Second International Calcium Channel Conference - Placencia, Belize
March 28 – April 2, 2010

Impact of protein interactions for gating modulation of $Ca_V1.3$ L-type calcium channels

Alexandra Koschak, Gabriella Juhasz-Vedres, Mathias Gebhart, Andreas Lieb, Martina Sinnegger-Brauns, Annalisa Zucchotti, Jutta Engel, Marlies Knipper and Jörg Striessnig

Pharmacology and Toxicology, Institute of Pharmacy, Center for Molecular Biosciences, University of Innsbruck, Austria; Institute of Physiology II and Tübingen Hearing Research Centre, University of Tübingen, Tübingen, Germany

$Ca_V1.3$ L-type channels control inner hair cell (IHC) sensory and sinoatrial node (SAN) function, and excitability in central neurons by means of their low-voltage activation and inactivation properties. In SAN cells $Ca_V1.3$ inward calcium current (I_{Ca}) inactivates rapidly whereas in IHCs inactivation is slow. We have recently discovered that $Ca_V1.3$ channel gating is modulated by an intramolecular C-terminal mechanism (CTM). This mechanism was elicited during analysis of human C-terminal splice variants that differ in the length of their C-terminus and that modulates the channel's negative activation range and slows calcium-dependent inactivation (CDI). Interestingly, this regulation has not been reported for rat $Ca_v1.3$ analogues but is present in mouse. We further report a new short $Ca_v1.3$ splice variant in human and mouse brain also revealing CTM modulation. Under action potential-like stimulations short channels show pronounced accumulation in I_{Ca} inactivation which is due to slower recovery from inactivation compared to long channels. Another candidate suggested in slowing $Ca_V1.3$ channel inactivation is the presynaptically located ribbon-synapse protein RIM which we detected in the organ of Corti before onset of hearing and also in IHC preparations. RIM shifted the voltage-dependence of I_{Ca} activation and inactivation significantly to more depolarized potentials and slowed CDI. In an early developmental stage, RIM might therefore partly account for the slow inactivation of $Ca_V1.3$ IHC currents. No human diseases resulting from mutations in the *CACNA1D* gene have been reported so far. However, a loss-of-function in humans might cause deafness and sinoatrial node dysfunction. Support: FWF (P-20670), EC (MRTN-CT-2006-035367), University of Innsbruck.