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Gating determinants in L-type (Ca_v1.2) channels

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Mutations in the lower third of pore lining segments IS6 and IIS6 of the Ca_v1.2 α_1 subunit shift the activation curve to the left and decelerate the activation kinetics (Hohaus et al. 2005, Kudrnac et al. 2008). In the closed state S6 segments in this area are believed to cross over thereby forming a tightly packed region constricting the pore near the inner channel mouth. Kinetic studies revealed that mutations in this region destabilize the closed and simultaneously stabilize the open channel state (Beyl et al. 2009). In segment IIS6 a strong correlation between changes in hydrophobicity (ΔH) and the shifts of the activation curve was observed ($\Delta V_{0.5}$, Hering et al. 2008). By mutating residues in the lower third of segments IIS6 and IVS6 we identified novel gating sensitive residues that shift the activation curve and affected channel activation kinetics. Potential interactions between gating sensitive residues in segments IS6-IVS6 were disclosed by double mutant cycle analysis. Our study revealed specific impacts of gating determinants in all four S6 segments and enabled insights into the molecular determinants of pore stability. A homology model of the Ca_v1.2 pore will be discussed. Supported by FWF-Project P19614-B11