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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
	Rat: 683aa, NM_053497, NP_445949, chr. 14p11
	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
	Rat: 664aa, NM_012928, NP_037060, chr. Xq37
	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 Rat: 611aa, NM_053495, NP_445947, chr. 9q21 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 Rat: 575aa, NM_053496, NP_445948, chr. 1q32 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.

1. Bradley J, Li J, Davidson N, Lester HA, and Zinn K (1994) Heteromeric factory cyclic nucleotide-gated channels: a subunit that confers increased sensitivity to cAMP. *Proc Natl Acad Sci USA* **91:**8890–8894.

2. Liman ER and Buck LB (1994) A second subunit of the olfactory cyclic nucleotide-gated channel confers high sensitivity to cAMP. *Neuron* **13:**611–621.

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 Rat CNGB1a: 1339aa, NM_031809, NP_113997, chr. 19p12 Rat CNGB1b: 858aa, CAA04152, AAC19120 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.

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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 Rat: not cloned 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 Rat: 910aa, NM_053375, NP_445827, chr. 2q15 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 Rat: 834aa, NM_053684, NP_446136, chr. 7q11 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 $\sim$ +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 Rat: 780aa, NM_053685, NP_446137, chr. 2q34 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 Rat: 1198aa, NM_021658, NP_067690, chr. 8q24 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.