Review

Neural functions of calcineurin in synaptic plasticity and memory

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Major brain functions depend on neuronal processes that favor the plasticity of neuronal circuits while at the same time maintaining their stability. The mechanisms that regulate brain plasticity are complex and engage multiple cascades of molecular components that modulate synaptic efficacy. Protein kinases (PKs) and phosphatases (PPs) are among the most important of these components that act as positive and negative regulators of neuronal signaling and plasticity, respectively. In these cascades, the PP protein phosphatase 2B or calcineurin (CaN) is of particular interest because it is the only Ca^{2+}-activated PP in the brain and a major regulator of key proteins essential for synaptic transmission and neuronal excitability. This review describes the primary properties of CaN and illustrates its functions and modes of action by focusing on several representative targets, in particular glutamate receptors, striatal enriched protein phosphatase (STEP), and neuromodulin (GAP43), and their functional significance for synaptic plasticity and memory.

The neural basis of higher-order brain functions has been the subject of intense research in the neurosciences over the past decades. This work led to the concept that major brain functions rely on brain plasticity and involve changes in synaptic efficacy. The mechanisms that underlie synaptic plasticity in the developing and adult brain are complex and depend on cascades of molecular events that engage multiple components. Protein kinases (PKs) and their counterpart enzymes, protein phosphatases (PPs), are among the most critical of these components. While PKs generally act as positive regulators of neuronal signaling and as potentiators of synaptic efficacy, PPs generally act as negative regulators that constrain synaptic efficacy. Although PKs were long considered to be more important than PPs due to their higher number (about 500 known PKs for only two dozen PPs), recent research has established that PKs and PPs are equally important for brain plasticity and are both essential components of neuronal signaling that underlie complex brain functions.

One of the major PPs in this respect is the Ca^{2+}-dependent Ser/Thr phosphatase protein phosphatase 2B or calcineurin (CaN). CaN is one of the most abundant PPs in the nervous system and acts on multiple substrates in synaptic, cytoplasmic, and nuclear compartments in neuronal cells. Dysregulation of CaN in the diseased brain is one of the major causes of pathological Ca^{2+} signaling associated with cognitive disorders, and of severe diseases such as Alzheimer's disease and Down syndrome (Dineley et al. 2010; Rachidi and Lopes 2010; Berridge 2011; Mohmmad Abdul et al. 2011). This review describes some of the mechanisms and biochemical targets by which CaN exerts its actions in synaptic plasticity and brain functions.

Basic properties of CaN

CaN is a protein Ser/Thr phosphatase composed of a large catalytic (CaNA) and a small regulatory subunit (CaNB) (Klee et al. 1979). Its Ca^{2+} dependence is mediated by CaNB and calmodulin (CaM)

(Klee et al. 1998). Upon Ca^{2+} binding, CaNB changes conformation, which induces conformational changes in CaNA and exposes the CaM binding site (Yang and Klee 2000). Ca^{2+}/CaM then activates CaN by displacing CaNA's autoinhibitory domain from the catalytic domain (Shen et al. 2008). CaN has very high affinity for Ca^{2+} and is activated by nanomolar concentrations of Ca^{2+} (Cohen and Klee 1988). It can also be reversibly inactivated after prolonged Ca^{2+}/CaM exposure (Stemmer et al. 1995; Shen et al. 2008) by, for instance, oxidation of a critical amino acid in the CaM binding domain of CaNA that blocks Ca^{2+}/CaM binding and CaN activation (Carruthers and Stemmer 2008).

In the mouse, three distinct genes encode CaNA (α, β, γ) and have different splice variants, while only one gene encodes CaNB in two different forms ($\alpha1$, $\alpha2$) (Kuno et al. 1989; Kincaid et al. 1990; Ueki et al. 1992; Chang et al. 1994). CaN is highly enriched in the brain (Su et al. 1995), and while several CaNA isoforms are differentially expressed in different areas (Takaishi et al. 1991; Kuno et al. 1992; Buttini et al. 1993; Chang et al. 1994), only CaNB$\alpha1$ is expressed in the brain (Ueki et al. 1992; Chang et al. 1994). In neurons, CaN protein is present in the perikarya, processes, and the nucleus (Sola et al. 1999), and is particularly enriched in synaptic terminals (Kuno et al. 1992). Different binding partners restrict CaN to distinct subcellular compartments, such as NFAT1 in the nucleus (Clipstone and Crabtree 1992; Luo et al. 1996; Beals et al. 1997) and AKAP scaffold proteins in dendrites (Coghlan et al. 1995; Abrenica et al. 2009). Each of the CaN subcellular pools exerts different functions and allows CaN-dependent control of neuronal structure, transcription, or neurotransmission depending on the substrates in the vicinity of CaN (for review, see Groth et al. 2003).

CaN in neuronal plasticity and memory

Experimental models of neuronal plasticity

Increased neuronal activity is associated with changes in synaptic efficacy and neuronal excitability that confer plasticity to neuronal circuits, a property necessary for memory formation. The cellular and molecular mechanisms of neuronal plasticity are complex and have been experimentally studied in different

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neuronal models. Plasticity is most commonly induced by artificial electrical stimulation of populations of neurons or axonal fibers in acute brain sections, for instance, from the hippocampus, a brain region required for spatial and episodic memory. Stimulation at high frequency increases synaptic efficacy and induces long-term potentiation (LTP), a strengthening of plasticity. In contrast, prolonged stimulation at low frequency decreases synaptic efficacy and results in long-term depression (LTD), a form of synaptic weakening. Potentiated synapses can be reset by synaptic depression and by undergoing depotentiation. Several brain regions can express LTP, LTD, and/or depotentation, and CaN has been shown to be involved in the underlying mechanisms, in particular, in the hippocampus. One of the most prominent actions of CaN is to constrain LTP. LTP is increased when CaN activity is decreased whether by antisense knockdown of CaNA (Ikegami et al. 1996), forebrain-restricted expression of a CaN inhibitor, knockout (KO) of CaNB (α1) in excitatory neurons (Winder et al. 1998; Malleret et al. 2001; Zeng et al. 2001), or by pharmacological inhibition (Wang and Stelzer 1994; Wang and Kelly 1996). Conversely, LTP is impaired when CaN activity is increased by, for instance, expression of an active CaN in forebrain excitatory neurons (Mansuy et al. 1998b).

CaN is also essential for LTD and depotentiation. LTD is blocked when CaN is inhibited either pharmacologically (Mulkey et al. 1994; Hodgkiss and Kelly 1995) or by injection of a CaN autoinhibitory peptide in postsynaptic neurons (Mulkey et al. 1994). It is also strongly diminished by CaNB (α1) gene KO in forebrain excitatory neurons (Zeng et al. 2001). Likewise, depotentiation is blocked by CaN inhibition whether achieved pharmacologically, by neuron-specific expression of a CaN inhibitor in forebrain, or by CaNA (α) KO (Zhuo et al. 1999; Jouvenceau et al. 2003; Kang-Park et al. 2003; Lin et al. 2003a; Jouvenceau and Dutar 2006).

Further to being essential to plasticity at excitatory synapses, CaN is also implicated in plasticity at inhibitory synapses. LTD at inhibitory synapses is blocked by CaN inhibition (Lu et al. 2000). Because of such a dual role in excitatory and inhibitory synapses, CaN manipulations that are not cell-type-specific can produce confounding results. Thus, an alteration in inhibitory synapses may oppose or interfere with an alteration in excitatory synapses at the level of a population of neurons, which may explain why CaNA (α) KO mice have been shown to display normal LTP and LTD (Zhuo et al. 1999), despite a clear involvement of CaN in both forms of plasticity. It may also explain why LTP is precluded if inhibitory neurotransmission is not specifically blocked during LTP induction (Lu et al. 1996). In contrast, when CaN inhibition is restricted to excitatory neurons or occurs during LTP induction, it facilitates LTP and blocks LTD (Hodgkiss and Kelly 1995; Wang and Kelly 1996; Winder et al. 1998; Malleret et al. 2001; Zeng et al. 2001; Jouvenceau et al. 2003; Jouvenceau and Dutar 2006).

Experience-dependent plasticity and memory

LTP, LTD, and depotentiation are artificial models of neuronal plasticity generally used in vitro, but similar forms of plasticity have also been observed in vivo (Whitlock et al. 2006; Yoon et al. 2009; Cooke and Bear 2012). In mammals, plasticity can be induced by physiological stimuli that mimic a sensory episode. In cats and rodents, a popular model of experience-dependent plasticity is ocular dominance shift (OD) resulting from monocular deprivation (MD). OD occurs in a region of the visual cortex that receives input from both eyes. Usually, the input from the contralateral eye is stronger than from the ipsilateral eye, but after occlusion of the contralateral eye during the critical period, this can be permanently reversed. OD has been shown to involve a three-step process involving plasticity: (1) the response to the oc-

cluded eye is weakened through LTD-like mechanisms; (2) the threshold for synaptic activation is decreased, which favors LTP; (3) the response to the open eye is strengthened via LTP-like mechanisms (Smith et al. 2009; Yoon et al. 2009). These mechanisms are fully blocked by an increase in CaN (Yang et al. 2005), suggesting that CaN is likely engaged as a negative regulator of OD-dependent plasticity.

Experience-dependent plasticity is also a fundamental mechanism for learning and memory. LTP-like synaptic enhancement occurs at thalamo-cortical synapses during perceptual learning on a visual task (Cooke and Bear 2012) and in the hippocampal CA1 region during inhibitory avoidance learning (Whitlock et al. 2006). The molecular requirement for experimental models of neuronal plasticity, experience-dependent forms of plasticity, and memory overlap significantly (Izquierdo et al. 2008; Smith et al. 2009; Ye and Carew 2010; Johansen et al. 2011; Korb and Finkbeiner 2011), and altering this requirement by molecular manipulations frequently alters all three processes (Nedivi 1999). Accordingly, CaN inhibition enhances memory, whether achieved pharmacologically (Christie-Fougere et al. 2009), by expression of a CaN inhibitor in forebrain excitatory neurons (Malleret et al. 2001; Baumgartel et al. 2008), or through antisense oligonucleotide-mediated knockdown, applied pre-training (Ikegami and Inokuchi 2000) or post-training (Gerdjikov and Beninger 2005). Pharmacological CaN inhibition in the amygdala also blocks a specific form of learning, the extinction of associative fear memory (Lin et al. 2003a, b). In associative fear memory, mice learn to associate a conditioned stimulus (CS) that is non-aversive (a tone or context), with an unconditioned stimulus (US) that is aversive (footshock). Extinction of fear memory is achieved by repeatedly exposing the animal to the CS alone, which weakens the aversive memory trace (CS-US) and strengthens a new non-aversive memory trace (CS with no US) (Delamater 2004). Extinction relies on the relearning that a CS no longer predicts a US. This dependence on learning may explain why it involves CaN. However, CaN may not be involved in all forms of extinction, and, for instance, it was shown that its inhibition in forebrain neurons does not affect extinction of taste aversion, another form of associative aversive memory (Baumgartel et al. 2008). Another explanation for the discrepancy between the extinction effects in the two different memory tasks may be the distinct roles of excitatory or inhibitory cells in extinction (Yee et al. 2004; Jacobson et al. 2006; Jungling et al. 2008; Sangha et al. 2009; Lin et al. 2010, 2011a; Meins et al. 2010). For studies on fear extinction, CaN was inhibited broadly and in every cell type (using a pharmacological inhibitor), while it was inhibited only in forebrain excitatory neurons in taste aversion studies, again suggesting the importance of CaN compartimentalization.

CaN and the control of membrane receptors and channels

The recruitment and activity of membrane receptors and voltage-gated ion channels in neurons are strongly regulated by protein phosphorylation, and many receptors and channels are controlled by CaN. The following section describes some of the most important receptors and channels targeted by CaN, the effect of their dephosphorylation by CaN, and their contribution to neuronal plasticity and memory.

CaN regulates synaptic transmission in part through the AMPA receptor

Most of the fast synaptic transmission at excitatory synapses in the brain is mediated by the glutamatergic AMPA-(α-amino-3-

hydroxy-5-methyl-4-isoxazolepropionic acid) receptor (AMPA-R) (Collingridge et al. 1992). In the adult brain, AMPA-Rs are usually composed of heterotetramers of GluR1, GluR2, GluR3, or GluR5 subunits. Their composition is highly dynamic (Greger et al. 2007) and greatly influences the electrophysiological features of the AMPA-R, in particular its permeability to cations, and its interaction with postsynaptic partners (for review, see Burnashev and Rozov 2000). AMPA-R activity and abundance critically affect the efficacy of glutamatergic synapses. Both activity and trafficking into and out of synapses are modulated by the phosphorylation state of the AMPA-R (Kessels and Malinow 2009). Several sites on different GluR subunits are subject to phosphorylation, but Ser845 on GluR1, a site phosphorylated by the cAMP-dependent protein kinase (PKA) (Price et al. 1999) and dephosphorylated by CaN (Fig. 1; Beattie et al. 2000), is one of the most important for AMPA-R regulation. Phosphorylated Ser845 increases AMPA-R peak response open probability (Banke et al. 2000), AMPA-R current (Roche et al. 1996), and insertion into the membrane (Man et al. 2007), and thereby strengthens synaptic transmission. In contrast, Ser845 dephosphorylation triggers AMPA-R internalization and weakens transmission (Man et al. 2007). It has therefore been suggested to be a mechanism for LTD (Lee et al. 1998). Since CaN dephosphorylates Ser845 (Beattie et al. 2000) and CaN inhibition blocks LTD (Mulkey et al. 1994; Hodgkiss and Kelly 1995; Lu et al. 2000; Zeng et al. 2001), its interaction with the AMPA-R likely constitutes an important means by which CaN regulates plasticity. This interaction involves common binding partners that are part of a postsynaptic scaffold. In this scaffold, the protein AKAP150 (Fig. 1; Gomez et al. 2002; Tavalin et al. 2002; Jurado et al. 2010) binds the AMPA-R, CaN, and PKA, and the balanced activity of CaN and PKA determines the phosphorylation state of Ser845 on GluR1. In this balance, CaN can directly dephosphorylate Ser845 but can also lead to a decrease in local kinase activity. After NMDA-R activation, it triggers the redistribution of AKAP150 and PKA from the postsynaptic membrane to the cytoplasm (Gomez et al. 2002; Smith et al. 2006). Since it remains in its postsynaptic location at the same time (Gomez et al. 2002; Smith et al. 2006), this further favors dephosphorylation of GluR1, AMPA-R internalization, and decreased synaptic efficacy.

CaN regulates dendritic excitability through the voltage gated A-type K$^+$ channel Kv4.2

A target of CaN that contributes to its ability to regulate neuronal excitability is the voltage-gated A-type K$^+$ channel Kv4.2 (Fig. 1; Lin et al. 2011b). Kv4.2 is enriched in dendrites (Jinno et al. 2005) and specifically in postsynaptic terminals (Alonso and Widmer 1997; Gardoni et al. 2007). It is involved in neuronal repolarization after an action potential (AP) (Kim et al. 2005) and controls the amplitude of back-propagating APs in dendrites (Hoffman et al. 1997). In hippocampal slice culture, overexpression of Kv4.2 shortens AP duration and decreases back-propagation, while overexpression of dominant-negative Kv4.2 increases AP duration and enhances AP back-propagation (Kim et al. 2005). Consistently, in mice, Kv4.2 overexpression prevents LTP, while dominant-negative Kv4.2 enhances LTP (Jung et al. 2008), and Kv4.2 KO increases AP amplitude and lowers the threshold for LTP (Chen et al. 2006). Kv4.2 KO also results in deficits in spatial learning (Lockridge and Yuan 2011). Thus, much like CaN, Kv4.2 acts as a negative regulator of neuronal plasticity. Further to its direct effects on dendritic excitability, it may also influence plasticity indirectly. Kv4.2 overexpression reduces relative synaptic NR2B/NR2A subunit ratios, while Kv4.2 blockade increases synaptic NR2B/NR2A ratios (Jung et al. 2008). An increased NR2B/NR2A ratio has been hypothesized to support plasticity (Yashiro and Philpot 2008) and/or to function as a mechanism of metaplasticity (Xu et al. 2009b). In contrast, a low NR2B/NR2A ratio likely favors CaN, and LTD over LTP (Yashiro and Philpot 2008).

One of the consequences of Kv4.2 dephosphorylation by CaN is its stabilization at the membrane, a process that depends on AKAP150 (Lin et al. 2011b). However, besides CaN, NMDA-R activation and Ca^{2+} influx can also directly control Kv4.2 and act on its internalization (Kim et al. 2007; Lei et al. 2008). The dissociation between stabilization and internalization depends on the spatial location of NMDA-R activation and Ca^{2+} influx. When occurring at synapses, it favors Kv4.2 phosphorylation and internalization (Kim et al. 2007; Hammond et al. 2008), while when occurring at extrasynaptic NMDA-R, dephosphorylation and stabilization are increased (Lei et al. 2008, 2010; Mulholland and Chandler 2010). Kv4.2 phosphorylation and internalization co-occur with AMPA-R insertion in dendritic spines (Kim et al. 2007). AMPA-R insertion and Kv4.2 internalization may thus be mediated by the identical CaN-containing complexes in response to NMDA-R activation.

Internalization of Kv4.2 also requires cleavage by calpain (Lei et al. 2010), an enzyme that participates to the internalization of different membrane receptors and signaling molecules including NMDA-R (Wu et al. 2005a; Yuen et al. 2008) and AMPA-R (Wu et al.
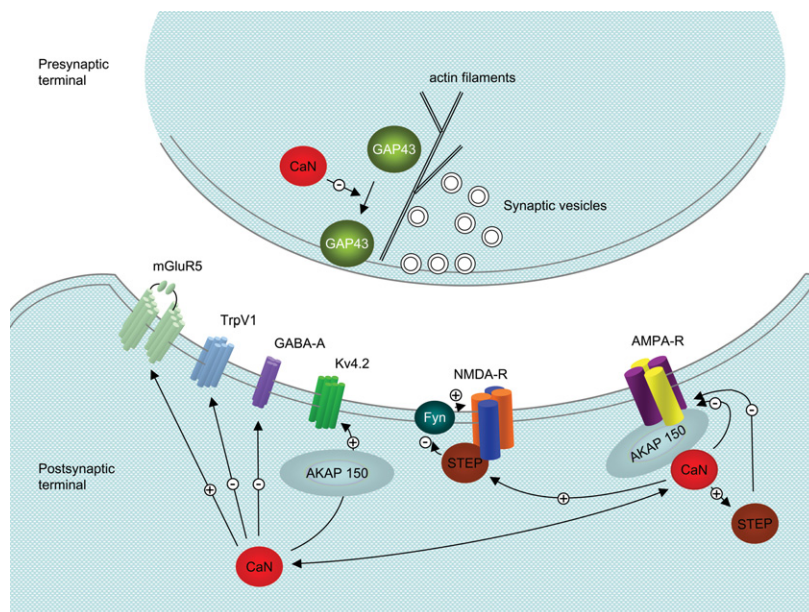
Figure 1. CaN has targets both in the pre- and the postsynaptic terminal. In the pre-synaptic terminal, the main target is GAP43. In the postsynaptic terminal, CaN either targets proteins directly or via STEP. Many proteins are dephosphorylated in an AKAP150-dependent manner. (⊕) Activates protein or increases its abundance at membrane; (⊖) inhibits protein or decreases its abundance at membrane.

2005a; Yuen et al. 2008). Calpain-mediated cleavage also contributes to generate a Ca^{2+}/calmodulin-independent form of CaN (Tallant et al. 1988; Wang et al. 1989). Furthermore, when activated after extrasynaptic NMDA-Rs activation, calpain can also cleave and relocate the striatal-enriched phosphatase (STEP), another CaN target (see below), from postsynaptic terminals to the cytoplasm (Xu et al. 2009a), as well as neuromodulin (GAP43), also a CaN target (see below) (Zakharov and Mosevitsky 2001).

CaN can further regulate Kv4.2 trafficking by an indirect mechanism involving the downstream regulatory element antagonist modulator (DREAM/KChIP3). DREAM belongs to the potassium channel–interacting protein (KChIP) family and is a direct target of CaN (Ruiz-Gomez et al. 2007). Its dephosphorylation by CaN is required for DREAM and Kv4.2 membrane localization when coexpressed in cell culture (Ruiz-Gomez et al. 2007). The interaction of Kv4.2 and DREAM with the membrane decreases in the hippocampus after training on a hippocampal-dependent task in mice (Alexander et al. 2009), an effect associated with lower CaN activity (Havekes et al. 2006). While a direct link between this interaction and memory processes is still unclear, it is interesting to note that DREAM KO, like CaN inhibition, improves memory performance (Malleret et al. 2001; Alexander et al. 2009; Fontan-Lozano et al. 2009) and enhances LTP (Ikegami et al. 1996; Wang and Kelly 1996; Malleret et al. 2001; Zeng et al. 2001; Lilliehook et al. 2003).

Other receptors and channels targeted by CaN

The metabotropic glutamate receptor mGluR5

The metabotropic glutamate receptor mGluR5 is a CaN target that modulates the responsiveness of neurons to different extracellular signals. Activation of mGluR5 induces phosphatidylinositol hydrolysis via phospholipase C, which releases intracellular IP3-sensitive Ca^{2+} stores. It further activates ryanodine-sensitive Ca^{2+} stores and alters the activity of different voltage-gated channels (Gerber et al. 1992; Swartz and Bean 1992; Fagni et al. 2000; Sanchez-Prieto et al. 2004; Park et al. 2010; Zheng and Raman 2011). Additionally, mGluR5 activation enhances glutamate-evoked currents through the NMDA receptor (Fitzjohn et al. 1996). However, this results in a rapid desensitization of mGluR5, which is counteracted by CaN. By dephosphorylating the receptor, CaN can prolong its activity after glutamate release (Fig. 1; Alagarsamy et al. 2005). This effect of CaN is likely important for the induction of LTD, some forms of which rely on mGluR5 in the hippocampus (Camodeca et al. 1999; Sung et al. 2001; Huang and Hsu 2006; Naie et al. 2007; Neyman and Manahan-Vaughan 2008). But further, mGluR5 is also involved in LTP and its inhibition prevents LTP at both, excitatory (Rodrigues et al. 2002; Neyman and Manahan-Vaughan 2008) and inhibitory, synapses (Le Vasseur et al. 2008; Le Duigou et al. 2011). These effects on multiple forms of neuronal plasticity are consistent with the involvement of mGluR5 in experience-dependent plasticity in visual cortex, which requires both, LTD- and LTP-like, mechanisms, through mechanisms that remain unclear (Hensch and Stryker 1996; Daw et al. 1999). mGluR5 also plays an important function in memory. Its activation in the basolateral amygdala enhances fear conditioning (Rudy and Matus-Amat 2009), while its inhibition blocks the acquisition of fear memory (Schulz et al. 2001; Rodrigues et al. 2002). Furthermore, mGluR5 inhibition in the amygdala blocks the extinction of CTA memory (Simonyi et al. 2009) similarly to CaN inhibition and may also involve LTD-like mechanisms. Together, these findings suggest that mGluR5 is likely an important mediator of CaN's action in memory regulation, through complex mechanisms that are still not fully understood.

Some of the mechanisms by which mGluR5 contributes to LTD involve activation of the vanilloid receptor TrpV1 (Bennion et al. 2011; Puente et al. 2011). TrpV1 is a non-selective cation channel highly permeable to Ca^{2+} and is also a direct target of CaN. But while mGluR5 prevents TrpV1 desensitization that limits the effects of repeated or persistent TrpV1 activation (Li et al. 2008), CaN favors this desensitization (Fig. 1; Mohapatra and Nau 2005). On a circuit level, this depends on whether Trpv1 is activated in excitatory or inhibitory neurons (Bennion et al. 2011). Through an indirect mechanism involving LTD at inhibitory synapses, activation of TrpV1 can facilitate LTP (Bennion et al. 2011) and suppress LTD (Li et al. 2008) in hippocampal networks. This likely reflects differential action of Trpv1 on excitatory/inhibitory circuits, reminiscent of that observed for CaN (Lu et al. 2000). Finally, further to regulating TrpV1 directly, CaN may also act downstream from this channel since it was shown to be activated by Ca^{2+} after TrpV1 stimulation and to regulate the activity of voltage-gated calcium channels (Wu et al. 2005b) and Kv7.2/3 (Zhang et al. 2011). Further investigation of this pathway will certainly provide interesting insight into CaN's contribution to different types of plasticity.

CaN targets membrane receptors at inhibitory synapses

A major property of CaN that makes it an essential regulator of bidirectional plasticity is its ability to control inhibitory synapses in addition to excitatory synapses (Jones and Westbrook 1997). It can bind to and dephosphorylate A-type GABA receptors ($GABA_A$-R) in an NMDA-R dependent manner (Fig. 1; Chen and Wong 1995; Robello et al. 1997; Lu et al. 2000). This dephosphorylation suppresses $GABA_A$-R responses (Chen and Wong 1995), reduces inhibitory transmission (Jones and Westbrook 1997; Wang et al. 2003), and mediates LTD at inhibitory synapses (Lu et al. 2000). Reduction of GABAergic drive can disinhibit excitatory neurotransmission, thus opposing the decrease in neurotransmission mediated by CaN at excitatory synapses. Depending on the cellular localization of CaN activation, the net effect may be different. In line with its important role in shaping excitatory transmission, GABAergic inhibition has been strongly implicated in experience-dependent plasticity (Heimel et al. 2011), as well as synaptic plasticity and memory (Mohler 2007).

A protein phosphatase cascade involving CaN and STEP

Phosphorylation is an essential mechanism that allows cells to integrate information from different extracellular signals. PK cascades are ubiquitous and have multiple effector functions in many cell types. Likewise, although not as numerous as PKs, PPs can act on several sets of substrates and integrate extracellular signals. A major substrate of CaN that plays an important role in these cascades is STEP (Fig. 1; Paul et al. 2003). STEP is a tyrosine phosphatase present as at least six different polypeptides (Lombroso et al. 1993; Sharma and Lombroso 1995). Polypeptides of 61, 46, 38, and 20 kDa are generated by alternative splicing of the same transcript (Sharma and Lombroso 1995; Bult et al. 1997), and at least one of the shorter polypeptides (33 kDa) results from calcium-dependent cleavage of STEP61 by calpain (Nguyen et al. 1999). STEP61 (Boulanger et al. 1995; Bult et al. 1996), STEP46 (Oyama et al. 1995), and STEP38 (Bult et al. 1997) are localized to the membrane, specifically at postsynaptic terminals and in the endoplasmic reticulum, but the shortest polypeptides are predominantly in the cytoplasm and lack a catalytic domain (Boulanger et al. 1995). Cleavage may thus be a mechanism of relocating STEP to the cytoplasm and may determine its activity toward specific targets (Braithwaite et al. 2008; Xu et al. 2009a). The

longest uncleaved splice isoforms, STEP61 and STEP46, are phosphorylated by PKA and dephosphorylated by CaN (Paul et al. 2000, 2003).

CaN and STEP are tightly linked; they are coactivated (Yang et al. 2006) and have comparable effects on LTD, LTP, and memory. Inhibition of CaN (Wang and Kelly 1996, 1997) or STEP (Pelkey et al. 2002) in postsynaptic terminals causes synaptic potentiation and occludes LTP. Conversely, overexpression of CaN or STEP impairs long-lasting LTP (Mansuy et al. 1998b; Winder et al. 1998; Pelkey et al. 2002; Paul et al. 2007). On a behavioral level, CaN or STEP inhibition improves memory (Malleret et al. 2001; Venkitaramani et al. 2011), while their overexpression disrupts learning and memory consolidation (Mansuy et al. 1998a,b; Paul et al. 2007). Interestingly, both STEP and CaN have been implicated in the molecular pathways of Aβ toxicity in Alzheimer's disease (Abdul et al. 2009; Kurup et al. 2010). These findings suggest that STEP is likely an important mediator of cross talk between CaN-dependent pathways and tyrosine phosphorylation.

STEP has multiple substrates, and one of the most important for synaptic plasticity is the NMDA-R (Pelkey et al. 2002; Braithwaite et al. 2006). It can directly bind to and dephosphorylate the receptor and thereby regulate its surface expression and activity (Pelkey et al. 2002; Braithwaite et al. 2006). STEP can also modulate the NMDA-R indirectly through the membrane-bound Src family tyrosine kinase Fyn. STEP binding and dephosphorylation of Fyn reduce its kinase activity (Nguyen et al. 2002), which decreases NMDA-R phosphorylation and activity (Yu et al. 1997). PKA has been suggested to interfere with STEP association with Fyn (Yang et al. 2011), suggesting an important balance between CaN and PKA activity for its regulation. Further to NMDA-R, STEP is involved in AMPA-R endocytosis after activation of mGluRs 1 and 5 (group 1) (Zhang et al. 2008). This is interesting since activation of this mGluR group is sufficient to induce LTD (Camodeca et al. 1999) and suggests that the involvement of CaN in AMPA-R endocytosis and LTD induction may be both direct (see above) and indirect via STEP.

CaN regulates presynaptic parameters via GAP43

Neuronal plasticity is not restricted to mechanisms in postsynaptic terminals, but also depends on pre-synaptic processes (Powell 2006). Pre-synaptic plasticity primarily shapes the probability and the amount of neurotransmitter release triggered by a given AP. This involves synaptic vesicle-, cytoplasmic, or active zone-associated proteins that regulate vesicle availability, docking, priming, Ca^{2+} triggering, and even Ca^{2+} entry. Pre-synaptic output changes are mostly transient, and, accordingly, they support short-term plasticity. Long-term plasticity rather involves structural changes, by which the size or presence of existing synapses is altered or new synapses are formed (Gogolla et al. 2007). The growth-associated protein 43 (GAP43, neuromodulin, F1, B-50, pp46, P-57) is a nervous system–specific protein (Kristjansson et al. 1982) that is involved in both short- and long-term pre-synaptic plasticity. In short-term plasticity, GAP43 may act in at least two ways. By binding rabaptin-5, an effector of the small GTPase Rab5 (Neve et al. 1998), GAP43 negatively regulates endosomal size and vesicle recycling (Neve et al. 1998). GAP43 only binds rabaptin-5 at high Ca^{2+} concentrations (Neve et al. 1998). At low Ca^{2+} concentrations, this binding is blocked by CaM (Alexander et al. 1987; Neve et al. 1998). CaM binding, in turn, is prevented by GAP43 phosphorylation, and CaM can thus be rapidly released locally through activation of the respective kinase, PKC (Van Hooff et al. 1988). This CaM release facilitates Ca^{2+}/CaM-dependent events in the pre-synaptic terminal, such as regulation of neurotransmitter release (Dekker et al. 1989)

through CaMKII and Rab3A (Wang et al. 2008). CaMKII's association with Ca^{2+}/CaM triggers its autophosphorylation, which persists even after Ca^{2+} levels fall and Ca^{2+}/CaM dissociates from the enzyme (Lisman et al. 2002). Since this results in lasting CaMKII activation, it has been proposed to function as a biochemical memory trace of previous Ca^{2+} influx (Lisman et al. 2002). It may thus potentially serve as a transition between short- and long-term synaptic changes and/or as a substrate for long-term plasticity and memory.

GAP43's main contribution to long-term plasticity, however, is through regulation of membrane and actin dynamics. GAP43 expression is strongest and most widespread during development (Jacobson et al. 1986), when the nervous system structure is subject to extensive changes and rearrangements. Here, GAP43 regulates neurite and growth cone morphology (Aigner and Caroni 1993). GAP43 achieves this by stabilizing long actin filaments (He et al. 1997). This has been suggested to involve direct mechanisms by actin binding as well as binding to $PI(4,5)P_2$ to regulate its availability for actin binding proteins that stabilize filaments and promote growth (Laux et al. 2000). It is not required for neurite outgrowth or growth cone formation per se but for neuronal pathfinding at decision points (Strittmatter et al. 1995). Accordingly, expression of a non-phosphorylatable form of GAP43 causes ectopic axonal growth (Holahan et al. 2010). This finding suggests that GAP43 function is tightly regulated by phosphorylation. Indeed, the ability of GAP43 to stabilize actin filaments depends on its phosphorylation status (He et al. 1997). When dephosphorylated, GAP43 binds to CaM and is inactive, an event triggered by dephosphorylation by CaN (Liu and Storm 1989; Seki et al. 1995). This dephosphorylation has been proposed to underlie the inhibition of neurite outgrowth by Ca^{2+} waves (Lautermilch and Spitzer 2000). GAP43 is also targeted to the membrane through phosphorylation (Kristjansson et al. 1982) and specifically enriched at pre-synaptic membranes in the adult nervous system (Sorensen et al. 1981; Gispen et al. 1985).

GAP43 expression declines after synaptogenesis (Jacobson et al. 1986) except in layer 1 of cortex, the CA1 region of the hippocampus, nucleus accumbens, the amygdala, and several subcortical structures (Benowitz et al. 1988), brain regions with high plasticity. In the hippocampus, GAP43 phosphorylation is dynamically regulated by synaptic activity. It is increased immediately after LTP induction whether by high-frequency stimulation (Lovinger et al. 1986; Gianotti et al. 1992; Leahy et al. 1993; Ramakers et al. 1999) or chemical depolarization (Ramakers et al. 2000b). Moreover, the extent of GAP43 phosphorylation correlates with the amount of potentiation (Lovinger et al. 1986). The increase persists for 60 min if induced in hippocampal slices (Ramakers et al. 1999) and for several days if induced in vivo (Routtenberg and Lovinger 1985). This supports the notion that GAP43 phosphorylation mediates long-term plasticity and memory and fits nicely with our own observation of a sustained decrease in CaN activity after learning (Baumgartel et al. 2008). Overexpression of wild-type GAP43 enhances in vivo LTP in the perforant path (Routtenberg et al. 2000), but not in the Schaffer collaterals (Hulo et al. 2002), possibly because GAP43 is still expressed in the adult CA1 (Benowitz et al. 1988). However, overexpression of a pseudophosphorylated GAP43 enhances LTP in Schaffer Collaterals (Hulo et al. 2002), which shows that GAP43 activity is more important than its level per se. In line with this, expression of a non-phosporylatable form of GAP43 has no effect on LTP induction (Routtenberg et al. 2000; Hulo et al. 2002). Pseudophosphorylated GAP43 also enhances short-term plasticity, in particular paired pulse facilitation and synaptic response summation during high-frequency stimulation (Hulo et al. 2002), demonstrating again its dual function in short- and long-term plasticity. In line with the absence of a gross morphological

phenotype in the brain of GAP43 KO mice (Strittmatter et al. 1995), LTP in hippocampal slices is normal (Hulo et al. 2002).

Consistent with the effects of LTP, LTD induction transiently decreases GAP43 phosphorylation in a CaN-dependent manner in the CA1 region of the hippocampus when achieved by low-frequency stimulation (Ramakers et al. 1999, 2000a), but not when achieved by NMDA incubation that will primarily induce postsynaptic plasticity (van Dam et al. 2002). With respect to natural forms of plasticity such as ocular dominance plasticity, there are currently no data implicating GAP43, except the observation that the level and phosphorylation of membrane-associated GAP43 are elevated during the critical period in cat visual cortex (McIntosh et al. 1990; Sheu et al. 1990); GAP43 association with the membrane is not altered by monocular deprivation (McIntosh et al. 1990).

However, GAP43 is strongly implicated in memory. GAP43 phosphorylation is increased after training on a memory task in the hippocampus (Cammarota et al. 1997), which correlates nicely with a reduction in CaN activity (Havekes et al. 2006). GAP43 KO mice do not survive after weaning and thus do not allow any behavioral analysis of cognitive function (Maier et al. 1999). However, heterozygous GAP43 mice have deficits in spatial learning but also have multiple sensorimotor deficits and decreased sociability, which may bias the results (Rekart et al. 2005; Zaccaria et al. 2010). Consistently, GAP43 overexpression has an effect on memory. First, it enhances learning on a working and spatial memory version of the delayed matching-to-place task in the radial arm maze (Routtenberg et al. 2000) but not on purely spatial tasks, such as contextual fear conditioning or the water maze (Holahan and Routtenberg 2008). However, it favors the extinction of contextual fear memory and enhances reversal learning in the radial arm maze (Holahan and Routtenberg 2008). Overexpression of a pseudophosphorylated GAP43 does not affect spatial learning but enhances contextual fear memory and blocks its extinction (Holahan and Routtenberg 2008). Additionally, while it does not affect learning on the radial arm maze (Routtenberg et al. 2000), it alters its reversal (Holahan and Routtenberg 2008). Overexpression of a non-phosphorylatable GAP43 also interferes with spatial learning in the water maze but not in other forms of learning (Holahan and Routtenberg 2008). These findings suggest that the phosphorylation status of GAP43 and the amount of GAP43 protein are equally important, and both need to be fine-tuned. Dysregulation of GAP43 (increase) in the hippocampus has been associated with Alzheimer's disease (Rekart et al. 2004), a finding that correlates with the CaN overactivation observed in Alzheimer's patients (Berridge 2011; Qian et al. 2011), which may further activate GAP43 and contribute to memory impairments. In summary, CaN is an important determinant of presynaptic neurotransmitter release and restructuring through regulation of GAP43 activity. GAP43 dephosphorylation provides an important pre-synaptic mechanism by which membrane-targeted CaN contributes to plasticity and memory.

Conclusion

CaN is an important regulator of neuronal plasticity in the brain that targets multiple substrates in distinct subcellular compartments. Each of these targets contributes to the functions of CaN in plasticity and learning and memory and has multiple and intricate relationships. Manipulations of these targets in vitro and in vivo have provided some mechanistic insight into their modes of action. However, some of CaN's functions still remain poorly understood, in particular in pathological conditions and diseases, and will therefore require more work in the future, with the hope to provide new potential targets for therapeutic treatments.

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Neural functions of calcineurin in synaptic plasticity and memory

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