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REVIEW

The voltage-gated calcium-channel β subunit: more than just an accessory

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Abstract Voltage-gated Ca^{2+} channels (VGCCs) are involved in a number of excitatory processes in the cell that regulate muscle contraction, neurotransmitter release, gene regulation, and neuronal migration. They consist of a central pore-forming α_1 subunit together with a number of associated auxiliary subunits including a cytoplasmic β subunit. With the aid of X-ray crystallography, it has been found that the β subunits of VGCCs (β_{2a}, β_3, and β_4) interact strongly with the I–II loop of the pore-forming α_1 subunit. Here we discuss the potential interaction sites of β_{1a} with its α_1 subunit as well as the skeletal ryanodine receptor. We suggest that not only can β_{1a} interact with the α_1 subunit I–II loop, but more subtle interactions may be possible through the II–III loop via the β_{1a} SH3 domain. Such findings could have important implications with respect to EC coupling.

Keywords Voltage-gated calcium channels · Dihydropyridine receptor · Beta subunit · Excitation contraction (EC) coupling

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Introduction

Voltage-gated Ca^{2+} channels (VGCCs) are activated in response to membrane depolarization and are essential in cytoplasmic Ca^{2+} signaling processes in a variety of cells. VGCCs regulate a number of cellular processes including muscle contraction, secretion, neurotransmitter release, gene regulation, and neuronal migration. Two classes of VGCCs have been described and are summarized in Table 1. The first class includes high-voltage-activated (HVA) channels, which are activated by strong depolarization. These are further classified according to their electrophysiological and pharmacological properties into the P/Q, N, R, and L types. The second class of channels are low-voltage activated (LVA) and are known as T-type calcium channels.

Voltage-gated Ca^{2+} channels are multi-subunit membrane complexes that are composed of a pore-forming α_1 subunit together with associated auxiliary subunits, α_2, δ, and β, and in skeletal muscle, the γ subunit. Although significant biophysical and pharmacological properties of VGCCs are conferred by the $\alpha 1$ subunit, the auxiliary subunits dramatically influence the gating properties and surface expression of these channels. Among the auxiliary subunits, β is unique in that it is located entirely in the cytoplasm where it acts as the most potent regulator of channel function and expression.

Here we review information relating to the structural and functional role of β subunits in VGCCs and focus particularly on the skeletal isoform of this protein. In skeletal muscle, excitation–contraction (EC) coupling is the signal transduction process that allows a surface membrane action potential to initiate Ca^{2+} release from intracellular stores, thus leading to muscle contraction. This process requires the conformational coupling between the skeletal

Table 1 Ca^{2+}-channel types based on their electrophysiological and pharmacological properties

Ca^{2+}-current type	Voltage	α1 Subunit (gene name)	Specific blockers	Primary locations
L	HVA	$Ca_v1.1$ (CACNA1S)	Dihydropyridines	Skeletal muscle
L	HVA	$Ca_v1.2$ (CACNA1C)	Dihydropyridines	Cardiac muscle, smooth muscle, endocrine cells, neurons
L	HVA	$Ca_v1.3$ (CACNA1D)	Dihydropyridines	Endocrine cells, neurons
L	HVA	$Ca_v1.4$ (CACNA1F)	Dihydropyridines	Retina
P/Q	HVA	$Ca_v2.1$ (CACNA1A)	ω-Agatoxin	Nerve terminals, dendrites
N	HVA	$Ca_v2.2$ (CACNA1B)	ω-Conotoxin	Nerve terminals, dendrites
R	Intermediate-voltage activated	$Ca_v2.3$ (CACNA1E)	None	Nerve terminals, dendrites
T	LVA	$Ca_v3.1$ (CACNA1G)	None	Cardiac muscle, smooth muscle, neurons
T	LVA	$Ca_v3.2$ (CACNA1H)	None	Cardiac muscle, neurons
T	LVA	$Ca_v3.3$ (CACNA1I)	None	Neurons

HVA High-voltage activated, *LVA* low-voltage activated

dihydropyridine receptor ($Ca_v1.1$) Ca^{2+} channel in the surface membrane and the ryanodine receptor (RyR) Ca^{2+} release channel in the sarcoplasmic reticulum (SR) Ca^{2+} store. We raise the possibility that specific protein–protein interactions involving the skeletal β subunit may be responsible for some of the unique properties observed in skeletal EC coupling.

History and nomenclature of the β-subunit

The $Ca_v\beta$ subunit was first identified in 1987 and classified as a 54-kD auxiliary subunit through its association with the purified dihydropyridine receptor (DHPR); it is now referred to as $Ca_v\beta_{1a}$ (Takahashi et al. 1987). The protein was partially sequenced, and the gene for the β_{1a} subunit was cloned (Ruth et al. 1989). Three subsequent β subunit genes, $Ca_v\beta_2$, β_3, and β_4, were identified by homology and cloned (Castellano et al. 1993a, b; Hullin et al. 1992; Perez-Reyes et al. 1992). According to the HUGO/GDB nomenclature, the genes encoding the β subunits are referred to as CACNB1–4 and numerous splice variants for each gene are known (Table 2). Notably, all four isoforms are expressed in the brain. In addition, each β subunit is differentially expressed in other tissue types. β_{1a} is a distinct β_1 variant that is uniquely associated with the skeletal muscle voltage-gated L-type calcium channel.

Structural modularity of the β subunit

All β subunits possess a common structure consisting of five domains (Fig. 1). Homology modelling and X-ray crystallographic studies have shown that these molecules consist of a core structure made up of an Src homology 3 (SH3)

Table 2 Ca^{2+}-channel β subunits—classification and tissue distribution

Subunit isoform	HUGO/GDB gene nomenclature	Tissue distribution
β1	CACNB1	β1a: skeletal muscle, β1b: brain
β2	CACNB2	Heart, lung, trachea, aorta, brain
β3	CACNB3	Smooth muscle, trachea, aorta, lung, brain
β4	CACNB4	Brain

Fig. 1 Schematic domain modules of Ca^{2+}-channel β subunits. The SH3 and guanylate kinase (*GK*) domains are conserved in all β subunits with the greatest sequence variability observed in the N and C termini and the hook region

domain and a guanylate kinase (GK)-like domain. This core module is highly conserved amongst the four isoforms (Chen et al. 2004; Opatowsky et al. 2004; Van Petegem et al. 2004) while the region connecting these two domains (hook region) and the N and C termini are relatively unconserved and are subject to alternative splicing. The core domain of the β subunits is similar to a group of scaffolding proteins dubbed membrane-associated guanylate kinases (MAGUKs), which contain several protein–protein interaction domains and are involved in the assembly of multiprotein complexes (Dolphin 2003; Hanlon et al. 1999).

Although the GK domain of the β subunit is enzymatically inactive due to the absence of an ATP binding motif (Kistner et al. 1995), it interacts with the SH3 domain to form a stable core. It should be noted that so far, crystallographic analysis has only been carried out on this central

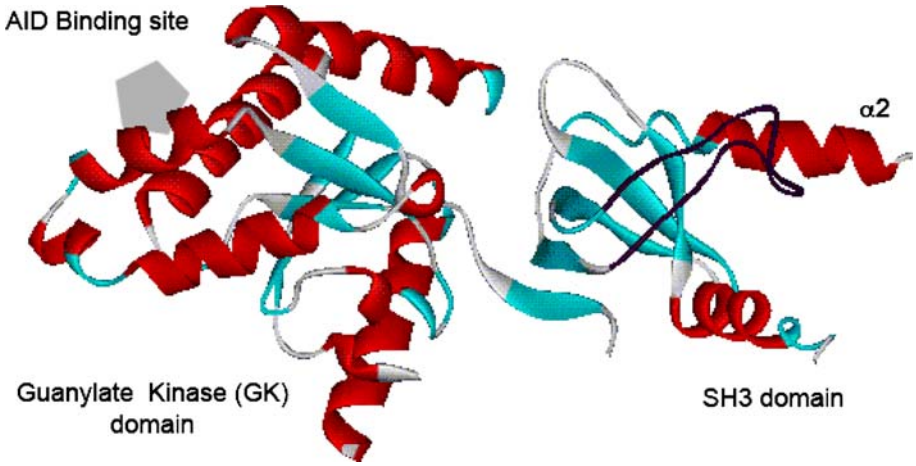

Fig. 2 Crystal structure of the β3 core protein (Chen et al. 2004). The molecule is made up of a guanylate kinase (*GK*) and SH3 domain. An α_1 binding partner AID has been located on the GK domain. The loop highlighted in *black* represents a potential SH3 binding site that is predicted to be occluded by helix α2. The hook region is not visible due to poor electron density

core region containing a short (β3, β4) or absent (β2) hook sequence (Chen et al. 2004; Opatowsky et al. 2004; Van Petegem et al. 2004). In fact the β2 structure was solved by co-crystalization of separate SH3 and GK domains (minus the hook region). The nonconserved N terminal, C terminal, and hook region have been shown to be exposed in a protease-sensitive manner (Opatowsky et al. 2003), and no crystallographic data are available on these regions, presumably due to their dynamic nature. It is noteworthy that unlike real MAGUK proteins, which contain PDZ domains upstream to their SH3 domains, no comparable PDZ regions have been identified in the β subunits. The hook region of MAGUK proteins has been shown to be involved in docking with other proteins (Chishti 1998), whereas no such binding partners have yet been attributed to the hook region of the β subunit. The nonconserved C-terminal tail of the β subunit is highly divergent amongst the different isoforms and is predicted to have less secondary structure (Hanlon et al. 1999). Interestingly, in vitro experiments have shown that this region binds to the RyR calcium release channel in skeletal muscle (Cheng et al. 2005).

The β subunit associates predominantly with the α1 subunit through a highly conserved, high-affinity interaction between the alpha interaction domain (AID) in the α1 subunit and the GK domain of the β subunit (Fig. 2). All three structural studies that investigated the binding of the AID peptide to the β subunit core provided similar evidence that the interaction site of AID is located in a deep groove on the GK domain called the AID binding pocket (ABP) (Van Petegem et al. 2004). Binding of the AID peptide does not significantly alter the core structure of the β subunit (Chen et al. 2004). The binding affinity of the β subunits to either the AID peptide or the full length I–II linker has been determined for a variety of combinations of subunits and shown, using several methods, to be in the low nanomolar range (Richards et al. 2004). In addition to this high-affinity interaction, two other lower-affinity β-subunit interaction sites have also been identified on the C terminus (Qin et al. 1997; Walker et al. 1999) and the N terminus (Stephens et al. 2000) of the α1 subunit.

Although the GK domain is responsible for the high-affinity binding to the AID, the functional significance of the other structural motif, the SH3 domain, remains unclear. Typically, SH3 are protein interaction domains that mediate the assembly of specific protein complexes, generally involving proline-rich recognition sites such as PXXP or XPPPX (McPherson 1999). Crystallographic studies have shown the arrangement of the first four β strands of the β subunit SH3 to be similar to canonical SH3 domains, however the fifth β strand is separated by an unstructured central hook region that gives the SH3 domain of the β subunit a "split architecture." In addition, two long helices that are absent in canonical SH3 domains are appended to the SH3 domains of the β subunit (Fig. 2) (Chen et al. 2004; Van Petegem et al. 2004).

Within the β-subunit SH3 domain, there is good sequence homology (Fig. 3) amongst the residues noted to form the hallmark proline binding residues of all SH3 domains (Hanlon et al. 1999). Although the crystal structures have shown this putative polyproline binding site to be occluded (see Fig. 2), this does not preclude the possibility of dynamic structural rearrangements exposing these interaction sites for binding. Indeed such an interaction has been shown to occur between the β2a subunit and a GTPase involved in receptor-mediated endocytosis (Gonzalez-Gutierrez et al. 2007). Also, SH3 domain binding sites have been identified in the cardiac α1 II–III loop and C terminal (Dubuis et al. 2006). Interestingly, the II–III loop has been shown to be important in skeletal EC coupling (Tanabe et al. 1990), and we have preliminary in vitro evidence that this loop is able to bind with the SH3 domain of the β_{1a} isoform (Y. Karunasekara et al., unpublished observations). This raises a possibly controversial issue about the role of the β subunit in regulating or being part of the physical coupling between the α_{1s} and RyR1 in skeletal EC coupling.

Fig. 3 Amino acid sequence alignment of SH3 domains within Ca^{2+}-channel β-subunit isoforms. Regions with the highest sequence homology are shown, with *red* denoting conserved residues for all isoforms

Role in membrane expression and modulation of calcium channels

The β subunit has a marked effect on DHPR channel expression and modulation of the pore-forming α_1 subunit. A number of research groups have shown that overexpression of the β subunit increased the density of endogenous calcium currents, indicating an increase in the functional expression of HVA α1 subunits (Colecraft et al. 2002; Neuhuber et al. 1998; Raghib et al. 2001). The β subunit aids in the trafficking of α_1 to the plasma membrane, partly by its ability to mask an endoplasmic reticulum retention signal in the α1 subunit (Bichet et al. 2000). According to He et al. (2007), the AID–GK domain interaction is necessary for β-subunit-stimulated P/Q-type Ca^{2+}-channel surface expression, and the GK domain alone can carry out this function.

In addition to its role in membrane trafficking, the β subunit modulates a host of biophysical properties of the channel with characteristics specific to the α_1-β combination. The β subunit can accomplish these dual functions independently, as illustrated by its ability to modulate the biophysical properties of channels in the presence of a mutation in the AID region, which disrupts its ability to enhance membrane trafficking of α_1 (Gerster et al. 1999). It has been suggested that this is due to the ability of some β subunits to associate with other intracellular loops of the channel through weaker interactions. This supports a model in which the conserved high-affinity binding of the β subunit to the AID anchors it to the α1 subunit and facilitates low-affinity interactions of other β-subunit domains/regions with different parts of the α1 subunit, which in turn are responsible for the modulation of gating (He et al. 2007; Van Petegem et al. 2008).

All four β-subunit isoforms hyperpolarize the voltage-dependent activation of all high-voltage-activated VGCCs. In contrast, steady-state inactivation properties reveal differences, both with regard to different α_1 subunits and different β subunits. In general, the β1, β3, and β4 subunits expressed with α1 result in the hyperpolarization of voltage-dependent inactivation, so that channels inactivate at more negative potentials and speed up the inactivation kinetics. On the other hand, partly due to palmitoylation of two cysteines in its N terminus, the rat and human β_{2a} subunit depolarizes the voltage dependence of inactivation, making the channels inactivate at more positive potentials, and dramatically slowing down the kinetics of inactivation (He et al. 2007). Furthermore, the β core containing the SH3-hook-GK module governs the modulatory effects upon activation, and the hook region and the N terminus (especially the distal variable region) are critical for modulating inactivation (He et al. 2007; Richards et al. 2007). However, Hidalgo et al. have recently reported that the structural determinants of inhibition of inactivation by β2a are encoded, not in variable regions, but rather within the GK domain (Gonzalez-Gutierrez et al. 2008). Although the C terminus constitutes a large portion of the β subunits, the deletion of it did not have any effect on activation or inactivation of, at least, $Ca_v2.1$ channels (He et al. 2007).

Regulation of calcium channels also occurs through modification of the β subunits and/or their interactions with other proteins. β_{2a} is a substrate for protein kinase A, and phosphorylation of β_{2a} is important for the ability of protein kinase A to stimulate the currents generated by the $\alpha_1$1.2 channels in mammalian expression systems and in cardiac myocytes. The β subunit also plays a role in the modulation of the $\alpha_1$2.2 channels through the mitogen-activated protein kinase (MAPK) pathway (Fitzgerald 2002). Gem is a small Ras-related G protein that has a high affinity for the β subunit, the binding of which interferes with the β subunit's ability to traffic the α1 to the plasma membrane (Beguin et al. 2001).

$Ca_v\beta$ subunit in skeletal muscle

The β_{1a} isoform is specific to skeletal muscle. Similar to other isoforms, it has five domains, including the conserved

SH3 and GK domains, and has also been shown to perform a dual role as a chaperone and modulator of the α_{1s} subunit (Bichet et al. 2000; Gerster et al. 1999). We have preliminary data showing that the β_{1a} isoform also binds to the α_{1s} AID binding site with nanomolar affinity (K_d: 15.2 ± 1.8 nM, Y. Karunasekara et al., unpublished observations). Consistent with its role in membrane expression of the α_{1s} subunit, patch-clamp analyses of β_{1a}-null myotubes show that their L-type calcium currents are strongly decreased (Strube et al. 1996). Although these observations indicate a failure of EC coupling due to a reduction of voltage sensors, further experiments have shown a direct role of the β subunit in the transmission of the signal from the voltage sensor (α_{1s}) to the calcium release channel (RyR1) (Beurg et al. 1999; Sheridan et al. 2004). β1-null myotubes transfected with the cardiac β_{2a} isoform show cardiac-type EC coupling, and deletion/chimeric studies of β_{1a} and β_{2a} in knock-out cells have identified a region in the C terminus of β_{1a} that enables skeletal-type EC coupling (Beurg et al. 1999). This group has further shown that the β_{1a} is able to bind to a cluster of positively charged residues (3495–3502) in the foot region of the RyR1 and that this interaction strengthens EC coupling (Cheng et al. 2005). It is of interest that the region of the RyR1 involved in the binding with β_{1a} subunit is immediately adjacent to a variably spliced region implicated in myotonic dystrophy (Kimura et al. 2007). These results reinforce the interesting question about the precise role of β_{1a} in skeletal EC coupling.

The recent analysis of a novel β-null zebrafish mutant "*Relaxed*" has demonstrated that the lack of EC coupling in this system is caused by the disruption in the structural network involving the DHPR relative to the RyR1s (Schredelseker et al. 2005, 2009). This suggests that β_{1a} may act as a scaffolding protein and that at least in skeletal muscle cells, the reduced number of channels in the membrane may result from a decreased stabilization in the signalling complex rather than from reduced trafficking to the membrane (Obermair et al. 2008). However, fluorescent protein-tagged β_{1a} subunits failed to colocalize with RyR1 in dysgenic (α1s-null) myotubes, indicating that triad targeting of β_{1a} may require an association with α1s (Leuranguer et al. 2006).

Role of $Ca_v\beta$ subunit in disease

The significance of β subunit is emphasized by diseases associated with its knockout and through mutations. Knockout of the β1 isoform (CACNB1), present in skeletal muscle as β_{1a} and in heart and brain as β_{1b}, results in a lethal phenotype. Homozygous $\beta1^{-/-}$ mice show reduced skeletal muscle mass with structural abnormalities and die at birth from asphyxiation. Interestingly, heterozygotes are asymptomatic, indicating that there is normally a sufficient excess of β1 subunit, such that loss of 50% has no effect (Strube et al. 1996).

Deletion of the $Ca_v\beta$2 gene (CACNB2) gives rise to an embryonic lethal phenotype, underlining the essential role of β_2 in cardiac contraction (Ball et al. 2002). In contrast, knockout of the β_3 isoform (CACNB3) does not result in a major phenotype, indicating that other β subunits are able to substitute for its function. The lethargic mouse is a spontaneous mutation in the gene encoding the β4 subunit (CACNB4). This causes a premature stop codon resulting in no detectable protein as it is a null mutation. Lethargic mice exhibit ataxia, lethargic behavior, and spontaneous focal motor seizures (Burgess et al. 1999). Mutations in the $Ca_v\beta$4 subunit gene have been found in patients with idiopathic generalized epilepsy and episodic ataxia (Escayg et al. 2000). In cardiac myopathy associated with failed cardiac myografts, there was a large reduction in β subunit mRNA and protein by up to 80%, and the major species detected was β_{1b} (Hullin et al. 1999). There was also an increase in the amount of truncated relative to full-length β3 transcript in human left ventricular tissue showing ischemic cardiomyopathy, compared to nonfailing tissue (Hullin et al. 2003).

Conclusions

All $Ca_v\beta$ subunit isoforms play a vital role in the membrane expression and modulation of HVA calcium channels. In skeletal muscle, the β_{1a} subunit is essential in the structural organization of the DHPR complex opposite the RyR1, thus enabling the direct coupling of the voltage sensor and the Ca^{2+} release channel in EC coupling. There is strong evidence that β_{1a} also has a modulatory function in EC coupling. Although the interaction between the α1 and β subunits involves the AID of α1 and GK domain of β, there is sufficient evidence to suggest that there may be other interaction sites between these two subunits that may explain the unique modulatory properties that are observed for different β-subunit isoforms. The unique role of the β_{1a} subunit in relation to the α_{1s}–RyR1 interaction in skeletal EC coupling remains unclear and forms the basis of future studies.

References

Ball SL, Powers PA, Shin HS, Morgans CW, Peachey NS, Gregg RG (2002) Role of the beta(2) subunit of voltage-dependent calcium channels in the retinal outer plexiform layer. Invest Ophthalmol Vis Sci 43:1595–1603

Beguin P, Nagashima K, Gonoi T, Shibasaki T, Takahashi K, Kashima Y, Ozaki N, Geering K, Iwanaga T, Seino S (2001) Regulation of

Ca^{2+} channel expression at the cell surface by the small G-protein kir/Gem. Nature 411:701–706. doi:10.1038/35079621

Beurg M, Ahern CA, Vallejo P, Conklin MW, Powers PA, Gregg RG, Coronado R (1999) Involvement of the carboxy-terminus region of the dihydropyridine receptor beta1a subunit in excitation–contraction coupling of skeletal muscle. Biophys J 77:2953–2967. doi:10.1016/S0006-3495(99)77128-6

Bichet D, Cornet V, Geib S, Carlier E, Volsen S, Hoshi T, Mori Y, De Waard M (2000) The I–II loop of the Ca^{2+} channel alpha1 subunit contains an endoplasmic reticulum retention signal antagonized by the beta subunit. Neuron 25:177–190. doi:10.1016/S0896-6273(00)80881-8

Burgess DL, Biddlecome GH, McDonough SI, Diaz ME, Zilinski CA, Bean BP, Campbell KP, Noebels JL (1999) Beta subunit reshuffling modifies N- and P/Q-type Ca^{2+} channel subunit compositions in lethargic mouse brain. Mol Cell Neurosci 13:293–311. doi:10.1006/mcne.1999.0748

Castellano A, Wei X, Birnbaumer L, Perez-Reyes E (1993a) Cloning and expression of a neuronal calcium channel beta subunit. J Biol Chem 268:12359–12366

Castellano A, Wei X, Birnbaumer L, Perez-Reyes E (1993b) Cloning and expression of a third calcium channel beta subunit. J Biol Chem 268:3450–3455

Chen YH, Li MH, Zhang Y, He LL, Yamada Y, Fitzmaurice A, Shen Y, Zhang H, Tong L, Yang J (2004) Structural basis of the alpha1-beta subunit interaction of voltage-gated Ca^{2+} channels. Nature 429:675–680. doi:10.1038/nature02641

Cheng W, Altafaj X, Ronjat M, Coronado R (2005) Interaction between the dihydropyridine receptor Ca^{2+} channel beta-subunit and ryanodine receptor type 1 strengthens excitation–contraction coupling. Proc Natl Acad Sci USA 102:19225–19230. doi:10.1073/pnas.0504334102

Chishti AH (1998) Function of p55 and its nonerythroid homologues. Curr Opin Hematol 5:116–121

Colecraft HM, Alseikhan B, Takahashi SX, Chaudhuri D, Mittman S, Yegnasubramanian V, Alvania RS, Johns DC, Marban E, Yue DT (2002) Novel functional properties of Ca(2+) channel beta subunits revealed by their expression in adult rat heart cells. J Physiol 541:435–452. doi:10.1113/jphysiol.2002.018515

Dolphin AC (2003) β subunits of voltage-gated calcium channels. J Bioenerg Biomembr 35:599–620. doi:10.1023/B:JOBB.0000008026.37790.5a

Dubuis E, Rockliffe N, Hussain M, Boyett M, Wray D, Gawler D (2006) Evidence for multiple Src binding sites on the alpha1c L-type Ca^{2+} channel and their roles in activity regulation. Cardiovasc Res 69:391–401. doi:10.1016/j.cardiores.2005.11.006

Escayg A, De Waard M, Lee DD, Bichet D, Wolf P, Mayer T, Johnston J, Baloh R, Sander T, Meisler MH (2000) Coding and noncoding variation of the human calcium-channel beta4-subunit gene CACNB4 in patients with idiopathic generalized epilepsy and episodic ataxia. Am J Hum Genet 66:1531–1539. doi:10.1086/302909

Fitzgerald EM (2002) The presence of Ca^{2+} channel beta subunit is required for mitogen-activated protein kinase (MAPK)-dependent modulation of alpha1B Ca^{2+} channels in COS-7 cells. J Physiol 543:425–437. doi:10.1113/jphysiol.2002.022822

Gerster U, Neuhuber B, Groschner K, Striessnig J, Flucher BE (1999) Current modulation and membrane targeting of the calcium channel alpha1C subunit are independent functions of the beta subunit. J Physiol 517(Pt 2):353–368. doi:10.1111/j.1469-7793.1999.0353t.x

Gonzalez-Gutierrez G, Miranda-Laferte E, Neely A, Hidalgo P (2007) The Src homology 3 domain of the beta-subunit of voltage-gated calcium channels promotes endocytosis via dynamin interaction. J Biol Chem 282:2156–2162. doi:10.1074/jbc.M609071200

Gonzalez-Gutierrez G, Miranda-Laferte E, Nothmann D, Schmidt S, Neely A, Hidalgo P (2008) The guanylate kinase domain of the beta-subunit of voltage-gated calcium channels suffices to modulate gating. Proc Natl Acad Sci USA 105:14198–14203. doi:10.1073/pnas.0806558105

Hanlon MR, Berrow NS, Dolphin AC, Wallace BA (1999) Modelling of a voltage-dependent Ca^{2+} channel beta subunit as a basis for understanding its functional properties. FEBS Lett 445:366–370. doi:10.1016/S0014-5793(99)00156-8

He LL, Zhang Y, Chen YH, Yamada Y, Yang J (2007) Functional modularity of the beta-subunit of voltage-gated Ca^{2+} channels. Biophys J 93:834–845. doi:10.1529/biophysj.106.101691

Hullin R, Singer-Lahat D, Freichel M, Biel M, Dascal N, Hofmann F, Flockerzi V (1992) Calcium channel beta subunit heterogeneity: functional expression of cloned cDNA from heart, aorta and brain. EMBO J 11:885–890

Hullin R, Asmus F, Ludwig A, Hersel J, Boekstegers P (1999) Subunit expression of the cardiac L-type calcium channel is differentially regulated in diastolic heart failure of the cardiac allograft. Circulation 100:155–163

Hullin R, Khan IF, Wirtz S, Mohacsi P, Varadi G, Schwartz A, Herzig S (2003) Cardiac L-type calcium channel beta-subunits expressed in human heart have differential effects on single channel characteristics. J Biol Chem 278:21623–21630. doi:10.1074/jbc.M211164200

Kimura T, Pace SM, Wei L, Beard NA, Dirksen RT, Dulhunty AF (2007) A variably spliced region in the type 1 ryanodine receptor may participate in an inter-domain interaction. Biochem J 401:317–324. doi:10.1042/BJ20060686

Kistner U, Garner CC, Linial M (1995) Nucleotide binding by the synapse associated protein SAP90. FEBS Lett 359:159–163. doi:10.1016/0014-5793(95)00030-D

Leuranguer V, Papadopoulos S, Beam KG (2006) Organization of calcium channel beta1a subunits in triad junctions in skeletal muscle. J Biol Chem 281:3521–3527. doi:10.1074/jbc.M509566200

McPherson PS (1999) Regulatory role of SH3 domain-mediated protein–protein interactions in synaptic vesicle endocytosis. Cell Signal 11:229–238. doi:10.1016/S0898-6568(98)00059-X

Neuhuber B, Gerster U, Mitterdorfer J, Glossmann H, Flucher BE (1998) Differential effects of Ca^{2+} channel beta1a and beta2a subunits on complex formation with alpha1S and on current expression in tsA201 cells. J Biol Chem 273:9110–9118. doi:10.1074/jbc.273.15.9110

Obermair GJ, Tuluc P, Flucher BE (2008) Auxiliary Ca(2+) channel subunits: lessons learned from muscle. Curr Opin Pharmacol 8:311–318. doi:10.1016/j.coph.2008.01.008

Opatowsky Y, Chomsky-Hecht O, Kang MG, Campbell KP, Hirsch JA (2003) The voltage-dependent calcium channel beta subunit contains two stable interacting domains. J Biol Chem 278:52323–52332. doi:10.1074/jbc.M303564200

Opatowsky Y, Chen CC, Campbell KP, Hirsch JA (2004) Structural analysis of the voltage-dependent calcium channel beta subunit functional core and its complex with the alpha 1 interaction domain. Neuron 42:387–399. doi:10.1016/S0896-6273(04)00250-8

Perez-Reyes E, Castellano A, Kim HS, Bertrand P, Baggstrom E, Lacerda AE, Wei XY, Birnbaumer L (1992) Cloning and expression of a cardiac/brain beta subunit of the L-type calcium channel. J Biol Chem 267:1792–1797

Qin N, Platano D, Olcese R, Stefani E, Birnbaumer L (1997) Direct interaction of gbetagamma with a C-terminal gbetagamma-binding domain of the Ca^{2+} channel alpha1 subunit is responsible for channel inhibition by G protein-coupled receptors. Proc Natl Acad Sci USA 94:8866–8871. doi:10.1073/pnas.94.16.8866

Raghib A, Bertaso F, Davies A, Page KM, Meir A, Bogdanov Y, Dolphin AC (2001) Dominant-negative synthesis suppression of voltage-gated calcium channel Cav2.2 induced by truncated constructs. J Neurosci 21:8495–8504

Richards MW, Butcher AJ, Dolphin AC (2004) Ca^{2+} channel beta-subunits: structural insights AID our understanding. Trends Pharmacol Sci 25:626–632. doi:10.1016/j.tips.2004.10.008

Richards MW, Leroy J, Pratt WS, Dolphin AC (2007) The HOOK-domain between the SH3 and the GK domains of Cavbeta subunits contains key determinants controlling calcium channel inactivation. Channels Austin 1:92–101

Ruth P, Rohrkasten A, Biel M, Bosse E, Regulla S, Meyer HE, Flockerzi V, Hofmann F (1989) Primary structure of the beta subunit of the DHP-sensitive calcium channel from skeletal muscle. Science 245:1115–1118. doi:10.1126/science.2549640

Schredelseker J, Di Biase V, Obermair GJ, Felder ET, Flucher BE, Franzini-Armstrong C, Grabner M (2005) The beta 1a subunit is essential for the assembly of dihydropyridine-receptor arrays in skeletal muscle. Proc Natl Acad Sci USA 102:17219–17224. doi:10.1073/pnas.0508710102

Schredelseker J, Dayal A, Schwerte T, Franzini-Armstrong C, Grabner M (2009) Proper restoration of excitation-contraction coupling in the dihydropyridine receptor beta 1-null zebrafish relaxed is an exclusive function of the beta 1a subunit. J Biol Chem 284:1242–1251

Sheridan DC, Cheng W, Carbonneau L, Ahern CA, Coronado R (2004) Involvement of a heptad repeat in the carboxyl terminus of the dihydropyridine receptor beta1a subunit in the mechanism of excitation–contraction coupling in skeletal muscle. Biophys J 87:929–942. doi:10.1529/biophysj.104.043810

Stephens GJ, Page KM, Bogdanov Y, Dolphin AC (2000) The alpha1B Ca^{2+} channel amino terminus contributes determinants for beta subunit-mediated voltage-dependent inactivation properties. J Physiol 525(Pt 2):377–390. doi:10.1111/j.1469-7793.2000.t01-1-00377.x

Strube C, Beurg M, Powers PA, Gregg RG, Coronado R (1996) Reduced Ca^{2+} current, charge movement, and absence of Ca^{2+} transients in skeletal muscle deficient in dihydropyridine receptor beta 1 subunit. Biophys J 71:2531–2543. doi:10.1016/S0006-3495(96)79446-8

Takahashi M, Seagar MJ, Jones JF, Reber BFX, Catterall WA (1987) Subunit structure of dihydropyridine-sensitive calcium channels from skeletal muscle. Proc Natl Acad Sci USA 84:5478–5482. doi:10.1073/pnas.84.15.5478

Tanabe T, Beam KG, Adams BA, Niidome T, Numa S (1990) Regions of the skeletal muscle dihydropyridine receptor critical for excitation-contraction coupling. Nature 346:567–569

Van Petegem F, Clark KA, Chatelain FC, Minor DL Jr (2004) Structure of a complex between a voltage-gated calcium channel beta-subunit and an alpha-subunit domain. Nature 429:671–675. doi:10.1038/nature02588

Van Petegem F, Duderstadt KE, Clark KA, Wang M, Minor DL Jr (2008) Alanine-scanning mutagenesis defines a conserved energetic hotspot in the CaValpha1 AID-CaVbeta interaction site that is critical for channel modulation. Structure 16:280–294. doi:10.1016/j.str.2007.11.010

Walker D, Bichet D, Geib S, Mori E, Cornet V, Snutch TP, Mori Y, De Waard M (1999) A new beta subtype-specific interaction in alpha1A subunit controls P/Q-type Ca^{2+} channel activation. J Biol Chem 274:12383–12390. doi:10.1074/jbc.274.18.12383