The role of neuronal calcium sensors in balancing synaptic plasticity and synaptic dysfunction

Talitha L. Kerrigan1, Daniel J. Whitcomb1,*, Philip L. Regan1,2 and Kwangwook Cho1,2*

1 Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, School of Clinical Sciences, Faculty of Medicine and Dentistry, University of Bristol, Bristol, UK
2 MRC Centre for Synaptic Plasticity, University of Bristol, Bristol, UK
*Correspondence: d.j.whitcomb@bristol.ac.uk; kw.cho@bristol.ac.uk

INTRODUCTION

Ca2+ signaling plays an important role in diverse biological processes, ranging from gene expression to cellular development (Sheng et al., 1991; Means, 1994; Park et al., 2007). Cellular Ca2+ sources are abundant and include the mitochondria, endoplasmic reticulum, lysosome, and extracellular environment. Changes in Ca2+ mobilization from this array of “Ca2+ stores” serve as the primary factor in the regulation of Ca2+ sensors and the subsequent activity of various substrates (Rosen et al., 1994; Moldoveanu et al., 2002; Burgoyne, 2007). Accordingly, uncovering the mechanisms underlying the activation and function of various Ca2+ sensors is fundamental to developing our understanding of dynamic neuronal responses to Ca2+ signals. Controlling synaptic transmission, modulating neuronal excitability, and, in particular, the focus of this review, regulating synaptic plasticity (Berridge, 2000).

Although a few exceptional cases of Ca2+-independent forms of synaptic plasticity have been reported (Fitzjohn et al., 2001; Dickman et al., 2009), it is widely accepted that the majority of synaptic long-term plasticity operates through Ca2+-dependent mechanisms. Tetanic high frequency stimulation of presynaptic regions in the hippocampus induces a rise in postsynaptic Ca2+, leading to long-term potentiation (LTP) (Malenka et al., 1986, Lisman, 1989). Conversely, low frequency stimulation induces a low-to-moderate rise in free intracellular Ca2+, producing long-term depression (LTD) (Mulkey et al., 1994). These different and specific effects suggest that Ca2+ is involved in the induction of LTP as well as LTD, and that the magnitudes of activity-dependent rises in free Ca2+ and Ca2+-mobilization from different sources determines the induction of LTP and LTD (Lisman, 1989; Artola and Singer, 1993; Cho et al., 2001).

Thought to be central to this functional dichotomy are Ca2+-regulated enzymes. For example, LTP-inducing Ca2+ rises are detected by calmodulin (CaM; Mulkey et al., 1993) and activate Ca2+/calmodulin-dependent kinases (CaMKs; Malenka et al., 1986), while LTD-inducing Ca2+ signals activate a calcineurin/inhibitor-1 phosphatase cascade (Mulkey et al., 1994). These Ca2+-sensitive molecules play a key role in neuronal function through the regulation of glutamate receptor trafficking and synaptic plasticity in various regions of the brain (Palmer et al., 2005; Burgoyne, 2007; Jo et al., 2008, 2010). This is achieved either through direct interaction with cargo molecules, or through regulation of protein membrane trafficking (Palmer et al., 2005; Jo et al., 2008, 2010).

Recently, neuronal calcium sensors (NCS) have been shown to interact with endocytic molecules involved in glutamate receptor trafficking (Figures 1A,B; Palmer et al., 2005; Jo et al., 2008, 2010). More specifically, these Ca2+ sensors interact with several downstream effectors involved in AMPAR trafficking, including ARB/Grip (Chung et al., 2000), adaptor protein 2 (AP2; Lee et al., 2002; Palmer et al., 2005), the Arp2/3 complex (Bocca et al., 2008), and PSD-95 (Kim et al., 2007). Here we will discuss how NCS proteins serve to orchestrate LTD signaling, and what makes them unique to one another in their roles in synaptic plasticity.

Neuronal calcium sensors (NCS) readily bind calcium and undergo conformational changes enabling them to interact and regulate specific target molecules. These interactions lead to dynamic alterations in protein trafficking. Emerging evidence suggests that NCS and alterations in Ca2+ mobilization modulate glutamate receptor trafficking, subsequently determining the expression of different forms of synaptic plasticity. In this review, we aim to discuss the functional relevance of NCS in protein trafficking and their emerging role in synaptic plasticity. Their significance within the concept of “translational neuroscience” will also be highlighted, by assessing their potential as key molecules in neurodegeneration.

Keywords: neuronal calcium sensor, long-term synaptic plasticity, Alzheimer’s disease
FIGURE 1 | Ca^{2+} sensors and LTD. Schematic diagram showing different Ca^{2+} sensors regulate distinct forms of LTD. (A) The activation of NMDARs results in Ca^{2+} entry in the neuron. Ca^{2+} entry through NMDARs is sensed by hippocalcin, activating the myristoyl switch and stimulating the binding to β-adaptin of the AP2 complex, resulting in its translocation to the plasma membrane. AP2 is then able to bind with the GluA2 subunit of AMPARs, recruiting clathrin. Finally, hippocalcin is displaced by clathrin, and AMPARs are internalized. (B) AMPARs are stabilized at the synapse through interactions with GRIP. Activation of the G-protein coupled metabotropic glutamate receptor (mGluR), specifically the mGluR5-isoform containing receptor, induces the release of Ca^{2+} from intracellular stores. Increased levels of Ca^{2+} trigger the association of PICK1 with NCS-1. PICK1 interacts with PKC. NCS-1 localizes PICK1 in close proximity with AMPARs, facilitating the PKC-mediated phosphorylation of GluA2. This releases AMPARs from the GRIP interaction, matching them for synaptic removal via endocytosis. (C) Hippocalcin in bound with the SH3 domain of PSD-95. This interacts with the NMDAR subunit GluN2B. These interactions prevent the binding of AP2, required for dynamin and clathrin-dependent endocytosis. Activation of the G-protein coupled mAChR induces the release of Ca^{2+} from intracellular stores. Increased levels of Ca^{2+} are sensed by hippocalcin. As a consequence of this, PSD-95 dissociates from NMDARs. AP2 is now free to bind with NMDARs and initiate their endocytosis. (D) The hypothetical model of Ca^{2+}-mediated Aβ toxicity. The aberrant activation of synaptic receptors leads to enhanced Ca^{2+} influx from both extracellular sites and intracellular Ca^{2+} stores. Ca^{2+} entry via NMDARs can impair mitochondrial function, leading to the release of cytochrome c and the formation of the apoptosome. This activates caspase-3, which cleaves and inhibits Akt-1. Given that Akt-1 ordinarily functions to phosphorylate GSK-3β and thereby downregulate the activity of GSK-3β, without this constitutive inhibition GSK-3β is now able to induce AMPAR endocytosis (Lopez et al., 2008; Li et al., 2009; Jo et al., 2011). Similarly, sustained release of Ca^{2+} from intracellular stores is likely to be sensed by, for example, PICK1. One likely consequence of this is the induction of LTD-signaling mechanisms and the endocytosis of AMPARs.

NEURONAL CALCIUM SENSORS

Neuronal calcium sensors proteins are a subgroup of proteins belonging to the EF-hand super family (Pongs et al., 1993; for detail of their structural and functional properties, we refer the reader to a number of excellent comprehensive reviews that cover these issues in great depth; Burgoyne, 2007; Ames et al., 2012; Burgoyne and Haynes, 2012). NCS proteins are widely expressed in neurons throughout the nervous system, and are able to regulate axonal outgrowth and synaptic transmission (Pongs et al., 1993; Olafsson et al., 1997). Upon Ca^{2+} binding, they exhibit the distinct property of being able to associate with the plasma membrane, via the post-translational addition of a myristoyl group (Ames et al., 1997). Such functional characteristics (among others to be discussed) render these proteins particularly adept at regulating synaptic receptor movement in response to neuronal activation, a fundamental prerequisite for the regulation of synaptic plasticity.

NCS AND LTD

Activation of NMDAR and metabotropic glutamate receptor (mGluR) induces both NMDAR-dependent and mGluR-dependent
LTD (NMDAR-LTD, mGluR-LTD respectively; see review Anwyl, 2006). Importantly, induction mechanisms of NMDAR- and mGluR-LTD are mediated by different Ca²⁺-dependent signaling pathways, involving different Ca²⁺ sensors (Jo et al., 2008; Figure 1B). These two distinct forms of LTD are conferred by different Ca²⁺ sensitivities and/or conformational changes of particular intracellular Ca²⁺ binding proteins. Accordingly, whilst NMDAR-LTD requires CaM and hippocalcin, mGluR-LTD involves NCS-1, protein kinase C (PKC), and IP3 (Jo et al., 2008). This suggests that distinct properties of Ca²⁺ sensors not only control the induction of LTD, but also maintain and regulate specificity of various signaling cascades. Given the physiological importance of different forms of Ca²⁺ sensors in LTD, the selective behavior of these proteins is undoubtedly significant in receptor trafficking, particularly receptor endocytosis.

**NCS-1, PICK1, AND AMPA RECEPTOR ENDOCYTOSIS**

Neuronal calcium sensor-1, first described as a regulator of synaptic transmission at the neuromuscular junction in *Drosophila* and Xenopus (Pongs et al., 1991; Olafsson et al., 1997), is highly expressed throughout the brain (Paternini et al., 2000). NCS-1 interacts with protein kinase interacting with C kinase 1 (PICK1) and regulates synaptic plasticity in the perirhinal cortex (Jo et al., 2008). NCS-1 binds directly to PICK1 via its Bin/Ampiphysin/Rvs (BAR) domain, in a Ca²⁺-dependent manner. The PICK1-BAR domain dimerizes, forming a concave arrangement. This unique conformation is thought to act as a "curvature sensor" (Peter et al., 2004), serving as a means of interaction between PICK1 and curved lipid membranes, like those of endocytic vesicles (He et al., 2011). The surface of the PICK1-BAR domain consists of positively charged regions, which mediate non-covalent interactions with negatively charged lipids. Accordingly, changes in membrane charges could dynamically regulate the membrane-localization of PICK1 (Jin et al., 2006), a possible crucial factor in synaptic plasticity. PICK1 plays a key role in mediating the interaction between GluA2 of AMPARs and synaptic stabilizing structures, and accordingly can function to promote receptor endocytosis (Chung et al., 2000; Xia et al., 2000; Hanley and Henley, 2003). Again, the BAR domain plays a central part here; PICK1 binds with phosphoinositide lipids through the BAR domain, and this lipid/BAR interaction is essential for the synaptic targeting of PICK1 (Jin et al., 2006). Specifically, the BAR domain interacts with lipids of endocytic vesicles, mediating the internalization of PICK1 and associated synaptic receptors. Accordingly, it was shown that expression of a mutant BAR domain-containing PICK1 (K266, 268E) prevented the endocytosis of GluA2-containing AMPARs and enhanced AMPAR-mediated synaptic transmission (Jin et al., 2006). Interestingly, PICK1 itself is also a Ca²⁺ sensor (Hanley and Henley, 2003), and can regulate AMPAR endocytosis through an actin depolymerization (Rocca et al., 2008). Thus, it is thought that the association of PICK1 with NCS-1 might serve to target PICK1 to the vicinity of AMPARs to initiate their removal from the synapse, providing a distinctive role for NCS-1 in LTD (Jo et al., 2008).

**Ca²⁺ DYSREGULATION AND NEURODEGENERATION: ARE CALCIUM SENSORS THE KEY?**

Dysregulation of Ca²⁺ is well documented in the "Ca²⁺-theory" of neurodegenerative diseases, involving excitatory toxicity and mitochondria-mediated apoptosis (Khachaturian, 1987; Schneider et al., 2001). For example, changes in [Ca²⁺], can induce a concomitant change in mitochondrial Ca²⁺ ([Ca²⁺]m), leading to an increase of reactive oxygen species (ROS) production and the release of cytochrome c (Jiang et al., 2001; Brustovetsky et al., 2003). Released cytochrome c binds apoptotic protease activating factor 1 (Apaf-1) and triggers the caspase cascade and cell death (Hengartner, 2000). Given the significance of disrupted Ca²⁺ homeostasis to enhanced oxidative stress and neuronal loss evident in neurodegenerative diseases, here we discuss how Ca²⁺ and Ca²⁺ sensor-mediated receptor trafficking may affect synaptic function during Alzheimer’s disease (AD).

Large bodies of evidence support that amyloid-β peptide (Aβ) induces the dysregulation of Ca²⁺ homeostasis and leads to activation of pro-apoptotic signal cascades (Ekinci et al., 2008;
VILIP-1 was reduced in AD brains compared with age-matched controls. Artola, A., and Singer, W. (1993). Neuron 8, 198–202.

Ames, J. B., Sunghyuk, L., and Ikura, M. (2001). Nucleic Acids Res. 30, 489–497.

Ames, J. B., Sunghyuk, L., and Ikura, M. (2012). Molecular structure and target recognition of neuronal calcium sensors. Trends Neurosci. 35, 673–686.

Bernstein, H. G. (2001). Abnormal localization of two neuronal calcium-sensor proteins, vizinin-like proteins (vilips)-1 and -3, in neocortical brain areas of Alzheimer disease patients. Dement. Geriatr. Cogn. Disord. 12, 110–116.

Berridge, M. J. (2000). Neuronal calcium signaling. Physiol. Rev. 80, 185–235.

Berridge, M. J. (2007). Neuronal calcium sensor proteins: generalizing diversity in neuronal signalling. Nat. Rev. Neurosci. 8, 182–193.

Bortolotto, Z. A. (2013). Long-term depression of excitatory synaptic transmission and its relationship to long-term potentiation. Trends Neurosci. 36, 489–497.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.

Bourgeois, É. D., Bogerts, B., and Gundelfinger, E. D. (1997). Molecular mechanics of hippocampal L TD. J. Neurosci. 17, 7362–7370.
Neuronal calcium sensors and synaptic plasticity

Heikinheimo, K. (2001). CREB: a Ca2+-regulated transcription factor phosphorylated by calmodulin-dependent kinase. Science 292, 1420-1423.

Smith, Z. J., Groen, K. N., and Laferla, F. M. (2005). Calcium dysregulation in Alzheimer's disease: recent advances gained from genetically modified animals. Cell Calcium 38, 427-457.

Windsor, J. M. (2001). Mutant presenilins disturb neuronal calcium homeostasis in the brain of transgenic mice, decreasing the threshold for excitotoxicity and facilitating long-term potentiation. J. Biol. Chem. 276, 15359-15364.

Schiano, R., Bernstein, H. G., Riederer, P., and Braunewell, K. H. (2001). The neuronal calcium sensor VILIP-1 is associated with amyloid plaques and extracellular tangles in Alzheimer's disease and promotes cell death and tau phosphorylation in vitro: a link between calcium sensors and Alzheimer's disease. Neurobiol. Dis. 8, 903-909.

Shanker, G. M., Bloodgood, B. L., Towne, M., Walsh, D. M., Selkoe, D. J., and Sabatini, B. L. (2007). Natural oligomers of the Alzheimer amyloid-beta protein induce reversible enzalutema loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. J. Neuroscience 27, 2866-2875.

Sheng, M., Greenberg, M. E., and Schinder, J. (1991). CREB: a Ca2+-regulated transcription factor phosphorylated by calmodulin-dependent kinase. Science 252, 1420-1423.

Smith, Z. J., Groen, K. N., and Laferla, F. M. (2005). Calcium dysregulation in Alzheimer's disease: recent advances gained from genetically modified animals. Cell Calcium 38, 427-457.
Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 01 March 2012; accepted: 07 April 2012; published online: 04 May 2012.

Citation: Kerrigan TL, Whitcomb DJ, Regan PL and Cho K. (2012) The role of neuronal calcium sensors in balancing synaptic plasticity and synaptic dysfunction. Front. Mol. Neurosci. 5:57. doi: 10.3389/fnmol.2012.00057

Copyright © 2012 Kerrigan, Whitcomb, Regan and Cho. This is an open-access article distributed under the terms of the Creative Commons Attribution Non Commercial License, which permits non-commercial use, distribution, and reproduction in other forums, provided the original authors and source are credited.