

# Neuronal calcium sensor proteins: emerging roles in membrane traffic and synaptic plasticity

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*F1000 Biology Reports* 2010, **2**:5 (doi:10.3410/B2-5)

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## Abstract

Ca<sup>2+</sup> plays a crucial role in the regulation of neuronal function. Recent work has revealed important functions for two families of neuronally expressed Ca<sup>2+</sup> sensor proteins. These include roles in membrane traffic and in alterations in synaptic plasticity underlying changes in behaviour.

## Introduction and context

Intracellular Ca<sup>2+</sup> regulates many distinct aspects of neuronal function over a very wide range of timescales. The transduction of changes in Ca<sup>2+</sup> concentration into a specific physiological outcome involves the action of Ca<sup>2+</sup>-binding proteins that act as sensors and regulate the activity of various target proteins. Many Ca<sup>2+</sup> sensors bind Ca<sup>2+</sup> via so-called EF-hand domains and the best known of these is the ubiquitous protein calmodulin. During vertebrate evolution, however, there has been an expansion in the number of EF-hand proteins, particularly in protein families expressed in neurons [1]. Amongst these are the neuronal calcium sensor (NCS) proteins [1] and the calcium-binding proteins (CaBPs) [2,3]. The CaBPs are more similar to calmodulin than the NCS proteins are but they all have in common a high affinity for Ca<sup>2+</sup>, allowing them to respond with high sensitivity to small increases in neuronal cytosolic Ca<sup>2+</sup> concentration.

The NCS family consists of 14 genes in mammals, and some of these genes are expressed as multiple splice variants [1]. These include NCS-1, hippocalcin, neurocalcin  $\delta$ , visinin-like protein (VILIP) 1-3, recoverin, guanylyl cyclase-activating proteins (GCAPs) 1-3, and K<sup>+</sup> channel-interacting protein (KChIP) 1-4. NCS-1 was discovered in flies and named frequenin due to its ability to enhance neurotransmitter release in a frequency-dependent manner and was thought to be a neuronal-specific protein [4]. NCS-1 has, however, an orthologue

in yeast [5] and other fungi whereas other NCS proteins appeared at later stages of evolution and in some cases have a more restricted neuronal expression. The NCS proteins have varied patterns of intracellular localisation, and some of these proteins are cytosolic whereas others are associated with membrane organelles due to the lipid modifications of myristoylation or palmitoylation. It was originally shown for recoverin [6] and later for some other NCS proteins such as hippocalcin [7] that they can reversibly associate with membranes on Ca<sup>2+</sup> binding and extrusion of their myristoyl tail (the Ca<sup>2+</sup>/myristoyl switch). Other NCS proteins such as NCS-1 have their myristoyl tail exposed even in the absence of Ca<sup>2+</sup> [8] and therefore can associate with membranes even at resting intracellular Ca<sup>2+</sup> concentrations [9], allowing them to respond to short-duration and local Ca<sup>2+</sup> signals.

The CaBPs are expressed in fish onwards and are encoded by seven genes with alternate splice forms of CaBP1 (including caldendrin) and CaBP2 [2]. CaBP7 and 8 are also known as calneurons 2 and 1, respectively [10]. Again, these proteins can be found to be either cytosolic or membrane-associated [11] although none shows the Ca<sup>2+</sup>/myristoyl switch mechanism that appears to be unique to members of the NCS family.

Recoverin and the GCAPs have defined roles in regulating signalling pathways specifically in the retina [12,13].

Recent work has begun to reveal the physiological functions of other NCS and CaBP proteins: for example, roles in the regulation of plasma membrane  $\text{Ca}^{2+}$  channels [14-18]. They have also been suggested to regulate intracellular ion channels such as the inositol 1,4,5-trisphosphate receptor [19-21], although the effect of CaBPs initially reported [19] was opposite to that seen in later studies [20,22]. The molecular basis for the functions of these proteins has been revealed in part by identification of some of their target proteins. Below, we will highlight recent advances in our understanding of the roles of these  $\text{Ca}^{2+}$  sensors in membrane traffic and in forms of synaptic plasticity.

## Major recent advances

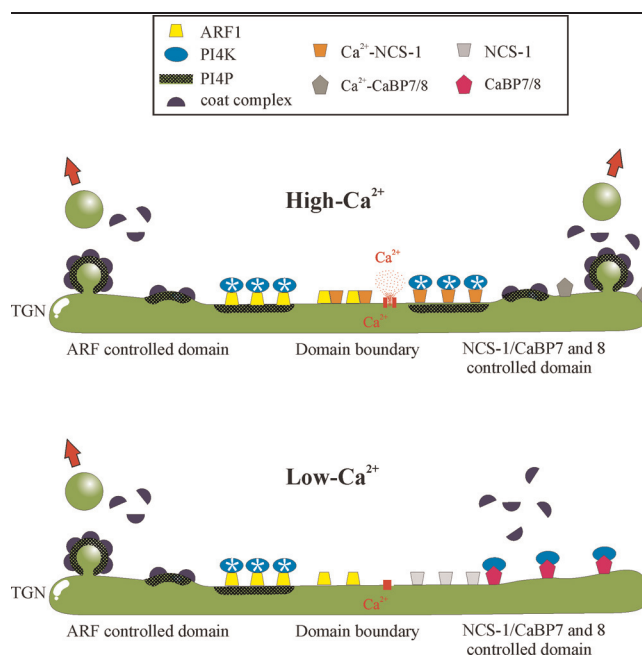
### Regulation of membrane traffic

It has become increasingly apparent that NCS and CaBP proteins have roles in regulating intracellular traffic in cells either through interaction with specific cargo molecules or through general effects on membrane traffic processes. The first example to be characterised was the ability of KChIPs to stimulate the traffic of the Kv4 potassium channels to the cell surface [16]. This requires a direct physical interaction of the KChIPs with the Kv4 channel subunits [23,24]. For KChIP1, traffic with Kv4 channels occurs via a novel non-conventional pathway, from the endoplasmic reticulum to the Golgi apparatus, that is dependent on functional EF-hands in KChIP1 [25] before subsequent traffic to the plasma membrane. This pathway may be related to the local satellite traffic pathways present within neuronal dendrites [26]. Other specific effects of NCS proteins include stimulation by VILIP-1 of the cell surface expression of  $\alpha 4\beta 2$  nicotinic acetylcholine receptors [27] and inhibition by NCS-1 of dopamine D2 receptor internalisation [28], which is further discussed below.

A more general effect of NCS-1 and CaBP7/8 (calneurons 2/1) on membrane traffic is exerted through regulation of a key enzyme in phosphoinositide metabolism, phosphatidylinositol-4-kinase (PI4K) III $\beta$ . A role for NCS-1 in stimulating this enzyme was first shown in yeast [5] and subsequently the mammalian NCS-1 protein was shown to stimulate PI4KIII $\beta$  and also to interact with both the enzyme and the small GTPase ADP-ribosylation factor 1 (ARF1) on the Golgi complex [29,30]. These interactions regulate general traffic from the trans-Golgi network (TGN) to the plasma membrane [29], with the effects of NCS-1 and ARF1 being antagonistic. The importance of these interactions is indicated by findings that NCS-1, ARF1 and PI4KIII $\beta$  control inner ear development in zebrafish [31]. Recently, CaBP7 and 8 were found to interact with PI4KIII $\beta$  but, in contrast to NCS-1, inhibited the enzyme

activity at resting  $\text{Ca}^{2+}$  levels [32]. This inhibition was released on binding of NCS-1 at elevated  $\text{Ca}^{2+}$  levels, providing a tight  $\text{Ca}^{2+}$  threshold for control of the traffic from the TGN to the plasma membrane in neurons (Figure 1).

**Figure 1. Regulation of vesicular trafficking from the trans-Golgi network (TGN) in neurons by neuronal calcium sensor-1 (NCS-1) and calcium-binding protein (CaBP) 7 and 8 (calneurons)**



The Golgi apparatus is an important  $\text{Ca}^{2+}$  store. Release of  $\text{Ca}^{2+}$  from the Golgi through channels such as the inositol 1,4,5-trisphosphate receptor may influence trafficking through and from this organelle. Under conditions of high local  $\text{Ca}^{2+}$  concentration (high- $\text{Ca}^{2+}$ ), NCS-1 binds to and activates phosphatidylinositol-4-kinase III $\beta$  (PI4KIII $\beta$ ) (activated PI4KIII $\beta$  is indicated by an asterisk) to drive the production of phosphatidylinositol 4-phosphate (PI4P) (shown enriched in hatched regions of the membrane), a lipid essential for stimulation of vesicular traffic from the TGN. CaBP7 and CaBP8 do not interact with PI4KIII $\beta$  at high  $\text{Ca}^{2+}$ . A further level of complexity in this model stems from a  $\text{Ca}^{2+}$ -dependent interaction between NCS-1 and the key Golgi trafficking GTPase ADP-ribosylation factor 1 (ARF1). At high  $\text{Ca}^{2+}$ , NCS-1 and ARF1 interact, preventing activation of PI4KIII $\beta$  in regions where the two proteins coexist. Since ARF1 activates PI4KIII $\beta$  independently of  $\text{Ca}^{2+}$ , this interplay may represent a mechanism for spatial organisation of the TGN into discrete subdomains tasked with serving either  $\text{Ca}^{2+}$ -dependent or  $\text{Ca}^{2+}$ -independent trafficking functions that are segregated by domain boundaries populated by non-productive ARF1/NCS-1 complexes. Under conditions of low local  $\text{Ca}^{2+}$  concentration (low- $\text{Ca}^{2+}$ ), NCS-1 no longer activates PI4KIII $\beta$  and instead CaBP7 and CaBP8 are able to interact with the kinase to inhibit its activity. Lack of PI4P production under such circumstances would prevent vesicular traffic from  $\text{Ca}^{2+}$ -dependent trafficking domains. Trafficking from ARF1-controlled domains could occur at both high and low  $\text{Ca}^{2+}$ .

### Roles in synaptic plasticity

NCS-1 has functions in the control of neuronal development [15] and neuronal survival [33]. It has also become clear that NCS-1 has key roles in aspects of synaptic plasticity underlying learning and memory. There are three NCS-1 homologues in *Caenorhabditis elegans* and knockout of the one most similar to the mammalian protein impaired learning and memory in the worms [34]. Increased levels of NCS-1 switched the mode of short-term plasticity in hippocampal synapses in culture from depression to facilitation [35]. Further progress was made when it was shown that NCS-1 was required for a form of synaptic plasticity, known as long-term depression (LTD), induced through metabotropic glutamate receptor activation in cortical neurons [36]. In this system, NCS-1 acted as a  $\text{Ca}^{2+}$  sensor in conjunction with another  $\text{Ca}^{2+}$ -binding protein, PICK1 (protein interacting with C kinase 1).

As noted above, NCS-1 interacts with and controls the surface expression of dopamine D2 receptors. Most recently, a study extended these findings to directly link NCS-1 regulation of dopamine D2 receptor activity with the processes of learning and memory in adult mice. Inducible targeted expression of NCS-1 specifically in the dentate gyrus of transgenic animals enhanced acquisition of spatial memory and had the novel effect of increasing exploratory behaviour. Importantly, these effects could be abolished through antagonism of the NCS-1/dopamine D2 receptor interaction by use of a membrane-permeant inhibitory peptide [37].

Another NCS protein, hippocalcin, has been of interest in considerations of synaptic plasticity as it is expressed to the highest extent in the hippocampus, which is a site of memory formation. Hippocalcin knockout mice have impaired memory formation [38]. Like NCS-1, hippocalcin has been suggested to act as a  $\text{Ca}^{2+}$  sensor for LTD but in this case in the hippocampus [39].

KChIP3 was independently discovered and named the downstream regulatory element antagonistic modulator (DREAM) [40]. DREAM can act in the nucleus by binding in a  $\text{Ca}^{2+}$ -dependent manner to a specific DNA sequence and may control aspects of synaptic plasticity through changes in gene expression. In fact, one of its major physiological roles revealed in a knockout mouse is in pain modulation [41]. A recent novel role that has been discovered is that of caldendrin in regulating nuclear signalling in neurons by interaction with the protein Jacob. This leads to changes in dendritic remodelling following NMDA (*N*-methyl-D-aspartic

acid) receptor activation [42], which could also be important for synaptic plasticity.

### Future directions

Major issues still to be resolved include the physiological roles of the NCS family members that have been less studied (e.g., neurocalcin  $\delta$  and most of the CaBP family). All of the knockouts of NCS proteins have differing phenotypes, indicating a lack of redundancy of these proteins. To date, the only knockouts in mice for the CaBP family are for CaBP4 and 5 that may be expressed only in the retina in mice [43,44]. These mice have abnormalities in retinal function, and indeed mutations in human CaBP4 result in congenital stationary night blindness [45]. Knockouts of other CaBPs that are expressed in the brain would be informative. Various studies have made indirect links between NCS proteins and neuronal disease states, and the relationship of these proteins to neurological deficits requires further work as they could potentially be targets for pharmacological treatment of these disease processes [46]. Of further interest is the relationship between the described effects of these proteins on membrane traffic and on synaptic plasticity and whether these two aspects are causally related. Finally, while the structures of several of the NCS and CaBP proteins have been solved, there are still only a few examples of structural analysis of the sensors bound to their target proteins [23,24,47-49] and so additional structure/function studies would help to reveal more about the molecular basis of their actions as we currently know relatively little about how they regulate their target proteins.

### Abbreviations

ARF1, ADP-ribosylation factor 1; CaBP, calcium-binding protein; DREAM, downstream regulatory element antagonistic modulator; GCAP, guanylyl cyclase-activating protein; KChIP,  $\text{K}^+$  channel-interacting protein; LTD, long-term depression; NCS, neuronal calcium sensor; NMDA, *N*-methyl-D-aspartic acid; PI4K, phosphatidylinositol-4-kinase; PICK1, protein interacting with C kinase 1; TGN, trans-Golgi network; VILIP, visinin-like protein.

### Competing interests

The authors declare that they have no competing interests.

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