Chapter 7
Protein Interaction Partners of $Ca_v2.3$ R-Type Voltage-Gated Calcium Channels

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Abstract The $Ca_v2.3$ voltage-gated calcium channel represents the most enigmatic of all voltage-gated calcium channels due to its pharmacological inertness and to its mixed characteristics of HVA and LVA calcium channels. Protein interaction partners of the cytosolic II-III linker of $Ca_v2.3$ contribute to calcium homeostasis by regulating the channels surface expression and activation. Specific regulation of $Ca_v2.3$ by proteins interacting with the carboxy terminal region plays an important role in exocytosis and presynaptic plasticity, linking channel function to long-term potentiation. Modulation of $Ca_v2.3$ by its interaction partners thus contributes

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to several physiologic processes such as signal transduction in the retina, insulin secretion and generation of rhythmic activity in the heart and in the brain.

Keywords $Ca_v2.3$ • R-type current • Amyloid precursor protein • Calmodulin • Rab5A • Heat shock proteins vacuolar ATPase

Abbreviations

APP	Amyloid precursor protein
APLP1	Amyloid precursor-like protein 1
CaM	Calmodulin
CDF	Calcium-dependent facilitation
CDI	Calcium-dependent inactivation
DHP	Dihydropyridines
EGFR	Epidermal growth factor receptor
HVA	High-voltage activated
LVA	Low-voltage activated
PKC	Protein kinase C
V-ATPase	Vacuolar ATPase
VGCC	Voltage-gated calcium channel

7.1 Introduction

7.1.1 Voltage-Gated Calcium Channels

Voltage-gated calcium channels (VGCCs) are expressed on the plasma membrane of excitable cells, where they regulate calcium ion permeability. Calcium ions are the most versatile second messengers and also serve as charge carriers. VGCCs respond to changes in membrane potential and convert cellular electrical excitability into intracellular signaling. Calcium channels are multi-subunit integral membrane proteins, with a large (>250 kD) pore-forming and voltage-sensing α1 subunit and smaller auxiliary transmembrane α2δ and cytoplasmic β subunits (Catterall 2011). The auxiliary β subunits regulate proteasomal degradation of the α1 subunit (Altier et al. 2011; Rougier et al. 2011 Waithe et al. 2011) making them crucial for cellular trafficking and stable surface expression of the α1 subunit. The function of plasma membrane calcium channels can be critically modulated by various signaling pathways, and frequently involves transient or persistent interaction of certain cellular proteins with the α1 subunit. These interactions also tightly regulate the amount of calcium channels expressed on the cell surface. These processes are important because small changes in the number of surface channels can greatly affect cell signaling.

Based on their biophysical and pharmacological properties, VGCCs can be classified into three groups. (i) L-type high-voltage-activated (HVA) calcium channels comprising the $Ca_V1.1$, 1.2, 1.3, and 1.4 channels, which can be inhibited by dihydropyridines (DHPs), phenylalkylamines and benzodiazepines (Striessnig 1999; Catterall and Few 2008; Dolphin 2009), (ii) non-L-type HVA channels $Ca_V2.1$ (P/Q-type), $Ca_V2.2$ (N-type), and $Ca_V2.3$ (R-type) that are sensitive to ω-agatoxin IVA and ω-conotoxin GVIA and SNX 482, respectively (Reid et al. 2003; Kamp et al. 2005; Catterall and Few 2008), and (iii) the low-voltage-activated (LVA) T-type calcium channel family ($Ca_V3.1$, 3.2, and 3.3) (Perez-Reyes 2003). Among the calcium channels, the R-type/$Ca_V2.3$ calcium channel has been less explored due to its pharmacological inertness (it's only known peptide inhibitor SNX-482 also antagonizes L- and N-type calcium channels at concentrations higher than 300 nM). Under the perforated patch configuration it has been shown in chromaffin cells that 20 % of I_{Ca} can be accounted for by toxin-resistant, R-type calcium currents (Albillos et al. 2000; Hernandez et al. 2011).

7.2 Discovery of R-Type/E-Type Voltage-Gated Calcium Channels

The first evidence for increased structural diversity of high-voltage gated calcium channels came from the cloning of new calcium channel types from the rabbit brain (Niidome et al. 1992) and from the forebrain of the marine ray *Discopyge ommata* (Horne et al. 1993). The complete amino acid sequence from rabbit, designated BII, showed structural similarity to the so-called BI sequence, encoding the non-L-type voltage-gated calcium channel i.e. the P-/Q-type calcium channel (Mori et al. 1991). Transcripts of BII were predominantly identified in the brain and most abundant in the cerebral cortex, the hippocampus and the corpus striatum (Niidome et al. 1992).

The consecutive approach to identify calcium current components homologous to the ray doe-1 channel in the CNS of mammalia was successful for rat cerebellar granule cells (Zhang et al. 1993). Doe-1 formed high voltage-activated calcium currents when expressed in *Xenopus* oocytes, and inactivated more rapidly than any of the previously identified calcium channels. The high voltage-activated Ca^{2+} current component, which persisted after blocking L-, N- and P-/Q-type calcium channels, was defined as the "resistant"/R-type voltage-gated Ca^{2+} current (Ellinor et al. 1993; Zhang et al. 1993). The mammalian counterpart of doe-1 was cloned from rat (Soong et al. 1993) and finally also from human (Williams et al. 1994) and was occasionally referred to as the "E-type" voltage-gated calcium channel (Schneider et al. 1994). After functional expression of the rat $Ca_v2.3$ clone, it was speculated that this channel may represent the low voltage-activated T-type calcium channel, which at that time had yet to be structurally identified (Soong et al. 1993). Instead, cloning and expression of human and rabbit $Ca_v2.3$ splice variants

revealed a high-voltage-activated calcium channel (R-type), at least in heterologous expression systems (Schneider et al. 1994; Wakamori et al. 1994; Williams et al. 1994).

The R-type calcium channel received its name from "resistant" and indeed to date no highly selective antagonists exist. SNX-482, a toxin found in the venom of the tarantula *Hysterocrates gigas* does show selectivity for R-type channels but also inhibits L-type and N-type channels at concentrations beyond 200 nM (Bourinet et al. 2001). Although the structure of $Ca_v2.3$ deduced from sequencing of cDNA has been known for several years (Perez-Reyes and Schneider 1994; Pereverzev et al. 2002a), its physio- and pathophysiological role remain only partially recognized (Kamp et al. 2005; Weiergräber et al. 2006). Evidence suggests that $Ca_v2.3$ developed very early in evolution (Zhang et al. 1993; Perez-Reyes 2003; Spafford and Zamponi 2003), which may underline its great significance in vivo.

In heterologous expression systems, $Ca_v2.3$ inward currents are activated at test potentials of about –20 mV (De Waard et al. 1996). The single channel conductance is about 14 pS (Perez-Reyes and Schneider 1995), and the channel kinetics measured by patch-clamp recordings reveal a fast activating and inactivating channel type with transient inward current characteristics (Pereverzev et al. 2002a; Leroy et al. 2003), similar but not as fast as observed for T-type voltage-gated calcium channels (Nakashima et al. 1998).

7.3 Expression of $Ca_v2.3$ Voltage-Gated Calcium Channels in Various Regions of the Vertebrate Organism

The $Ca_v2.3$ VGCC is widely expressed throughout the vertebrate organism, not only in the central nervous system (for details, see Table 2 in Kamp et al. 2012b) Its initial detection in the endocrine system of mice and rats (Pereverzev et al. 2002b, 2005; Jing et al. 2005; Trombetta et al. 2012) was recently confirmed for the human organism as well (Muller et al. 2007; Trombetta et al. 2012). Endothelial and myocardial expression of R-type calcium channels (Lu et al. 2004; Weiergräber et al. 2005; Galetin et al. 2010) has been well established on a transcriptional and functional level, however, detecting myocardial $Ca_v2.3$ protein has proven to be problematic (Tevoufouet and Schneider, unpublished results). Interestingly, $Ca_v2.3$ is also expressed in the reproductive system (Sakata et al. 2002) and the gastrointestinal tract (Grabsch et al. 1999; Naidoo et al. 2010), where in the latter case its functional importance during autonomous excitation generation must be analyzed in greater detail. More recently, the involvement of R-type calcium channels in delayed cerebral ischemia has been shown in animal models of subarachnoid haemorrhage, in which blood metabolites induce expression of R-type calcium channels in cerebral arteries (Ishiguro et al. 2008; Wang et al. 2010). Furthermore, the subcellular distribution of $Ca_v2.3$ has been investigated to some detail revealing both, somatodendritic as well as presynaptic expression (Yokoyama et al. 1995) with additional functional specificities (Brenowitz and Regehr 2003).

7.3.1 *Expression of $Ca_v2.3$ Splice Variants*

Originally, $Ca_v2.3d$ was cloned as a fetal splice variant from human brain (Schneider et al. 1994). Splice variants of $Ca_v2.3$ from different species as well as auxiliary subunits are tissue-specifically expressed. Besides the expression in neuronal (Han et al. 2002; Sochivko et al. 2002, 2003; Dietrich et al. 2003; Osanai et al. 2006) and endocrine tissues (Vajna et al. 1998; 2001; Grabsch et al. 1999; Wang et al. 1999; Albillos et al. 2000; Matsuda et al. 2001; Pereverzev et al. 2002b; Mergler et al. 2003; Watanabe et al. 2004; Jing et al. 2005; Ortiz-Miranda et al. 2005; Pereverzev et al. 2005; Holmkvist et al. 2007; Muller et al. 2007; Zhang et al. 2007), $Ca_v2.3$ transcripts have also been detected in heart (Weiergräber et al. 2000, 2005; Lu et al. 2004), kidney (Vajna et al. 1998; Schramm et al. 1999; Weiergräber et al. 2000; Natrajan et al. 2006), sperm (Lievano et al. 1996; Wennemuth et al. 2000; Sakata et al. 2002; Carlson et al. 2003), spleen (Williams et al. 1994), and retina (Kamphuis and Hendriksen 1998; Lüke et al. 2005) (for details, see Table 2 in Kamp et al. 2012b).

Structurally, a broad set of $Ca_v2.3$ splice variants can be predicted from different cloning approaches (Fig. 7.1) resulting from alternate use of exon 19 encoded arginine-rich segment in the II-III loop, as well as from the alternate use of exon 45 in the carboxyterminal region (Pereverzev et al. 2002a).

7.4 Structure and Function of the $Ca_v2.3$ Voltage-Gated Calcium Channel

The complete quaternary structure of native VGCCs containing $Ca_v2.3$ is unknown, but may resemble purified calcium channel complexes (Perez-Reyes and Schneider 1994) and thus may contain additional subunits including the well known auxiliary $Ca_v\beta$-subunits, which modulate $Ca_v2.3$-mediated inward currents in heterologous expression systems (Parent et al. 1997; Nakashima et al. 1998). To date, VGCCs containing $Ca_v2.3$ have not been purified as has been accomplished for L-type calcium channels from rabbit skeletal muscle (Flockerzi et al. 1986; Sieber et al. 1987; Takahashi et al. 1987; Striessnig et al. 1987), and bovine heart (Schneider and Hofmann 1988) and for the neuronal N-type calcium channels (Witcher et al. 1993a, b).

Sequence comparison of the deduced primary sequence revealed a well known intra-molecular homology pattern, which is found in all VGCCs as well as in voltage-gated Na^+ channels. This pattern contains four internal repeats, which have been termed domains I, II, III, and IV. Secondary structure analysis predicts 6 transmembrane segments including a random coiled short part between transmembrane segment 5 and 6, the pore forming segment (P-loop) (Guy and Conti 1990). Many of these structure predictions resemble the confirmed structural elements in the bacterial and rat voltage-gated K^+-channel (Doyle et al. 1998; Long et al. 2005).

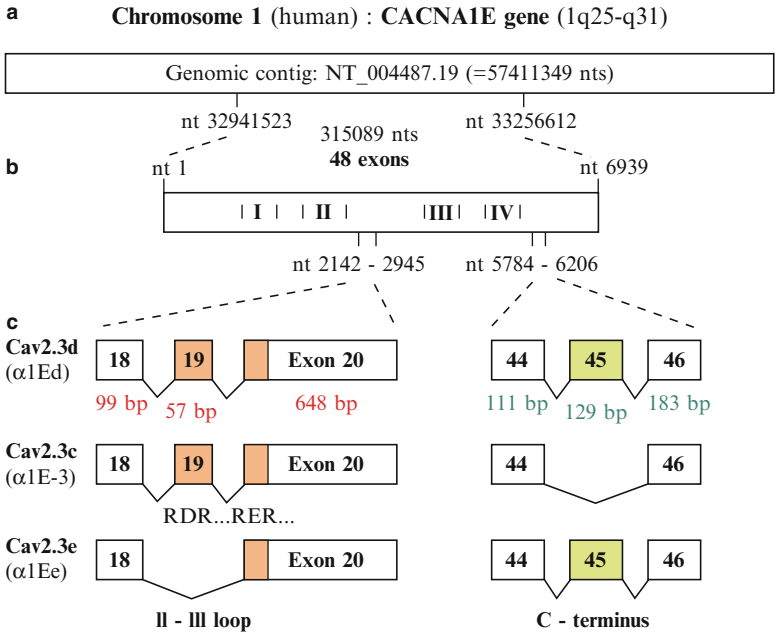

Fig. 7.1 Splice variants of $Ca_v2.3$ (alternative skipping of exon 19 and exon 45). Partial intron-exon structure of the human $Ca_v2.3$ subunit demonstrates the major splice variants reported in the literature (for details see: Pereverzev et al. 2002a). (**a**) The human gene of $Ca_v2.3$ is located on chromosome 1. Aligning the cloned human cDNA (GenBank L27745) to the Human Genome data bank led to the detection of the contig NT_004487.19, with a length of 54,411,349 nucleotides. The human cDNA aligned to the region between nt 32,941,523 and nt 33,256,612 within this contig and comprising 48 exons. (**b**) Two regions of the $Ca_v2.3$ subunit were investigated for structural variations, the II–III linker, containing exon 18 to exon 20 at the position 2142–2945, and the carboxy terminus, showing exon 44 to exon 46 at the position 5784–6206 of the human $Ca_v2.3$ cDNA. (**c**) Three major splice variants of the mammalian $Ca_v2.3$ subunit have been determined in vivo. The splice variant which was cloned from human fetal brain contains both exon 19 and exon 45 ($Ca_v2.3d$). The neuronal $Ca_v2.3c$ and the endocrine $Ca_v2.3e$ splice variant lack exon 19 and exon 45, respectively. The 57 nt of exon 19 encode an arginine-rich region similar to the first 19 aa of exon 20, which is shown by the first three amino acids of each segment (RDR . . . and RER . . .)

Additional elements may contribute to the kinetic properties of $Ca_v2.3$-mediated inward currents as reported for structurally similar ion channels. The segments S6 participate in gating the ion channels (Hofmann et al. 1999; Zhen et al. 2005; Xie et al. 2005), and the P-loops form essential components of the selectivity filters, thus also influencing the speed of the ion flux through the pore (Kim et al. 1993; Tang et al. 1993; Yang et al. 1993; Ellinor et al. 1995; Parent and Gopalakrishnan 1995; Dirksen et al. 1997; Cibulsky and Sather 2000; Cibulsky and Sather 2003). The segment S4 acts mainly as the voltage sensor (Jiang et al. 2003; Lacinova 2005), and its detailed orientation to the pore region has been elucidated in crystals from bacterial K^+ and Na^+ channels to a great extent (Lee et al. 2009; Payandeh

et al. 2011). Furthermore, mutational analysis revealed that separate regions of $Ca_v2.3$, like the conserved hydrophobic locus VAVIM in the S6 transmembrane segment of domain IV, are involved in voltage-dependent gating (Raybaud et al. 2007). Hydrophobic residues in the VAVIM locus (and other residues) promote the channel's closed state rendering them critical for the stability of the channel's closed and open states. Additionally, mutational analysis of a leucine residue in S4S5 provides the first evidence that the IIS4S5 and the IIS6 regions are energetically coupled during the activation of a VGCC (Wall-Lacelle et al. 2011).

7.5 Interaction Sites of $Ca_v2.3$ Voltage-Gated Calcium Channels

Interactions of $Ca_v2.3$ with its few known interaction partners have yet to be visualized by crystallization, but have been modeled (e.g. interaction with $Ca_v\beta$-subunits (Berrou et al. 2005)) and investigated in heterologous expression systems (Krieger et al. 2006). The interaction site of $Ca_v\beta$ with $Ca_v1.1$ and $Ca_v1.2$ is located in a conserved region between domain I and II (De Waard et al. 1994; Pragnell et al. 1994), which also contains the interaction site of $Ca_v2.3$ with $Ca_v\beta$-subunits (Berrou et al. 2001, 2005). The affinity of G-protein $\beta\gamma$ complexes towards the $Ca_v2.3$ I-II loop is similar as towards the I-II loops of the related $Ca_v2.1$ and $Ca_v2.2$ $\alpha1$-subunits, which are all three six to eight-fold higher as towards L-type $\alpha1$ subunits (De Waard et al. 1997).

Segments of the cytosolic loops of $Ca_v1.2$ L-type calcium channels have been co-crystallized with functional auxiliary subunits of VGCCs (Van Petegem et al. 2004) or functionally interacting calmodulin (Petegem et al. 2005; Dick et al. 2008; Kim et al. 2008; Tadross et al. 2008). For $Ca_v2.3$ this interaction was compared and predicted by modelling. Molecular replacement analyses were carried out using a three-dimensional homology model for the AID with the auxiliary $Ca_v\beta$-subunits (Berrou et al. 2005). Together with other data (Van Petegem et al. 2004), these results revealed detailed information about how the AID may functionally interact with $Ca_v\beta$-subunits in high voltage-activated calcium channels.

The II-III linker of the $Ca_v2.3$ subunit is lacking the classical so called "synprint-site", which in $Ca_v2.1$ (P-/Q-type) and $Ca_v2.2$ (N-type) was shown to be responsible for the excitation secretion coupling (Mochida et al. 1996; Rettig et al. 1996) and which is responsible for synaptic vesicle endocytosis (Watanabe et al. 2010). The II-III linker of $Ca_v2.3$ however harbors a unique site located within the arginine-rich stretch, which is responsible for a novel calcium-mediated modulation of the $Ca_v2.3$ voltage-gated calcium channel (Leroy et al. 2003). This site may be involved in protein kinase C (PKC) mediated signaling (Klöckner et al. 2004), connecting $Ca_v2.3$ to muscarinic receptor activation (Mehrke et al. 1997; Meza et al. 1999; Melliti et al. 2000; Bannister et al. 2004), possibly representing the mechanism behind muscarinic enhancement of the "toxin-resistant" R-type calcium

current in hippocampal CA1 pyramidal neurons (Tai et al. 2006). The relation of this mechanism to experimentally induced epilepsy was recently summarized (Weiergräber et al. 2006, 2010; Siwek et al. 2012).

$Ca_v2.3$ contains a carboxyterminal calcium/calmodulin interaction site (Liang et al. 2003; Kamp et al. 2012a), like other voltage-gated ion channels, for example the DIII-IV linker of the cardiac sodium channel involved in action potential generation and propagation (Sarhan et al. 2012).

7.6 Interaction Partners of the Cytosolic II-III Linker of the $Ca_v2.3$

Protein interaction partners of the II-III linker of the $Ca_v2.3$ VGCC have been shown to modulate surface expression of the channel and are thought to enable binding of PKC. The amyloid-precursor-like protein APLP1 interacts with the II-III loop of the $Ca_v2.3$ VGCC increasing internalization of the channel. The small G-protein Rab5a on the other hand, which also binds to the II-III linker, modestly increasing internalization, reduces APLP1-mediated internalization of the $Ca_v2.3$ VGCC. Both interactions may represent a mechanism that maintains calcium homeostasis by regulating surface expression of the $Ca_v2.3$ VACC. Hsp70 also binds to the II-III linker of the $Ca_v2.3$ VGCC, possibly enabling phosphorylation of the channel by its known interaction partner PKC, increasing activation, as found in other VGCCs.

7.6.1 APLP1-Mediated Internalization of $Ca_v2.3$ Voltage-Gated Calcium Channels

Recently, the amyloid-precursor-like protein APLP1 was identified as a novel interaction partner of the II-III loop of the $Ca_v2.3$ VGCC, which consists of a part of the extracellular region, the transmembrane domain, and a short part of the cytosolic domain, predicted to be 6 aa in length, representing the minimum length for possible protein-protein interaction (Radhakrishnan et al. 2011b).

Amyloid precursor proteins compose a highly conserved gene family which includes APLP1 and APLP2 as well as APP, a protein crucial in Alzheimer's disease. Although various functions of these proteins have been suggested, it remains unclear whether they act as signaling receptors and/or adhesion molecules or whether their physiological function may be primarily related to their shedded soluble fragments (Jacobsen and Iverfeldt 2009). APP and APLP2 are predominantly located in intracellular compartments, whereas APLP1 is found mainly on the cell surface (Kaden et al. 2009), and is restricted to the nervous system (Slunt et al. 1994). Interestingly, synthetic peptides corresponding to the cytoplasmic domain of APLP1 and APLP2 have been shown to be phosphorylated by protein kinase C, which also

phosphorylates APP (Gandy et al. 1988; Suzuki et al. 1997; da Cruz e Silva et al. 2009). Like APP and APLP2, APLP1 also undergoes intra-membrane proteolysis (Cong et al. 2011). Furthermore, it has recently been shown that APP regulates the expression of $Ca_v1.2$ (L-type) calcium channels in striatal and hippocampal GABAergic inhibitory neurons (Yang et al. 2007, 2009).

APLP1 consists of 650 amino acids and interacts with the II-III loop of the $Ca_v2.3$ VGCC via a site between 999 and 1,899 bp, referred to here as APLP1S. Interaction of APLP1 and $Ca_v2.3$ causes an increase in internalization of $Ca_v2.3$ in stably transfected HEK 293 cells (Radhakrishnan et al. 2011b). Interestingly, the full length protein alone, and not APLP1S, which lacks part of the extracellular region, causes internalization of $Ca_v2.3$, suggesting that a signal which the extracellular region of APLP1 receives is important for endocytosis of $Ca_v2.3$. Furthermore, full length APLP1 affects inactivation kinetics of $Ca_v2.3$ VGCCs (Radhakrishnan et al. 2011b). The necessity of full length APLP1 as opposed to APLP1S, the interaction site identified in a Y2H screen in which the II-III loop of $Ca_v2.3$ was used as bait, for internalization and modulation of $Ca_v2.3$, may be based on the need for oligomerization of APLP1 via the extracellular domain, which is not uncommon for proteins of this family (Kaden et al. 2012).

APLP1 plays an important role in α_2-adrenergic receptor trafficking and may similarly act as a negative-feedback mechanism of $Ca_v2.3$ by mediating its internalization. This mechanism could represent a neuroprotective role of APLP1, reducing calcium influx into neurons, possibly activated by increased calcium influx. This is in line with findings demonstrating that expression of APLP1 mRNA is down regulated in pilocarpine-induced epileptic rats (Wang et al. 2009). Under these circumstances non-availability of APLP1 for endocytosis of $Ca_v2.3$ could lead to elevated intracellular calcium levels, possibly contributing considerably to pilocarpine-induced epilepsy and neurodegeneration. Further support of this view is given by the observation that $Ca_v2.3$ knockout mice are neuroprotected after kainate injection compared to wild type mice (Weiergräber et al. 2007), pointing to possible role of APLP1 in neurodegenerative disease.

7.6.2 Rab5A-Mediated Internalization of $Ca_v2.3$ Voltage-Gated Calcium Channels

Rab5A belongs to the Rab protein family, which comprises more than 60 proteins and can be classed as members of the small G protein superfamily. GTP-dependent Rab proteins regulate various steps of vesicular trafficking, behaving as membrane-associated molecular switches (Pochynyuk et al. 2007). Rab GTPases can associate with motor complexes, and thus, can allow for membrane association and directional movement of various vesicular cargos along the microtubule cytoskeleton (Horgan and McCaffrey 2011). Rab5A is found on the cell membrane, early endosomes and melanosomes, and is known to support the fusion of endocytotic vesicles and the

formation and transport of early endosomes (Zerial and McBride 2001). Recently it has been demonstrated that Rab5A regulates EGFR endocytosis and signaling by interacting with a protein complex consisting of TIP30, endophilin B1 and acyl-CoA synthetase long-chain family member 4, underlining its role as an endocytotic protein (Zhang et al. 2011).

Rab5A has recently been found to interact with the II-III loop of $Ca_v2.3$, modestly increasing internalization of the $Ca_v2.3$ VGCC. Intriguingly however, Rab5A reduces APLP1-mediated internalization of the channel by increasing endocytosis of APLP1 itself thus limiting the availability of APLP1 at the cell surface (Radhakrishnan et al. 2011b). These findings are in agreement with data reporting co-localization of Rab5A with APP family proteins (Marquez-Sterling et al. 1997; Kyriazis et al. 2008). One may conclude that Rab5A together with APLP1 is involved in a mechanism that maintains calcium homeostasis by regulating surface expression of the $Ca_v2.3$ VGCC.

7.6.3 Interaction of HSP-70 with $Ca_v2.3$ Voltage-Gated Calcium Channels

Heat shock 70-kDa proteins (Hsp70s) represent the most conserved family of proteins found in all organisms (Gupta 1998) and are known to be inducible by cellular stress, hyperthermia and infection (Gupta et al. 2007, 2010). Although the 13 Hsp70 isoforms account for 2 % of all proteins in stressed human cells (Zylicz and Wawrzynow 2001), they are also found in unstressed cells in which they act as chaperones (Sfatos et al. 1996; Bukau et al. 2006). In co-immunoprecipitation experiments the II-III loop of $Ca_v2.3$ was found to interact with Hsp70 (Krieger et al. 2006), which is known to interact with PKC (Newton 2003). When PKC is activated, it becomes highly sensitive to dephosphorylation. Hsp70 is capable of binding to the dephosphorylated motif and stabilizing it. PKC becomes rephosphorylated and is able to re-enter the pool of signalling-competent PKC (Gao and Newton 2002; Newton 2003).

It has been reported that $Ca_v2.2$ (N-type) $\alpha 1$ subunits are regulated by PKC dependant phosphorylation of the cytosolic linker that connects domain I and II (Zamponi et al. 1997). Similarly, $Ca_v2.3$ currents are potentiated by PKC-dependant phosphorylation at common sites shared with $Ca_v2.1$ and $Ca_v2.2$ channels but also at sites unique to $Ca_v2.3$. Examination of the effect of the PKC activator phorbol ester on $Ca_v2.3$ currents revealed that the II-III loop is an important determinant of activation, however no phosphorylation of the II-III loop could be detected therein (Krieger et al. 2006). It is assumable that PKC does not bind directly to the channel, but that Hsp70 mediates binding of PKC to the II-III loop to support phosphorylation of other regions of the channel protein to increase activation (Kamatchi et al. 2003, 2004). The interaction of Hsp70, PKC and the II-III loop of Cav2.3 has not been understood completely and it is assumable that additional proteins participate in

forming a multimeric activation complex, however involvement of Hsp70 with $Ca_v2.3$ has several possible implications for pathologies in which both proteins are involved like ischemic heart disease, diabetes and neurodegeneration.

7.7 Interaction Partners of the Carboxy-Terminal Region of $Ca_v2.3$ Voltage-Gated Calcium Channels

Specific regulation of $Ca_v2.3$ by carboxy terminal protein interaction partners plays an important role in neurotransmitter release and in presynaptic plasticity (Dietrich et al. 2003; Kamp et al. 2005). A novel calmodulin splice variant was recently shown to interact with $Ca_v2.3$, possibly modulating its gating properties and/or trafficking, linking $Ca_v2.3$ to regulation of long-term potentiation (Kamp et al. 2012a). Furthermore the G1 subunit of vacuolar ATPase, a critical protein in vesicular fusion, also binds to the C-terminus of $Ca_v2.3$. Inhibition of V-ATPase attenuates the $NiCl_2$ mediated increase of the R-type-dependent b-wave measured in electroretinograms and reduces $Ca_v2.3$ peak currents indicating a role for $Ca_v2.3$ in exocytosis and thus neurotransmitter release.

7.7.1 Interaction of $Ca_v2.3$ Voltage-Gated Calcium Channels and Calmodulin

Because calcium is an important second messenger and is involved in major cellular processes, such as exocytosis and induction of apoptosis, regulation of calcium influx and thus of calcium homeostasis is critical for the cell. Calmodulin (CaM) is a central molecule in cellular calcium regulation acting on over 300 different target proteins (Findeisen and Minor 2010). Structurally, CaM is composed of two independent lobes (C- and N-lobe) each with two EF-hands as calcium-binding motifs.

CaM regulates VGCCs by interacting with the IQ-domain, in the carboxyterminus (Zühlke et al. 2000). Generally, CaM has two different modulatory effects on VGCCs: (i) calcium-dependent facilitation (CDF) and (ii) calcium-dependent inactivation (CDI). CDI of Ca_v1 channels is mediated by the C-lobe of CaM whereas the N-lobe of CaM drives CDI in the Ca_v2 subfamily (Peterson et al. 1999; DeMaria et al. 2001; Liang et al. 2003). It has been suggested that the differences in lobe-specific function of CaM between Ca_v1 and Ca_v2 subfamilies are due to differences in binding orientation of Ca_v1 and Ca_v2 calcium channels (Findeisen and Minor 2010).

Recently, a novel splice variant of CaM-2 (CaM-2-ext) with a 46 nucleotide- long insertion retained from a 5666 nucleotide-long intron between exon 1 and 2 of the

classic calmodulin-2 has been found in two human cell lines and was identified as an interaction partner of the carboxyterminus of $Ca_v2.3$ by yeast-two-hybrid screening and co-immunoprecipitation (Kamp et al. 2012a). CaM-2-ext significantly decreases $Ca_v2.3$ peak current density, which may be caused by modulation of $Ca_v2.3$ channel gating properties or impairment of its trafficking (Kamp et al. 2012a). The physiological and pathophysiological significance of CaM-2-ext as well as its expression pattern must be further investigated in future studies.

Modulation of VGCCs, particularly of $Ca_v2.3$ by CaM appears to be important for presynaptic calcium regulation. It is conceivable that CDI of $Ca_v2.3$ relies on the global presynaptic calcium concentration sensed by CaM, indicating an important role of CaM as a sensitive calcium concentration sensor (Liang et al. 2003). Furthermore, there is strong evidence that both $Ca_v2.3$ and CaM, are involved in the induction of presynaptic long-term potentiation (LTP) in certain synapses such as in mossy fibers and cerebellar Purkinje cell terminals (Dietrich et al. 2003; Breustedt et al. 2003; Myoga and Regehr 2011). Calcium entering the cell through $Ca_v2.3$ binds to CaM, which may activate adenylyl cyclases and subsequently protein kinase A (PKA) leading to induction of presynaptic LTP (Kamp et al. 2005, 2012). LTP also involves PKC activation, which in turn modulates $Ca_v2.3$ by increasing presynaptic calcium influx through $Ca_v2.3$ (Stea et al. 1995; Klöckner et al. 2004).

7.7.2 Interaction of $Ca_v2.3$ Voltage-Gated Calcium Channels with Vacuolar ATPase

Recently, the G1 subunit of the vacuolar ATPase (V-ATPase) was identified as a novel interaction partner of the carboxyterminus of $Ca_v2.3$ voltage-gated calcium channels. V-ATPases are highly conserved multi-enzyme complexes, which consist of a peripheral, catalytic (V1) and a membrane-integrated sector (V0) (Nelson and Harvey 1999; Nishi and Forgac 2002). The G1 subunit is part of a peripheral stalk connecting both sectors and is involved in the regulation of the multi-enzyme complexes' stability (Charsky et al. 2000). As V-ATPases pump protons under ATP-hydrolysis through cellular membranes they are involved in various cellular processes such as vesicle acidification, protein processing, and their trafficking and targeting (Palokangas et al. 1998; Gruber et al. 2001; Schoonderwoert and Martens 2001).

Recently, the G1 subunit of the V-ATPase was identified as a novel interaction partner of the full length $Ca_v2.3$ C-terminus by yeast-2-hybrid screening (Radhakrishnan et al. 2011a). This interaction was confirmed by FLAG immunoprecipitation in 293 T cells. Similarly, Gao and Hosey identified the homolog G2 subunit of V-ATPase as an interaction partner of the L-type calcium channel $Ca_v1.2$ by similar methods and using a GST-pull down assay (Gao and Hosey 2000). Nevertheless, the physiological significance of the interaction between the V-ATPase and VGCCs remains unclear. The V-ATPase inhibitor bafilomycin

A1 reduces $Ca_v2.3$ peak currents and attenuates the $NiCl_2$ mediated increase of the R-type-dependent b-wave measured in electroretinograms (Radhakrishnan et al. 2011a). Whether bafilomycin affects the interaction between $Ca_v2.3$ and the V-ATPase however, is uncertain. More likely, trafficking of VGCCs to the plasma membrane is affected by the V-ATPase antagonist leading to reduced calcium channel currents. This interpretation is in line with the previous results from Gao and Hosey who observed disturbed trafficking of $Ca_v1.2$ calcium channels to the plasma membrane and their intracellular accumulation after treatment with the V-ATPase inhibitor folimycin (Gao et al. 2001).

Furthermore, interaction of VGCCs with V-ATPase could be critical in the mechanism of exocytosis: the V0 sector of V-ATPase was suggested to act as a fusion pore during exocytosis (Morel et al. 2001; El Far and Seagar 2011). The V0 sector is composed of a ring of homolog subunits enriched in the presynaptic membrane (Taubenblatt et al. 1999; Morel et al. 2001). It interacts with several proteins of the exocytotic machinery such as VAMP, syntaxin and synaptobrevin (Galli et al. 1996; Shiff et al. 1996; Morel et al. 2003) and is calcium-sensitive and permeable to acetylcholine. The V0-proteolipid rings have shown to be involved in membrane fusion in yeast vacuoles (Peters et al. 2001; Bayer et al. 2003). Thereby, two proteolipid rings in both membranes dimerize in a "head-to-head" position forming a channel. Membrane proteolipids can invade the V0-proteolipid ring connecting both membranes promoted by lateral separation of the V0 proteolipid ring subunits (Peters et al. 2001; Bayer et al. 2003). A similar mechanism was suggested to occur during exocytosis, however more data is needed on this subject. During docking of the synaptic vesicle to the active zone of neurotransmitter release, the interaction between VGCCs and V-ATPase may help organize of the synaptosome and possibly destabilize the V-ATPase holoenzyme leading to dissociation of the V1 sector from the V0 sector. It is conceivable that formation of a loose and—after rising of presynaptic calcium—tight SNARE complex positions the V0 sector in the vesicle and the plasma membrane, rendering dimerization of V0 sectors and subsequent neurotransmitter release highly dependent on direct interaction with VGCCs, however, experimental data in support of this hypothetical model has yet to be provided.

7.8 Future Outlook: Role of $Ca_v2.3$ Channels and Their Interaction Partners in Cardiac Activity

L-type channels are not the only VGCCs in cardio myocytes: T-type and more recently R-type channels have been identified in the myocardium, however the influence of $Ca_v2.3$ VGCCs on cardiac activity is still being debated. $Ca_v2.3$ deficient mice display arrhythmic patterns like uncoordinated atrial activation, second degree atrioventricular block type II (Mobitz type II) and QRS-dysmorphology. The exact mechanism of action has yet to be elucidated, however a role of $Ca_v2.3$ in

successive activation of voltage-gated calcium channels has been suggested. Thus, further studies of the functional role of $Ca_v2.3$ and its modulation by interaction partners in cardiac activity could be of great physiological and pathophysiological importance.

The VGCCs investigated in greatest detail in the myocardium are the L-type channels. Of particular importance among these, is the $Ca_v1.2$ channel as the main contributor of excitation-contraction coupling (Wang et al. 2004; Brette et al. 2006). Upon cardiomyocyte depolarization, L-type calcium channels open allowing influx of calcium ions which activates ryanodine receptors (RyR)—particularly RyR2—, resulting in a release of calcium ions from the sarcoplasmic reticulum into the cytosol, i.e. calcium-induced calcium release (Valdeolmillos et al. 1989). The importance of $Ca_v1.2$ in the myocardium is underlined by the non-viability of mice lacking the channel, which die before day 14.5 p.c., i.e. 1 day after the embryonic heart starts beating (Seisenberger et al. 2000).

Nevertheless, $Ca_v1.2$ channels are not the only VGCCs in cardiomyocytes. Other L-type channels ($Ca_v1.3$) (Mangoni et al. 2003; Marger et al. 2011; Qu et al. 2011), T-type channels ($Ca_v3.1$ and 3.2) (Cribbs 2010; Ono and Iijima 2010; Marger et al. 2011), and more recently R-type channels ($Ca_v2.3$) (Mitchell et al. 2002; Lu et al. 2004; Weiergräber et al. 2005; Murakami et al. 2007) and Galetin, Schneider et al., unpublished) have been identified in the myocardium. The role of $Ca_v1.3$ channels in cardiac activity is generally well accepted and is reported to play a compensatory role after $Ca_v1.2$ ablation (Xu et al. 2003). The function of $Ca_v2.3$VGCCs on the other hand, is still being debated.

Significant evidence pointing towards a non-negligible role of $Ca_v2.3$ channels in cardiac pacemaking is continuously being raised. Weiergräber et al. and Mitchell et al. detected both $Ca_v2.3$ channel expression at both mRNA and protein in rat atrial and ventricular myocytes (Weiergräber et al. 2000; Mitchell et al. 2002). Shortly thereafter, a significantly increased coefficient of variation in heart rate was found in isolated embryonic hearts of $Ca_v2.3$ deficient mice, reflecting increased variability of heart rate and an irregular beating pattern (Lu et al. 2004). In hearts of adult $Ca_v2.3$ deficient mice, telemetric ECG recording also revealed arrhythmic patterns, including ECG dysmorphology, uncoordinated atrial activation (partially non-transducted), second degree atrioventricular block type II (Mobitz type II) and QRS-dysmorphology (Weiergräber et al. 2005). Taken together, these findings point toward an important role of $Ca_v2.3$ in sustaining a regular heart beat, due to their expression in pacemaker cells, both in embryonic and adult hearts.

Despite all the previously-mentioned data, some doubts still exist as to whether $Ca_v2.3$ truly contributes to cardiac pacemaking in the myocardium or only via the autonomic nervous system. In effect, knockout animals not only display pacemaking disturbances, but also altered autonomic nervous system control after ablation of $Ca_v2.3$ (Weiergräber et al. 2005). Modified sympathetic regulation of cardiac activity is found in mice lacking Ca_v2 subfamily channels $Ca_v2.3$ and $Ca_v2.2$ (Murakami et al. 2007). In addition, expression of $Ca_v2.3$ in rat intra-cardiac neurons (although only at low levels of 7 %) has been proven (Jeong and Wurster 1997). These doubts are additionally exacerbated by difficulties in detecting $Ca_v2.3$ protein in mouse

heart microsomes so far. However, using the isolated perfused heart experimental set up (Langendorff), similar arrhythmic patterns could be recorded in spontaneously beating hearts extracted from $Ca_v2.3$-deficient mice (Tevoufouet and Schneider, unpublished). Using the Langendorff method, significantly increased heart rates were recorded from isolated perfused hearts of $Ca_v2.3$-deficient mice (Tevoufouet and Schneider, unpublished), an outcome observed in telemetric ECG recordings of $Ca_v2.3$-deficient mice (Weiergräber et al. 2005). However, in embryonic isolated hearts of $Ca_v2.3$-deficient mice, heart rate was found to be reduced

Altogether, these facts suggest that the ablation of $Ca_v2.3$ channels causes abnormalities in cardiac activity, which cannot be fully compensated by upregulation of $Ca_v3.1$ channels (Weiergräber et al. 2005), thus confirming a significant role of $Ca_v2.3$ in pacemaking of cardiac activity. The exact mechanism of action has yet to be elucidated, however a role of $Ca_v2.3$ in successive activation of VGCCs (Lakatta et al. 2010) has been suggested: after activation of T-type channels, activation of $Ca_v2.3$ could be required to achieve the potential necessary for activation of L-type calcium channels (Galetin, Schneider et al., unpublished). Thus, further studies of the functional role of $Ca_v2.3$ and its interaction partners in cardiac activity could be of great physiologic and pathophysiologic importance.

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