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Review

Voltage- and calcium-dependent inactivation in high voltage-gated Ca^{2+} channels

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Abstract

Calcium influx into cardiac myocytes via voltage-gated Ca channels is a key step in initiating the contractile response. During prolonged depolarizations, toxic Ca^{2+} overload is prevented by channel inactivation occurring through two different processes identified by their primary trigger: voltage or intracellular Ca^{2+}. In physiological situations, cardiac L-type ($Ca_V1.2$) Ca^{2+} channels inactivate primarily via Ca^{2+}-dependent inactivation (CDI), while neuronal P/Q ($Ca_V2.1$) Ca^{2+} channels use preferentially voltage-dependent inactivation (VDI). In certain situations however, these two types of channels have been shown to be able to inactivate by both processes.

From a structural view point, the rearrangement occurring during CDI and VDI is not precisely known, but functional studies have underlined the role played by at least 2 channel sequences: a C-terminal binding site for the Ca^{2+} sensor calmodulin, essential for CDI, and the loop connecting domains I and II, essential for VDI. The conserved regulation of VDI and CDI by the auxiliary channel β subunit strongly suggests that these two mechanisms may use a set of common protein–protein interactions that are influenced by the auxiliary subunit. We will review our current knowledge of these interactions. New data are presented on L-P/Q ($Ca_V1.2/Ca_V2.1$) channel chimera that confirm the role of the I–II loop in VDI and CDI, and reveal some of the essential steps in Ca^{2+} channel inactivation.

Keywords: Voltage-gated calcium channels; Ca-dependent inactivation; Voltage-dependent inactivation; Calmodulin; Auxiliary subunits

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Contents

1. Voltage-dependent and Ca^{2+}-dependent inactivation of voltage-gated Ca^{2+} channels

Calcium channels are key molecular assemblies of the plasma membrane that generate electrical and chemical signals essential for cell physiology (Catterall, 2000). These channels are composed of a central pore-forming subunit encoded by one of the ten genes ($Ca_V1.1$–4; $Ca_V2.1$–3, or $Ca_V3.1$–3) identified in the human genome. Each of these subunits can form a Ca^{2+} selective pore in the plasma membrane that is opened (activated) by membrane depolarization and closed by intrinsic mechanisms triggered by the same stimulating depolarization (voltage-dependent inactivation or VDI). The high-threshold Ca^{2+} channel subfamilies (encoded by $Ca_V1.x$ or $Ca_V2.x$ pore forming subunits) have additional mechanisms that regulate their pore opening. These include modulation by the Ca^{2+} influx generated by their own opening (Ca-dependent inactivation or CDI) and fine tuning of their electrophysiological properties by a set of modulatory subunits ($\alpha 2-\delta$, 4 known genes; γ, 10 genes; and β, 4 genes; Arikkath and Campbell, 2003), of which the β subunit appears to be critical, modifying channel expression, activation, inactivation, regulation and pharmacology. The regulation of high-threshold Ca^{2+} channel inactivation by both voltage and Ca^{2+} has been shown to be essential to ensure the pertinence of the electrical and chemical signals generated by channel opening in both muscle cells and neurons (Alseikhan et al., 2002; Splawski et al., 2004), and consequently the analysis of their underlying mechanisms has been a major center of interest for many laboratories involved in the field of Ca^{2+} signaling (for review on inactivation, see Hering et al., 2000; Stotz and Zamponi, 2001b; Budde et al., 2002; Findlay, 2004).

Most of these efforts have been centered on two types of Ca^{2+} channels: the L-type ($Ca_V1.2$) and P/Q-type ($Ca_V2.1$). These channels constitute the major channel type in cardiac ventricular and cerebellar Purkinje cells, respectively. Inactivation of $Ca_V1.2$ channels is driven by both voltage and Ca^{2+} (Budde et al., 2002) and these two processes are easily separated by replacing extracellular Ca^{2+} by Ba^{2+}, a divalent cation that cannot induce CDI (see Fig. 1). Although this type of CDI can be induced by a global change in intracellular Ca^{2+} (such as that generated by the release of intracellular stores or neighboring Ca^{2+} channels), single channel recordings clearly