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Review article

Presynaptic calcium channels

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ABSTRACT

At the presynaptic terminal, neuronal firing activity induces membrane depolarization and subsequent Ca^{2+} entry through voltage-gated Ca^{2+} (Ca_V) channels triggers neurotransmitter release from the active zone. Presynaptic Ca^{2+} channels form a large signaling complex, which targets synaptic vesicles to Ca^{2+} channels for efficient release and mediates Ca^{2+} channel regulation. The presynaptic Ca_V2 channel family (comprising $Ca_V2.1$, $Ca_V2.2$ and $Ca_V2.3$ isoforms) encode the pore-forming $\alpha1$ subunit. The cytoplasmic regions are the target of regulatory proteins for channel modulation. Modulation of presynaptic Ca^{2+} channels has a powerful influence on synaptic transmission. This article overviews spatial and temporal regulation of Ca^{2+} channels by effectors and sensors of Ca^{2+} signaling, and describes the emerging evidence for a critical role of Ca^{2+} channel regulation in control of synaptic transmission and presynaptic plasticity. Sympathetic superior cervical ganglion neurons in culture expressing $Ca_V2.2$ channels represent a well-characterized system for investigating synaptic transmission. The exogenously expressed $\alpha1$ subunit of the $Ca_V2.1$ as well as endogenous $Ca_V2.2$ was examined for modulation of channel activity, and thereby regulation of synaptic transmission. The constitutive and Ca^{2+}-dependent modulation of $Ca_V2.1$ channels coordinately act as spatial and temporal molecular switches to control synaptic efficacy.

Contents

Abbreviations: Ca_V2 channels, voltage-gated Ca^{2+} channels; AZ, active zone; SCG, superior cervical ganglion; EPSPs, excitatory postsynaptic potentials; CaM, calmodulin; CaBP1, Ca^{2+}-binding protein-1; VILIP-2, visinin-like protein-2; CaMKII, Ca^{2+}/CaM-dependent protein kinase II; APs, action potentials; SVs, synaptic vesicles; ISI, interstimulus interval; PPF, paired-pulse facilitation; PPD, paired-pulse depression; PTP, posttetanic potentiation; nCaS, neuron specific Ca^{2+} sensor proteins.

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1. Introduction

At the presynaptic terminal, neuronal firing activity induces membrane depolarization and subsequent Ca^{2+} entry through voltage-gated Ca^{2+} (Ca_V) channels triggers neurotransmitter release from the active zone (AZ). Multiple mechanisms directly or indirectly modulate the function of presynaptic Ca^{2+} channels (Catterall and Few, 2008; Dunlap et al., 1995; Snutch and Reiner, 1992; Tedford and Zamponi, 2006). The ability of Ca_V channels to open, close, or inactivate in response to membrane depolarization changes temporally during and after neuronal firing activity and alters efficacy of synaptic transmission (Catterall and Few, 2008; Tedford and Zamponi, 2006). Following brief overviews of Ca^{2+} channel structure/function, this article reviews progress toward understanding the cellular and molecular mechanisms that modulate the activity of presynaptic Ca^{2+} channels, regulate synaptic transmission, and induce short-term synaptic plasticity. I focus here on the spatial and temporal regulation of Ca^{2+} channels that have been shown to regulate synaptic transmission in functional synapses, mostly in a model synapse formed between superior cervical ganglion (SCG) neurons in culture, including regulation by G protein coupled receptors, SNARE proteins, and residual intracellular Ca^{2+}.

2. Presynaptic Ca^{2+} channels

Ca^{2+} currents in different cell types have diverse physiological roles and pharmacological properties, and an alphabetical nomenclature has evolved for the distinct classes of Ca^{2+} currents (Tsien et al., 1988). N-type, P/Q-type, and R-type Ca^{2+} currents require strong depolarization for activation (Tsien et al., 1991) and are blocked by specific polypeptide toxins from snail and spider venoms (Miljanich and Ramachandran, 1995). N-type and P/Q-type Ca^{2+} currents are observed primarily in neurons, where they initiate neurotransmission at most fast conventional synapses (Catterall, 2000; Dunlap et al., 1995; Olivera et al., 1994). The Ca^{2+} channels that have been characterized biochemically are composed of four or five distinct subunits (Fig. 1A) (Catterall, 2000; Takahashi et al., 1987). The α1 subunit of 190–250 kDa is the largest subunit, and it incorporates the conduction pore, the voltage sensors and gating apparatus, and most of the known sites of channel regulation by second messengers, drugs, and toxins. The α1 subunit is composed of about 2000 amino acid residues organized in four homologous domains (I–IV) (Fig. 1B). Each domain of the α1 subunit consists of six transmembrane α helices (S1 through S6) and a membrane-associated P loop between S5 and S6. The S1 through S4 segments serve as the voltage sensor module, whereas transmembrane segments S5 and S6 in each domain and the P loop between them form the pore module (Yu et al., 2005). The large intracellular segments of Ca^{2+} channels serve as a signaling platform for Ca^{2+}-dependent regulation of neurotransmission, as discussed below.

Ca^{2+} channel α1 subunits are encoded by ten distinct genes in mammals, which are divided into three subfamilies by sequence similarity (Catterall, 2000; Ertel et al., 2000; Snutch and Reiner, 1992). Division of Ca^{2+} channels into these three subfamilies is phylogenetically ancient, as single representatives of each are found in the *C. elegans* genome. The Ca_V2 subfamily members ($Ca_V2.1$, $Ca_V2.2$, and $Ca_V2.3$) conduct P/Q-type, N-type, and R-type Ca^{2+} currents, respectively (Catterall, 2000; Ertel et al., 2000; Olivera et al., 1994; Snutch and Reiner, 1992).

The α1 subunits are associated with four distinct auxiliary protein subunits (Catterall, 2000) (Fig. 1A). The intracellular β subunit is a hydrophilic protein of 50–65 kDa. The transmembrane, disulfide-linked α2δ subunit complex is encoded by a single gene, but the resulting prepolypeptide is posttranslationally cleaved and disulfide-bonded to yield the mature α2 and δ subunits. A γ subunit having four transmembrane segments is a component of skeletal muscle Ca^{2+} channels, and related subunits are expressed in heart and brain. The auxiliary subunits of Ca^{2+} channels have an important influence on their function (Dolphin, 2003; Hofmann et al., 1999). $Ca_V\beta$ subunits greatly enhance cell surface expression of the α1 subunits and shift their kinetics and voltage dependence of activation and inactivation. The α2δ subunits also enhance cell surface expression of α1 subunits (Davies et al., 2007), and set presynaptic release probability (Hoppa et al., 2012). The γ subunits modulate cardiac Ca^{2+} channel function together with the β subunit (Yang et al., 2011). The functional role of the γ subunits of Ca^{2+} channels is the least well-defined. Although these four auxiliary subunits modulate the functional properties of the Ca^{2+} channel complex, the pharmacological and physiological diversity of Ca^{2+} channels arises primarily from the existence of multiple α1 subunits.

3. Modulation of presynaptic Ca^{2+} channel activity

3.1. Interaction with G proteins

Most neurotransmitters, including acetylcholine, glutamate, GABA, biogenic amines, and many neuropeptides inhibit presynaptic N-type and P/Q-type Ca^{2+} currents through activation of G protein-coupled receptors in nerve terminals (Hille, 1994; Ikeda and Dunlap, 1999). The most prominent form of G protein-induced inhibition causes a positive shift in the voltage dependence of activation of the Ca^{2+} current (Bean, 1989; Marchetti et al., 1986; Tsunoo et al., 1986). Gβγ subunits released from heterotrimeric G proteins of the Gi/Go class are responsible for this form of Ca^{2+} channel inhibition (Hille, 1994; Ikeda and Dunlap, 1999). Gβγ binds directly to the N-type Ca^{2+} channel α1 subunits (Herlitze et al., 1996; Ikeda, 1996) at three sites; the N $terminus_{45\text{-}55}$ (Canti et al., 1999), the intracellular loop connecting domains I and II $(LI\text{-}II)_{377\text{-}393}$ (Herlitze et al., 1996; Zamponi et al., 1997), and the C $terminus_{2257\text{-}2336}$ (Li et al., 2004). The sites in the N terminus and loop I–II exert the most potent effects. The Gβγ-induced inhibition can be reversed by strong positive depolarization (Bean, 1989; Marchetti et al., 1986; Tsunoo et al., 1986). Reversal of this inhibition by depolarization provides a point of intersection between chemical and electrical signal transduction at the synapse and can potentially provide novel forms of short-term synaptic plasticity that do not rely on residual Ca^{2+}.

In addition to this voltage-dependent inhibition of Ca_V2 channels by direct interaction with G proteins, many neurons also exhibit voltage-independent inhibition of Ca_V2 channels that is