Abstract

Ion channels are proteins that form ion-permeable pores in the cell membrane and thereby determine the membrane potential of cells. Hyperpolarization-activated and cyclic nucleotide-gated (HCN) channels belong to the superfamily of voltage-gated ion channels and are composed of four identical subunits. Each subunit has a modular architecture and contains a voltage-sensing domain (VSD), a pore domain (PD), and a cyclic nucleotide-binding domain (CNBD). The PD contains the ion-permeation pathway and the selectivity filter, which consists of a conserved motif (CIGYG) that makes HCN channels selective for sodium and potassium. Recently, a new HCN channel termed HCN-like 1 (HCNL1) with an unusual selectivity-filter motif has been identified in zebrafish sperm.

In my thesis, I characterized the HCNL1 channel with electrophysiological methods and revealed its profound differences to classical HCN channels. Surprisingly, HCNL1 selectively conducts protons (H^+ ions). Conduction of other ions is below the detection limit of the patch-clamp technique. Pharmacological and mutagenesis experiments indicate that protons permeate through the VSD, and not through the canonical PD. In the S4 segment of the VSD, a methionine residue (M169), located at a position that is occupied by an arginine in “classical” HCN channels, plays a key role for proton permeation.

HCNL1 is found in several other cyprinoid fish. I could confirm proton conduction in HCNL1 of the common carp and a Chinese cave fish. The evolution of a highly selective proton channel from the “classical” HCN channels might have a particular physiological relevance in sperm of freshwater fish. Freshwater is scarce in sodium ions. Protons, however, can be conducted from the freshwater into sperm via HCNL1 channels, thereby depolarizing sperm, which might be important for an intracellular signaling cascade that controls sperm motility.