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

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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 that significantly impact upon synaptic function. Emerging evidence suggests that NCS and alterations in Ca^{2+} 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

INTRODUCTION

Ca^{2+} 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 Ca^{2+} sources are abundant and include the mitochondria, endoplasmic reticulum, lysosome, and extracellular environment. Changes in Ca^{2+} mobilization from this array of "Ca^{2+} stores" serve as the primary factor in the regulation of Ca^{2+} 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 Ca^{2+} sensors is fundamental to developing our understanding of dynamic neuronal responses to Ca^{2+}; controlling synaptic transmission, modulating neuronal excitability, and, the particular focus of this review, regulating synaptic plasticity (Berridge, 2000).

Although a few exceptional cases of Ca^{2+}-independent forms of synaptic plasticity have been reported (Fitzjohn et al., 2001; Dickinson et al., 2009), it is widely accepted that the majority of synaptic long-term plasticity operates through Ca^{2+}-dependent mechanisms. Tetanic high frequency stimulation of presynaptic regions in the hippocampus induces a rise in postsynaptic Ca^{2+}, 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 Ca^{2+}, producing long-term depression (LTD) (Mulkey et al., 1994). These different and specific effects suggest that Ca^{2+} is involved in the induction of LTP as well as LTD, and that the magnitudes of activity-dependent rises in free Ca^{2+} and Ca^{2+} 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 Ca^{2+}-regulated enzymes. For example, LTP-inducing Ca^{2+} rises are detected by calmodulin (CaM; Mulkey et al., 1993) and activate Ca^{2+}/calmodulin-dependent kinases (CaMKs; Malenka et al., 1986), while LTD-inducing Ca^{2+} signals activate a calcineurin/inhibitor-1 phosphatase cascade (Mulkey et al., 1994). These Ca^{2+}-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 Ca^{2+} sensors interact with several downstream effectors involved in AMPAR trafficking, including ABP/GRIP (Chung et al., 2000), adaptor protein 2 (AP2; Lee et al., 2002; Palmer et al., 2005), the Arp2/3 complex (Rocca 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.

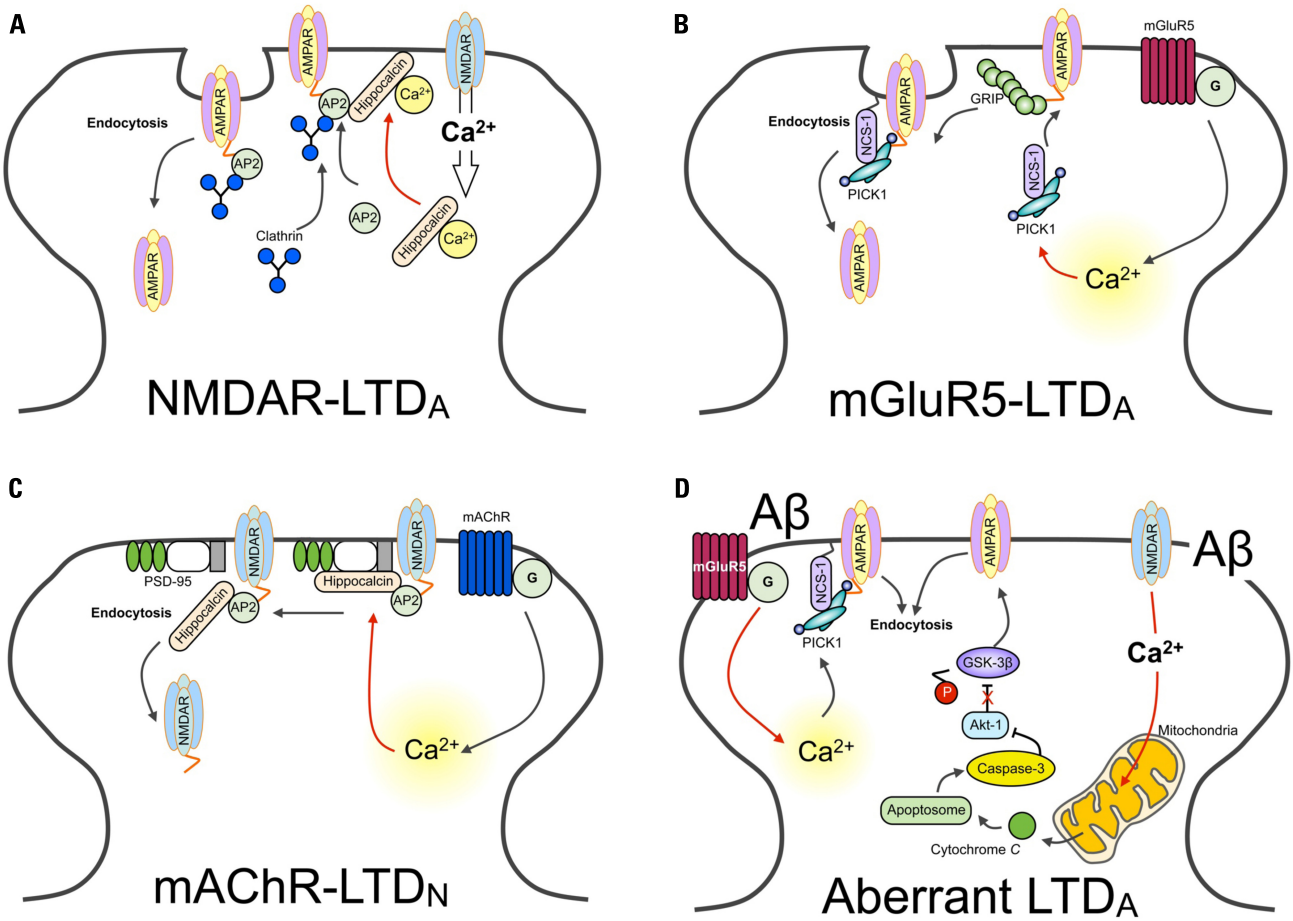

FIGURE 1 | Ca^{2+} sensors and LTD. Schematic diagram showing different Ca^{2+} sensors regulate distinct forms of LTD. **(A)** The activation of NMDARs results in Ca^{2+} entry in the neuron. Ca^{2+} entry through NMDARs is sensed by hippocalcin, activating the myristoyl switch and stimulating the binding 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, mobilizing 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 disassociates 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 Ca^{2+}-dependent signaling pathways, involving different Ca^{2+} sensors (Jo et al., 2008; **Figure 1B**). These two distinct forms of LTD are conferred by different Ca^{2+} sensitivities and/or conformational changes of particular intracellular Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} 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., 1993; Olafsson et al., 1997), is highly expressed throughout the brain (Paterlini 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/Amphiphysin/Rvs (BAR) domain, in a Ca^{2+}-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 GluA2/3 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, 2005). 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 Ca^{2+} sensor (Hanley and Henley, 2005), and can regulate AMPAR endocytosis through 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).

HIPPOCALCIN AND LTD

Emerging findings have outlined an important role for hippocalcin, a member of the visinin-like (VSNL) family proteins (VSNLs), in regulating dynamic neuronal synaptic change. It has previously been shown that NMDAR-mediated Ca^{2+} entry into neurons results in the hippocalcin-dependent internalization of AMPARs (Palmer et al., 2005). Here, it was shown that hippocalcin interacts with the AP2 adaptor complex subunit β2-adaptin (**Figure 1A**). This, in turn, binds with the GluA2/3 AMPAR subunit – an interaction that is Ca^{2+}-dependent – and promotes its clathrin-mediated endocytosis. In this study, the infusion of a dominant negative truncated form of hippocalcin (Hip^{2-72}), an N-terminal region of the protein that does not include Ca^{2+} binding domains and is required for β2-adaptin interaction, inhibits the induction of LTD. Critically, this hippocalcin-mediated mechanism appears to be specific for LTD, as there was no effect found on the induction of LTP, though the same NMDAR-mediated Ca^{2+} influx is involved in LTP and LTD.

A more recent study has found evidence to suggest that under basal conditions, hippocalcin binds with the SH3 region of PSD-95, and that muscarinic acetylcholine receptor (mAChR)-induced intracellular Ca^{2+} release induces the translocation of hippocalcin to the plasma membrane (**Figure 1C**). This leads to the dissociation of PSD-95 from NMDARs, allowing for the binding of AP2 to NMDARs to result in their endocytosis (Jo et al., 2010). Therefore, given the associate relationship between hippocalcin and the endocytosis of AMPARs, it is likely that hippocalcin could discriminate and respond to two distinct forms of intracellular Ca^{2+} mobilization (i.e., NMDAR- and mAChR-mediated). It is clear, therefore, that NCS-1 and hippocalcin are central regulators of receptor trafficking, pivotal in the expression of physiological LTD. Here, these NCS proteins activate key LTD molecules to induce both AMPAR and NMDAR internalization. Further work is required, however, to fully characterize how the same Ca^{2+} sensor can detect two distinct Ca^{2+} mobilizations and induce distinct receptor trafficking.

Ca^{2+} DYSREGULATION AND NEURODEGENERATION: ARE CALCIUM SENSORS THE KEY?

Dysregulation of Ca^{2+} is well documented in the "Ca^{2+} theory of neurodegenerative disease," involving excitatory toxicity and mitochondria-mediated apoptosis (Khachaturian, 1987; Schneider et al., 2001). For example, changes in $[Ca^{2+}]_i$ can induce a concomitant change in mitochondrial Ca^{2+} ($[Ca^{2+}]_m$), 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 Ca^{2+} homeostasis to enhanced oxidative stress and neuronal loss evident in neurodegenerative diseases, here we discuss how Ca^{2+} and Ca^{2+} sensor-mediated receptor trafficking may affect synaptic function during Alzheimer's disease (AD).

Large bodies of evidence support that amyloid-beta peptide (Aβ) induces the dysregulation of Ca^{2+} homeostasis and leads to activation of pro-apoptotic signal cascades (Ekinci et al., 2000;

Smith et al., 2005; Lopez et al., 2008). Surprisingly however, a role for Ca^{2+} sensors in this pathogenesis has not yet been unambiguously demonstrated. Aβ-induced $[Ca^{2+}]_i$ rises have been shown to regulate calsenilin, a KChIP subfamily of NCS, and its binding with the pro-apoptotic C-terminus of presenilin-2 (PS2; Buxbaum et al., 1998; Jo et al., 2005). The calsenilin–PS2 association leads to an increase in apoptosis and APP production (Jo et al., 2005; Jang et al., 2011). Additionally, the Ca^{2+} sensor visinin-like protein (VILIP) has been shown to associate with amyloid plaques and its expression enhances phosphorylation of tau, an additional hallmark of AD brains (Schnurra et al., 2001). In contrast to this finding, however, expression of VILIP-1 was reduced in AD brains compared with age-matched brain samples (Braunewell et al., 2001). Together, such studies currently paint a somewhat undefined picture as the exact role of NCS in AD pathology. Nevertheless, these studies do indicate that the aberrant regulation of Ca^{2+} sensors could underlie the development of AD, and this concept certainly warrants future investigation.

Caspase has been implicated as a key LTD molecule in the hippocampus and is involved in Aβ-mediated synaptic dysfunction (Li et al., 2010; Jo et al., 2011). Recently, it has been revealed that synaptic impairment caused by Aβ is mediated by a caspase–Akt-1–GSK3β signal cascade (termed the CAG cascade; Li et al., 2010; Jo et al., 2011). Interestingly, Aβ induces aberrant synaptic plasticity, leads to the inhibition of LTP but facilitation of LTD, and causes AMPAR endocytosis (Kim et al., 2001; Walsh et al., 2002; Hsieh et al., 2006; Shankar et al., 2007, 2008; Li et al., 2009). Thus, it is perhaps not surprising that the Aβ-mediated activation of the CAG cascade leads to the facilitation of LTD (**Figure 1D**). As we have described in this review, NCS-1, hippocalcin, and PICK1 are key molecules in the signaling underlying the induction of LTD and AMPAR and NMDAR endocytosis (Hanley and Henley, 2005; Citri et al., 2010; Jo et al., 2010). It would therefore be of great interest to investigate whether NCS could be aberrantly regulated during AD pathology.

As suggested in **Figure 1C**, activation of mAChR regulates NMDAR trafficking through a hippocalcin and PSD-95-mediated mechanism. Given the importance of enhancing cholinergic transmission and downregulating NMDAR transmission – strategies used as clinically approved AD treatments (e.g., memantine) – the role played by this NCS in receptor trafficking could provide a potential therapeutic target for Aβ-mediated synaptic dysfunction.

CONCLUDING REMARKS

Ca^{2+} signals can be "detected (sensor)" and "translated (switch)" to effectors. "Sensing" and "switching" should be tightly controlled to maintain effective homeostatic regulation in neurons. Growing evidence supports the notion that NSC and PICK1 have a key role in the endocytosis of glutamate receptors, a major molecular mechanism of LTD at excitatory synapses. Interestingly, Aβ-mediated neurotoxicity has been linked with excessive intracellular Ca^{2+} and aberrant synaptic plasticity. Thus our assumption is that overactive AMPAR endocytosis (or excessive LTD) caused by hyperactive NCS is likely to be found in AD or Aβ-induced neurotoxicity models. Therefore, it is of great interest to examine how NCS are involved in neurotoxicity and synaptic dysfunction. What is evident is the fact that intracellular Ca^{2+} mobilization, which includes mitochondrial Ca^{2+} flux and Ca^{2+} sensing, is a fundamental process in both physiological and pathological states. Through this review, we have aimed to bring new insight into NCS and synaptic plasticity, and provide a potential translation to synaptic disease models.

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