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Abstract

Naturally occurring mutations (causing "channelopathies" [7-9] or mutations introduced to establish structure-activity relationships in Cav may influence gating properties [1-3]. It is generally believed that the voltage-dependent upward movement of VS triggers the opening of CaV1.2 pore while repolarization and the downward movement initiates the channel's closure [4]. In our study we investigated the individual roles of VSs in the Cav1.2 channel gating.

In order to elucidate the input of individual VSs in CaV1.2 gating, charged residues of segments IS4- IVS4 were replaced by glutamine and the corresponding effects on gating processes (activation, deactivation and inactivation) of calcium channels were analysed [4]. Since, inactivation of L-type calcium channel (Cav1.2) determines the length of the cardiac action potential, our studies mainly focused on this gating process.

During my doctoral thesis work I also contributed to the clarification of the role of individual S 4 segments in activation gating [4]. We identified a key role of segment IS4 and IIIS4 in activation. Almost all replacements of charges in IS4 and IIIS4 decreased the slope of the Boltzmann curve of channel activation (activation curve) suggesting a key role of these voltage sensors in channel activation.

The main focus of my project was, however, on the role of S4 segments in inactivation gating. I discovered, that segment IS4 affects not only activation but additionally has a key role in CaV1.2 inactivation. Impairing IS4 function by charge neutralization had by far the largest and regular (charge dependent) effects on voltage-dependent inactivation compared to no or less impact of equivalent charge neutralizations in segments IIS4 and IIIS4 [5].

Interestingly, shifts in the voltage-dependence of inactivation curves induced by IS4 neutralisations showed significant correlation with shifts of the voltage dependence of channel activation. This finding indicates that IS4 movement is not only rate limiting for activation but also initiates inactivation [6].