Control of HCN channel opening and closing by cyclic nucleotide binding and action

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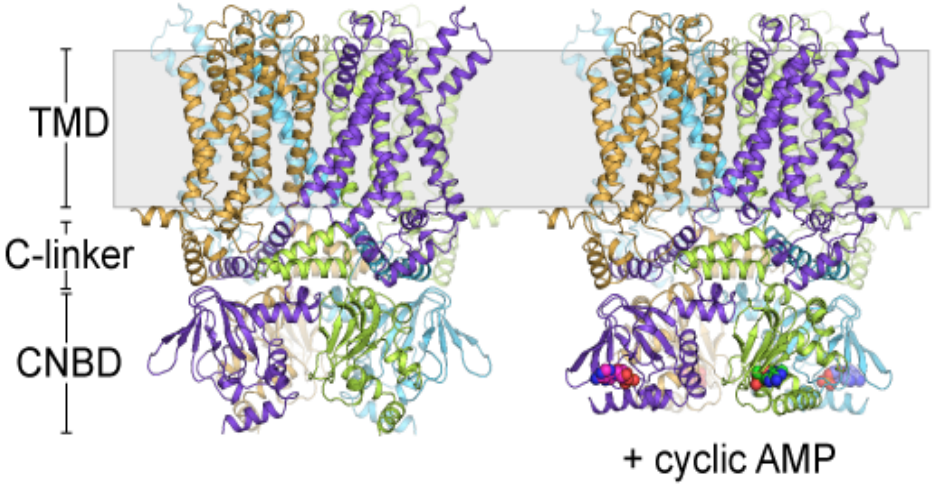
Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels contribute to membrane potential and electrical pacemaker activity in various cells of the body. The four mammalian HCN channel isoforms arise from four separate genes and are similar in structure and function to other voltage-gated ion channels, especially those in the KCNH (including HERG) and cyclic nucleotide-gated (CNG) channel families in animals and KAT1 channel family in plants. HCNs are non-swapped, tetrameric channels that open in response to hyperpolarization of the membrane potential. The C- and N-termini of individual subunits are intracellular and theypossess a cyclic-nucleotide binding domain (CNBD) in the proximal C-terminus. In mammalian HCN2 and HCN4 isoforms, binding of cAMP and cGMP (intracellular messenger molecules) shift the activation curve to less-negative voltages to about the same maximum extent but greater amounts of cGMP are required. Single mutations in the CNBD can also shift the range of effective concentrations of cAMP and cGMP. We have combined functional measurements from the literature and direct binding information by isothermal titration calorimetry with a mathematical model to determine whether differences in effective concentrations between different ligands, or in the effects of single mutations in the CNBD on effective concentration, are due mainly to alterations in binding affinity or gating transitions that follow the initial binding event. The findings highlight regions of the CNBD that may contribute specifically to binding or gating effects of ligands. Such information could be used to design molecules to treat diseases including those that are associated with growing number of mutations identified in human HCN genes.



Mercoledi 19 giugno 2024 - ore 10:00
Aula Videoconferenze, DIMA - Via Eudossiana 18, Roma
Link Google Meet: meet.google.com/evw-rmex-psb

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