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Single channel manifestations of L-type calcium channel inactivation

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L-type calcium channels (L-VDCC) are inactivated through voltage- (VDI) and calcium- (CDI) dependent mechanisms. Single-channel studies addressing these phenomena are rare, perhaps because of the *bona fide* biophysical concept of inactivation as a singular event leading to an absorbing closed state. We elaborate on two examples challenging this simplistic view.

VDI of L-VDCC ismodulated by the N-terminus of its β-subunits (Herzig et al., FASEB J 2007;21:1527-38). We took advantage of this phenomenon by creating and studying N-terminal truncation mutants of a β_1-subunit coexpressed with Cav1.2 and $\alpha_2\delta$-2. The full-length β_1-subunit construct strongly induced VDI (compared to mock-transfection) of the multimeric channel. Deletion of the N-terminus progressively mitigated the modulation. The single-channel representation of this selective effect (other whole-cell parameters being unaffected) was revealed by Markov modeling: here, inactivation is best represented by slow yet reversible entry into a non-absorbing, non-conducting state.

CDI has been described in single channels from cardiomyocytes as a dynamic process, involving the reduction of open times (“mode Ca “ gating, Imredy and Yue, Neuron 1994;12:1301-18, Josephson et al., J Physiol 2010;588:213-23). We confirm this phenomenon using recombinant human Cav1.3 channels. Furthermore, we examine the role of the alternatively spliced C-terminal modulator (CTM) of this pore subunit (Singh et al., J Biol Chem 2008;283:20733-44). Our data raise the intriguing possibility that CTM affects CDI indirectly, i.e. through its modulatory effect on open probability.

In conclusion, both CDI and VDI are complex and highly dynamic phenomena. Detailed understanding of inactivation can be greatly aided by single-channel studies.