Hyperpolarization-activated, cyclic nucleotide-gated (HCN)

Overview: The hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels are cation channels that are activated by hyperpolarization at voltages negative to ~–50 mV. The cyclic nucleotides cAMP and cGMP directly activate the channels and shift the activation curves of HCN channels to more positive voltages, thereby enhancing channel activity. HCN channels underlie pacemaker currents found in many excitable cells including cardiac cells and neurons (DiFrancesco, 1993; Pape, 1996). In native cells, these currents have a variety of names, such as I_h, I_q and I_f. The four known HCN channels have six transmembrane domains and form tetramers. It is believed that the channels can form heteromers with each other, as has been shown for HCN1 and HCN4 (Altomare *et al.*, 2003). A standardized nomenclature for HCN channels has been proposed by the NC-IUPHAR subcommittee on voltage-gated ion channels (see Hofmann *et al.*, 2005).

Nomenclature	HCN1	HCN2	HCN3	HCN4
Ensembl ID	ENSG00000164588	ENSG00000099822	ENSG00000143630	ENSG00000138622
Activators	cAMP > cGMP (both weak)	cAMP > cGMP	–	cAMP > cGMP
Inhibitors	Cs^+, ZD7288, ivabradine	Cs^+, ZD7288, ivabradine	Cs^+, ZD7288, ivabradine	Cs^+, ZD7288, ivabradine

HCN channels are permeable to both Na^+ and K^+ ions, with a Na^+/K^+ permeability ratio of about 0.2. Functionally, they differ from each other in terms of time constant of activation with HCN1 the fastest, HCN4 the slowest and HCN2 and HCN3 intermediate. The compounds ZD7288 (BoSmith *et al.*, 1993) and ivabradine (Bucchi *et al.*, 2002) have proven useful in identifying and studying functional HCN channels in native cells.

Abbreviations: ivabradine (S16257-2), (3-(3-{[((7*S*)-3,4-dimethoxybicyclo [4,2,0] octa-1,3,5-trien7-yl) methyl] methylamino} propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one hydrochloride; **ZD7288**, [4-(*N*-ethyl-*N*-phenyl-amino)-1,2-dimethyl-6-(methylamino) pyrimidinium chloride

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