Nestler EJ (2000) Cloning and localization of the hyperpolarization-activated cyclic nucleotide-gated channel family in rat brain. *Brain Res Mol Brain Res* **81:**129–139.

TABLE 10
*HCN4 channels*

| | |
|---|---|
| Channel name | HCN4[1–4] |
| Description | Hyperpolarization-activated, cyclic nucleotide-gated cation channel |
| Other names | HAC4, BCNG3 |
| Molecular information | Human: 1203aa, NM_005477, NP_005468, chr. 15q24-q25<br>Rat: 1198aa, NM_021658, NP_067690, chr. 8q24<br>Mouse: 1201aa, XM_287905, XP_287905, chr. 9 B |
| Associated subunits | Not established |
| Functional assays | Voltage-clamp |
| Current | $I_h$, $I_f$, or $I_q$ |
| Conductance | Not established |
| Ion selectivity | $K^+$, $Na^+$ ($P_{Na}/P_K \sim 0.2$); divalents also permeate |
| Activation | $V_{0.5}$ = −65 mV to −100 mV; $t_a$ = 260 ms–30s at −140 mV to −70 mV (values are strongly influenced by experimental parameters such as temperature, pH, and pulse protocol) |
| Inactivation | No inactivation |
| Activators | cAMP > cGMP (both include a positive shift of $V_{0.5}$ in the range of +10 mV to +25 mV) |
| Gating modifiers | ZD7288 |
| Blockers | $Cs^+$, ZD7288, ivabradine, zatebradine, cilobradine |
| Radioligands | None |
| Channel distribution | Thalamus, retina, olfactory bulb, sinus node, taste cells, testis |
| Physiological functions | Development of cardiac pacemaker cells, heart rate control, transduction of sour taste |
| Mutations and pathophysiology | D553N and HCN4-573X mutations associated with sick sinus node disease |
| Pharmacological significance | Not established |

aa, amino acids; chr., chromosome.

1. Ishii TM, Takano M, Xie LH, Noma A, and Ohmori H (1999) Molecular characterization of the hyperpolarization-activated cation channel in rabbit heart sinoatrial node. *J Biol Chem* **274:**12835–12839.
2. Ludwig A, Zong X, Stieber J, Hullin R, Hofmann F, and Biel M (1999) Two pacemaker channels from human heart with profoundly different activation kinetics. *EMBO J* **18:**2323–2329.
3. Monteggia LM, Eisch AJ, Tang MD, Kaczmarek LK, and Nestler EJ (2000) Cloning and localization of the hyperpolarization-activated cyclic nucleotide-gated channel family in rat brain. *Brain Res Mol Brain Res* **81:**129–139.
4. Seifert R, Scholten A, Gauss R, Mincheva A, Lichter P, and Kaupp UB (1999) Molecular characterization of a slowly gating human hyperpolarization-activated channel predominantly expressed in thalamus, heart, and testis. *Proc Natl Acad Sci USA* **96:**9391–9396.