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Biochimica et Biophysica Acta 1742 (2004) 59–68
BIOCHIMICA ET BIOPHYSICA ACTA
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Review

The neuronal calcium-sensor proteins

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Received 16 July 2004; accepted 16 August 2004
Available online 27 August 2004

Abstract

Changes in intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) affect many different aspects of neuronal function ranging from millisecond regulation of ion channels to long term changes in gene expression. These effects of Ca^{2+} are transduced by Ca^{2+}-binding proteins that act as Ca^{2+} sensors by binding Ca^{2+}, undergoing a conformational change and then modifying the function of additional target proteins. Mammalian species express 14 members of the neuronal calcium sensor (NCS) family of EF hand-containing Ca^{2+}-binding proteins which are expressed mainly in photoreceptor cells or neurons. Many of the NCS proteins are membrane targeted through their N-terminal myristoylation either constitutively or following exposure of the myristoyl group after Ca^{2+} binding (the Ca^{2+}/myristoyl switch). The NCS proteins have been implicated in a wide range of functional roles in neuronal regulation, several of which have been confirmed though molecular genetic analyses.

Keywords: NCS-1; Hippocalcin; KChIP; Neurocalcin; Calcium; VILIP

1. Introduction

An elevation of intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) is the trigger for neurotransmitter release from synaptic vesicles at neuronal synapses [1, 2]. Alterations in $[Ca^{2+}]_i$ also bring about many different changes in neuronal function including modulation of ion channels, gene expression and effects on neuronal survival and apoptosis. The varied effects of changes in $[Ca^{2+}]_i$ depend on the magnitude, duration and location of the Ca^{2+} signal [3] and are mediated through various Ca^{2+}-binding proteins acting as Ca^{2+}-sensors. The most common Ca^{2+}-binding motif in mammalian genomes is the EF hand motif that is best known due to its presence in the ubiquitous Ca^{2+}-sensor protein calmodulin. Calmodulin is involved in multiple aspects of Ca^{2+} signalling in neurons including in the regulation of neurotransmitter release [4], function of K^+ and Ca^{2+} channels [5] and various receptors [6, 7] and gene transcription [8] and synaptic plasticity via activation of Ca^{2+}/calmodulin-dependent protein kinase type II [9]. It is not, however, the only important EF hand protein and the related EF-hand containing neuronal Ca^{2+} sensor (NCS) proteins also have many important roles in neuronal signalling [10]. We discuss the functional importance of the NCS protein family in this review.

2. The NCS protein family

NCS proteins (Table 1) have been identified in many organisms ranging from yeast to man. The human genome encodes 14 members of the family [11] and it is likely that these are conserved and represented in all mammalian species. Various aspects of these proteins have been the subject of previous reviews [10,12,13]. In this article, therefore, a brief overview of the NCS proteins based on the five known classes within the family will be given along with mention of more recent information on their functional roles. The NCS proteins are Ca^{2+} sensors as they bind Ca^{2+} with micromolar or submicromolar affinities, undergo conformational changes on Ca^{2+} binding and interact with and regulate other proteins leading to changes in physiological function. Recoverin and the guanylyl cyclase activating proteins (GCAPs) are expressed only in the retina where they regulate phototransduction [14]. Other NCS proteins are

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doi:10.1016/j.bbamcr.2004.08.008

Table 1
The NCS protein family and their identified functions

NCS protein	Function	Genetic evidence
NCS-1 (frequenin)	Regulation of neurotransmission, learning, channel regulation, PI(4) kinase activation	Overexpression in *Drosophila*. Null mutants in *C. elegans* and yeast
Neurocalcin δ	Endocytosis	
Hippocalcin	Phospholipase D activation, anti-apoptotic, MAP kinase signalling	
VILIP-1	Guanylyl cyclase activation, traffic of nicotinic receptors	
VILIP-2	?	
VILIP-3	?	
Recoverin	Inhibition of rhodopsin kinase in photoreceptors	KO in mouse
GCAP-1	Activation of guanylyl cyclase in photoreceptors	KO in mouse, human mutations
GCAP-2	Activation of guanylyl cyclase in photoreceptors	KO in mouse
GCAP-3	Activation of guanylyl cyclase in photoreceptors	
KChIP1	K^+ channels, repression of transcription	
KChIP2	K^+ channels, repression of transcription	KO in mouse
KChIP3 (DREAM, calsenilin)	K^+ channels, presenilin-binding, repression of transcription, pro-apoptotic	Two KO mouse strains
KChIP4	K^+ channels, repression of transcription	

The table lists the 14 NCS proteins that have been identified in mammalian genomes.

expressed in the nervous system, either in specific classes of neurons (e.g., hippocalcin) or as NCS-1 in essentially all neuronal cell types [15]. The latter protein is also expressed by many non-neuronal cell types [16–19] and an orthologue is even present in yeast (Frq 1) [20]. The existence of multiple members of this family may relate to differences in their subcellular targeting and responsiveness to $[Ca^{2+}]_i$ as well as differences in the proteins that they interact with and regulate. In addition, each neuronal class expresses a different cocktail of NCS proteins that would allow the manifestation of neuron-specific responses to differing Ca^{2+} signals.

3. Structure of the NCS proteins

The NCS proteins all possess four EF hand motifs but only three (or two in the case of recoverin and KChIP1) are able to bind Ca^{2+}. In all cases the first, most N-terminal EF hand is non-functional in Ca^{2+}-binding due to the presence of a cysteine and a proline in the putative Ca^{2+}-binding loop. Eleven of the mammalian NCS proteins are N-terminally myristoylated. The structures of several NCS proteins have been solved by X-ray crystallography or use of NMR including those for Ca^{2+}-bound forms of human [21] and yeast [22] NCS-1, GCAP-2 [23], neurocalcin δ [24] and KChIP1 [25,26]. Recoverin, the first of the NCS proteins to be discovered, has been most extensively characterised by biochemical and structural approaches with structures of the myristoylated protein in the Ca^{2+}-free [27,28], Ca^{2+}-bound [29] and intermediate forms [30,31] being known (Fig. 1). In recoverin, the myristoyl group is sequestered in a hydrophobic pocket in the Ca^{2+}-free condition [27] and binding of two Ca^{2+} ions to EF hands 2 and 3 leads to a conformational

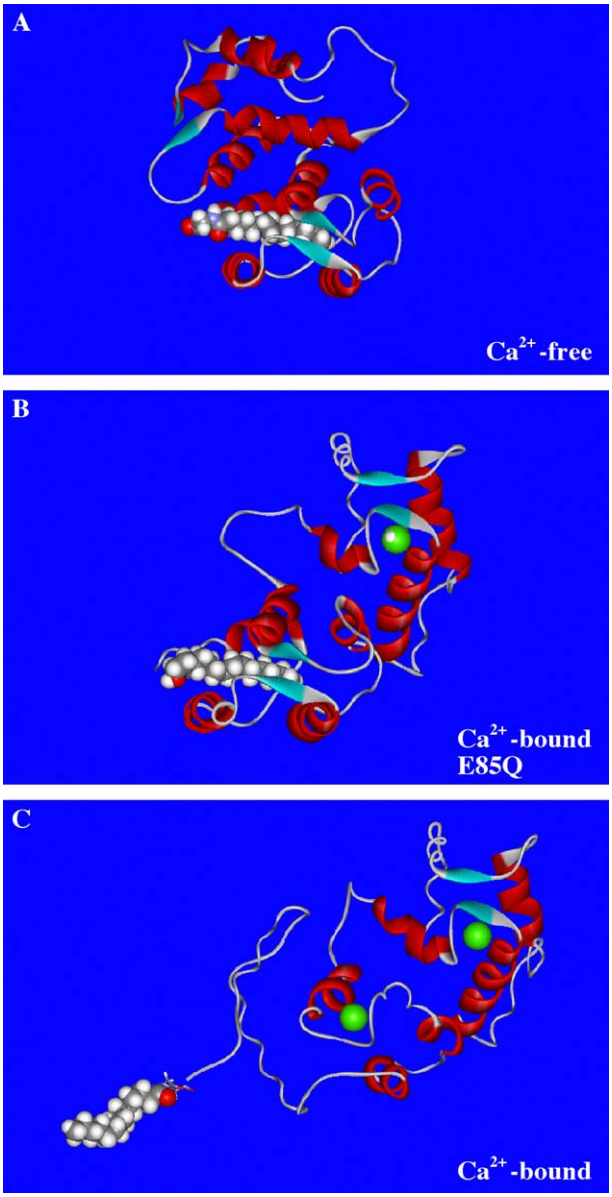

Fig. 1. Structures of myristoylated recoverin from NMR analysis. The structures shown are for (A) Ca^{2+} free recoverin (PDB 1IKU), (B) recoverin E85Q with a single Ca^{2+} ion bound to EF hand 3 (PDB 1LA3), and (C) recoverin with two Ca^{2+} ions bound to EF hands 2 and 3 (PDB 1JSA). The structure of recoverin E85Q is believed to reflect that of an intermediate following binding of the first Ca^{2+} to wild-type protein. The structural data were from Refs. [27,29,30].

change in which the myristoyl group flips out [29] allowing reversible association of the protein via this lipid moiety with membranes. Some but not all other myristoylated NCS proteins share this Ca^{2+}/myristoyl switch mechanism [32]. Information on the behaviour of the individual mammalian NCS proteins along with information on their functions is summarised below.

4. Class A proteins: NCS-1 (frequenin)

NCS-1 was originally discovered as frequenin from the study of a *Drosophila* mutant in which it is overexpressed [33]. The mutant flies showed an enhancement of activity-dependent facilitation of neurotransmission implicating the protein in the regulation of neurotransmitter release. Such a role was subsequently also demonstrated in *Xenopus* neurons in experiments using micro-injection of the protein [34]. Overexpressed mammalian NCS-1 was shown to enhance evoked exocytosis from dense-core secretory granules in PC12 cells [16, 35] and subsequently in other cell types [18,36]. Genetic manipulations of NCS-1 in *C. elegans* have also demonstrated that NCS-1 levels have a positive correlation with learning and memory in this organism [37]. In addition, overexpresion of NCS-1 in hippocampal neurons in culture switched the form of short-term plasticity that could be elicited from paired-pulse depression to facilitation [38]; this was not due to an effect on Ca^{2+} currents in transfected neurons. NCS-1 has been found, however, to regulate the function of N- and P/Q-type voltage-gated Ca^{2+} channels [39–43] and potentially A-type K^+ channels [44] [45] as well as the down-regulation of D2 dopamine receptors by endocytosis [46]. NCS-1 and its *S. cerevisiae* orthologue (Frq1) do not appear to possess a conventional Ca^{2+} myristoyl switch [22, 47] and much of the NCS-1 is associated with the plasma membrane and the trans-Golgi network in neurons and other cell types even at low $[Ca^{2+}]_i$ [47,48]. A significant advance in the understanding of NCS-1 function was the discovery that Frq1 is essential for survival in yeast due to its ability to activate Pik1, one of the two phosphatidylinositol-4-OH kinases (PI(4)K) [20]. It was subsequently shown that NCS-1 can activate the closest mammalian enzyme PI(4)K type IIIβ [49]. Since this enzyme converts phosphatidylinositol to phosphatidylinositol-4-phosphate, the precursor of phosphatidylinositol 4,5-bisphosphate, its activity can affect IP_3-dependent signalling and also membrane traffic events in the secretory pathway that require these lipids. Some of the physiological effects of NCS-1, notably its ability to enhance agonist-evoked secretion, have been attributed to its activation of PI(4)K III β leading to up-regulation of IP_3 receptor signalling and Ca^{2+} mobilisation [18,50,51]. It is known, however, that several other effectors for NCS-1 exist but the functional significance of most of these interactions remains to be explored. Nevertheless, it is clear that the effect of NCS-1 on dopamine D2 receptor internalisation is likely to be mediated through its direct interactions with the receptor itself and with G-protein coupled receptor kinase (GRK) 2 [46].

The targeting of NCS-1 to plasma and TGN membranes requires its N-terminal myristoylation [47] and, in addition, basic residues within the myristoylation motif of NCS-1 and hippocalcin at positions 5, 7 and 9 determine their specific localisation to these rather than other intracellular membranes [52]. The tight membrane association of NCS-1 is not dependent on Ca^{2+}-binding [35,47] suggesting that the myristoyl group is constitutively exposed and this is supported by structural data on the *S. cerevisiae* protein [22]. Analysis by use of mutagenesis suggests that residues within the N-terminus but outside the myristoylation motif lock the myristoyl group in an exposed conformation [53]. The constitutive membrane association would allow NCS-1 to respond rapidly, on a millisecond time scale, to local changes in $[Ca^{2+}]_i$ close to its membrane location, and thereby respond much more quickly to Ca^{2+} signals than NCS proteins that operate a Ca^{2+}/myristoyl switch and need to translocate from the cytosol to membranes.

The full range of functions of NCS-1 still remains to be determined. It is known to interact directly with at least six distinct proteins including, in addition to those mentioned above, calcineurin and cyclic nucleotide phosphodiesterase [35,54]. Also NCS-1 interacts with a protein, in which mutations lead to X-linked mental retardation, known as IL1-receptor associated-protein-like protein (IL1RAPL) [55]. The functional significance of this interaction remains to be fully explored but it suggests that NCS-1 and IL1RAPL are required for normal brain development. Further work will be needed to identify all of the NCS-1 effectors and to determine how they contribute to the various physiological roles of NCS-1.

5. Class B proteins: VILIPs, neurocalcin and hippocalcin

This group of five NCS proteins are closely similar in sequence to each other (Fig. 2) with between 66% and 94% sequence identity between each protein [56]. A related neurocalcin-like protein is one of the first NCS proteins to be recognisable as having appeared after NCS-1 during evolution with *Drosophila* expressing NCS-1, neurocalcin [33,57] and a KChIP-like protein. These Class B proteins appear to be largely or entirely neuronal-specific. The expression of VILIPs 1–3 and hippocalcin in brain have been well characterised by in situ hybridisation which showed a distinct expression pattern for each protein [15]. For example, hippocalcin is most highly expressed in hippocampal pyramidal neurons [58] and VILIP-3 in cerebellar Purkinje cells. The expression of neurocalcin δ was not mapped in this study. With a couple of notable exceptions, immunocytochemical studies on the localisation of this group of proteins are unreliable due to a lack of characterisation of the extent of cross-reactivity of antisera.

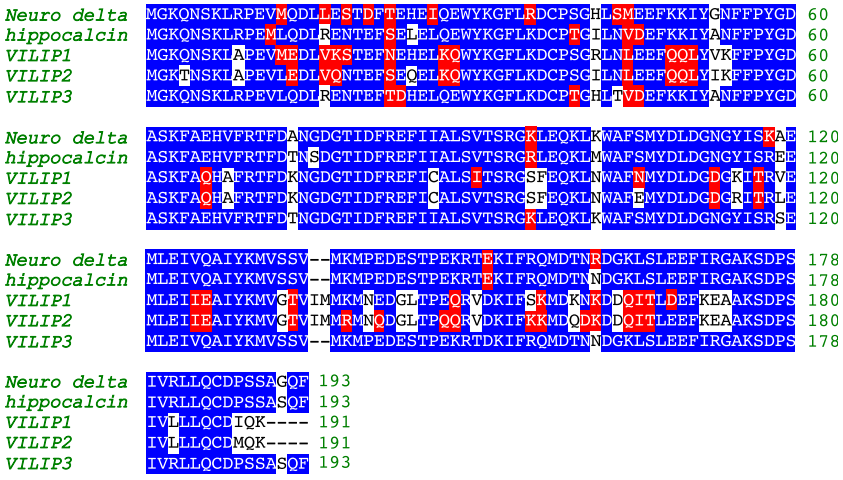

Fig. 2. Alignment of the sequences of the human neurocalcin and VILIP subfamily of NCS proteins. Residues outlined in blue are identical in at least three of the proteins.

Where specific, characterised antisera have been used, the data confirm the distinct expression patterns of these proteins [59].

The existence of a Ca^{2+}/myristoyl switch has been shown biochemically [59–62] and has been examined within live cells for hippocalcin [47,63], neurocalcin δ [47,64], VILIP-1 [65] and VILIP-3 [66] and all four proteins were found to exhibit this property. The translocation of hippocalcin from the cytosol to membranes (plasma membrane and TGN) has been examined in detail using hippocalcin-EYFP in living cells [63]. The heterologously expressed protein in HeLa cells showed a maximal rate of translocation with a time constant of around 1 s and translocation was half maximal at around 300 nM free Ca^{2+} with the protein having a dynamic range of Ca^{2+}-sensitivity of 200–800 nM $[Ca^{2+}]_i$. This suggests that hippocalcin would be able to affect its target proteins on membranes only if $[Ca^{2+}]_i$ is elevated globally within the cell for sufficient time to allow translocation (seconds) but requires only a small $[Ca^{2+}]_i$ elevation above resting levels. This class of protein would therefore require a more prolonged Ca^{2+} signal for their full activation than the membrane-associated NCS-1.

Much remains to be learnt about the functions of this group of proteins. A few clues on their function are available, however. VILIP-1, but not VILIP-3, has been shown to interact with and activate membrane guanylyl cyclases [56,67] and VILIP-1 has been implicated in stimulation of the cell surface expression of the α4 nicotinic acetylcholine receptor [68]. Recently, biochemical analyses have shown a Ca^{2+}-dependent interaction of VILIP-3 with the microsomal protein cytochrome b_5 [69]; the functional significance of this interaction is currently unknown. The most convincing functional data on hippocalcin show it to be an inhibitor of apoptosis through its interaction with the neuronal apoptosis inhibitor proteins [70,71]. It has also been suggested, however, to be involved in the activation of phospholipase D [72] and in MAP kinase signalling pathways [73]. Little evidence is available on the function of neurocalcin δ in neurons apart from its ability to interact directly in a Ca^{2+}-dependent manner with actin, tubulin and clathrin [64,74]. It is present on isolated brain coated vesicles [75] and, in conjunction with its direct interaction with clathrin heavy chain [64], this supports a possible role in endocytosis in neurons. Neurocalcin δ may also be involved in the inhibition of rhodopsin kinase in certain retinal cell types [76]. Given the close similarity of these proteins, it will be interesting to see if they turn out to have distinct or overlapping functions in the different neurons in which they are expressed. It is possible that like NCS-1 they will interact with multiple effector proteins and that some of their functions could also overlap with NCS-1.

6. Class C proteins: recoverin

Recoverin is expressed only in photoreceptor cells of the retina and there is a single mammalian gene. Orthologues of recoverin are expressed in photoreceptors in species from amphibia onwards. As noted above, this protein has been characterised in detail using structural approaches allowing insight into its Ca^{2+}-free and Ca^{2+}-bound structures and also its intermediate forms with a single bound Ca^{2+} ion [30, 31] [27–29]. The only known function of recoverin is to bind to [77] and inhibit rhodopsin kinase (otherwise known as GRK1) [78–80]. Recoverin is believed to have a role in the regulation of phototransduction by preventing the down-regulation of rhodopsin due to its phosphorylation and thereby prolonging the light response [14] Its physiological role in vivo has recently been examined in knock-out mice. Analysis of photo-responses of rods in the absence of recoverin established that it prolongs the dark-adapted response and increases sensitivity at low light levels [81]. The results were consistent with a molecular function for recoverin through its inhibition of rhodopsin kinase. Several other NCS proteins can inhibit GRK1 in vitro [82] and this, coupled with the interaction of NCS-1 with GRK2 [46],

suggests that inhibition of these receptor kinases might be a general function of NCS proteins other than recoverin.

7. Class D proteins: GCAPs

The GCAPs are all expressed only in the retina where their only known function is in regulating photoreceptor guanylyl cyclase (ret GC) activity [14]. Mutations in human GCAP1 have been shown to lead to cases of retinal dystrophy due to death of photoreceptors [83]. All three GCAP proteins stimulate ret GC at low Ca^{2+} concentrations found in mammalian photoreceptors (<100 nM) but inhibit ret GC activity at higher Ca^{2+} levels to below basal activity of the cyclase [84–87]. The actual Ca^{2+} sensitivity of the GCAP inhibition is determined by the ambient Mg^{2+} concentration [88]. The interaction of GCAPs with ret GC has been extensively characterised biochemically [89,90] and the structure of GCAP-2 has been solved by NMR [23]. These NCS proteins do not use a Ca^{2+}/myristoyl switch mechanism although myristoylation of GCAP-1 increased its sensitivity to Ca^{2+} in the inhibition of ret GC [91, 92]. The requirement for three different GCAPs is unclear but they are not all expressed in the same photoreceptor cells or with the same subcellular localisation [93]. GCAP-1 and GCAP-2 are expressed in rod and cone photoreceptors but GCAP-3 is expressed only in cone outer segments. Differences between GCAP-1 and GCAP-2 have been reported with GCAP-1 stimulating ret GC-1 and GCAP-2 stimulating both retinal guanylyl cyclase 1 and 2. Nevertheless, expression of only GCAP-1 in mice with both GCAP-1 and 2 knocked out is sufficient to recover normal function in both rods and cones [94,95].

8. Class E proteins: KChIPs

There are four KChIP proteins and additional splice variants [96–98] which are expressed in CNS neurons and in the case of KChIP2 also in cardiac myocytes [99]. The term KChIP is derived from their discovery as K^+ channel interacting proteins based on interaction with and regulation of A-type (Kv4) K^+ channels. A KChIP-related protein with about 40% identity to all of the mammalian KChIPs is present in the *Drosophila* genome and KChIPs are also present in fish. This class of NCS proteins illustrates the potential that the NCS proteins have to mediate distinct and diverse aspects of neuronal regulation. KChIP3, before its discovery as a K^+ channel regulator [96], had already been independently discovered as DREAM [100], a Ca^{2+}-dependent repressor of transcription which has a direct interaction with a specific DNA motif to control transcription. In addition, it was earlier known as calsenilin [101] due to its interaction with the two presenilins that are mutated in certain forms of familial Alzheimer's disease. Calsenilin was found to modify the processing of the presenilins [101] and later was implicated as a regulator of amyloid precursor processing [102]. KChIP3 is expressed by many different types of neurons [103, 104] and the multiple roles of KChIP3/DREAM/Calsenilin in K^+ channel regulation, transcriptional repression and amyloid processing have been confirmed by analysis of two strains of knock-out mice [102,105]. The functional importance of KChIP2 in cardiac myocytes has also been demonstrated in vivo in null mice [99].

KChIPs 1–4 and their various splice isoforms have all been found to interact directly with K^+ channels of the Kv4 family. These K^+ channels play crucial roles in cardiac myocytes and neurons in regulating excitability. The KChIPs appear to be constitutive subunits of Kv4 channels and they modify the gating properties of expressed Kv4 channels to convert them to the native neuronal form of the channel [96,106]. In addition, they are also required when expressed in heterologous cell types for efficient traffic of the channels to the cell surface, and can stimulate surface expression when co-expressed with the Kv4 subunit by up to 40-fold [96]. The KChIPs are membrane targeted through distinct mechanisms including N-terminal myristoylation [52] and palmitoylation [107]. The myristoylated KChIP1 appears to be localised to post ER transport vesicles so that it interacts with and enhances the traffic of Kv4 channels from the Golgi complex to the plasma membrane [52]. The mechanisms involved are not known in detail but seem to involve the masking of an intracellular retention signal in the N-terminus of the channel by binding of KChIP to this domain [108]. Mutation of an R-X-R putative ER retention signal in the N-terminus of Kv4.2 did not affect intracellular retention [109] suggesting that there must be a novel motif that unusually may operate at the Golgi rather than the ER [52]. Recent structural analysis has illuminated the interaction of this N-terminal domain with KChIP1 [25,26] showing that this involves a hydrophobic pocket on KChIP1 that is exposed in the Ca^{2+}-bound form (Fig. 3) and the formation of a dimeric assembly between the channel and KChIP1. This has not, however, provided any clues as to why a Ca^{2+}-binding protein is required to mask the retention signal. Mutation of the EF hands of KChIP1 did not affect its interaction with Kv4 but did prevent its stimulatory effects on channel expression at the plasma membrane and its effects on channel gating [96]. Chelation of Ca^{2+} was found to disrupt the dimeric assembly between KChIP1 and the Kv4.2 N-terminus giving a possible structural basis for this Ca^{2+} requirement [26].

KChIP3 as DREAM [100,110] has a confirmed role in inhibiting transcription and binds directly to specific DNA motifs [111,112]. DREAM has been shown to have roles in the control of prodynorphin expression [100,105], in the silencing of the apoptotic hrk gene in hematopoietic progenitor cells [113] and in the circadian regulation of gene expression in the pineal gland [114]. It has also been shown to act in the regulation of expression of thyroblobulin in the thyroid gland but through interaction with the

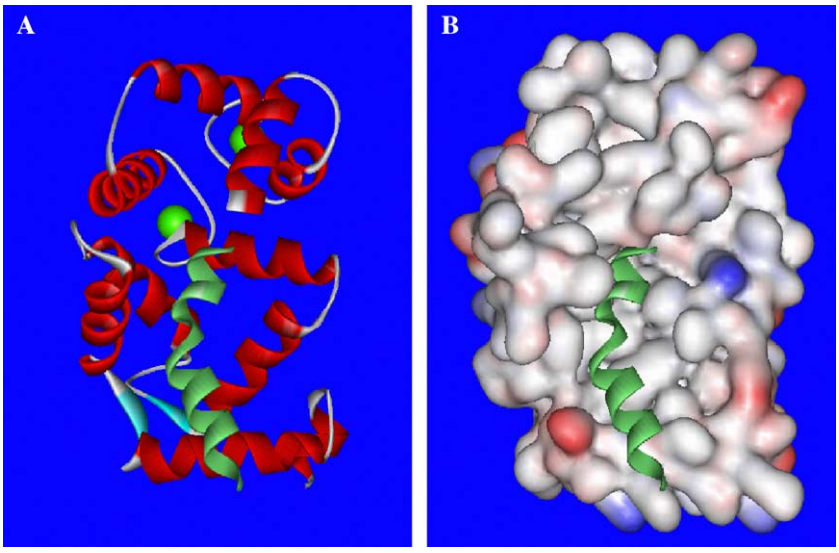

Fig. 3. Structure of Ca^{2+}-bound KChIP1 in a complex with the N-terminal domain of the potassium channel Kv4.2. The two images are shown in ribbon format (A) and with surface rendering (B) of mKChIP1 with Kv4.2(1–30) shown as a green ribbon. Zhou et al. [26] solved the crystal structure of a fusion protein consisting of the N-terminal 30 residues of Kv4.2 linked to the C-terminus of KChIP1 (PDB 1S6C). In the crystal structure the KChIP1 formed dimers with each of the two N-terminal KV4.2 domains buried in exposed hydrophobic cavities of the KChIPs. For clarity the figure shows only the interaction of a single copy of KChIP1 and Kv4.2(1–30). In the surface rendering, charged residues are shown in red and blue and polar residues in white.

transcription factor TTF-1 [115]. In its guise as calsenilin, it has been implicated in neuropathology not only through its effects on processing of amyloid precursor protein but also as a stimulator or initiator of apoptosis when expressed heterologously in non-neuronal cell types [116,117]. Interestingly, the KChIPs overlap not only in their functions as Kv4 K^+ channel regulators but also as repressors of gene transcription through binding to the DRE sequence [114]. The existence of three completely distinct functions of KChIP3 raises the possibility that it may have yet more functional roles and that other KChIPs also have functions distinct from the regulation of Kv4 K^+ channels or gene transcription.

9. Why do multiple NCS proteins exist?

Some early studies suggested that NCS proteins had overlap with calmodulin in their target proteins. It is now clear, however, that the NCS proteins have specific targets that are not regulated by calmodulin and therefore have distinct physiological functions. It seems that certain NCS proteins such as recoverin and GCAPs have evolved as specialised Ca^{2+}-binding proteins that carry out very specific functions in the retina. It is not clear, however, why three different GCAPs are required. In the case of the neuronally expressed NCS proteins, differing neurons express a particular cocktail of these proteins. Their requirement, in addition to calmodulin, may be due to the need for more specific Ca^{2+} sensors that are involved in a more limited range of intracellular events. In addition, they have a higher (around 10 fold) affinity for Ca^{2+} than calmodulin with a high cooperativity of binding, allowing them to sense Ca^{2+} elevations not far above basal levels. The NCS proteins most likely have distinct target or effector proteins although the extent of overlap between them has not been examined in more than a few cases. The diversity of these proteins may also be related to their differential use of N-terminal myristoylation so that some NCS proteins are already membrane targeted awaiting a $[Ca^{2+}]_i$ rise at basal Ca^{2+} levels and others require a more prolonged $[Ca^{2+}]_i$ elevation to allow translocation from cytosol to membranes. As seen for GCAPs, it is also possible that certain functions are exerted at low Ca^{2+} concentrations through Ca^{2+}-independent protein–protein interactions. Overall the variable properties of the NCS proteins would increase the diversity of possible neuronal responses to different Ca^{2+} signals.

Acknowledgment

Work in the author's laboratory is supported by grants by the Wellcome Trust.

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