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Review

AMPA receptor regulation during synaptic plasticity in hippocampus and neocortex

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ABSTRACT

Discovery of long-term potentiation (LTP) in the dentate gyrus of the rabbit hippocampus by Bliss and Lømo opened up a whole new field to study activity-dependent long-term synaptic modifications in the brain. Since then hippocampal synapses have been a key model system to study the mechanisms of different forms of synaptic plasticity. At least for the postsynaptic forms of LTP and long-term depression (LTD), regulation of AMPA receptors (AMPARs) has emerged as a key mechanism. While many of the synaptic plasticity mechanisms uncovered in at the hippocampal synapses apply to synapses across diverse brain regions, there are differences in the mechanisms that often reveal the specific functional requirements of the brain area under study. Here we will review AMPAR regulation underlying synaptic plasticity in hippocampus and neocortex. The main focus of this review will be placed on postsynaptic forms of synaptic plasticity that impinge on the regulation of AMPARs using hippocampal CA1 and primary sensory cortices as examples. And through the comparison, we will highlight the key similarities and functional differences between the two synapses.

Contents

1. Introduction

Rapid activity-dependent mechanisms of synaptic plasticity, such as LTP and LTD, are believed to be central for the proper development of brain connectivity and for the coding and storage of memory. Because both LTP and LTD have innate built-in positive-feedback propensity, there is a requirement for global homeostatic plasticity mechanisms acting on a slower time scale to provide stability to the overall neuronal activity [1,2]. Most of our understanding on synaptic plasticity mechanisms derives from hippocampal studies, in part because this structure is critical for memory formation, but also because synaptic plasticity is

Abbreviations: AKAP79/150, A-kinase anchoring protein 79/150; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CA1, cornus ammonis 1 of hippocampus; CaMKI, Ca^{2+}/calmodulin-dependent protein kinase I; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CP-AMPAR, Ca^{2+}-permeable AMPA receptor; GABA, gamma-aminobutyric acid; GAD65, glutamate decarboxylase 65; LTP, long-term potentiation; LTD, long-term depression; mEPSC, miniature excitatory postsynaptic current; MPR, membrane proximal region; NMDAR, N-methyl-D-aspartate receptor; PAK, p21-activated kinase; PKA, cAMP-dependent protein kinase or protein kinase A; PLC, phospholipase C; PSD, postsynaptic density; PSD-95, postsynaptic density protein 95; STP, short-term potentiation.

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particularly robust in this area. Although multiple forms of LTP and LTD are expressed in the hippocampus, even at the same synapses [3], the most commonly studied form of LTP/LTD is NMDAR receptor (NMDAR)-dependent, and is predominantly studied at the Schaffer collateral to CA1 synapses. The mechanisms of LTP and LTD induced at the CA1 synapses are known to an extensive molecular detail, which mainly involve regulation of AMPARs [4,5] (see Section 2.3). While many of the basic mechanisms of AMPAR regulation during synaptic plasticity in the hippocampus apply to synapses else where, there are critical differences, which underscores the specific functional requirement of the synapses under study.

Hippocampus is part of the archicortex, which is structurally different from the 6-layered neocortex. Despite the anatomical and functional distinctions, synapses in both brain areas display common forms of synaptic plasticity. Early studies done by Mark Bear's group reported that the bidirectional regulation of synapses in layer 2/3 of visual cortex shares common induction mechanisms with synapses in the CA1, including the dependence on NMDARs [6]. Later studies uncovered further commonalities, including mechanisms of AMPAR regulation, but also revealed important differences in the induction mechanisms of LTP and LTD across neocortical layers [7,8]. However, for the purpose of meaningful comparisons we will limit our discussions to the NMDAR-dependent forms of LTP/LTD in layer 2/3 of the neocortex and the Schaffer collateral to CA1 synapses. NMDAR-dependent LTP and LTD are expressed postsynaptically via regulation of AMPARs, which are also utilized by global homeostatic synaptic plasticity. Therefore we will compare AMPAR regulation during LTP/LTD and homeostatic synaptic plasticity in these two brain areas.

2. LTP/LTD in CA1 and neocortex

Kirkwood et al. first convincingly demonstrated that common forms of NMDAR-dependent of LTP and LTD are present at the Schaffer collateral synapses in the hippocampal CA1 and the layer 4 to 2/3 synapses in the visual cortex [6]. At both types of synapses, theta burst stimulation induces LTP and low frequency stimulation (1-Hz, 900 pulses) produces LTD. Also in both areas, the induction of LTP is Hebbian, requiring co-incident pre- and post-synaptic activity [9], which is a property conferred by its dependence on the activation of NMDARs [6,9]. NMDAR-dependent LTP and LTD have since been demonstrated in other sensory cortices and higher order cortical areas in diverse species [10], including the human inferior and middle temporal cortex [11].

Besides the common induction rules, neocortical and hippocampal LTP/LTD also share downstream signaling. In the CA1, LTP and LTD require activation of various protein kinases and protein phosphatases, respectively, which suggest involvement of phosphoproteins [12]. Similarly, neocortical LTP also depends on protein kinases, such as Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) [13–16] and cAMP-dependent protein kinase (PKA) [17,18], and neocortical LTD requires protein phosphatase activity [19]. One of the phosphoproteins implicated in the expression of LTP/LTD in CA1 is the AMPAR [20,21], and AMPAR phosphorylation also appears crucial in neocortical LTP/LTD [22,23]. As discussed later (Section 2.2.2), altering AMPAR phosphorylation regulates synaptic transmission by either changing single channel properties or receptor trafficking.

2.1. Overview on the known differences in synaptic plasticity between hippocampus and neocortex

While there are many similarities between LTP/LTD observed at CA1 and neocortical synapses, apparent differences were noted even from early studies. For instance, CA1-LTP normally displays a prominent short-term potentiation (STP), which decays into a long-lasting potentiation, whereas neocortical LTP typically lacks STP and develops gradually over time [6]. In the CA1, STP can be observed in isolation under conditions of blocking protein kinases [20,24]. Interestingly, neocortical LTP is more susceptible to inhibition of protein kinases such that mice lacking only 1 copy of the αCaMKII gene (αCaMKII+/–mice) completely lack LTP in the cortex [13,14], while the CA1-LTP is minimally affected [14]. The rather specific LTP deficits in neocortex of αCaMKII+/–mice correlated with a selective impairment of permanent memory formation [14]. These studies were one of the first demonstrations that LTP in the neocortex can be selectively targeted for disruption, and supports a role of neocortex in the storage of remote memories, which is distinct from the role of hippocampus in the initial formation of memories [25]. Similarly, mice expressing a dominant negative form of p21-activated kinase (PAK) display abnormal spine morphology and LTP/LTD in the temporal cortex, but not in CA1, which correlated with impairments in long-term memory [26].

There are other examples that indicated that synaptic plasticity in the neocortex occurs under more restricted conditions and vulnerable to manipulations than in the CA1. For instance, knockout mice lacking glutamate decarboxylase 65 (GAD65), the gamma-aminobutyric acid (GABA) synthesizing enzyme enriched at GABAergic boutons [27], lack LTD in the visual cortex, but exhibit normal synaptic plasticity in the CA1 [28]. This suggests that neocortical LTD is more vulnerable to changes in GABAergic function. Neocortical LTD is also more sensitive to blockers of phospholipase C (PLC)-linked receptors. Blocking multiple PLC-linked receptors abolish LTD in the visual cortex, but leaves a portion of LTD intact in the CA1 [29]. This suggests that neocortical LTD is regulated more drastically by changes in the tone of PLC-linked neuromodulators. In line with this, activation of PLC-linked neuromodulator receptors in visual cortex produces LTD even under spike-timing windows that are known to favor LTP [22], as well as with induction protocols that normally yield pairing-induced LTP [30]. This may explain the strong requirement of neuromodulatory systems in cortical reorganization [31–33]. Recent studies also show that there are specific differences in AMPAR regulation in the neocortex compared to that in the hippocampus (Section 2.3 and Table 1).

2.2. AMPAR regulation during synaptic plasticity

It is now widely accepted that AMPAR regulation is a key component in the expression of postsynaptic forms of LTP and LTD, as well as homeostatic synaptic plasticity of excitatory synapses. There are largely 2 modes of AMPAR regulation that contribute to synaptic plasticity: one is via regulation of its synaptic trafficking and the other is via alterations in phosphorylation of its subunits. These two key regulation mechanisms may not be independent, because some phosphorylation sites have been implicated in regulating synaptic trafficking of AMPARs [12,20].

2.2.1. AMPAR synaptic trafficking in LTP and LTD

One of the first evidence supporting synaptic trafficking of AMPARs in synaptic plasticity came from studies in CA1 demonstrating the existence of "silent" synapses, which lack functional AMPARs [34,35]. In particular, these studies showed that "silent" synapses convert to functional ones (i.e. express functional AMPARs) following LTP induction. These results paved a way for subsequent studies addressing how AMPARs could traffic in and out of synapses following LTP and LTD. By expressing specific AMPAR subunits that allow electrophysiological detection (i.e. electrophysiological tagging method), Malinow's group demonstrated that LTP is associated with synaptic incorporation of GluA1 (or GluR1) subunit containing AMPARs [36,37]. Although over-expressing the GluA1 subunit, which assemble into homomers, allow detection of functional GluA1-homomers at synapses following LTP [36,37],

Table 1
Comparison of AMPAR regulation in CA1 and neocortex.

	CA1	Neocortex
Cell surface GluA1/GluA2 ratio	Higher [54,67].	Lower [66,117].
CP-AMPARs	Mostly perisynaptic and extrasynaptic [54,107]. Limited synaptic and extrasynaptic expression [39,127].	Synaptic expression during development and via changes in sensory experience [66,95,108–113].
GluA1-S831 phosphorylation	Increased phosphorylation with LTP [57,58]. Not necessary for LTP or LTD [71]. Not necessary for synaptic AMPAR trafficking [36].	Necessary for spike-timing dependent LTD and pairing LTD [22,30]. Not necessary for spike-timing dependent LTP [22]. Necessary for normal experience-dependent synaptic scaling [66].
GluA1-S845 phosphorylation	Dephosphorylation with LTD [58,62]. Necessary for NMDAR-dependent LTD [71,128]. "Primes" associative LTP [69].[a] Increases cell surface AMPAR without changes in synaptic AMPAR function [53,67].[a]	Increased phosphorylation with sensory deprivation [66,95]. Necessary for both LTP and LTD [22]. "Primes" associative spike-timing dependent LTP [22]. Necessary for experience-dependent synaptic scaling [66]. Increases cell surface AMPAR and synaptic AMPAR function [66].[a]

[a] In these studies, GluA1-S845 phosphorylation was pharmacologically increased by β-adrenergic receptor agonist application, and the necessity of S845 was not directly tested.

the incorporation of native Ca^{2+}-permeable GluA1-homomers at CA1 synapses during LTP is debated [38–40]. Nevertheless, there is a clear consensus in the field that new AMPARs are mobilized to synapses following LTP. Recent studies using single molecule tracking of individual AMPARs showed that one mode of increasing the synaptic content of AMPARs is via activity-dependent "diffusional trapping" [41,42]. Individual AMPARs tagged with a quantum dot has been shown to diffuse laterally across the plane of the plasma membrane, often traversing into synaptic regions. While the dwell time of AMPARs at synapses is longer than that seen at extrasynaptic sites, synaptic activity dramatically limits the mobility of synaptic AMPARs. This led to the idea that synaptic activity accumulates AMPARs at synapses via limiting the lateral diffusion rate [43]. In support of this, there is a strong correlation between cell surface and synaptic AMPAR levels [44], and the AMPARs recruited to synapses following LTP predominantly originate from pre-existing surface population [45]. However, LTP inducing stimuli also increases the exocytosis rate of AMPARs [45], and disrupting exocytosis microdomains located close to the postsynaptic density (PSD) prevents LTP [46]. Collectively, these findings suggest that exocytosis of AMPARs is crucial for increasing the surface population of AMPARs, which are then trapped at synapses in an activity dependent manner (Fig. 1).

On the flip side, convergent evidence supports a role of AMPAR endocytosis following LTD induction and interfering with AMPAR endocytosis impairs LTD in the CA1 region [47]. Endocytosis of AMPARs occurs at discrete perisynaptic and extrasynaptic endocytic "hot zones", and the close proximity of perisynaptic endocytic zones to the PSD is maintained by protein–protein interactions involving the long forms of Homer, Shank, and dynamin-3 [48]. Expression of Homer1a, which is an activity induced dominant negative form of Homer, decreases the fraction of spines containing endocytic zones [48]. This suggests that neural activity can regulate the availability of perisynaptic endocytic zones. Unexpectedly, synapses lacking endocytic zones had lower synaptic AMPAR levels [48], consistent with findings that recycling endosomes are a source for providing AMPARs that can be trafficked to synaptic sites following LTP [49]. Thus, endocytic zones are not only involved in endocytosis of AMPARs, but also are critical for supplying AMPARs to recycling endosomes for synaptic insertion (Fig. 1).

2.2.2. AMPAR phosphorylation and LTP/LTD

Phosphorylation of specific AMPAR subunits is essential for the regulation of plasma membrane and synaptic trafficking of AMPARs [20] (Fig. 1). In the case of LTP, phosphorylation of GluA1 S818 by PKC and S845 by PKA are thought critical for synaptic targeting of GluA1-containing AMPARs following LTP induction [50–52]. Our current understanding is that the GluA1-S845 phosphorylation plays a more permissive role in LTP by increasing the amount of AMPARs at extrasynaptic plasma membrane [53] or stabilizing perisynaptic GluA1 homomers [54], while the GluA1-S818 site is thought critical for the actual synaptic targeting of AMPARs following LTP by increasing the rate of extrasynaptic and synaptic insertion [50,52]. In addition, the GluA1-S831 site, a major CaMKII phosphorylation site [55,56], might contribute LTP [57,58] by regulating the single channel conductance [59,60]. In the case of LTD, GluA1-S845 dephosphorylation [58,61,62] and GluA2-S880 phosphorylation [63,64] have been implicated to play a role. How the regulation of these two subunits coordinate LTD expression remains unclear.

PKA phosphorylation of GluA1-S845 has been proposed to "prime" the receptors for synaptic targeting by promoting plasma membrane insertion [53]. Interestingly, GluA1-S845 phosphorylation is highly regulated by neuromodulators linked to the cAMP signaling cascade. For instance, in both the CA1 and the visual cortex

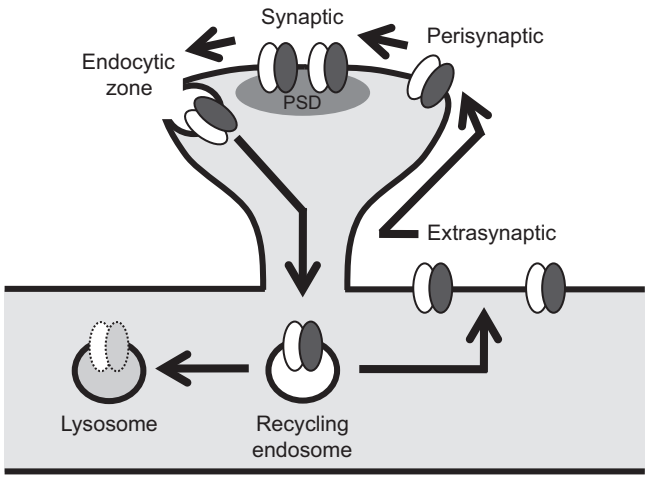

Fig. 1. A model of AMPAR regulation. AMPARs reside in distinct subcellular compartments as depicted. Exocytosis from recycling endosome to extrasynaptic sites depends on GluA1-S845 phosphorylation. PKA-linked neuromodulators increase the extrasynaptic GluA1 population via acting on GluA1-S845. Interestingly, cortical synapses have a smaller basal extrasynaptic GluA1 population compared to CA1. Extrasynaptic population can laterally diffuse into synaptic areas, and synaptic activity traps and anchors them to the PSD. Synaptic targeting depends on GluA1-S818 phosphorylation and CaMKII activity, as well as prior phosphorylation on the GluA1-S845, but not on the GluA1-S831. Synaptic AMPARs can be endocytosed via perisynaptic endocytic zones, which also act to supply AMPAR to recycling endosomes. Dephosphorylation of GluA1-S845 targets endocytosed AMPARs to lysosome for degradation, while phosphorylation of this site allows recycling back to the plasma membrane. CP-AMPARs predominantly accumulate at perisynaptic sites in CA1, while accumulate at cortical synapses with changes in sensory experience.

activation of β-adrenergic receptors increases GluA1-S845 phosphorylation [22,65] and cell surface expression of GluA1 [66–68], and promotes LTP induction [22,69]. These effects are likely due to the close proximity of β-adrenergic receptors and PKA signaling molecules to the synaptic AMPARs. Indeed, β2-adrenergic receptors are localized at PSDs and form a macromolecular complex with GluA1, stargazin, and PSD-95 [68]. And PKA is linked to this macromolecular complex via anchoring to A-kinase anchoring protein 79/150 (AKAP79/150), which interacts with PSD-95 [70]. While GluA1-S845 promotes LTP induction, it is not necessary for CA1-LTP, as mice carrying an alanine mutation of this site (GluA1-S845A) express normal LTP at these synapses [71]. This contrasts the necessity of GluA1-S845 in neocortical LTP (see Section 2.3).

GluA1-S818 is located within a membrane proximal region (MPR) right after the last transmembrane domain of the GluA1, which is a region that interacts with an actin cytoskeleton binding protein 4.1N [72]. The role of GluA1-S818 in LTP is rather complex, because it requires concomitant action of other phosphorylation sites (e.g. GluA1-S816) and depalmitoylation of a cysteine residue (i.e. GluR1-C811) within the MPR [50,52]. In any case, mutations that prevent S818 and S816 phosphorylation decreases, while phosphomimic mutation of these two serines (S816D and S818D) increases, the membrane insertion rate of AMPARs [52]. The membrane targeting of GluA1 by the MPR serines was due to regulating the interaction between the GluA1 and 4.1N, and disrupting this interaction inhibits LTP [52].

In addition to the GluA1-S845 and S818 sites, GluA1-S831 might also play a role in LTP. CaMKII is both necessary [73,74] and sufficient [75] for LTP, and consistent with being one of the CaMKII substrates [55,56], phosphorylation of GluA1-S831 increases with LTP [57,58]. However, while CaMKII activity is required to drive AMPARs to synapses, this is independent of GluA1-S831 [36]. Because phosphorylation of GluA1-S831 increases single channel conductance [59], it is likely to mediate the increase in AMPAR conductance with LTP [76,77]. However, CA1 LTP is quite normal in mice specifically lacking the GluA1-S831 site [71], hence it is not necessary for LTP expression.

LTD, on the other hand, is accompanied by a dephosphorylation of GluA1-S845 [58,62], phosphorylation of GluA2-S880 [63,64], and endocytosis of AMPARs [78,79]. The role of GluA1-S845 dephosphorylation is likely via targeting GluA1-containing AMPARs for endocytosis and eventual degradation in the lysosomes [80]. GluA2-S880 phosphorylation is also involved in receptor endocytosis by preferentially shifting GluA2 interaction from Grip to Pick-1 [63,81]. Mimicking phosphorylation of the GluA2-S880 site (GluA2-S880E mutation) depresses synaptic transmission and partially occludes LTD [82]. However, GluA2 is not necessary for LTD, since NMDAR-dependent CA1 LTD [83,84] and activity-dependent endocytosis of AMPARs [85] can occur in the absence of the GluA2 subunit. Because LTD is absent in mice lacking the GluA1-S845 site (GluA1-S845A mutant) [71], GluA1 may play a more dominant role.

2.2.3. AMPAR regulation during synaptic scaling

Activity-dependent regulation of AMPARs is not limited to LTP/LTD, but also occurs during homeostatic synaptic plasticity. The latter form of synaptic plasticity acts to maintain balance in the overall network activity by working on global variables that act on a longer time scale than those needed for LTP/LTD. One form of homeostatic synaptic plasticity is termed "synaptic scaling", because homeostasis is achieved via adjustment of synaptic gain [2]. It is now well documented that a prolonged decrease and increase in input activity, respectively, scales up and down excitatory synapses. Early evidence for synaptic scaling came from neuronal cultures where pharmacological blockade of neural activity globally increases the gain of excitatory synapses, and pharmacologically increasing neuronal firing reduces the strength of excitatory synapses [86,87]. Synaptic scaling was found to respond to global cell-wide variables, such as somatic action potentials [88,89], and produce changes across most of the synapses on a neuron. However, some studies suggest that synaptic scaling can happen locally at single synapses [90–92]. Global and local homeostatic synaptic plasticity may serve distinct roles in regulating neuronal function [93].

Regardless of the extent of change, the most prominent postsynaptic change related to synaptic scaling is the regulation of AMPARs, which often tap into similar mechanisms used during LTP/LTD. For instance, prolonged inactivity leads to accumulation of AMPARs at synapses, which correlated with an increase in AMPAR-mediated miniature excitatory postsynaptic current (mEPSC) [87]. On the other hand, prolonged increase in neural activity removes synaptic AMPARs and decrease mEPSCs [87,94]. Most studies find that the main regulation is at the level of controlling synaptic GluA1 content [66,95–100], but disrupting GluA2-dependent mechanisms also impact synaptic scaling [101,102]. Molecular details of AMPAR regulation during synaptic scaling is quite similar to that observed during LTP/LTD, such as modulation of GluA1 phosphorylation [66,95] and GluA2 interaction with Pick-1 [102] and/or other carboxy-tail binding partners [101]. At this point, how seemingly opposite changes in neural activity (i.e. increase in activity for driving LTP versus a decrease in neural activity that produce scaling up) lead to similar AMPAR regulation (i.e. up-regulation of synaptic AMPAR function) is not clear. One possibility is that distinct signaling occurs for LTP/LTD versus synaptic scaling. For instance, LTP/LTD that lead to AMPAR regulation are mainly NMDAR-dependent, while synaptic scaling can happen in the absence of NMDAR activity, such as requiring mGluR signaling [103]. However, NMDAR activity can influence the kinetics of synaptic scaling [104], and may be critical for local synapse-specific scaling [93].

2.3. Contrasting AMPAR regulatory mechanisms in hippocampus and neocortex

So far the available data suggest that neocortical synapses may be more permissive to synaptic trafficking of Ca^{2+}-permeable (CP-) AMPARs than synapses in the CA1. In the CA1, synaptic incorporation of CP-AMPARs, such as GluA1-homomers, is debated [38–40], and may occur under certain conditions such as activation of CaMKI signaling [105,106]. In addition, there is evidence that CP-AMPARs are predominantly localized to perisynaptic sites in the CA1 [54,107]. On the other hand, CP-AMPARs are observed at neocortical synapses early in development [108–110], and changes in sensory experience regulate synaptic expression of CP-AMPARs [95,111–113]. For instance, single-whisker experience increases synaptic CP-AMPARs in the barrel cortex [111,112], which requires Pick-1 [114]. In the visual cortex, CP-AMPARs appear at synapses following binocular visual deprivation, which then are subsequently removed by visual experience [66,95]. Furthermore, visual deprivation-induced cross-modal changes in barrel cortex also involve regulation of CP-AMPARs [95,113]. While the CP-AMPAR regulation seen in the barrel cortex by single whisker experience mimics LTP [111,112], the regulation in visual cortex after binocular deprivation follows the rules of synaptic scaling [66,95]. The cross-modal changes seem to involve both LTP-like [113] and homeostatic synaptic plasticity mechanisms [95] depending on the duration of visual deprivation. Regardless, these results suggest that CP-AMPAR, especially GluA1-homomer, regulation may be a key mechanism in which sensory cortices respond to changes in the sensory environment.

In mice lacking the GluA1-S845 phosphorylation site, CP-AMPARs accumulate at visual cortical synapses [66], but are actively removed and degraded in the CA1 [54]. While further

study is required to determine how CP-AMPARs are differentially regulated in the two brain regions, it is tempting to speculate that the cortical synapses may be more tolerant to the presence of CP-AMPARs. CP-AMPARs have faster decay kinetics and larger conductance than Ca^{2+}-impermeable AMPARs [115]. Hence it is possible that changes in the temporal dynamics of synaptic responses conferred by the presence of CP-AMPARs may provide benefit to the cortical synapses, which may outweigh any potential negative impact of having the extra Ca^{2+} signal. Interestingly, the basal expression of GluA1 is lower in visual cortex compared to CA1 [116] (unpublished observations H.-K. Lee). Furthermore, the percentage of GluA1 present on the cell surface is lower in visual cortex (about 15–30%) [66,117] than in CA1 (about 40–45%) [54,67]. These measurements reflect predominantly extrasynaptic surface population suggesting that the size of this "reserve" pool of GluA1-containing AMPARs is less in the neocortex.

There is also potential difference in the role of AMPAR phosphorylation for synaptic plasticity in hippocampus and neocortex. As discussed previously, GluA1-S845 site is specifically involved in the expression of LTD in the CA1 without effect on LTP [54,58,71]. However, mice lacking the site (GluA1-S845A mutants) display impairment of both LTP and LTD in the visual cortex [22,30]. This is interesting in light of the findings that neocortical plasticity is highly dependent on neuromodulatory systems, such as norepinephrine and acetylcholine [31–33]. Furthermore, the polarity of neocortical synaptic plasticity critically depend on the neuromodulatory system, such that activation of PKA-linked neuromodulator receptors produces LTP and PLC-linked receptors result in LTD with the same stimulation protocol [22,30]. It is noteworthy that activating β-adrenergic receptor, which is linked to PKA signaling, increases GluA1-S845 phosphorylation [22,66] and cell surface expression of AMPARs [66] in the visual cortex. Whether the "priming" effect of GluA1-S845 plays a more critical role in neocortical plasticity needs further study, but this would be consistent with the findings that synaptic plasticity in neocortex is more vulnerable to manipulations of PKA. For instance, inhibiting PKA completely blocks both LTP and LTD in the visual cortex [17,22]. In contrast, while PKA inhibitors are effective at blocking LTP in the CA1 in neonates [118,119], beyond the second postnatal week LTP is usually not severely impacted until the late maintenance phase [58,120,121] (but see [122]). The role of PKA in neocortical LTP may be complicated, because in barrel cortex PKA-dependent LTP is only revealed following sensory deprivation [18]. However, considering that sensory deprivation leads to homeostatic synaptic plasticity [66,95,117,123–125], and that the state of synapses determines the distinct signaling for LTP/LTD [20], this may not be a surprise. Indeed, sensory deprivation changes the state of AMPAR phosphorylation [66,95], which may influence the expression of PKA-dependent LTP.

Another potential difference in AMPAR regulation is on the role of GluA1-S831. In CA1, GluA1-S831 phosphorylation correlates with [57,58], but is not necessary for LTP [71]. However, in the visual cortex GluA1-S831 is necessary for associative spike-timing dependent and pairing-induce LTD [22,30]. This is paradoxical, considering that GluA1-S831 is phosphorylated by CaMKII [55,56] and PKC [126], but LTD in the visual cortex is normal in αCaMKII knockouts [13] or in the presence of PKC inhibitors [29]. How the GluA1-S831 site contributes to cortical LTD remains to be determined, but we recently found that basal phosphorylation of GluA1-S845 is abnormally high [66] in the visual cortex of GluA1-S831A mutants, which would explain the absence of LTD. However, this abnormal regulation is specific to the cortex, because GluA1-S845 site is not significantly altered or negatively impacted in the CA1 of GluA1-S831A mutants [71]. These results suggest that CA1 and neocortex may respond differently to changes in GluA1-S831 phosphorylation.

3. Conclusions

Hippocampal synapses, especially the Schaffer collateral inputs to CA1, have been instrumental in unraveling many of the fundamental mechanisms of synaptic plasticity. While many of the basic mechanisms are conserved across brain areas, there are specific differences. Recent studies highlight that the neocortex has a distinct functional role in that it contributes to the long-term storage of memories, and in particular sensory cortices need to respond to changes in sensory demand that is tied to the behavioral state and the sensory environment. Therefore, it is perhaps not a surprise that the sensory neocortices show more restricted plasticity than the CA1, and have somewhat different AMPAR regulatory mechanisms in place to respond to their specific functional demands.

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