Calcium sensors in neuronal function and dysfunction

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Abstract

Calcium signalling in neurons as in other cell types can lead to varied changes in cellular function. Neuronal Ca^{2+} signalling processes have also become adapted to modulate the function of specific pathways over a wide variety of time domains and these can have effects on, for example, axon outgrowth, neuronal survival and changes in synaptic strength. Ca^{2+} also plays a key role in synapses as the trigger for fast neurotransmitter release. Given its physiological importance, abnormalities in neuronal Ca^{2+} signalling potentially underlie many different neurological and neurodegenerative diseases. The mechanisms by which changes in intracellular Ca^{2+} concentration in neurons can bring about diverse responses is underpinned by the roles of ubiquitous or specialised neuronal Ca^{2+} sensors. It has been established that synaptotagmins have key functions in neurotransmitter release, and in addition to calmodulin, other families of EF-hand-containing neuronal Ca^{2+} sensors including the NCS and the CaBP protein families play important physiological roles in neuronal Ca^{2+} signalling. It has become increasingly apparent that these various Ca^{2+} sensors may also be crucial for aspects of neuronal dysfunction and disease either indirectly or directly as a direct consequence of genetic variation or mutations. An understanding of the molecular basis for the regulation of the targets of the Ca^{2+} sensors and the physiological roles of each protein in identified neurons may contribute to future approaches to the development of treatments for a variety of human neuronal disorders.

Introduction

Calcium signalling in many cell types can mediate a diverse range of changes in cellular function affecting gene expression, cell growth, development, survival and cell death. In addition, neuronal calcium signalling processes have become adapted to modulate the function of other important pathways in the brain, including neuronal survival, axon outgrowth (Spitzer 2006), and changes in synaptic strength (Catterall and Few 2008; Catterall et al. 2013). Changes in the concentration of intracellular free Ca^{2+} ($[Ca^{2+}]i$) are essential for the transmission of information through the nervous system as the trigger for neurotransmitter release at synapses. In addition, alterations in $[Ca^{2+}]i$ can lead to a wide variety of different physiological changes that can modify neuronal functions over a range of time domains of milliseconds through 10s of minutes to days or longer (Berridge 1998). It has long been believed that the physiological outcome from a change in $[Ca^{2+}]i$ depends on its location, amplitude, and duration. The importance of location becomes even more pronounced in neurons due to their complex morphologies. Pathological changes in Ca^{2+} signalling pathways have been suggested to underlie various neuropathological disorders (Braunewell 2005; Berridge 2010; Brini et al. 2014; Brini et al. 2017; Berridge 2018) including neurological abnormalities and neurodegenerative disorders (Popugaeva and Bezprozvanny 2013; Egorova and Bezprozvanny 2017; Pchitskaya et al. 2018; Secondo et al. 2018; Wegierski and Kuznicki 2018). Such changes have implicated Ca^{2+} entry pathways and release of Ca^{2+} from intracellular stores (Popugaeva and Bezprozvanny 2013; Egorova and Bezprozvanny 2017; Secondo et al. 2018; Wegierski and Kuznicki 2018) (Schampel and Kuerten 2017).

The nature, magnitude and location of the Ca^{2+} signal is crucial for the particular effect of neuronal physiology (Burgoyne 2007). Highly localised Ca^{2+} elevations due to Ca^{2+} entry though voltage-gated Ca^{2+} channels (VGCCs) lead to synaptic vesicle fusion with the presynaptic membrane for neurotransmitter release within less than a

millisecond (Burgoyne and Morgan 1998; Barclay et al. 2005). Differently localised and timed Ca^{2+} signals can result in changes to the properties of the VGCCs themselves (Catterall and Few 2008), to alterations in synaptic plasticity (Catterall et al. 2013) or lead to changes in gene expression (Bito et al. 1997). Postsynaptic Ca^{2+} signals arising from activation of NMDA receptors give rise to two important processes in synaptic plasticity, long term potentiation (LTP) and long-term depression (LTD). Interestingly, the Ca^{2+} signals that bring about either LTP or LTD differ only in their amplitude and duration (Yang et al. 1999).

Specific neuronal Ca^{2+} signals are likely to be decoded by various Ca^{2+} sensor proteins (McCue et al. 2010b). These are proteins that undergo a conformational change on Ca^{2+} binding allowing them to interact with and regulate various target proteins (Ikuro and Ames 2006; Burgoyne and Haynes 2015). Amongst the Ca^{2+} sensors that are important for neuronal function are the synaptotagmins that control neurotransmitter release (Fernandez-Chacon et al. 2001; Sudhof 2013), the ubiquitous EF-hand containing sensor calmodulin (Faas et al. 2011) that has many neuronal roles, and the more specific neuronal EF-hand containing proteins including the neuronal calcium sensor (NCS) proteins (Burgoyne and Weiss 2001; Burgoyne 2007; Burgoyne and Haynes 2012; Burgoyne and Haynes 2015) and the calcium-binding protein (CaBP)/calneuron families (Haeseleer et al. 2002; Mikhaylova et al. 2006; McCue et al. 2010a; Mikhaylova et al. 2011; Haynes et al. 2012). Potential involvement of members of these protein families in neuronal disorders studied in both experimental models and in human subjects has become apparent in recent years. In this review we assess the information available on the physiological roles of these various Ca^{2+} sensors and their modes of action, and also how they may contribute to neuronal dysfunction or be involved in disease-related processes in the nervous system.

SYNAPTOTAGMINS

The physiology and function of synaptotagmins

The synaptotagmins are transmembrane proteins predominantly associated with synaptic and secretory vesicles. There are multiple known isoforms of synaptotagmins (Craxton 2004) of which synaptotagmin I has been most widely studied. The role of synaptotagmins in neurotransmitter release has been the subject of intense investigations which have been extensively reviewed (Chapman 2008; Rizo and Rosenmund 2008; Sudhof and Rothman 2009). Synaptotagmins bind Ca^{2+} with relatively low affinity (K_d > 10 μM) through their two C2 domains (C2A and C2B) (Shao et al. 1998; Fernandez et al. 2001) which are functional in many but not all synaptotagmin isoforms. Ca^{2+} binding by C2 domains requires coordination of Ca^{2+} by both the protein and membrane lipids, and this lipid interaction is a key aspect for its function. In synaptotagmin 1 the C2A and C2B domains (Fig. 1) bind 3 and 2 Ca^{2+} ions respectively (Shao et al. 1998; Fernandez et al. 2001). It is now well established that synaptotagmin 1 is the key sensor for evoked, synchronous neurotransmitter release in many classes of neurons (Fernandez-Chacon et al. 2001). More recently, a key role for synaptotagmin 7 in neurotransmission has also been identified (Turecek and Regehr 2018) and synaptotagmin 2 has been shown to be a Ca^{2+} sensor in central inhibitory neurons (Chen et al. 2017). Structure-function studies of synaptotagmin 1 based on expression of specific mutants have been carried out in mice, worms and flies. For example, disruption of Ca^{2+} binding to the C2B domain of synaptotagmin 1 has been shown to have a more deleterious effect than disruption of Ca^{2+} binding to its C2A domain (Mackler et al. 2002; Robinson et al. 2002). The details of exactly how it

triggers exocytosis and the function of other synaptotagmin isoforms remain to be fully resolved. Membrane fusion requires the pairing and interaction of so-called SNARE proteins on vesicle and target membranes (Sollner et al. 1993). These can assemble into a SNARE complex that may form the minimal fusion machinery. For synaptic vesicle and neuroendocrine exocytosis, the SNARE proteins are SNAP-25, syntaxin 1 and synaptobrevin. In the case of neurotransmitter release, vesicle fusion is tightly regulated and requires a Ca^{2+} signal for activation. Ca^{2+} entry through VGCCs leading to Ca^{2+} elevation in local microdomains close to the mouth of the Ca^{2+} channels is able to trigger rapid (less than 1 ms) fusion of synaptic vesicles. Synaptotagmin can bind to both syntaxin and SNAP-25, and fast neurotransmitter release requires synaptotagmin (Geppert et al. 1994) probably pre-bound to assembled or partially assembled SNARE complexes (Schiavo et al. 1997; Rickman et al. 2006) so that Ca^{2+}-induced interaction with phospholipids can occur rapidly (Xue et al. 2008). It is still under debate how important synaptotagmin is in vesicle docking (de Wit et al. 2009; Chang et al. 2018) and how it acts at the plasma membrane in fusion itself (Tang et al. 2006; Hui et al. 2009) (Fig. 2). Synaptotagmin could act as a brake on fusion that is relieved by Ca^{2+} binding or have a positive role in membrane fusion (Chicka et al. 2008). A recent focus has been on the combined role of synaptotagmin and another SNARE-interacting protein, complexin, in timing synaptic vesicle fusion (Sudhof and Rothman 2009). The structure of a complex of synaptotagmin 1, complexin and the SNAREs has been characterised (Zhou et al. 2017). It was suggested that this tripartite complex could be a primed structure at the site of vesicle docking that would then need to be disrupted to allow fusion to occur. It has also been suggested that oligomerization of synaptotagmin is essential to control spontaneous fusion (Bello et al. 2018) but much still remains to be learnt about the molecular basis of its function (Kweon et al. 2018) (Bello et al. 2018)

Synaptotagmins and disease

Association of certain synaptotagmin isoforms with disease has been made. For example, synaptotagmin 7 has been implicated as a regulator of cancer cell proliferation (Wang et al. 2018b). In addition, synaptotagmin 11 has been identified as a Parkinson's disease risk gene and suggested to be involve in parkin-linked neurotoxicity in dopaminergic neurons (Wang et al. 2018a).

More significantly for central nervous system function and disease has been the discovery of *de novo* mutations in synaptotagmin 1 in patients associated with mental abnormalities. Synaptotagmin 1 has been shown to be essential for survival in model organisms but mutations that subtly change its function are not lethal (Chapman 2008). A rare variant in the gene *SYT1* was identified in a subject with movement and cognitive disorders (Baker et al. 2015). Expression of a rat SYT1 with this mutation in hippocampal neurons in culture was found to impair exocytosis and endocytosis suggesting that it is indeed responsible for the mental abnormalities. A second missense mutation in *SYT1* was later discovered (Cafiero et al. 2015). More recently, a series of further *de novo* mutations in SYT1 has been found in 9 more patients with various neurodevelopmental and movement abnormalities (Baker et al. 2018). Five of the mutations were found in the C2B domain clustered around the Ca^{2+} binding pocket. The effect of these mutations was functionally characterised by expression of the mutated proteins in rat hippocampal cultures. While all the proteins were correctly targeted to synapses, one of these mutations impaired expression and the other four mutations resulted in differing defects in the rates of exocytosis and endocytosis that could in part be correlated with the disease phenotypes of the patients. These results support the idea that the *SYT1* mutations were responsible for synaptic defects that resulted in the observed pathophysiology (Baker et al. 2018).

Interestingly, similar mutations to those found in the C2B domain of *SYT1* had been identified in the C2B domain of *SYT2* associated with Lambert-Eaton syndrome (Herrmann et al. 2014) that is due to a defect at peripheral motor neurons. Electrophysiological analysis in patients indicated that the mutations resulted in a

presynaptic defect (Whittaker et al. 2015). Further support for the significance of these mutations in *SYT2* has come from functional studies in *Drosophila* (Shields et al. 2017). A potential linkage of SYT2 to defects of central nervous function comes from the observation that SYT2 protein levels were reduced in brains of patients who had dementias (Bereczki et al. 2018).

CALMODULIN

The physiology and functions of calmodulin

Calmodulin s a ubiquitously expressed 16.7 kDa Ca^{2+}-binding protein playing a major role in regulating a wide variety of cellular events including motility, exocytosis, cytoskeletal assembly, muscle contraction and modulation of intracellular Ca^{2+} concentrations. This protein has been highly conserved throughout evolution, is found in all eukaryotes and is 100% identical across all vertebrates at the amino acid level. Calmodulin can bind four Ca^{2+} ions through its four EF-hand structural motifs (Chattopadhyaya et al. 1992). The N-terminal lobe of calmodulin is formed by the first two EF-hands, whereas the C-terminal lobe is formed by the third and fourth EF-hands. The C-terminal pair of EF-hands has a higher affinity for Ca^{2+} and slower binding kinetics than the N-terminal pair, which allows the two domains to behave independently at varying Ca^{2+} concentrations (Tadross et al. 2008). The highly flexible linker between the two domains can alter confirmation dramatically upon binding to target proteins (Fig. 3) and is an essential property of calmodulin, which permits this protein to interact with a large and diverse array of partners. It has been recently demonstrated that calmodulin's bilobal architecture is essential for VGCC regulation (Banerjee et al. 2018). The significant conformational changes on binding to its targets (Fallon et al. 2005) can increase its affinity for Ca^{2+}.

Calmodulin is present in brain at high concentrations (up to ~100 μM). In addition to its more general functions, calmodulin also has series of specific roles in transducing Ca^{2+} signals in neurons including the regulation of glutamate receptors (O'Connor 1999), ion channels (Saimi and Kung 2002), proteins in signalling pathways such as

neuronal nitric oxide synthase, and it can affect synaptic plasticity (Lisman et al. 2002; Xia and Storm 2005).

One key direct function of calmodulin is in regulating the activity of VGCCs by interacting with channel subunits (Catterall and Few 2008). As an example, Ca^{2+}-free (apo) calmodulin can bind to the IQ domain of the α_1 pore-forming subunit of the L-type Ca^{2+} channel $Ca_V1.2$ (Erickson et al. 2001; Pitt et al. 2001; Erickson et al. 2003) (Fig.4). Pre-bound apocalmodulin can then respond rapidly to Ca^{2+} elevation in local nanodomains and modulate the activity of the channel. Ca^{2+} binding to VGCC-associated calmodulin can have a range of effects on channel function including mediating Ca^{2+}-dependent facilitation (CDF) or Ca^{2+}-dependent inactivation (CDI) (Peterson 1999; Zuhlke et al. 1999; Lee et al. 2000; DeMaria et al. 2001; Catterall and Few 2008; Liu et al. 2010). For $Ca_V1.2$ channels, CDI is mediated by the C-terminal lobe of calmodulin (Peterson 1999). Whereas, for $Ca_V2.1$ (DeMaria et al. 2001; Lee et al. 2003), $Ca_V2.2$ (Liang et al. 2003) and $Ca_V2.3$ (Liang et al. 2003), CDI is controlled by the N-terminal lobe. Interestingly, for P/Q-type $Ca_V2.1$ channels, calmodulin is required for both CDI and CDF, with the N-terminal lobe of calmodulin involved in CDI and the C- terminal lobe underlying CDF (DeMaria et al. 2001; Lee et al. 2003). It is important to note that Ca^{2+}-dependent regulation of VGCCs is complex and involves several Ca^{2+} sensor proteins as modulators. As an example, CaBP1 can elicit CDI, but also reduces CDF by displacing calmodulin from the IQ domain in $Ca_V2.1$ channels (Lee et al. 2002; Findeisen and Minor 2010; Christel and Lee 2012; Findeisen et al. 2013; Oz et al. 2013). In addition to calmodulin and CaBP1, it has been shown that VILIP-2 inhibits calmodulin-mediated CDI and enhances CDF (Lautermilch et al. 2005; Nanou et al. 2012) through interaction with both the IQ and the calmodulin-binding domains (CBD). Calmodulin is also constitutively associated with, and regulates opening of, Ca^{2+}-activated potassium channels (Xia 1998; Schumacher et al. 2001), and other types of potassium channels (Wen and Levitan 2002). SK and IK Ca^{2+}-activated potassium channels lack Ca^{2+}-binding sites but their intracellular C-terminal region contains calmodulin-binding domains where

calmodulin binds tightly and confers Ca^{2+}-sensitivity to the channel. Two other major modes of action of calmodulin are exerted through Ca^{2+}/calmodulin-dependent kinases (CaMKs) and calcineurin. CaMKs contribute to several regulatory pathways involving, for example, phosphorylation of AMPA receptors (Barria et al. 1997) and the nuclear transcription factor CREB (Deisseroth et al. 1998). Calmodulin also positively regulates presynaptic neurotransmitter vesicle release probability, which is mediated via activation of CaMKII (Pang et al. 2010). The Ca^{2+}-activated phosphatase calcineurin can dephosphorylate a wide range of neuronal proteins leading to changes in gene transcription following activation of the transcription factor NFAT and its translocation into the nucleus. Calcineurin has also been implicated in synaptic plasticity (Malleret et al. 2001; Xia and Storm 2005).

Calmodulin and disease

The human genome contains three calmodulin genes (*CALM1*, *CALM2*, and *CALM3*) that encode for proteins with identical amino acid sequences. Despite the redundancy of calmodulin, single missense mutations, that change the way calmodulin functions, in any one of the six alleles are associated with disease phenotypes such as cardiac arrhythmia syndromes (Limpitikul et al. 2014; Makita et al. 2014; Yin et al. 2014; Boczek et al. 2016; Jimenez-Jaimez et al. 2016; Pipilas et al. 2016). In the brain, calmodulin dysfunction has also been suggested to be potentially linked to pathological conditions including epilepsy, memory loss and intellectual disability. CaMKIIγ , a serine/threonine-specific protein kinase involved in long-term plasticity, learning and memory, is a major target for calmodulin. A point mutation in γCaMKII (R292P) has been shown to interfere with calmodulin shuttling to the nucleus and therefore disrupted spatial learning, memory and caused intellectual disability (de Ligt et al. 2012; Cohen et al. 2018). In another study, it has been shown that mutations in Kv7 potassium channels can decrease calmodulin binding, and thereby disrupt channel trafficking to the plasma membrane. As a result, neuronal excitability and firing frequency can be affected, leading to pathological conditions from mild

epilepsy to early onset encephalopathy (Alaimo et al. 2018). Similarly, mutations in $Na_v1.2$ sodium channels can reduce calmodulin binding and lead to epilepsy (Yan et al. 2017). In addition, it has been experimentally verified that calmodulin is involved in the formation of amyloid-β plaques in Alzheimer's disease (O'Day et al. 2015). Altogether, these observations demonstrate the crucial role of calmodulin in regulating major signalling processes in neurons and show that mutations interfering with calmodulin binding or function can lead to serious neuropathological conditions.

NCS PROTEIN FAMILY

While many aspects of neuronal function are known to be regulated by calmodulin, proteins related to calmodulin have been discovered in recent years, which are exclusively expressed or enriched in neurons. Duplication and diversification of the calmodulin gene family may have given rise to these neuronal calcium sensing proteins, which are not all expressed in lower organisms, so that they can carry out neuronal functions specifically in higher organisms.

ThepPhysiology and function of NCS proteins

Whereas calmodulin is ubiquitously expressed, the expression of other calcium sensing proteins can be restricted to particular tissues and cell types. A good example of this is the neuronal calcium sensor (NCS) family of proteins, which are primarily expressed in neurons or retinal photoreceptors (Burgoyne 2007; Burgoyne and Haynes 2010). The NCS family of proteins are related in their protein sequence to calmodulin but have distinct properties, which allow them to carry out non-redundant roles that do not overlap with the functions of calmodulin (Fitzgerald et al. 2008). Members of the NCS protein family have been implicated, for example, in the regulation of neurotransmitter release, regulation of cell-surface receptors and ion channels, control of gene transcription (Carrion et al. 1999; Mellstrom and Naranjo 2001), cell growth and survival (Burgoyne 2007; Burgoyne and Haynes 2012), and specific retinal photoreceptor functions (Lim et al. 2014).

The NCS proteins are encoded by 14 genes in mammals, and with greater diversity from alternative splicing of transcripts from a number of the genes. All NCS gene products harbour four EF-hand motifs and display limited similarity (< 20%) to calmodulin (Burgoyne 2004; Weiss et al. 2010). NCS-1 is the most widely expressed of the NCS proteins in and outside of the nervous system. The protein was first discovered as frequenin in *Drosophila melanogaster* (Pongs et al. 1993) where there are two very closely related genes known as frq1 and frq2 (Sanchez-Gracia et al. 2010). Although initially thought to be neuronal specific (Nef et al. 1995), an NCS-1 orthologue with 59% sequence identity and closely related structure has been identified in *Saccharomyces cerevisiae* (Hendricks et al. 1999), the lowest organism with an NCS-like sequence. After this first evolutionary appearance of NCS-1 there has been a steady increase in the diversity of the family throughout evolution, which roughly correlates with increasing organism complexity. Five classes of NCS proteins have now been identified in higher organisms (Braunewell and Gundelfinger 1999; Burgoyne 2007). Class A contains NCS-1, which is present in yeast and all higher organisms. Class B consists of the visinin-like proteins (VILIPs), which appear first in *Caenorhabditis elegans*. Classes C and D evolved with the appearance of fish, and comprise recoverin and the guanylyl-cyclase-activating proteins (GCAPs) respectively. Finally, class E contains the K^+ channel-interacting proteins (KChIPs), which are found in insects and evolutionary subsequent species (Burgoyne 2004). Mammals have a single NCS-1, five VILIPs proteins (hippocalcin, neurocalcin δ, and VILIPs1-3), a single recoverin, three GCAPs and four KChIPs. Expression of the recoverins and GCAPs is restricted to the retina. Whereas, the rest of the NCS family are found in varied neuronal populations (Burgoyne 2007). It has been established that certain neurons express several, or all, of the NCS proteins, but in general the expression profile for each of the NCS proteins is unique (Paterlini et al. 2000; Rhodes et al. 2004). This suggests that despite the high sequence homology between the proteins (around 35-90% identity between each of the human family members for

example (Burgoyne and Weiss 2001)), each is likely to perform distinct functions in specific cell types (Burgoyne 2007).

Unlike calmodulin, not all EF-hands are functional in the NCS proteins, and the most N-terminal EF-hand is unable to bind Ca^{2+} in any of the family members. In the case of recoverin and KChIP1, only two of its four EF-hand motifs are functional in Ca^{2+} binding (Burgoyne et al. 2004; Burgoyne 2007). Unlike the dumbbell structure of calmodulin, the NCS proteins are compact and globular when in their Ca^{2+}-bound states, and they undergo limited conformational change following binding to their target proteins (Ames et al. 2006; Pioletti et al. 2006; Strahl et al. 2007; Wang et al. 2007) (Fig. 3). NCS proteins also differ from calmodulin in that many have motifs that allow membrane association (McFerran et al. 1999; O'Callaghan and Burgoyne 2003; O'Callaghan and Burgoyne 2004; Haynes and Burgoyne 2008). KChIP1 and all the members of classes A-D are N-myristoylated. Whereas, certain KChIP2, KChIP3 and KChIP4 isoforms possess palmitoylation motifs. In some cases the membrane association conferred by these moieties is dynamically regulated by Ca^{2+} binding when a sequestered myristoyl chain becomes exposed following a Ca^{2+}-driven shift in conformation. This is known as the reversible Ca^{2+}/myristoyl switch as originally described for recoverin (Ames et al. 1997). The VILIPs/neurocalcin/hippocalcin are also cytosolic at resting $[Ca^{2+}]_i$ but localise to the plasma membrane or Golgi complex upon Ca^{2+} elevation (O'Callaghan et al. 2002; Spilker et al. 2002; O'Callaghan et al. 2003b). In contrast, NCS-1 does not show the Ca^{2+}/myristoyl switch. Each of the NCS proteins displays distinct sub-cellular localisations, which are in part determined by additional interactions with specific phosphoinositides mediated by basic N-terminal residues immediately proximal to the site of acylation (O'Callaghan et al. 2003a; O'Callaghan et al. 2005).

NCS-1 is a multifunctional regulator of various processes, and it has been intensively studied (Burgoyne 2004; Burgoyne and Haynes 2012). MammalianNCS-1 is highly

evolutionarily conserved, retaining 59% identity with its yeast orthologue. It displays a high Ca^{2+}-binding affinity (Kd for Ca^{2+} around 200-300nM) and is able to respond to any fluctuations in $[Ca^{2+}]_I$ above resting levels. NCS-1 is N-terminally myristoylated and is constitutively associated with membranes including plasma and Golgi membranes (O'Callaghan et al. 2002), although it is able to rapidly exchange between membrane and cytosolic pools (Handley et al. 2010). In contrast to all other NCS family members, NCS-1 is not neuron specific and is expressed in neuroendocrine cells (McFerran et al. 1998), and at low levels in several non-neuronal cell types (Gierke et al. 2004). NCS-1 has three functional EF-hand motifs, which have differing cation specificities for Ca^{2+} versus Mg^{2+}. In the presence of elevated $[Ca^{2+}]_i$ EF2 and EF3 become Ca^{2+}-occupied simultaneously followed by Ca^{2+} binding to EF4 (Aravind et al. 2008; Mikhaylova et al. 2009). Two variants of NCS-! (frq1 and frq2) are expressed in *Drosophila* (Sanchez-Gracia et al. 2010) and may have distinct roles.. A second human variant has been described but it is likely not to play any physiological role being expressed at only low levels (Wang et al. 2016).

Much current understanding concerning the function of NCS-1 derives from over-expression or knockout studies. Over-expression in *Drosophila* caused a frequency-dependent facilitation of neurotransmitter release (Pongs et al. 1993), and its importance for neurotransmissions has been confirmed by knockout of the two *Drosophila* frequenin genes (Dason et al. 2009). In *Xenopus,* over-expression caused enhanced spontaneous and evoked transmission at neuromuscular junctions (Olafsson et al. 1995). Consistent with a role of NCS-1 in neurotransmitter release, over-expression was found to increase Ca^{2+}-dependent exocytosis of dense core granules in PC12 cells (McFerran et al. 1998), and to enhance associative learning and memory in *C. elegans* (Gomez et al. 2001).

Knockout of NCS-1 (frequenin) in the yeast *S. cerevisiae* is lethal due to its requirement for the activation of Pik1, one of the two yeast phosphatidylinositol-4 kinases (PI4Ks) (Hendricks et al. 1999). NCS-1 can also interact with the equivalent

mammalian Golgi enzyme PI4KIIIβ and enhances its activity (Taverna et al. 2002; Haynes et al. 2005; de Barry et al. 2006). The interaction with Golgi-associated PI4KIIIβ suggests that it may regulate secretion through the modulation of phosphatidylinositol-dependent trafficking steps (Hendricks et al. 1999; Zhao et al. 2001; Haynes et al. 2005). In support of this, NCS-1 has also been demonstrated to associate with another PI4KIIIβ regulator ARF1, a small GTPase critical to multiple trafficking steps in mammalian cells (Haynes et al. 2005; Haynes et al. 2007). The physiological significance of this interaction has been confirmed using genetic approaches in *C. elegans*. In this organism, knock out of NCS-1 impairs learning (Gomez et al. 2001) and affects temperature-dependent locomotion behaviour (Martin et al. 2013). The role of NCS-1 in the control of temperature-dependent locomotion was shown to require interaction with ARF1.1 and also potentially pifk1 the *C. elegans* orthologue of PI4KIIIβ (Todd et al. 2016).

Knock-out of NCS-1 in organisms other than *S. cerevisiae* is not lethal but does generate specific developmental phenotypes. In *Dictyostelium discoideum*, loss of NCS-1 function alters developmental rate (Coukell et al. 2004), and in *C. elegans* results in impaired learning and memory (Gomez et al. 2001). Knockdown of one of the two NCS-1 genes in zebrafish, *ncs-1*, prevents formation of the semi-circular canals of the inner ear (Blasiole et al. 2005). The signalling pathway involving NCS-1, ARF1 and PI4KIIIβ (Haynes et al. 2005) modulates the secretion of components important for the development of the vestibular apparatus of the inner ear (Petko et al. 2009). Knock-down of NCS-1, or expression of a dominant negative inhibitor based on an EF-hand mutation (Weiss et al. 2000), disrupted the induction of long-term depression in rat cortical neurons (Jo et al. 2008). Over-expression of NCS-1 in adult mouse dentate gyrus enhanced learning (Saab et al. 2009). Knock out of NCS-1 in mice was not lethal but caused behavioural changes and learning deficits (de Rezende et al. 2014; Nakamura et al. 2017).

Many different specific binding partners (Fig. 5) have been identified for NCS-1, which interact with either the Ca^{2+}-loaded or Ca^{2+}-free (apo) forms of NCS-1 (Haynes et al. 2006; Haynes et al. 2007). NCS-1 has a higher affinity for Ca^{2+} than calmodulin, and therefore may preferentially interact with certain Ca^{2+}-dependent binding partners when the amplitude of a Ca^{2+}-signal falls below the threshold for activation of calmodulin. For example, both calmodulin and NCS-1 have been shown to interact with, and desensitize, dopamine D2 receptors, but are likely to mediate their effects at different $[Ca^{2+}]_i$ (Kabbani et al. 2002) (Woods et al. 2008). Functional analyses have established that NCS-1 is a physiological regulator of D2 receptors (Saab et al. 2009; Dragicevic et al. 2014) (for clinical relevance of this regulation see below). Other NCS-1 target proteins appear to be specific for NCS-1 (Haynes et al. 2006).

Various studies have implicated NCS-1 in the regulation of VGCCs (Weiss et al. 2000; Weiss and Burgoyne 2001; Tsujimoto et al. 2002; Weiss and Burgoyne 2002; Dason et al. 2009). In *Drosophila*, the effects of Frq1 on both neurotransmission and nerve-terminal growth can be explained by a functional interaction with the VGCC *cacophony*, which is related the mammalian P/Q-type VGCCs, but despite the physiological evidence a direct interaction of the proteins was not demonstrated (Dason et al. 2009). In contrast, a direct interaction of mammalian NCS-1 with the Cav2.1 of VGCCs was subsequently shown to occur (Lian et al. 2014), and this may be of physiological significance for the Ca^{2+}-dependent regulation of these channels by NCS-1 underlying synaptic facilitation (Yan et al. 2014).

The structural basis of the interaction of NCS-1 with its target proteins has been well characterised. Key conserved residues within the hydrophobic groove that is exposed in the Ca^{2+}-bound state have been shown to interact with target peptides in structural studies (Huttner et al. 2003; Ames and Lim 2012; Burgoyne and Haynes 2015). Moreover, functional mutagenesis studies in worms have confirmed the importance of these hydrophobic residues (Martin et al. 2013). Direct analysis has been made of NCS-1interactions with two different target peptides based on structures solved in

parallel by X-ray crystallography (Pandalaneni et al. 2015) Comparison to complexes involving other NCS proteins has shown structural differences in how these interactions occur. Figure 6 illustrates the structure of Ca^{2+}-bound NCS-1 in complex with two peptides from the dopamine D2 receptor (Fig. 6A) or a single peptide from GRK1 (Fig. 6C) (Pandalaneni et al. 2015). In this figure NCS-1-target complexes are compared to earlier structures of *S. cerevisiae* frequenin in complex with two parts of a peptide from Pik1 (Strahl et al. 2007) (Fig.64B), of KCHIP1 with a fragment of Kv4.3 (Pioletti et al. 2006) (Fig. 6D) and of recoverin with one peptide from GRK1 (Ames et al. 2006) (Fig. 6F). The two examined interactions for mammalian NCS-1, as in the other reported structures, involve residues within the exposed hydrophobic groove, although these differ for each target peptide. There are also differences in interaction with a mobile C-terminal region of NCS-1, which can change its position in the complexes (Pandalaneni et al. 2015). The C-terminal tail of NCS-1 appears to be crucial for the nature and regulation of target protein interactions being able to potentially occlude the hydrophobic groove for certain substrates (Handley et al. 2010; Lian et al. 2011; Heidarsson et al. 2012). There are also differences in how two NCS proteins (NCS-1 and recoverin) interact with the same target peptide from GRK1 (Ames et al. 2006; Pandalaneni et al. 2015).

Much less is known about the VILIP/neurocalcin/hippocalcin proteins, although the VILIPs themselves appear to modulate various signal transduction pathways such as cyclic nucleotide and MAPK signalling (Braunewell and Klein-Szanto 2009). VILIP-1 has been found to regulate a class of purinergic receptors (Chaumont et al. 2008). They have been shown to have effects on gene expression and are also involved in trafficking of proteins to the plasma membrane (Lin et al. 2002; Brackmann et al. 2005). VILIP-3 (HPCAL1) was found to control the differentiation of neuroblastoma cells through its interaction with the transcriptional regulator PHOX2B (Wang et al. 2014).

Hippocalcin has been suggested to be involved as a Ca^{2+} sensor in long-term depression in (Palmer et al. 2005; Jo et al. 2010) . Consistent with this suggestion, it was observed that hippocalcin in cultured hippocampal neurons shows a rapid and reversible Ca^{2+}/myristoyl switch for translocation in response to acute stimuli (Markova et al. 2008; Dovgan et al. 2010). Hippocalcin has also been implicated in protection from neuronal apoptosis (Mercer et al. 2000; Korhonen et al. 2004), and in promoting neuronal differentiation (Park et al. 2017).

Recoverin is expressed exclusively in the retina and is believed to have a role in light adaptation and can enhance visual sensitivity (Polans et al. 1996; Sampath et al. 2005; Morshedian et al. 2018). Recoverin is found primarily in rod and cone cells of the retina (Yamagata et al. 1990; Dizhoor et al. 1991). Recoverin was predicted to prolong the lifetime of photolyzed rhodopsin by inhibiting its phosphorylation by rhodopsin kinase to extend the light response (Chen et al. 1995; Klenshin et al. 1995). The function of recoverin has been controversial and this hypothesis may be oversimplified. Discrepancies have been noted regarding the $[Ca^{2+}]_i$ required for rhodopsin kinase interaction which may lie outside normal physiological limits but analysis of recoverin knockout mice have shown changes in photoresponses consistent with a physiological role in inhibition of rhodopsin kinase (Makino et al. 2004).

The structure of recoverin has been extensively studied in its Ca^{2+}-bound and Ca^{2+}-free forms (Flaherty et al. 1993; Ames et al. 1995; Tanaka et al. 1995; Ames et al. 1997; Ames et al. 2002; Weiergraber et al. 2003). Recoverin is composed of two distinct domains connected through a linker and forms a compact structure in the absence of Ca^{2+}. Unlike other NCS proteins, recoverin has just two functional EF-hand motifs. Upon binding of Ca^{2+}, the N-terminal domain comprising EF1 and EF2 rotates through 45^{o} relative to the C-terminal domain driving extrusion of its buried myristoyl group. This permits recoverins to associate with membranes and reveals a hydrophobic surface, which can mediate interaction with the target protein rhodopsin kinase (Ames et al. 2006). The residues involved in the interaction of the myristoyl

group with the hydrophobic pocket are also conserved in the other members of the NCS family. However, not all of the other family members display the Ca^{2+}/myristoyl switch (O'Callaghan et al. 2002; Stephen et al. 2007). NCS-1 and KChIP1 expose a similar hydrophobic surface upon Ca^{2+}-binding which could be similarly important for target interactions (Bourne et al. 2001; Scannevin et al. 2004; Zhou et al. 2004b; Pioletti et al. 2006; Pandalaneni et al. 2015). In contrast, other NCS proteins are able to interact with certain binding proteins in their Ca^{2+}-free state therefore Ca^{2+}-driven exposure of a hydrophobic surface cannot be the sole mechanism by which these proteins bind to effectors.

GCAPs are activators of retinal guanylyl cyclases (GCs) (Palczewski et al. 2004) and are known to be physiological regulators of light adaptation (Mendez et al. 2001; Burns et al. 2002; Howes et al. 2002; Pennesi et al. 2003; Vinberg et al. 2018). They show the unusual property of activating GCs when in their Ca^{2+}-free form but become inhibitors of GCs at higher Ca^{2+} concentrations (Dizhoor and Hurley 1996). GCAP3 is expressed in cone cells whereas GCAP1 and GCAP2 are expressed in rod cells. While GCAP1 and GCAP2 having the same function in the same cell type the two proteins have different Ca^{2+} binding affinities for GC activation. This means that both proteins are required for GC activation over the full physiological Ca^{2+} concentration range maximising the dynamic range of GC activity (Koch 2006). The GCAPs are an example of how Ca^{2+} sensors have become adapted to increase dynamic Ca^{2+} sensitivity of regulatory mechanisms (Palczewski et al. 2004; Lim et al. 2014; Koch and Dell'Orco 2015).

Four KChIP genes and a large number of splice variants are expressed in mammals (Pruunsild and Timmusk 2005). KChIPs (K channel-interacting proteins) were so named as they were found to associate with transient voltage-gated potassium channels of the Kv4 family (An et al. 2000; Bahring 2018). The majority of the KChIPs can stimulate the trafficking of Kv4 channels to the plasma membrane (O'Callaghan et al. 2003a; Shibata et al. 2003; Hasdemir et al. 2005; Prechtel et al.

2018). Certain KChIP isoforms, in contrast, inhibit the trafficking of Kv4 channels (Jerng and Pfaffinger 2008). In addition, expression of KChIPs regulates the gating kinetics of Kv4 channels while acting as channel subunits (An et al. 2000; Bahring 2018) and can do so in response to Ca^{2+} (Groen and Bahring 2017; Bahring 2018). Knockout of KChIP1 has revealed a potential role in the GABAergic inhibitory system (Xiong et al. 2009). The KChIPs are expressed predominantly in the brain but KChIP2 is also expressed in the heart and knockout of KChIP2 causes a complete loss of calcium-dependent transient outward potassium currents and susceptibility to ventricular tachycardia (Kuo et al. 2001). KChIP3, is also known as DREAM or calsenilin, and has documented roles in transcriptional regulation (Carrion et al. 1999; Mellstrom and Naranjo 2001) and in the processing of presenilins and amyloid precursor protein which are important in the pathogenesis of Alzheimer's disease (Buxbaum et al. 1998a; Buxbaum et al. 1998b; Jo et al. 2004). While many of the KChIPs and their isoforms may have overlapping functions some differences between them have emerged (Holmqvist et al. 2002; Venn et al. 2008).

Despite KChIP3 being implicating in three quite distinct functions it is likely that they are all physiologically relevant. KChIP3 knockout mice show reduced responses in acute pain models due to changes in prodynorphin synthesis (Cheng et al. 2002), decreased β-amyloid production and physiological defects consistent with changes to the Kv4 channels (Lilliehook et al. 2003). DREAM/KChIP3/calsenilin has been found to interact with a wide range of target proteins (Rivas et al. 2011). Recently, functional effects for DREAM/KChIP3/calsenilin have been reported for the regulation of ryanodine receptors (Grillo et al. 2018) and via an interaction with RhoA on neurite growth (Kim et al. 2018).

The NCS protein family has evolved to carry out specialized neuronal functions separate to those of calmodulin. Of relevance is their approximately 10-fold higher affinity for Ca^{2+} when compared to calmodulin. The higher affinity allows the NCS proteins to be activated at lower Ca^{2+} concentrations and, in combination with

calmodulin, extends the dynamic range over which Ca^{2+} can regulate neuronal processes. In this way, the response of a cell to changes in $[Ca^{2+}]_i$ of different amplitude or kinetics would depend on which populations of Ca2+-binding proteins are activated under particular conditions. The individual expression patterns and sub-cellular localisation of each of the NCS proteins will also determine their specific roles in neuronal cell signalling. The characteristic N-terminal myristoylation or palmitoylation modifications which allow these proteins to associate with membranes may spatially partition them to distinct sub-cellular sites within the cell leading to a faster and more efficient response to particular Ca^{2+} signals. Specific physiological outcomes will also be determined by their distinct target proteins (Burgoyne and Haynes 2015). The various members of the NCS family arose at points in evolution corresponding to increasing neuronal sophistication in higher animals. As such, these proteins represent an example of how the properties of calcium binding proteins have been fine-tuned to act in specific neuronal signalling pathways.

NCS proteins and disease

In support of key roles for the NCS family in higher organisms, a number of studies have implicated these proteins in the pathological progression of human neurological diseases. Some evidence suggests indirect links such as with Alzheimer's disease, but evidence has emerged for more direct involvement based key physiological interactions and also on identification human genetic variants.

NCS-1 has been suggested to interact directly with and enhance the activity of inositol 1,4,5-trisphosphate receptors (IP_3Rs) (Schlecker et al. 2006; Nakamura et al. 2011) although this has not been seen in all studies (Haynes et al. 2004a). It has been suggested that the regulation of inositol 1,4,5-trisphosphate receptors IP_3Rs by NCS-1 and changes in Ca^{2+} signalling (Boehmerle et al. 2006) may underlie a potential role

of NCS-1 peripheral neuropathy (Mo et al. 2012) and also in tumour progression where it could be a therapeutic target (Moore et al. 2017; Boeckel and Ehrlich 2018).

Two other documented NCS-1 interactions are of possible significance for neuronal dysfunction. The importance of the regulation of dopamine D2 receptors by NCS-1, whereby NCS-1 inhibits receptor internalisation (Kabbani et al. 2002), comes from the fact that dopamine is of key importance for signalling within the CNS and in addictive behaviour (Koob 2006; Dagher and Robbins 2009). Regulation of D2 receptors by NCS-1underlies the effect of over-expression of NCS-1 on spatial memory acquisition (Saab et al. 2009). Dopamine D2 receptors are the targets for all known effective antipsychotic drugs (Seeman 1992), and NCS-1 is up-regulated in patients with bipolar disorder or schizophrenia (Koh et al. 2003) and in response to anti-psychotic drugs (Kabbani and Levenson 2006). NCS-1 is genetically associated with cocaine addiction (Multani et al. 2012), which is believed to be linked to effects of cocaine on dopamine transporters (Ritz et al. 1987). It has also been suggested that NCS-1 may be linked to the effects of lithium on bipolar disorders (D'Onofrio et al. 2015; D'Onofrio et al. 2017a; D'Onofrio et al. 2017b).

NCS-1 has been shown to be required for an adaptive response to dopaminergic agonists in substantia nigra neurons. Coupled with its up-regulation in the substantia nigra from Parkinson's disease patients, this suggested that it could be a target for modifying the vulnerability of neurons in the substantia nigra to neurodegeneration (Dragicevic et al. 2014; Poetschke et al. 2015; Duda et al. 2016). The binding of NCS-1 to the D2 receptor involves the short cytoplasmic C-terminal domain of the receptor (Kabbani et al. 2002). This interaction has been partially characterised using structural approaches (Lian et al. 2011; Pandalaneni et al. 2015) and this may allow exploration of the interaction as a therapeutic drug target (Kabbani et al. 2012).

Another clinically important interaction is with the interleukin 1 receptor accessory protein-like 1 protein (IL1RAPL1), which appears to be specific for NCS-1 (Bahi et al. 2003). Mutations in ILIRAPL1 have been shown to result in X-linked mental

retardation (Zhang et al. 2004; Tabolacci et al. 2006), and also have been linked to autistic spectrum disorder (ASD, (Piton et al. 2008)). Knock-out of IL1RAPL1 in mice leads to neurodevelopmental and learning abnormalities (Montani et al. 2017). Effects of Il1RAPL1 on exocytosis (Bahi et al. 2003), channel regulation and neurite growth (Gambino et al. 2007) appear to be mediated via NCS-1.

Interestingly, the study on Il1RAPL1 in ASD also identified a mutation (R120Q) within NCS-1 in an individual with ASD (Piton et al. 2008). This mutation was found to cause a functional deficit in NCS-1 (Handley et al. 2010) that appeared to be related to a change in the structural dynamics of the C-terminus of the protein (Handley et al. 2010) and overall structural flexibility (Zhu et al. 2014). However, the physiological relevance of this mutation and its exact relationship to the disease phenotype remains to be established.

A second almost identical homologue of frequenin expressed in *Drosophila* (Frq2) and human NCS-1 are able to interact with the guanine nucleotide exchange factor Ric8a and this interaction was shown to be physiologically relevant for development and neurotransmission in flies (Romero-Pozuelo et al. 2014). Characterisation of the structural basis for this interaction identified an interface that was used to examine potential therapeutic compounds that could prevent complex formation (Mansilla et al. 2017). As proof of principle, the authors showed that a potential therapeutic compound could alleviate the symptoms of fragile X syndrome in a fly model. These studies demonstrate the potential for such structural approaches to generate leads for new therapeutics that could be used in NCS-1-related pathologies (Roca et al. 2018).

The neurodegenerative disease known as Wolfram syndrome is caused by loss of function of the endoplasmic reticulum (ER) protein WF1. The molecular basis of the disorder appears to be due to a loss of coupling between mitochondria and the ER that is required for transfer of Ca^{2+} to the mitochondria (Angebault et al. 2018). This in turn leads to mitochondrial dysfunction and potential cell death. In exploring this mechanism further it was discovered that WF1 intersects directly with NCS-1.

Moreover, over-expression of NCS-1was able to compensate for the loss of WF1 function in fibroblasts from Wolfram syndrome patients (Angebault et al. 2018) suggesting that NCS-1 may be a useful target for development of new therapeutic approaches.

VILIP1 has been suggested to have a role in Alzheimer's disease due to an association with amyloid plaques in diseased brains (Schnurra et al. 2001). It is not clear, however, if there is any causal relationship, but VILIP1 in cerebrospinal fluid as been widely studied as an early stage biomarker Alzheimer's disease (Braunewell 2012; Groblewska et al. 2015; Babic Leko et al. 2016; Kirkwood et al. 2016).

A more direct involvement of neurocalcin delta in neuronal disease has come from a study(Riessland et al. 2017) showing that knock-down of this protein results in protective effects in various models of spinal muscular atrophy across a number of species. Neurocalcin delta had previously been found to interact with clathrin (Ivings et al. 2002), and the protective effects of neurocalcin delta were attributed to a consequence of the loss of neurocalcin delta as a negative regulator of endocytosis. Neurocalcin delta could therefore as a potential therapeutic target by inhibitors of its activity (Riessland et al. 2017).

Dystonia is an early onset movement disorder, which can be inherited in an autosomal-dominant manner linked to a defined set of genes or alternatively in an autosomal-recessive manner (the latter is classified as DYT2 dystonia). Missense mutations in hippocalcin were found in subjects with (DYT2-like dystonia (Charlesworth et al. 2015). It was suggested that the mutations could have disrupted hippocalcin's role in neuronal calcium signalling. Direct examination of the effect of dystonia mutations on the physiological function of hippocalcin showed that the mutations did not affect the protein structure but resulted in an oligomerization defect (Helassa et al. 2017). It is noteworthy that for another NCS protein, namely GCAP1, dimerization has been suggested to be functionally important (Ames 2018; Lim et al.

2018). In addition, an increase in Ca^{2+} influx through VGCCs of the Cav2 type in cells expressing the mutants was observed compared to wild type hippocalcin, thus suggesting a key role for perturbed Ca^{2+} homeostasis in DYT2 dystonia due to the mis-sense mutations (Fig. 7). The existence of other mutations that would produce truncated proteins have subsequently been discovered in two dystonia families (Atasu et al. 2018) further substantiating the link between hippocalcin and DYT2 dystonia.

The retinally-expressed NCS proteins, GCAPs, have known mutations that have been shown to result in retinal dystrophies and retinal degeneration (Behnen et al. 2010; Dell'Orco et al. 2010), consistent with their key functions in photoreceptors. For GCAP1, which is encoded by the human gene GUCA1A, nearly 20 point mutations have been identified in patients with autosomal dominant retinal dystrophy, leading to the suggestion that photoreceptor death is linked to an abnormality in calcium signalling. A recently identified mutation in GCAP1 (E111V) have been characterised biochemically and shown to decrease GCAP1's affinity for calcium, and thereby shift its regulation of GCs out of the physiological range of calcium concentration (Marino et al. 2018). In addition many mutations are known in the photoreceptor guanylate cyclase GUCY2D, the target for GCAPs, which result in retinal dystrophies. Characterisation of the effects of some of these mutations has indicated that their defects are in the Ca^{2+}-dependent regulation of their catalytic activity by GCAPs (Wimberg et al. 2018).

The idea that KChIPs may contribute to neuronal disease first arose when calsenilin (KChIP3) was discovered as an interactor with presenilins, and to regulate the processing of presenilins, which suggested a link to the pathogenesis of Alzheimer's disease (Buxbaum et al. 1998a; Jo et al. 2004). KChIP1 has been implicated in changes in behavioural anxiety in knock-out mice (Xia et al. 2010) and a human genetic variant associated with attention deficit disorder (Yuan et al. 2017). KChIPs have also been shown to be involved in pain control (Jin et al. 2012; Kuo et al. 2017;

Tian et al. 2018). More recently, DREAM has been shown to regulate the onset of cognitive decline in a mouse model of Huntington's disease (Lopez-Hurtado et al. 2018). The KChIPs may become targets for therapeutics that could be used for several types of neurological disorders. A major challenge will to be develop drugs that target specific KChIP isoforms.

CaBP protein family

The physiology and function of CaBPs

The CaBPs are a family of EF-hand containing Ca^{2+}-binding proteins, which are only found in vertebrates (Haeseleer et al. 2000), and appear to have arisen together in evolution as a family of genes (McCue et al. 2010a) (Fig. 8). They represent another example of a diverse family of Ca^{2+}-sensors capable of regulating discrete processes in the nervous systems of higher organisms. The CaBPs share sequence homology with calmodulin, and also display a similar structural arrangement of EF-hand motifs. Each of the CaBPs has four EF-hands although, like the NCS proteins, they display different patterns of EF-hand inactivation (Fig. 8). In CaBP1-5 the second EF-hand is inactive, with the exception of CaBP3, which also has an inactive EF-1 (although CaBP3 is believed to represent a pseudogene; (Haeseleer et al. 2000)). Two proteins were named CaBP7 and CaBP8 (Haeseleer et al. 2002), but bioinformatic analysis is more consistent with them being a conserved and distinct sub-family of CaBPs (McCue et al. 2010a). We will, therefore, refer to them by their alternative names calneuron 2 and calneuron 1, respectively (Wu et al. 2001; Mikhaylova et al. 2006). The calneurons, by contrast to the CaBPs, have a different pattern of EF-hand inactivation with active EF-hands 1 and 2 and inactive EF-hands 3 and 4 (Mikhaylova et al. 2006). The CaBPs also differ from calmodulin in that their central alpha helical linker domain connecting the C- and N-terminal EF-hand pairs is extended by 4 amino acid residues. This has been suggested to allow these proteins to interact with unique

targets (Haeseleer et al. 2000). Calneuron 1 has been shown to be expressed in essentially all rat and human brain regions (Hradsky et al. 2015).

A major difference compared with calmodulin is the ability of CaBP 1 CaBP2, calneurons 1 and calneuron 2 to target to specific cellular membranes (McCue et al. 2009). CaBP1 and CaBP2 are N-terminally myristoylated, which allows localisation to the plasma membrane and Golgi apparatus (Haeseleer et al. 2000; Haynes et al. 2004b). The precise N-terminal sequence to which the myristoyl group is attached is also important in the targeting of these two proteins, as exemplified by the long and short splice isoforms, which show subtle differences in their localisation. CaBP1-Long localises predominantly to the Golgi and also displays some cytosolic localisation. Whereas, CaBP1-Short localises most prominently to the plasma membrane and to Golgi structures (Haeseleer et al. 2000; McCue et al. 2009). Alternative splicing of the CaBP1 gene generates a third protein product, caldendrin (Seidenbecher et al. 1998). This splice isoform is significantly larger than either CaBP1-Long or CaBP1-Short due to an N-terminal extension, but caldendrin mRNA lacks the exon required for N-myristoylation and as a result the protein displays a markedly different sub-cellular localisation to its shorter relatives.

N-terminal acylation is important in the localisation of some CaBPs, but the calneurons appear to be targeted via a different mechanism. Like CaBP1 and CaBP2, calneuron 1 and calneuron 2 localise to internal membranes that co-label with Golgi specific markers and to vesicular structures (McCue et al. 2009; Mikhaylova et al. 2009). Calneuron 1 and calneuron 2 do not possess an N-terminal myristoylation motif and differ from the rest of the CaBP family due to a 38 amino acid extension at their C-terminus. Analysis of this sequence revealed a predicted C-terminal transmembrane domain with a cytosolic N-terminus (McCue et al. 2011). The C-terminal domain resembles tail-anchor motifs and directly localises calneuron 1 and calneuron 2 to membranes particularly of the trans-Golgi network (McCue et al. 2009; Hradsky et al. 2011).

To date, only a limited number of CaBP structures have been solved. These include CaBP1-Short (Wingard et al. 2005; Li et al. 2009; Findeisen and Minor 2010), CaBP4 ((Park et al. 2013; Park et al. 2014); PDB codes: 2M28 (Ca^{2+} bound C-lobe) and 2M29 (Ca^{2+} bound N-lobe)) and calneuron 2 (McCue et al. 2012). This information may provide insight into the structures of the rest of the CaBPs. Analogy to calmodulin would suggest that the CaBPs should adopt a dumbbell-like tertiary conformation consisting of an N-terminal domain containing EF-hand 1 and EF-hand 2, and a C-terminal domain containing EF-hand 3 and EF-hand 4 connected by a central linker. NMR analysis revealed that CaBP1 does indeed have two independent, non-interacting domains joined by a flexible linker (Wingard et al. 2005). The NMR structures of CaBP4 and calneuron 2 are of isolated N- or C-terminal domains, although in every instance these structures resemble compact, independently folded, helix-loop-helix arrangements very much like those observed in CaBP1 and calmodulin. Investigation into the effects of Mg^{2+} and Ca^{2+} binding has shown that, as predicted, the second EF-hand of CaBP1 is incapable of binding divalent cations. EF-hand 3 and EF-hand 4 bind to both Mg^{2+} and to Ca^{2+}. Whereas, EF-hand 1 is thought to be constitutively occupied by Mg^{2+} (Wingard et al. 2005; Li et al. 2009). The Mg^{2+}-bound form of CaBP1 is similar to that of apo-calmodulin but the Ca^{2+}-bound form appears markedly different. This is perhaps unsurprising as neither of the N-terminal EF-hands of CaBP1 bind to Ca^{2+} under saturating conditions and only EF-hand 1 binds to Mg^{2+}. This results in a constitutively closed conformation of the N-terminal domain while the C-terminal domain can switch to an open conformation upon Ca^{2+} binding to EF-hand 3 and EF-hand 4. Comparison of the C-terminal domain with that of calmodulin reveals differences in exposed hydrophobic residues thought to mediate target interactions (Wingard et al. 2005).

The structural differences between calmodulin and CaBP1 may go some way to explaining how they mediate differing effects on the same target molecules. For

instance, both CaBP1 and calmodulin bind to Cav1 VGCCs with calmodulin causing Ca^{2+}-induced channel closure, but CaBP1 promoting channel opening (Zhou et al. 2004a; Zhou et al. 2005a).

Both calmodulin and CaBP1 also regulate inositol 1,4,5-trisphosphate receptors (IP_3Rs) (Yang et al. 2002; Haynes et al. 2004b; Kasri et al. 2004) with CaBP1 binding the type I IP_3R with 100-fold higher affinity than calmodulin. This high affinity binding may result from the exposure of a distinct hydrophobic patch revealed in the C-terminus of CaBP1 upon Ca^{2+}-binding (Haynes et al. 2004b; Li et al. 2009). This unique surface hydrophobicity profile is likely to be important for the specialisation of CaBP1 function in the brain and retina and the existence of splice isoforms is also likely to further fine-tune the actions of this Ca^{2+} sensor. The higher affinity of CaBPs compared to calmodulin for the same target has led to the notion that the mechanism by which CaBPs differentially regulate such targets is through competition for binding to the same regulatory sites. It has been suggested that calmodulin, in spite of being present in a large molar excess over the various CaBPs, can be displaced from a target due to its lower affinity. Much of the experimental data leading to these conclusions has been derived from *in vitro* studies examining short binding motifs from a given effector protein (Kim et al. 2004; Zhou et al. 2005a; Oz et al. 2011; Findeisen et al. 2013). In order to assess the situation in an intact system, an elegant study by Yang and coworkers (Yang et al. 2014) tested Ca^{2+} channel regulation by calmodulin and CaBP4 in live cells. It was determined that in addition to a degree of competition for binding to the same target sites in $Ca_v1.3$ channels by calmodulin and CaBP4, an allosteric mechanism was also likely to exist whereby both proteins could simultaneously associate with the channel. This dual binding mode could potentially be favoured in resting conditions where apo-calmodulin has high affinity for the channel IQ motif. CaBP4 would simultaneously be associated with a distinct binding motif on the channel. Upon an increase in $[Ca^{2+}]_I$, a competitive interaction is unmasked by the higher affinity of CaBP4 for the calmodulin binding site on the

channel. This model accurately predicts the observed experimental data and loss of Ca^{2+}-dependent inactivation of $Ca_V1.3$ in the presence of CaBP4 and Ca^{2+} even when physiological levels of calmodulin are present (at least a 10-fold excess of calmodulin over CaBP4). It seems certain that for other effector proteins, including various VGCCs and ligand-gated Ca^{2+} channels, dual regulation by calmodulin and the CaBPs will represent a combination of allostery and direct competition.

In addition to novel modes of target interaction as discussed above, differing expression patterns, sub-cellular targeting mechanisms and Ca^{2+}-binding properties of the various members of the CaBP protein family likely bestow further specialisation in the regulation of important Ca^{2+}-channels in the central nervous system.

The majority of studies to date on CaBP1 have examined the functions of the longest splice isoform, caldendrin, and it is not yet clear whether the other splice isoforms of CaBP1 can carry out the same functions. Indeed, detection of CaBP1-Long and CaBP1-Short protein in rodent brain has proven elusive (Kim et al. 2014; Reddy et al. 2014), and it would appear that caldendrin is expressed at significantly higher levels. In spite of this, in simplified experimental systems CaBP1-Long and CaBP1-Short have been found to have roles in the regulation of various Ca^{2+}-channels including P/Q-type ($Ca_V2.1$) channels (Lee et al. 2002), L-type ($Ca_V1.2$) channels (Zhou et al. 2005b; Cui et al. 2007), TRPC5 channels (Kinoshita-Kawada et al. 2005) and IP_3Rs (Yang et al. 2002), which they inhibit (Haynes et al. 2004b; Kasri et al. 2004). A structural basis for the inhibition of IP_3Rs has been determined, whereby CaBP1 binding locks the receptor and prevents the inter-subunit motion required for initiation of channel opening (Li et al. 2013). The interaction of $Ca_V2.1$ with CaBP1 appears to rely acutely upon N-terminal myristoylation. Wild type, myristoylated, CaBP1-Long enhances channel inactivation and shifts the activation range to more depolarising voltages (Lee et al. 2002). An N-myristoylation mutant, however, was unable to mediate these effects, and instead modulated channels in a similar fashion to

calmodulin (Few et al. 2005). Differential modulation of L-type channels depending on the splice isoform of CaBP1 has also been observed. CaBP1-Short has been shown to completely inhibit inactivation of $Ca_V1.2$ channels (Zhou et al. 2005b), but caldendrin causes a more modest suppression and signals through a different set of molecular determinants (Tippens and Lee 2007). This suggests that the sub-cellular localisation of CaBP1 splice variants is important for their differing functions. In the auditory system, CaBP1 is expressed in spiral ganglion neurons (Yang et al. 2016), and CaBP1 knock-out mice exhibit progressive hearing loss albeit less severely than that observed in CaBP2 knock-out animals (Yang et al. 2016). In the visual system, CaBP1 appears to exert similar functions to CaBP2 (Sinha et al. 2016), and loss of the CaBP1 proteins induces defects in transmission of light responses by the retina. It should be noted that a number of these studies have used knockout animals that do not express any of the CaBP1 isoforms and therefore assigning a function to a specific splice variant is not possible.

Interactions of caldendrin with other types of proteins have also been reported, such as its interaction with light chain 3 of MAP1A/B, a microtubule cytoskeletal protein (Seidenbecher et al. 2004), and with myo1c a member of the myosin-1 family of motor proteins (Tang et al. 2007). A role for caldendrin in NMDA receptor (NMDAR) signalling has been reported involving an interaction with a novel neuronal protein, Jacob. Upon extra-synaptic NMDAR activation Jacob translocates to the nucleus to influence CREB activity resulting in the stripping of synaptic contacts and an associated simplification of dendritic architecture. Synaptic NMDAR-mediated synaptodendritic $[Ca^{2+}]_i$ elevation induces caldendrin binding to Jacob, thereby inhibiting nuclear trafficking and maintaining dendritic organisation. This interaction represents a novel mechanism of synapse to nucleus communication and highlights the important roles of CaBP family members in the mammalian central nervous system (Dieterich et al. 2008). Finally, caldendrin has recently been shown to control actin remodelling in dendritic spines in response to synaptic activity (Mikhaylova et al. 2018). Animals in which the caldendrin gene has been deleted exhibited impaired

dendritic spine plasticity, defective LTP and impaired hippocampus dependent learning (Mikhaylova et al. 2018). These findings are consistent with related studies highlighting a function for caldendrin in the hippocampus. It is required for efficient encoding of hippocampal-dependent spatial and fear-based memory (Yang et al. 2018a), and mice in which all CaBP1 isoforms are deleted, including caldendrin, exhibit defects in excitation/inhibition in hippocampal circuits (Nanou et al. 2018; Yang et al. 2018b).

Little information is available concerning the function of CaBP2. While it was initially detected exclusively in the retina it was also identified in auditory inner hair cells (Cui et al. 2007). CaBP5 was also detected in inner hair cells as well as in the retina, but in contrast to CaBP2 was found to have a modest inhibitory effect on the inactivation of $Ca_V1.3$ channels in transfected cells (Cui et al. 2007). Newer research points to an important role for CaBP2 in both the visual and auditory systems. Mice lacking CaBP2 have no gross morphological defects of the retina or retinal neuronal wiring, however, they do exhibit impaired transmission of retinal light responses (Sinha et al. 2016). CaBP2 is now known to be expressed in the cochlea in both inner and outer hair cells, and gene deletion of all CaBP2 splice variants leads to early onset hearing loss (Yang et al. 2016; Yang et al. 2018c). Some of the functions of CaBP2 may stem from its ability to stimulate CaMK activity, although this has only been reported *in vitro* (Cui et al. 2007). Little is known about the functions of CaBP5 but knockout mice displayed reduced sensitivity of retinal ganglion cells to light responses implicating CaBP5 in phototransduction pathways. CaBP5 was also found to interact with, and suppress, calcium-dependent inactivation of $Ca_V1.2$ channels (Rieke et al. 2008). One report has detailed an interaction of CaBP5 with components of the exocytotic machinery, and showed that expression of CaBP5 in a neuroendocrine cell line enhanced secretory granule exocytosis (Sokal and Haeseleer 2011). These data implicate CaBP5 as a potential regulator of visual and auditory processing, perhaps through modulation of neurotransmitter release in special sensory neurons.

CaBP4 is the most extensively characterised of the CaBP family. It is expressed in the retina where it localises to synaptic terminals and has also been detected in auditory inner hair cells. CaBP4 modulates VGCCs, and directly associates with the C-terminus of the $Ca_V1.4$ α1 pore-forming subunit, shifting the activation range of the channel to more hyperpolarised voltages in transfected cells (Haeseleer et al. 2004; Shaltiel et al. 2012). A plausible structural basis for this regulation has now been presented, whereby CaBP4 is speculated (through molecular docking predictions) to relieve an inhibitory self-interaction of the channel through binding to the IQ motif (Park et al. 2014). CaBP4 has also been shown to eliminate Ca^{2+}-dependent inactivation of $Ca_V1.3$ channels, which is likely to be important in the modulation of these channels in inner hair cells where Ca^{2+}-dependent inactivation is weak or absent probably allowing the audition of sustained sounds (Yang et al. 2006). A stronger inhibitory effect has been noted for CaBP1, however, suggesting that CaBP4 may not be the key Ca^{2+} sensor involved in this process (Cui et al. 2007). The function of CaBP4 is modulated by protein kinase Cζ in the retina, with increased CaBP4 phosphorylation in light-adapted tissue. Phosphorylation prolongs Ca^{2+} currents through $Ca_V1.3$ channels, which suggests that light-stimulated phosphorylation of CaBP4 might help to regulate presynaptic Ca^{2+} signals in photoreceptors (Lee et al. 2007). Conversely, dephosphorylation of CaBP4, studied in transfected HEK293T cells, by protein phosphatase 2A inhibited its ability to modulate $Ca_v1.3$ activity (Haeseleer et al. 2013). CaBP4 has also been implicated in neurotransmitter release at synaptic terminals due to its interaction with unc119, a synaptic photoreceptor protein important for neurotransmitter release and maintenance of the nervous system (Haeseleer 2008). Knockout of CaBP4 results in mice with abnormalities in retinal function where rod bipolar responses are approximately 100 times lower than those observed in wild-type animals (Haeseleer et al. 2004).

The functions of calneuron 1 and calneuron 2 have only recently begun to be investigated in detail. Both have been found to and inhibit the activity of PI4KIIIβ at low, or resting, $[Ca^{2+}]_i$. Over-expression of the proteins was also found to inhibit Golgi-to-plasma membrane trafficking, caused enlargement of the trans-Golgi network (TGN) and reduced the number of Piccolo-Bassoon positive transport vesicles. A molecular switch for the production of phosphoinositides at the TGN is thought to be created by the opposing roles of NCS-1 and calneuron 1 or calneuron 2. At elevated Ca^{2+} levels, NCS-1 preferentially binds to PI4KIIIβ displacing the calneurons thereby activating the enzyme to drive enhanced TGN-to-plasma membrane trafficking (Mikhaylova et al. 2009). Calneuron 2 was discovered in a genome-wide search for regulators of mitosis (Neumann et al. 2010). Analysis of the role of calneuron 2 during cell division has suggested that it plays a key role in cytokinesis through its inhibitory control of PI4KIIIβ (Rajamanoharan et al. 2015). Patch clamping experiments have shown that over-expressed calneuron 1 can inhibit N-type Ca^{2+}-channel currents in 293T cells, and this inhibition was not observed with a truncated calneuron lacking its hydrophobic C-terminus suggesting normal localisation is important in carrying out this function (Shih et al. 2009). Calneuron 1 and NCS-1 differentially regulate adenosine receptor activity, an important molecular target for the treatment of numerous human neurological diseases (Navarro et al. 2014). Similar differential regulation by calneuron 1 and NCS-1 has recently been reported for the CB_1 cannabinoid receptor, an important potential target in nociceptive signalling (Angelats et al. 2018).

CaBP proteins and disease

CaBPs have been directly or indirectly implicated in multiple neuronal diseases. Post-mortem brains of chronic schizophrenics have lower numbers of caldendrin-immunoreactive neurons, which express the protein at a much higher level. This loss of caldendrin in some neurons (or loss of the neurons themselves) and up-regulation

in others is likely to profoundly change synaptodendritic signalling in schizophrenic patients (Bernstein et al. 2007). Changes in the distribution of caldendrin have also been observed in kainate-induced epileptic seizures in rats. Caldendrin translocates to the post synaptic density only in rats that suffered epileptic seizures, which may implicate the protein in the pathophysiology of the disease (Smalla et al. 2003). Mutations in CaBP2 have now been identified and linked with hearing impairments in humans (Schrauwen et al. 2012; Markova et al. 2016). One of these studies identified a splice-site mutation in three consanguineous Iranian families, which likely generates a truncated CaBP2 protein with lower affinity for $Ca_v1.3$, leading to moderate-severe hearing loss (Schrauwen et al. 2012). Calneuron 1 has recently been shown to be over-expressed in aldosterone producing adenoma (Kobuke et al. 2018). The protein is required for stimulated aldosterone production and may therefore represent a therapeutic target for the control of excess hormone production in such tumours (Kobuke et al. 2018). CaBP4 function has been linked to disease, and mutations in this gene generate defects predominantly in retinal function. Knockout of CaBP4 was shown to cause a phenotype similar to that of incomplete congenital stationary night blindness in patients (Haeseleer et al. 2004), and mutations in CaBP4 can cause autosomal recessive night blindness (Zeitz et al. 2006). Patients with mutations in the CaBP4 gene have been identified that display congenital stationary night blindness. However, some patients with mutations display different phenotypes (Zeitz et al. 2006). In particular, a novel homozygous nonsense mutation has been reported in two siblings that resulted in severely reduced cone function but only negligible effects on rod function (Littink et al. 2009). CaBP4 null mutations have been observed in a consanguineous family with four members affected by Leber's congenital amaurosis (Aldahmesh et al. 2010). This condition is relatively rare, affecting about 1:80,000 of the general population, but is the most common cause of inherited loss of vision in children. Numerous studies now point to genetic mutations in CaBP4 as causative factors in a set of related cone-rod retinopathies (Littink et al. 2009; Aldahmesh et al. 2010; Bijveld et al. 2013; Hendriks et al. 2017; Smirnov et al. 2018). Multimodal

imaging of five genetically characterised patients affected by CaBP4 related retinopathy showed a variable amount of photoreceptor dysfunction but that this remained stable and did not deteriorate over a period of years (Schatz et al. 2017). This has led to the hope that CaBP4-based retinopathies might be tractable to gene therapy-mediated correction. More recently, a CaBP4 missense mutation (G155D) has been implicated in a rare inherited form of frontal lobe epilepsy. This would suggest a wider central function for CaBP4 outside of the visual system which requires further investigation in future studies.

CONCLUDING REMARKS

It has become increasing clear that a full understanding of how specific aspects of physiological neuronal function are regulated in response to spatially and temporally distinct Ca^{2+} signals will require a detailed knowledge of the Ca^{2+} sensors involved. In addition, many of these the Ca^{2+} sensors may be implicated indirectly due to abnormalities in Ca^{2+} signalling pathways in neurological or neurodegenerative disorders. In some cases, the Ca^{2+} sensors may be more directly implicated either due to their specific regulatory roles that impinge on key dysfunctional pathways. Alternatively, genetic mutations or variations of Ca^{2+} sensor activity may have a more direct effect on brain dysfunction. No matter how the Ca^{2+} sensors are involved they are likely to be potential therapeutic targets for new drugs that can be used to treat human disorders. For further understanding of the normal roles of each of the Ca^{2+} sensors further insight into the molecular basis for the regulation of their targets, and more detailed dissection of the physiological roles of each protein in identified neurons, is required. This knowledge will form the basis for future approaches to the development of treatments that could alleviate a variety of human neuronal disorders underpinned by defects in Ca^{2+} signalling.

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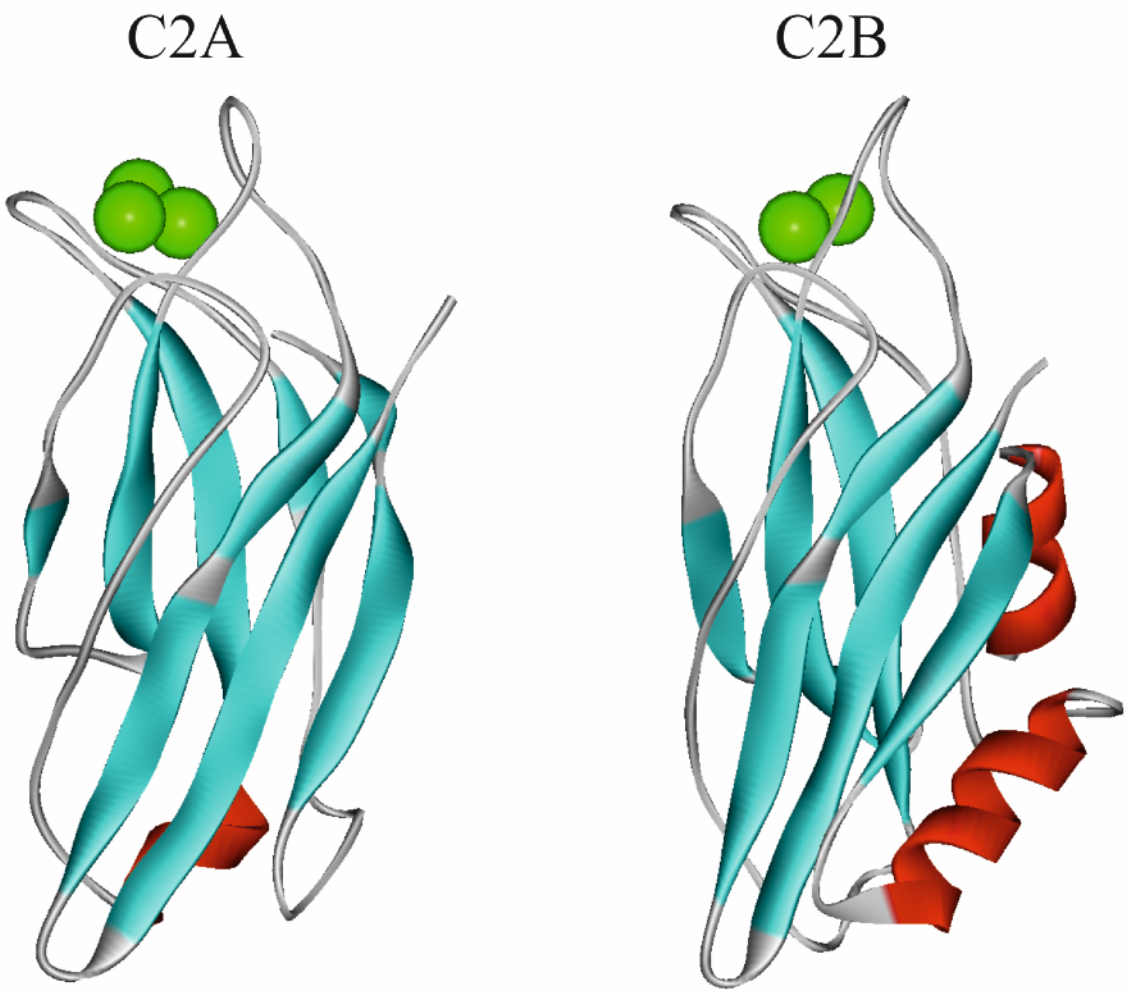

Figure 1. Structures of the C2A and C2B domains of synaptotagmin I. The structures show the isolated C2 domains in their Ca^{2+}-loaded state with the bound Ca^{2+} ions shown in green. The coordinates for the structures for the C2A and C2B domains come from the PDB files 1BYN and 1K5W, respectively.

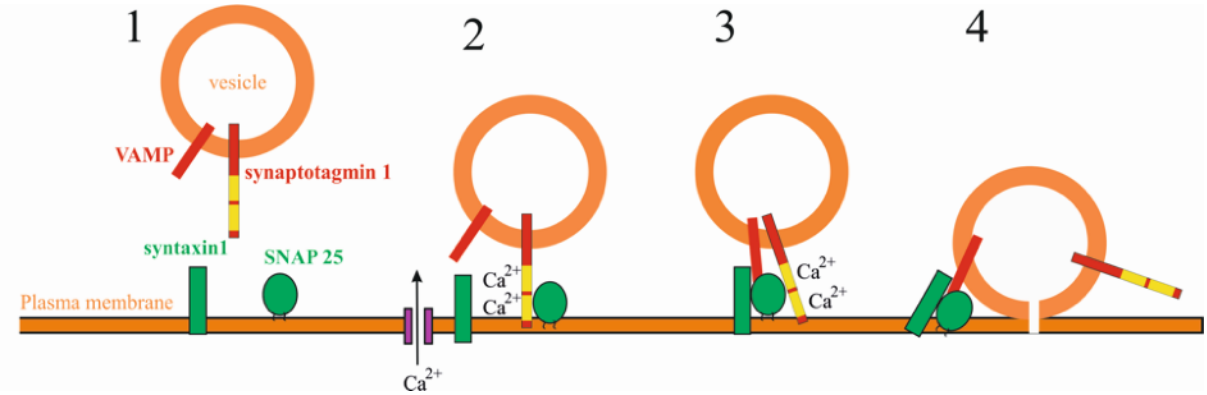

Figure 2. Potential role of synaptotagmin 1 in synaptic vesicle exocytosis. Key components of the minimal fusion machinery are associated with the synaptic vesicle and the plasma membrane (1). Neurotransmitter release is triggered by Ca entry though voltage gated calcium channels. Ca^{2+} binds to synaptotagmin 1 which may then lead to vesicle docking via interaction with phospholipids or with SNAP-25 on the plasma membrane (2). The SNARE complex assembles from the key components of VAMP, SNAP-25 and syntax and synaptotagmin associates with the complex (3). Through as yet undefined steps synaptotagmin become dissociated from the SNARE complex and fusion of the vesicle with the plasma membrane occurs to allow release of neurotransmitter from the vesicle (4).

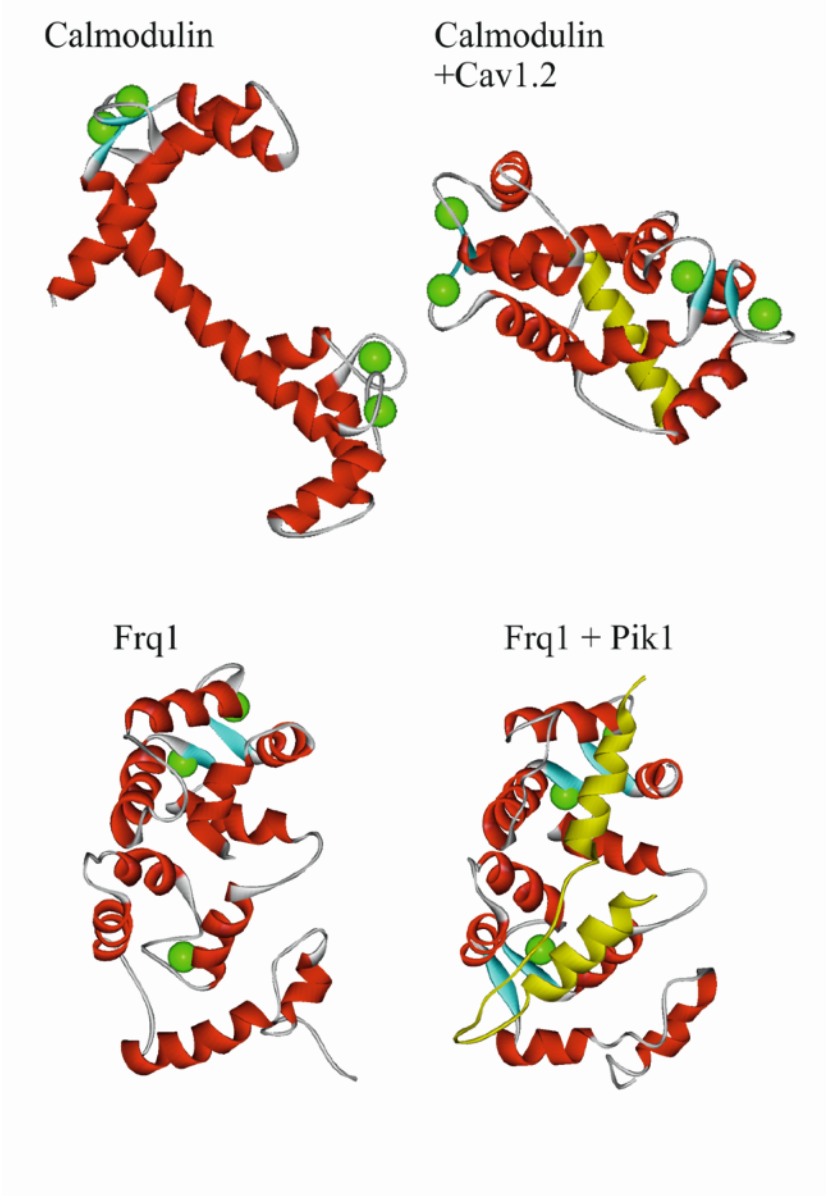

Figure 3. Comparison of the structures of Ca^{2+}-loaded calmodulin and yeast frequenin with and without bound target peptides. The structures at the top are of Ca^{2+}-bound calmodulin alone (PDB 1CLL) or in a complex with the IQ-like domain of the $Ca_v1.2$ Ca^{2+}-channel α-subunit (PDB 2F3Z). The structures at the bottom are of the Ca^{2+}-bound yeast frequenin (Frq1) alone (PDB 1FPW) or in a complex with the binding domain from Pik1 (PDB 2JU0). In each of the complexes the target peptide is shown in yellow.

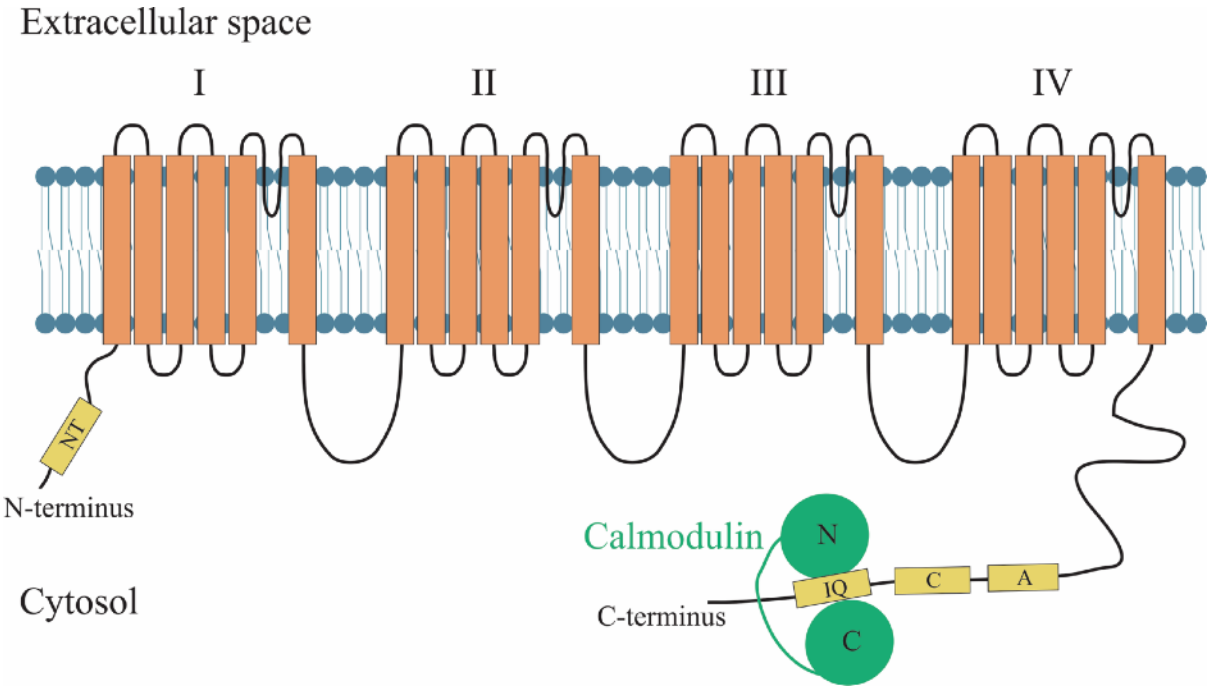

Figure 4.Schematic illustration of the pore-forming a_1 subunit of a $Ca_V1.2$ channel. The a_1 subunit is composed of 4 domains (I – IV), each consisting of six putative transmembrane segments (orange). Several potential binding sites for Ca^{2+} sensors (yellow) have been identified in the N-terminal (NT) and the C-terminal region (A, C and IQ) of $Ca_V1.2$ channels. Calmodulin (green), one of the major Ca^{2+} sensors, has been shown to be pre-associated to the channel through its interaction with the IQ motif. Once calmodulin becomes Ca^{2+}-loaded it exerts its effects on channel function through either its N- or its C-lobe.

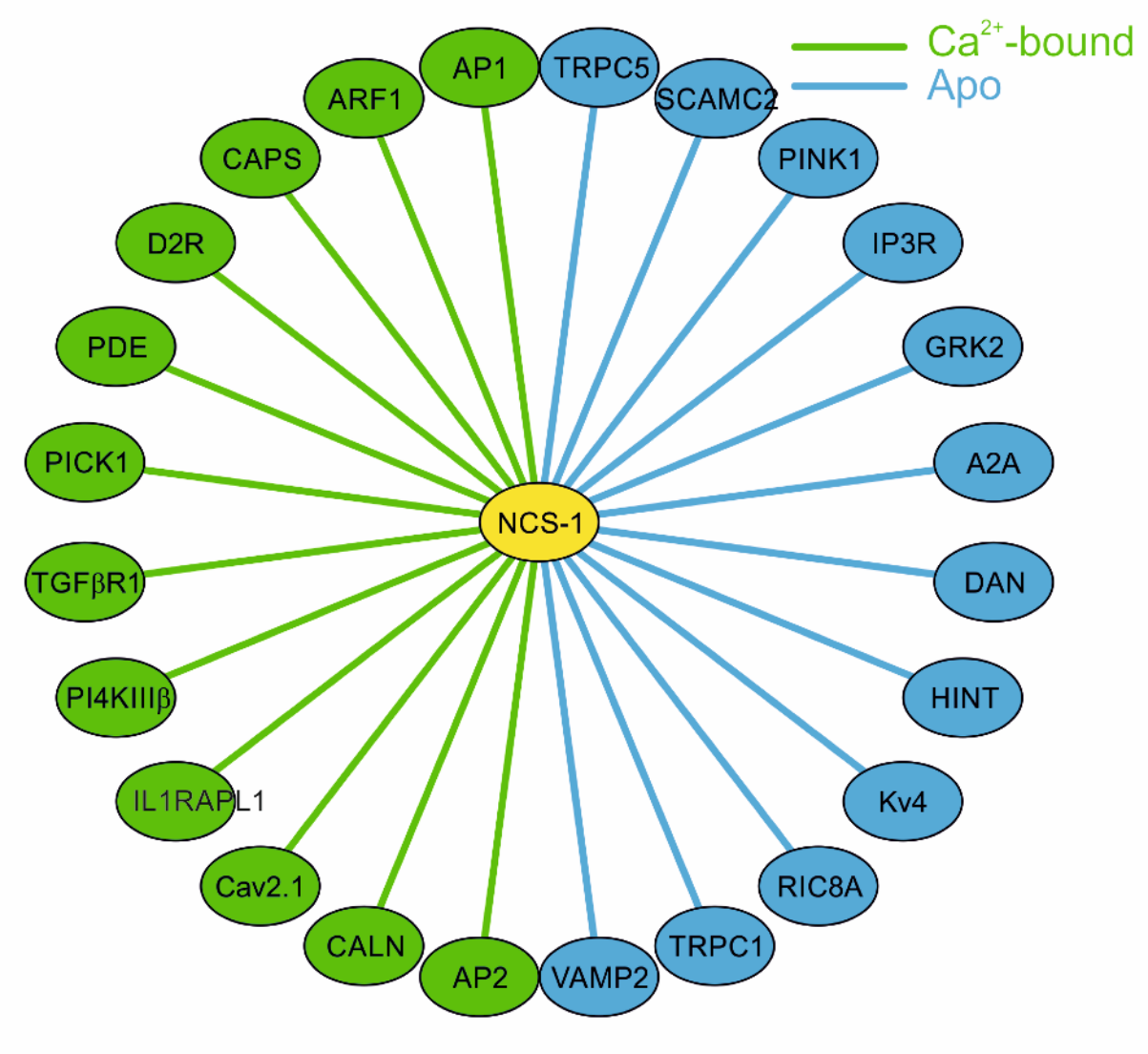

Figure 5. Major known target proteins for NCS-1 indicating interactions that require either the Ca^{2+}-bound or the apo form of NCS-1. The interactions shown include ones that are based on *in vitro* binding assays as well as interactions that have been substantiated and shown to have physiological relevance in functional studies.

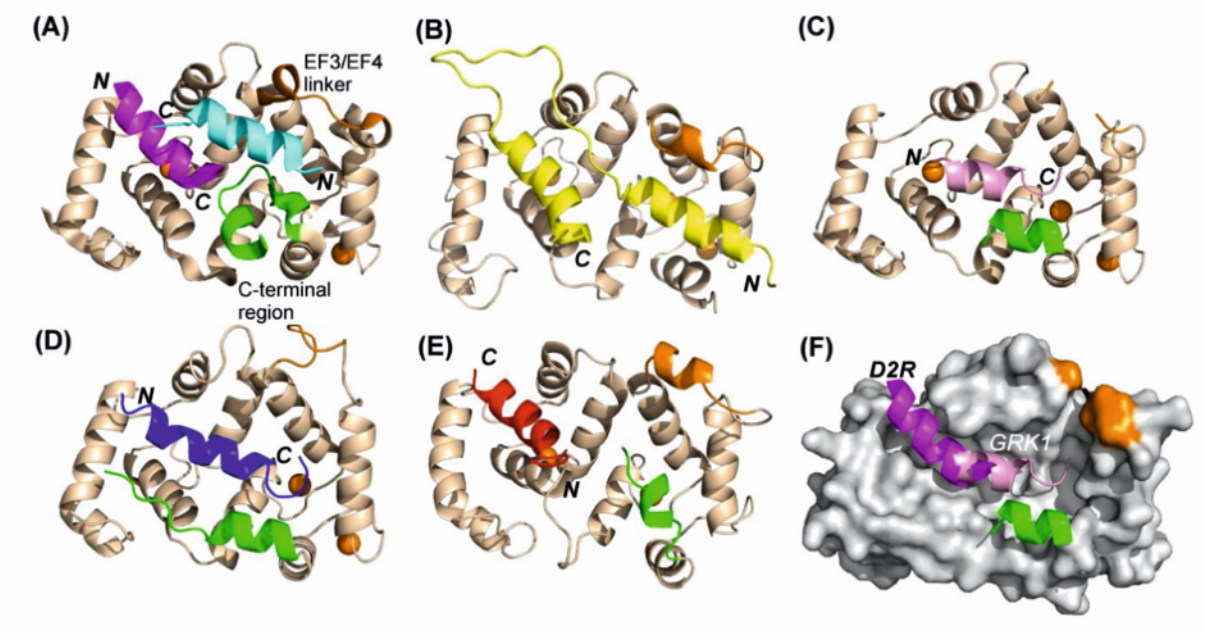

Figure 6. Comparison of the mode of binding of target peptides to NCS-1. Cartoon representation of the structures of (A) NCS-1 in complex with two molecules of D2R peptide (magenta and cyan) (PDB 5AER), (B) ScNcs1in complex with fragment of Pik1 (yellow) (2JU0) (45), (C) NCS-1 in complex with one molecule of GRK1 peptide (pink) (PDB 5AFP), (D) KChIP1 with a fragment of bound Kv4.3 (blue) (PDB 2I2R) (50). (E) Recoverin bound to the N- terminus of GRK1 residues 1-25 with GRK1 peptide (red; PDB 2I94) (52). (F) Overlay of structures 5AER and 5AFP showing the locations of the D2R bound in the N-site and GRK1 peptides. The peptide orientations are indicated as N, C in bold italics and the orientations of the NCS protein are identical in all the structures. The EF3/EF4 linker is coloured brown and the C-terminal region green; for clarity these regions are indicated only for

NCS-1-D2R peptide complex. In all the structures, Ca ions are shown as brown

spheres. Taken from (Pandalaneni et al. 2015).

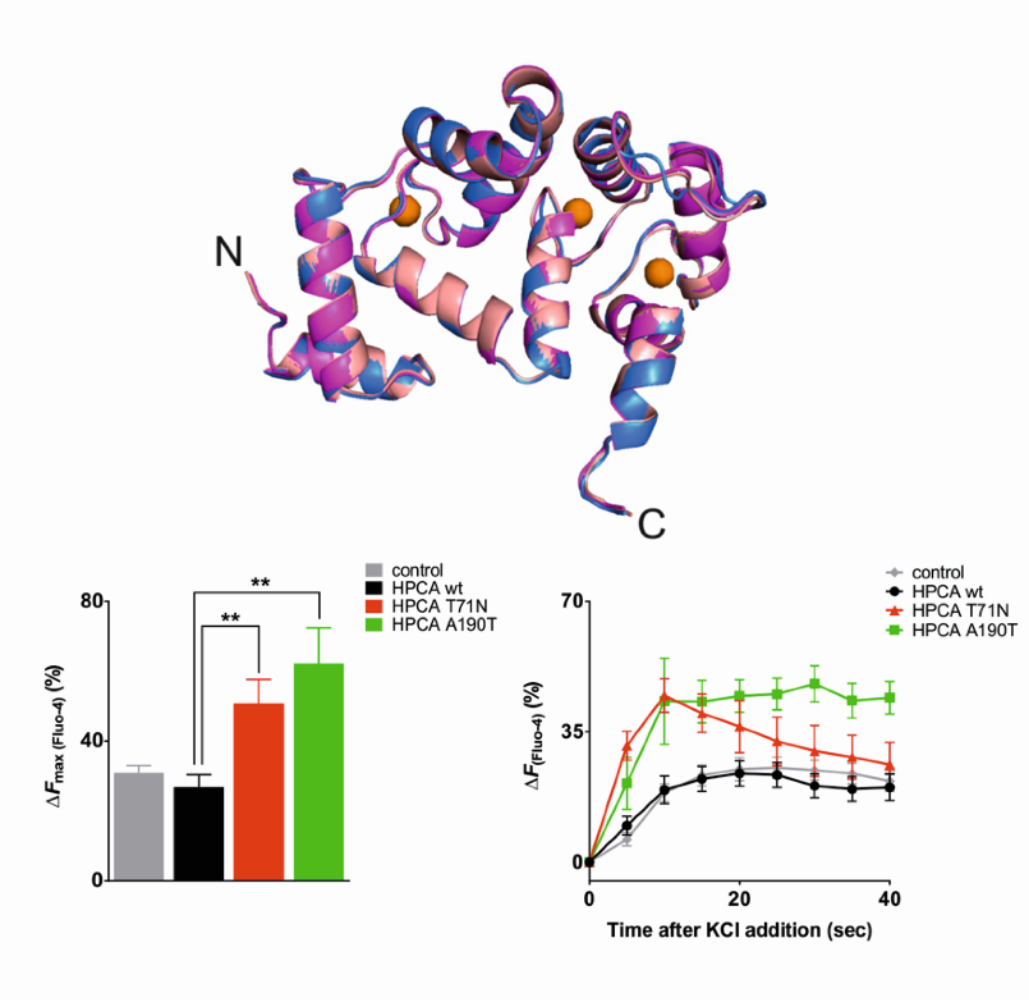

Figure 7. Effect of dystonia mutations of the structure of hippocalcin and its effect on calcium entry. Top. Alignment of hippocalcin crystal structure (magenta) with hippocalcin (T71N) (marine) and hippocalcin (A190T) (salmon) did not show any significant difference. Crystal structures were obtained for wild-type human hippocalcin (PDB 5G4P), hippocalcin (T71N) (PDB 5M6C) and hippocalcin (A190T) (PDB 5G58) at a resolution of the 2.42, 3.00 and 2.54 Å, respectively (Helassa et al. 2017). Bottom. Dystonia-causing hippocalcin mutants increase depolarisation-induced calcium influx. Differentiated SH-SY5Y cells transfected with hippocalcin-mCherry constructs were loaded with Fluo-4 to monitor calcium concentration changes. After KCl depolarisation, live cells were imaged on a spinning-disk confocal microscope. Maximum intracellular calcium increase and time course after KCl stimulation, showing that both hippocalcin(T71N) and hippocalcin(A190T) increased calcium entry in response to depolarisation. [Modified from (Helassa et al. 2017).]

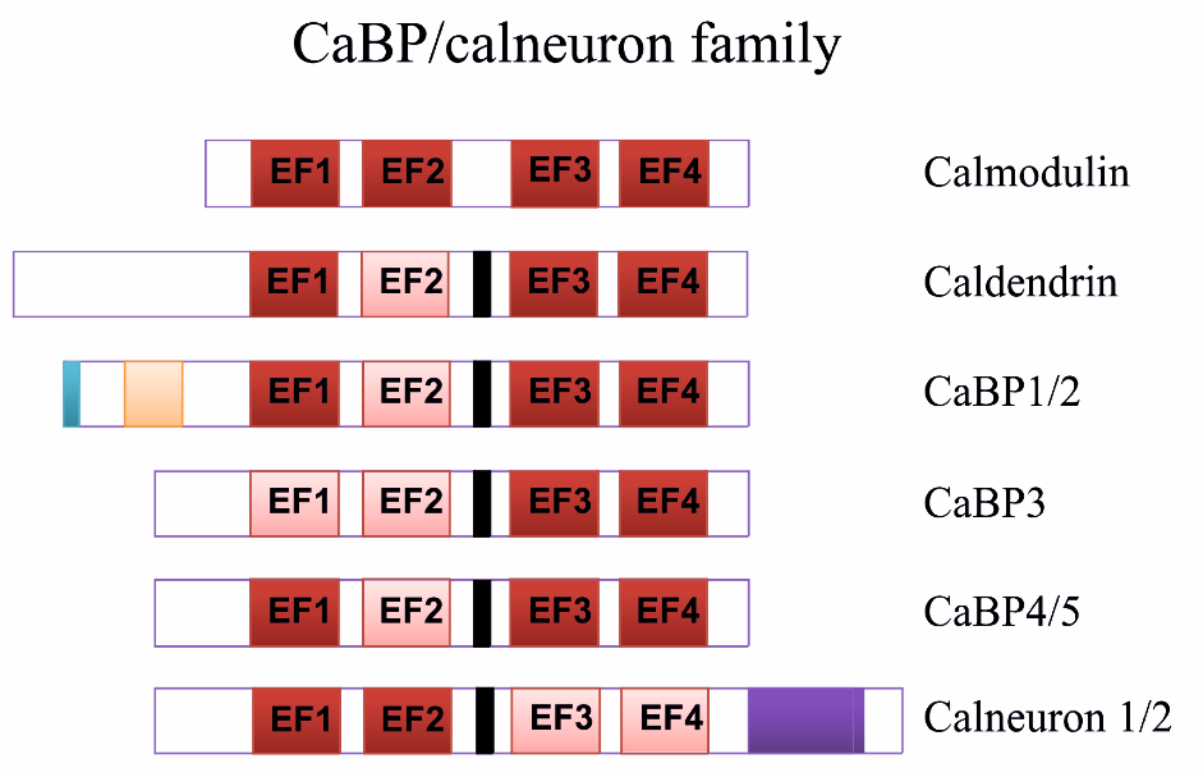

Figure 8. Schematic diagram showing the domain structure of calmodulin and members of the CaBP/calneuron protein family. Active EF-hand motifs are shown in red and inactive EF-hand motifs are shown in pink. Compared to calmodulin the CaBPs have an extended linker region between their first EF-hand pair and their second EF-hand pair (shown in black). CaBP1 and CaBP2 have an N-myristoylation site (shown in blue). CaBP1 and CaBP2 have alternative splice sites at their N-terminus which give rise to long and short isoforms (shown in orange). Calneurons 1 and 2 possess a 38 amino acid extension at their C-terminus (shown in purple).