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

Robert D Burgoyne* and Lee P Haynes

Address: The Physiological Laboratory, School of Biomedical Sciences, University of Liverpool, Crown Street, Liverpool, L69 3BX, UK

* Corresponding author: Robert D Burgoyne (burgoyne@liv.ac.uk)

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

The electronic version of this article is the complete one and can be found at: <http://f1000.com/reports/biology/content/2/5>

Abstract

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

Introduction and context

Intracellular Ca^{2+} regulates many distinct aspects of neuronal function over a very wide range of timescales. The transduction of changes in Ca^{2+} concentration into a specific physiological outcome involves the action of Ca^{2+} -binding proteins that act as sensors and regulate the activity of various target proteins. Many Ca^{2+} sensors bind Ca^{2+} 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^{2+} , allowing them to respond with high sensitivity to small increases in neuronal cytosolic Ca^{2+} 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 δ , visinin-like protein (VILIP) 1-3, recoverin, guanylyl cyclase-activating proteins (GCAPs) 1-3, and K^{+} 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^{2+} binding and extrusion of their myristoyl tail (the Ca^{2+} /myristoyl switch). Other NCS proteins such as NCS-1 have their myristoyl tail exposed even in the absence of Ca^{2+} [8] and therefore can associate with membranes even at resting intracellular Ca^{2+} concentrations [9], allowing them to respond to short-duration and local Ca^{2+} 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^{2+} /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 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 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 β . 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 β 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 β control inner ear development in zebrafish [31]. Recently, CaBP7 and 8 were found to interact with PI4KIII β but, in contrast to NCS-1, inhibited the enzyme

activity at resting Ca^{2+} levels [32]. This inhibition was released on binding of NCS-1 at elevated Ca^{2+} levels, providing a tight 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 Ca^{2+} store. Release of 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 Ca^{2+} concentration (high- Ca^{2+}), NCS-1 binds to and activates phosphatidylinositol-4-kinase III β (PI4KIII β) (activated PI4KIII β 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 β at high Ca^{2+} . A further level of complexity in this model stems from a Ca^{2+} -dependent interaction between NCS-1 and the key Golgi trafficking GTPase ADP-ribosylation factor 1 (ARF1). At high Ca^{2+} , NCS-1 and ARF1 interact, preventing activation of PI4KIII β in regions where the two proteins coexist. Since ARF1 activates PI4KIII β independently of Ca^{2+} , this interplay may represent a mechanism for spatial organisation of the TGN into discrete subdomains tasked with serving either Ca^{2+} -dependent or Ca^{2+} -independent trafficking functions that are segregated by domain boundaries populated by non-productive ARF1/NCS-1 complexes. Under conditions of low local Ca^{2+} concentration (low- Ca^{2+}), NCS-1 no longer activates PI4KIII β 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 Ca^{2+} -dependent trafficking domains. Trafficking from ARF1-controlled domains could occur at both high and low 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 Ca^{2+} sensor in conjunction with another 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 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 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 δ 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, 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.

References

1. Burgoyne RD: **Neuronal calcium sensor proteins: generating diversity in neuronal Ca^{2+} signalling.** *Nat Rev Neurosci* 2007, **8**:182-93.
2. Haeseleer F, Sokal I, Verlinde CLMJ, Erdjument-Bromage H, Tempst P, Pronin AN, Benovic JL, Fariss RN, Palczewski K: **Five members of a**

- novel Ca^{2+} binding protein (CABP) subfamily with similarity to calmodulin.** *J Biol Chem* 2000, **275**:1247-60.
3. Seidenbecher CI, Langnaese K, Sanmarti-Vila L, Boeckers TM, Smalla K-H, Sabel BA, Garner CC, Gundelfinger ED, Kreutz MR: **Caldendrin, a novel neuronal calcium-binding protein confined to the somato-dendritic compartment.** *J Biol Chem* 1998, **273**:21324-31.
 4. Pongs O, Lindemeier J, Zhu XR, Theil T, Endelkamp D, Krah-Jentgens I, Lambrecht H-G, Koch KW, Schwemer J, Rivosecchi R, Mallart A, Galceran J, Canal I, Barbas JA, Ferrús A: **Frequenin—a novel calcium-binding protein that modulates synaptic efficacy in the drosophila nervous system.** *Neuron* 1993, **11**:15-28.
 5. Hendricks KB, Wang BQ, Schnieders EA, Thorner J: **Yeast homologue of neuronal frequenin is a regulator of phosphatidylinositol-4-OH kinase.** *Nat Cell Biol* 1999, **1**:234-41.
 6. Ames JB, Ishima R, Tanaka T, Gordon JL, Stryer L, Ikura M: **Molecular mechanics of calcium-myristoyl switches.** *Nature* 1997, **389**:198-202.
 7. O'Callaghan DW, Tepikin AV, Burgoyne RD: **Dynamics and calcium-sensitivity of the Ca^{2+} -myristoyl switch protein hippocalcin in living cells.** *J Cell Biol* 2003, **163**:715-21.
 8. Ames JB, Hendricks KB, Strahl T, Huttner IG, Hamasaki N, Thorner J: **Structure and calcium-binding properties of Frq1, a novel calcium sensor in the yeast *Saccharomyces cerevisiae*.** *Biochemistry* 2000, **39**:12149-61.
 9. O'Callaghan DW, Ivings L, Weiss JL, Ashby MC, Tepikin AV, Burgoyne RD: **Differential use of myristoyl groups on neuronal calcium sensor proteins as a determinant of spatio-temporal aspects of Ca^{2+} -signal transduction.** *J Biol Chem* 2002, **277**:14227-37.
 10. Mikhaylova M, Sharma Y, Reissner C, Nagel F, Aravind P, Rajini B, Smalla KH, Gundelfinger ED, Kreutz MR: **Neuronal Ca^{2+} signaling via caldendrin and calneurons.** *Biochim Biophys Acta* 2006, **1763**:1229-37.
 11. McCue HV, Burgoyne RD, Haynes LP: **Membrane targeting of the EF-hand containing calcium-sensing proteins CaBP7 and CaBP8.** *Biochem Biophys Res Commun* 2009, **380**:825-31.
 12. Makino CL, Dodd RL, Chen J, Burns ME, Roca A, Simon MI, Baylor DA: **Recoverin regulates light-dependent phosphodiesterase activity in retinal rods.** *J Gen Physiol* 2004, **123**:729-41.
- F1000 Factor 6.0 Must Read
Evaluated by Roger Hardie 18 Oct 2004
13. Mendez A, Burns ME, Sokal I, Dizhoor AM, Baehr W, Palczewski K, Baylor DA, Chen J: **Role of guanylate cyclase-activating proteins (GCAPs) in setting the flash sensitivity of rod photoreceptors.** *Proc Natl Acad Sci U S A* 2001, **98**:9948-53.
- F1000 Factor 3.0 Recommended
Evaluated by Roger Hardie 17 Sep 2001
14. Lee A, Westenbroek RE, Haeseleer F, Palczewski K, Scheuer T, Catterall WA: **Differential modulation of Cav2.1 channels by calmodulin and Ca^{2+} -binding protein I.** *Nat Neurosci* 2002, **5**:210-7.
 15. Hui H, McHugh D, Hannan M, Zeng F, Xu SZ, Khan SU, Levenson R, Beech DJ, Weiss JL: **Calcium-sensing mechanism in TRPC5 channels contributing to retardation of neurite outgrowth.** *J Physiol* 2006, **572**:165-72.
 16. An WF, Bowlby MR, Betty M, Cao J, Ling HP, Mendoza G, Hinson JW, Mattsson KI, Strassle BV, Trimmer JS, Rhodes KJ: **Modulation of A-type potassium channels by a family of calcium sensors.** *Nature* 2000, **403**:553-6.
 17. Yang PS, Alseikhan BA, Hiel H, Grant L, Mori MX, Yang W, Fuchs PA, Yue DT: **Switching of Ca^{2+} -dependent inactivation of $\text{Ca}_v1.3$ channels by calcium binding proteins of auditory hair cells.** *J Neurosci* 2006, **26**:10677-89.
- F1000 Factor 3.0 Recommended
Evaluated by Gerald Zamponi 30 Oct 2006
18. Tzingounis AV, Nicoll RA: **Contribution of KCNQ2 and KCNQ3 to the medium and slow afterhyperpolarization currents.** *Proc Natl Acad Sci U S A* 2008, **105**:19974-9.
- F1000 Factor 6.0 Must Read
Evaluated by Karl-Peter Giese 04 Feb 2009
19. Yang J, McBride S, Mak D-OD, Vardi N, Palczewski K, Haeseleer F, Foskett JK: **Identification of a family of calcium sensors as protein ligands of inositol trisphosphate receptor Ca^{2+} release channels.** *Proc Natl Acad Sci U S A* 2002, **99**:7711-6.
- F1000 Factor 6.0 Must Read
Evaluated by Mitsuhiro Ikura 07 Apr 2003
20. Haynes LP, Tepikin AV, Burgoyne RD: **Calcium Binding Protein I is an inhibitor of agonist-evoked, inositol 1,4,5-trisphosphate-mediated calcium signalling.** *J Biol Chem* 2004, **279**:547-55.
 21. Iketani M, Imaizumi C, Nakamura F, Jeromin A, Mikoshiba K, Goshima Y, Takei K: **Regulation of neurite outgrowth mediated by neuronal calcium sensor-1 and inositol 1,4,5-trisphosphate receptor in nerve growth cones.** *Neuroscience* 2009, **161**:743-52.
 22. Kasri NN, Holmes AM, Bultynck G, Parys JB, Bootman MD, Rietdorf K, Missiaen L, McDonald F, De Smedt H, Conway SJ, Holmes AB, Berridge MJ, Roderick HL: **Regulation of InsP_3 receptor activity by neuronal Ca^{2+} -binding proteins.** *EMBO J* 2004, **23**:312-21.
 23. Pioletti M, Findeisen F, Hura GL, Minor DL: **Three-dimensional structure of the KChIP1-Kv4.3 T1 complex reveals a cross-shaped octamer.** *Nat Struct Mol Biol* 2006, **13**:987-95.
 24. Wang H, Yan Y, Liu Q, Huang Y, Shen Y, Chen L, Chen Y, Yang Q, Hao Q, Wang K, Chai J: **Structural basis for modulation of Kv4 K(+) channels by auxiliary KChIP subunits.** *Nat Neurosci* 2007, **10**:32-9.
 25. Hasdemir B, Fitzgerald DJ, Prior IA, Tepikin AV, Burgoyne RD: **Traffic of Kv4 K+ channels mediated by KChIP1 is via a novel post-ER vesicular pathway.** *J Cell Biol* 2005, **171**:459-69.
- F1000 Factor 4.9 Must Read
Evaluated by Elizabeth Smythe 29 Nov 2005, David Stephens 08 Dec 2005, Bettina Winckler 31 Oct 2006
26. Horton AC, Ehlers MD: **Dual modes of endoplasmic reticulum-to-golgi transport in dendrites revealed by live-cell imaging.** *J Neurosci* 2003, **23**:6188-99.
- F1000 Factor 6.4 Must Read
Evaluated by Robert Burgoyne 21 Jul 2003, Bettina Winckler 10 Sep 2003
27. Lin L, Jeanclous EM, Treuil M, Braunewell K-H, Gundelfinger ED, Anand R: **The calcium sensor protein visinin-like protein-1 modulates the surface expression and agonist sensitivity of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor.** *J Biol Chem* 2002, **277**:41872-8.
- F1000 factor 3.0 Recommended
Evaluated by Robert Burgoyne 31 Oct 2002
28. Kabbani N, Negyessy L, Lin R, Goldman-Rakic P, Levenson R: **Interaction with the neuronal calcium sensor NCS-1 mediates desensitization of the D2 dopamine receptor.** *J Neurosci* 2002, **22**:8476-86.
- F1000 Factor 3.0 Recommended
Evaluated by Robert Burgoyne 21 Oct 2002
29. Haynes LP, Thomas GMH, Burgoyne RD: **Interaction of neuronal calcium sensor-1 and ARF1 allows bidirectional control of PI(4) kinase and TGN-plasma membrane traffic.** *J Biol Chem* 2005, **280**:6047-54.
- F1000 Factor 3.0 Recommended
Evaluated by Antonella De Matteis 08 Dec 2004
30. Haynes LP, Sherwood MW, Dolman NJ, Burgoyne RD: **Specificity, promiscuity and localization of ARF protein interactions with**

- NCS-I and phosphatidylinositol-4 kinase-IIIb.** *Traffic* 2007, **8**:1080-92.
31. Petko JA, Kabbani N, Frey C, Woll M, Hickey K, Craig M, Canfield VA, Levenson R: **Proteomic and functional analysis of NCS-I binding proteins reveals novel signaling pathways required for inner ear development in zebrafish.** *BMC Neurosci* 2009, **10**:27.
 32. Mikhaylova M, Reddy PP, Munsch T, Landgraf P, Suman SK, Smalla KH, Gundelfinger ED, Sharma Y, Kreutz MR: **Calneurons provide a calcium threshold for trans-Golgi network to plasma membrane trafficking.** *Proc Natl Acad Sci U S A* 2009, **106**:9093-8.
- F1000 Factor 3.0 Recommended
Evaluated by Robert Burgoyne 14 Jul 2009
33. Nakamura TY, Jeromin A, Smith G, Kurushima H, Koga H, Nakabeppu Y, Wakabayashi S, Nabekura J: **Novel role of neuronal Ca^{2+} sensor-1 as a survival factor up-regulated in injured neurons.** *J Cell Biol* 2006, **172**:1081-91.
- F1000 Factor 3.0 Recommended
Evaluated by Robert Burgoyne 12 May 2006
34. Gomez M, De Castro E, Guarín E, Sasakura H, Kuhara A, Mori I, Bartfai T, Bargmann CI, Nef P: **Ca^{2+} signalling via the neuronal calcium sensor-1 regulates associative learning and memory in *C. elegans*.** *Neuron* 2001, **30**:241-8.
 35. Sippy T, Cruz-Martin A, Jeromin A, Schweizer FE: **Acute changes in short-term plasticity at synapses with elevated levels of neuronal calcium sensor-1.** *Nat Neurosci* 2003, **6**:1031-8.
- F1000 Factor 6.0 Must Read
Evaluated by Robert Burgoyne 21 Oct 2003
36. Jo J, Heon S, Kim MJ, Son GH, Park Y, Henley JM, Weiss JL, Sheng M, Collingridge GL, Cho K: **Metabotropic glutamate receptor-mediated LTD involves two interacting Ca^{2+} sensors, NCS-I and PICK1.** *Neuron* 2008, **60**:1095-111.
 37. Saab BJ, Georgiou J, Nath A, Lee FJ, Wang M, Michalon A, Liu F, Mansuy IM, Roder JC: **NCS-I in the dentate gyrus promotes exploration, synaptic plasticity, and rapid acquisition of spatial memory.** *Neuron* 2009, **63**:643-56.
- F1000 Factor 8.0 Exceptional
Evaluated by Robert Burgoyne 22 Sep 2009, Neil Burgess 30 Nov 2009
38. Kobayashi M, Masaki T, Hori K, Masuo Y, Miyamoto M, Tsubokawa H, Noguchi H, Nomura M, Takamatsu K: **Hippocalcin-deficient mice display a defect in cAMP response element-binding protein activation associated with impaired spatial and associative memory.** *Neuroscience* 2005, **133**:471-84.
 39. Palmer CL, Lim W, Hastie PG, Toward M, Korolchuk VI, Burbidge SA, Banting G, Collingridge GL, Isaac JT, Henley JM: **Hippocalcin functions as a calcium sensor in hippocampal LTD.** *Neuron* 2005, **47**:487-94.
 40. Carrion AM, Link WA, Ledo F, Mellstrom B, Naranjo JR: **DREAM is a Ca^{2+} -regulated transcriptional repressor.** *Nature* 1999, **398**:80-4.
 41. Cheng HY, Pitcher GM, Laviolette SR, Whishaw IQ, Tong KI, Kockeritz LK, Wada T, Joza NA, Crackower M, Goncalves J, Sarosi I, Woodgett JR, Oliveira-dos-Santos AJ, Ikura M, van der Kooy D, Salter MW, Penninger JM: **DREAM is a critical transcriptional repressor for pain modulation.** *Cell* 2002, **108**:31-43.
- F1000 Factor 6.5 Must Read
Evaluated by Stephen McMahon 18 Jan 2002, Ueli Schibler 24 Jan 2002, Peggy Mason 25 Jan 2002
42. Dieterich DC, Karpova A, Mikhaylova M, Zdobnova I, König I, Landwehr M, Kreutz M, Smalla KH, Richter K, Landgraf P, Reissner C, Boeckers TM, Zuschratter W, Spilker C, Seidenbecher CI, Garner CC, Gundelfinger ED, Kreutz MR: **Caldendrin-Jacob: a protein liaison that couples NMDA receptor signalling to the nucleus.** *PLoS Biol* 2008, **6**:e34.
- F1000 Factor 3.0 Recommended
Evaluated by Hilmar Bading 11 Mar 2008
43. Haeseleer F, Imanishi Y, Maeda T, Possin DE, Maeda A, Lee A, Rieke F, Palczewski K: **Essential role of Ca^{2+} -binding protein 4, a $\text{Ca}_v1.4$ channel regulator in photoreceptor synaptic function.** *Nat Neurosci* 2004, **7**:1079-87.
- F1000 Factor 4.8 Must Read
Evaluated by Annette Dolphin 04 Oct 2004, Gordon Fain 19 Nov 2004
44. Rieke F, Lee A, Haeseleer F: **Characterization of Ca^{2+} -binding protein 5 knockout mouse retina.** *Invest Ophthalmol Vis Sci* 2008, **49**:5126-35.
 45. Zeitz C, Kloeckener-Gruissem B, Forster U, Kohl S, Magyar I, Wissinger B, Mátyás G, Borruat FX, Schorderet DF, Zrenner E, Munier FL, Berger WW: **Mutations in *CABP4*, the gene encoding the Ca^{2+} -binding protein 4, cause autosomal recessive night blindness.** *Am J Hum Genet* 2006, **79**:657-67.
 46. Braunewell K-H: **The darker side of Ca^{2+} signaling by neuronal Ca^{2+} -sensor proteins: from Alzheimer's disease to cancer.** *Trends Pharmacol Sci* 2005, **26**:345-51.
 47. Li C, Chan J, Haeseleer F, Mikoshiba K, Palczewski K, Ikura M, Ames JB: **Structural insights into Ca^{2+} -dependent regulation of inositol 1,4,5-trisphosphate receptors by *CaBP1*.** *J Biol Chem* 2009, **284**:2472-81.
 48. Ames JB, Levay K, Wingard JN, Lusin JD, Slepak VZ: **Structural basis for calcium-induced inhibition of rhodopsin kinase by recoverin.** *J Biol Chem* 2006, **281**:37237-45.
 49. Strahl T, Huttner IG, Lusin JD, Osawa M, King D, Thorner J, Ames JB: **Structural insights into activation of phosphatidylinositol 4-kinase (*pik1*) by yeast frequenin (*Frq1*).** *J Biol Chem* 2007, **282**:30949-59.