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Review

Regulation of Ca_V2 calcium channels by G protein coupled receptors ☆

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ABSTRACT

Voltage gated calcium channels (Ca^{2+} channels) are key mediators of depolarization induced calcium influx into excitable cells, and thereby play pivotal roles in a wide array of physiological responses. This review focuses on the inhibition of Ca_V2 (N- and P/Q-type) Ca^{2+}-channels by G protein coupled receptors (GPCRs), which exerts important autocrine/paracrine control over synaptic transmission and neuroendocrine secretion. *Voltage-dependent* inhibition is the most widespread mechanism, and involves direct binding of the G protein βγ dimer (Gβγ) to the α1 subunit of Ca_V2 channels. GPCRs can also recruit several other distinct mechanisms including phosphorylation, lipid signaling pathways, and channel trafficking that result in *voltage-independent* inhibition. Current knowledge of Gβγ-mediated inhibition is reviewed, including the molecular interactions involved, determinants of voltage-dependence, and crosstalk with other cell signaling pathways. A summary of recent developments in understanding the voltage-independent mechanisms prominent in sympathetic and sensory neurons is also included. This article is part of a Special Issue entitled: Calcium channels.

Contents

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1. Introduction

Voltage gated calcium channels (Ca^{2+} channels) are key mediators of depolarization induced calcium influx into excitable cells, which in turn mediates a wide array of physiological responses including the activation of calcium dependent enzymes, smooth muscle contraction, pacemaker activity and neurotransmitter release [1–8]. Ca^{2+} channels are also associated with a wide range of pathologies, including pain, epilepsy, migraine, cardiac arrhythmias and autism [9–14]. It is widely known that there are subtypes of Ca^{2+} channels with different pharmacological and biophysical properties, and distinct cellular and physiological functions [15–17]. In neurons, certain L-type Ca^{2+} channel isoforms are expressed at cell bodies and dendrites, and one of their key functions is the initiation of calcium dependent gene transcription events [18–22]. Other L-type channel subtypes are expressed in cochlear hair cells and photoreceptor nerve terminals where they regulate neurotransmitter release at ribbon synapses [23,24]. T-type calcium channels are expressed in cell bodies as well as dendrites and one of their key functions is to regulate cellular excitability and neuronal firing properties [25–27], in addition to participating in secretion [28–30]. N-type and P/Q-type calcium channels are expressed at synaptic nerve terminals where their opening results in the release of neurotransmitters [1,19,31–34].

All Ca^{2+} channels are comprised of a pore forming Cavα1 subunit that contains the major structural features required for permeation, activation, and inactivation. The mammalian genome encodes ten different Cavα1 subunits that fall into three major families — Cav1 (L-type channels), Cav2 (N, P/Q- and R-types), and Cav3 (T-types) [17,35]. The Ca_V1 and Ca_V2 families are high voltage activated (HVA) channels, and are heteromers comprised of a pore forming Cavα1 subunit as well as Cavα2-δ and Cavβ subunits [36–38] (Fig. 1). In addition, these channels associate with calmodulin which is now considered part of the HVA channel macromolecular complex [39–44]. The Cavα1 subunit determines the Ca^{2+} channel subtype and is a large (~175–225 kDa) protein with four homologous transmembrane domains that are connected by cytoplasmic loops and bracketed by cytoplasmic N- and C-termini [37] (Fig. 1). These cytoplasmic regions are key targets for second messenger regulation including protein kinases and G proteins, as we discuss here in detail. The Cavβ subunits are cytoplasmic proteins that associate with HVA α1 subunits at a highly conserved region within the domain I–II linker (termed the Alpha Interaction Domain — AID) [45–47]. These subunits are encoded by four different genes (for reviews see [48,49]). The Cavα2-δ subunits are transcribed from one of four different Cavα2-δ genes, proteolytically cleaved and then reconnected via a disulfide bond (for a review, see [50]). The α2 portion is located at the extracellular side of the channel, whereas the δ portion either spans the membrane or may be linked to the extracellular leaflet of the plasma membrane through a glycosylphosphatidylinositol (GPI) anchor [51]. The function of these ancillary subunits is to regulate channel properties and promote Cavα1 subunit trafficking to and stabilization at the plasma membrane [52–54] (for reviews see [48,49,55–57]. As we will outline below, Cavβ subunits also alter second messenger regulation of the channel complex [58–61]. Finally, it should be noted that most Ca^{2+}

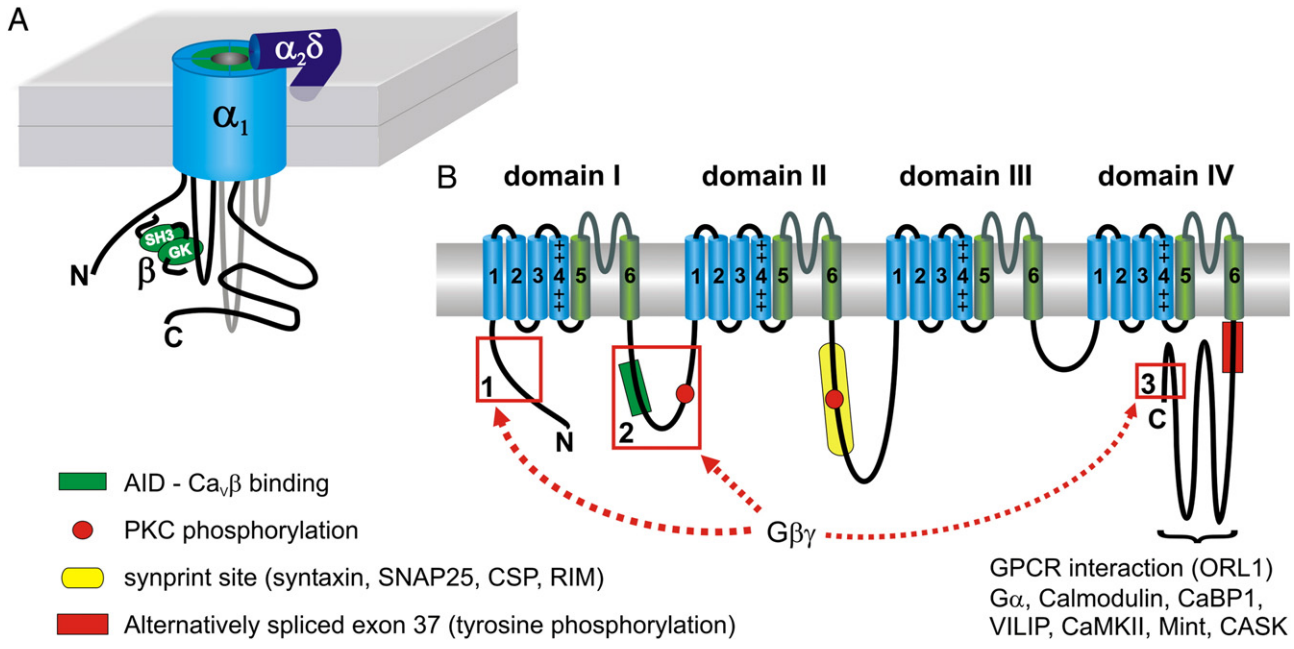

Fig. 1. Schematic depiction of the topology and subunit composition of Ca_V2 voltage-gated Ca^{2+} channels. (A) Cartoon showing the 3D topology along with channel auxiliary subunits. The intracellular β subunit interacts through its guanylate kinase-like domain (GK) with the I–II linker of the α1 subunit (at the α-interaction domain or AID). The α2δ subunit is largely extracellular and likely GPI-anchored to the plasma membrane. (B) Topology of the pore forming α_1 subunit. Four homologous repeats (domain I through domain IV) each consist of six transmembrane spanning α-helices (S1-S6) (blue or green cylinders) and a 'P-loop' between S5 and S6. The S5–S6 helices and P-loop comprise the pore domain of the channel (colored green), while S1–S4 (in particular S4 that has multiple charged residues) comprises the voltage sensor (colored blue). The intracellular N- and C-termini and the cytoplasmic loops connecting domains I–IV are important for interaction with other proteins including the auxiliary β subunit, synaptic proteins, Gβγ, GPCRs, calmodulin and other Ca^{2+} binding proteins (CaBP1, VILIP). These cytoplasmic domains are also targeted by second messenger pathways including phosphorylation by PKC, CaMKII, and tyrosine kinases. Alternative splicing greatly increases the functional diversity of the channels. For example, alternative splicing of exon37 on the proximal C-terminus controls inhibition of $Ca_V2.2$ channels by GPCRs in sensory neurons (see Section 11 for more details).