Review

THE EMBO JOURNAL

Postsynaptic localization and regulation of AMPA receptors and Cav1.2 by β2 adrenergic receptor/PKA and Ca^{2+}/CaMKII signaling

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Abstract

The synapse transmits, processes, and stores data within its tiny space. Effective and specific signaling requires precise alignment of the relevant components. This review examines current insights into mechanisms of AMPAR and NMDAR localization by PSD-95 and their spatial distribution at postsynaptic sites to illuminate the structural and functional framework of postsynaptic signaling. It subsequently delineates how β_2 adrenergic receptor (β_2 AR) signaling via adenylyl cyclase and the cAMP-dependent protein kinase PKA is organized within nanodomains. Here, we discuss targeting of β_2 AR, adenylyl cyclase, and PKA to defined signaling complexes at postsynaptic sites, i.e., AMPARs and the L-type Ca^{2+} channel $Ca_v1.2$, and other subcellular surface localizations, the role of A kinase anchor proteins, the physiological relevance of the spatial restriction of corresponding signaling, and their interplay with signal transduction by the Ca^{2+}- and calmodulin-dependent kinase CaMKII. How localized and specific signaling by cAMP occurs is a central cellular question. The dendritic spine constitutes an ideal paradigm for elucidating the dimensions of spatially restricted signaling because of their small size and defined protein composition.

Keywords AKAP; cAMP; NMDA receptors; norepinephrine; PSD-95
DOI 10.15252/embj.201899771 | Received 5 May 2018 | Revised 25 July 2018 | Accepted 17 August 2018 | Published online 24 September 2018
The EMBO Journal (2018) 37: e99771

See the Glossary for abbreviations used in this article.

Introduction

The mind-staggering capabilities of the brain depend on the complexity of neuronal connections formed by ~10^{15} synapses. Synapses not only transmit and process signals; they also constitute the basic unit for information storage such as episodic memory or motor skills utilizing different forms of synaptic plasticity such as long-term potentiation (LTP—see Glossary) and long-term depression (LTD). LTP is a permanent increase in the otherwise remarkably stable synaptic strength following brief synaptic stimulations at high frequency (1 s, 50–200 Hz), and LTD is a decrease induced by longer synaptic stimulations at modest frequency (Collingridge *et al,* 2004; Lisman & Hell *et al,* 2008; Sudhof & Malenka, 2008; Kessels & Malinow, 2009; Huganir & Nicoll, 2013; Morris, 2013). Furthermore, synapses decode and process signals in a dynamically regulated manner. For instance, spine Na^+ channels amplify (Araya *et al,* 2007) and K^+ channels dampen (Kim *et al,* 2007) postsynaptic excitation. Thus, the synapse integrates in its minute space a large number of signaling mechanisms, constituting a unique system for studying localized signaling.

Synaptic functions are modulated by various signaling pathways such as the prominent β_2 AR–PKA cascade (Lee *et al,* 2000; Oh *et al,* 2006; Hu *et al,* 2007; Lu *et al,* 2007; Joiner *et al,* 2010; Havekes *et al,* 2012; Qian *et al,* 2012, 2017; Murphy *et al,* 2014a; Patriarchi *et al,* 2016). The widely studied PKA is exemplary for localized signaling via formation of signaling complexes. It resides in stable complexes with AMPARs (Rosenmund *et al,* 1994; Tavalin *et al,* 2002; Joiner *et al,* 2010) and the L-type Ca^{2+} channel $Ca_v1.2$ (Davare *et al,* 1999; Balijepalli *et al,* 2006). Remarkably, these AMPAR and $Ca_v1.2$ complexes also contain the β_2 AR, trimeric Gs protein, and adenylyl cyclase (AC), for highly localized regulation via cAMP (Davare *et al,* 2001; Joiner *et al,* 2010; Wang *et al,* 2010). PKA is important for many forms of learning and memory in the broadest sense, which are as diverse as declarative and spatial memory (Lee *et al,* 2003), fear conditioning (Hu *et al,* 2007) and its reversal (Clem & Huganir, 2010; particularly relevant for posttraumatic stress disorder), drug addiction (Wolf & Tseng, 2012), and plasticity of sensory maps (Fischer *et al,* 2004). The β_2 AR is the main postsynaptic mediator of signaling by norepinephrine (Joiner *et al,* 2010; Qian *et al,* 2012, 2017; Patriarchi *et al,* 2016). Norepinephrine is important for arousal, acuity of behavioral tasks, and learning in novel and emotionally charged situations (Cahill *et al,* 1994; Berman & Dudai, 2001; Hu *et al,* 2007; Minzenberg *et al,* 2008; Carter *et al,* 2010; He *et al,* 2015).

After a thorough overview of the overall organization of the postsynaptic site of glutamatergic synapses, this review will assess our knowledge of the molecular details and spatial and functional

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Glossary

AC	adenylate cyclase
AKAP	A kinase anchor protein
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AMPA-type glutamate receptor
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase II
$Ca_v1.2$	class C L-type Ca^{2+} channel
$Ca_v1.3$	class D L-type Ca^{2+} channel
CI-AMPAR	Ca^{2+}-impermeable AMPAR
CNIH2/3	cornichon homologues 2 and 3
CP-AMPAR	Ca^{2+}-permeable AMPAR
EPSP	excitatory postsynaptic potential
GABA	γ-aminobutyric acid
GKAP	guanylate kinase domain-associated protein (also known as SAPAP)
GK	guanylate kinase
GluA	AMPA-type glutamate receptor subunit
GluN	NMDA-type glutamate receptor subunit
GRK	G protein-coupled receptor kinase
GsPCR	Gs protein-coupled receptor
LTD	long-term depression
LTP	long-term potentiation
MAP2B	microtubule-associated protein type 2B
mEPSC	miniature excitatory postsynaptic current
mGluR	metabotropic glutamate receptor
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NMDAR	N-methyl-D-aspartate receptor; NMDA-type glutamate receptor
PDZ	PSD-95–discs large–zonula occludens homology domain
PFC	prefrontal cortex
PKA	cAMP-dependent protein kinase; protein kinase A
PKC	protein kinase C
PP1	serine/threonine protein phosphatase 1
PP2B	protein phosphatase 2B/calcineurin
PSD-93	postsynaptic density protein of 93 kDa
PSD-95	postsynaptic density protein of 95 kDa
PSD	postsynaptic density
PTT-LTP	prolonged theta tetanus-long-term potentiation
Pyk2	protein tyrosine kinase 2; Ca-dependent tyrosine kinase (CADTK)
SAP102	synapse-associated protein of 102 kDa
SAP97	synapse-associated protein of 97 kDa
SAPAP	synapse-associated protein–associated protein (also known as GKAP)
SH3	Src homology domain 3
Src	proto-oncogene tyrosine-protein kinase
STEP	striatal-enriched protein tyrosine phosphatase
Stg	stargazing (γ2)
SynDIG1	synapse differentiation-induced gene 1
TARP	transmembrane AMPAR regulatory protein
TNF	tumor necrosis factor
γ8	transmembrane AMPAR regulatory protein (TARP) γ8

aspects of the classical postsynaptic signaling by β_2 AR–AC–PKA pathways. The review will then contrast those pre-assembled pathways with signaling by CaMKII, which is recruited to postsynaptic sites that experience heightened synaptic activity and Ca^{2+} influx through the NMDAR. This Ca^{2+} influx and the ensuing activation of CaMKII are absolutely critical for various forms of learning and LTP (Collingridge *et al,* 2004; Lisman & Hell *et al,* 2008; Sudhof & Malenka, 2008; Kessels & Malinow, 2009; Huganir & Nicoll, 2013; Morris, 2013). We propose that the diffuse signaling by NE throughout large brain regions by volume release sensitizes a broad population of synapses to induction of synaptic plasticity during alert states via preformed β_2 AR complexes with AMPARs and $Ca_v1.2$, whereas the activity-driven and highly specific recruitment of CaMKII to a small number of individual synapses that experience Ca^{2+} influx serves as the defining key step in the induction of LTP at those selected synapses for storage of specific information such as environmental maps or fear conditioning. Whether assembly of signaling complexes is constitutive or induced, target association is essential to minimize off target effects by cAMP, PKA, or CaMKII.

AMPARs and NMDARs

More than 80% of synapses in the cortex are glutamatergic (Micheva *et al,* 2010). The AMPAR mediates most of the basal postsynaptic response with the slower NMDAR contributing a smaller fraction especially during the later part of an EPSP. AMPARs consist of four homologous subunits (GluA1-4) (Traynelis *et al,* 2010). Diheterotetrameric GluA1/2 receptors account for ~80% and GluA2/3 receptors for most of the rest of postsynaptic AMPARs in forebrain under basal conditions (Wenthold *et al,* 1996; Lu *et al,* 2009; Traynelis *et al,* 2010; Fig 1). A minority of AMPARs consist of GluA1 only, which plays a role during the early phase of LTP at certain ages as well as LTD (see below). These AMPARs lack GluA2, which acquires via RNA editing an Arg at a position within its pore that is otherwise occupied by Gln in GluA1, GluA3, GluA4, and unedited GluA2. The positive charge reduces single-channel conductance and makes GluA2-containing AMPAR Ca^{2+}-impermeable (CI-AMPARs). GluA2-lacking AMPARs are Ca^{2+}-permeable (CP-AMPARs).

Like AMPARs, the homologous NMDARs are tetramers, which are formed by two GluN1 and two GluN2 subunits. One GluN1 and four GluN2 (A-D) genes exist, with GluN1/2A and GluN1/2B being the predominant isoforms in forebrain (Traynelis *et al,* 2010; Gray *et al,* 2011). Whereas most AMPARs are mainly permeable for Na^+ (and K^+), NMDARs also conduct Ca^{2+} (Fig 1). AMPARs and NMDARs are clustered at the postsynaptic density (PSD), a protein-dense meshwork, and precisely juxtaposed to the presynaptic active zone (Tang *et al,* 2016; Biederer *et al,* 2017) for fast and efficient postsynaptic responses (Clements *et al,* 1992).

Postsynaptic Distribution of AMPARs and NMDARs

A typical PSD is 300–400 nm in diameter (Harris & Stevens, 1989; Shepherd & Harris, 1998; Dani *et al,* 2010). It contains 30–150 AMPARs and 20–30 NMDARs according to immunogold EM (Nusser *et al,* 1998; Tanaka *et al,* 2005; Fukazawa & Shigemoto, 2012), EM tomography (Chen *et al,* 2008, 2015), electrophysiology (Bekkers & Stevens, 1989; Spruston *et al,* 1995; Smith *et al,* 2003), glutamate uncaging (Matsuzaki *et al,* 2001), and proteomic analysis of Triton X-100-treated PSDs (Sheng & Hoogenraad, 2007). PSD size is linearly correlated with AMPAR (Takumi *et al,* 1999; Shinohara *et al,* 2008; Fukazawa & Shigemoto, 2012; Chen *et al,* 2015) but not NMDAR content, which is fairly invariant between synapses of quite different sizes (Takumi *et al,* 1999; Racca *et al,* 2000; Shinohara *et al,* 2008; Chen *et al,* 2015). Because of the disproportional content of Ca^{2+}-permeable NMDARs, small spines have larger Ca^{2+} transients than large spines (Nimchinsky *et al,* 2004).

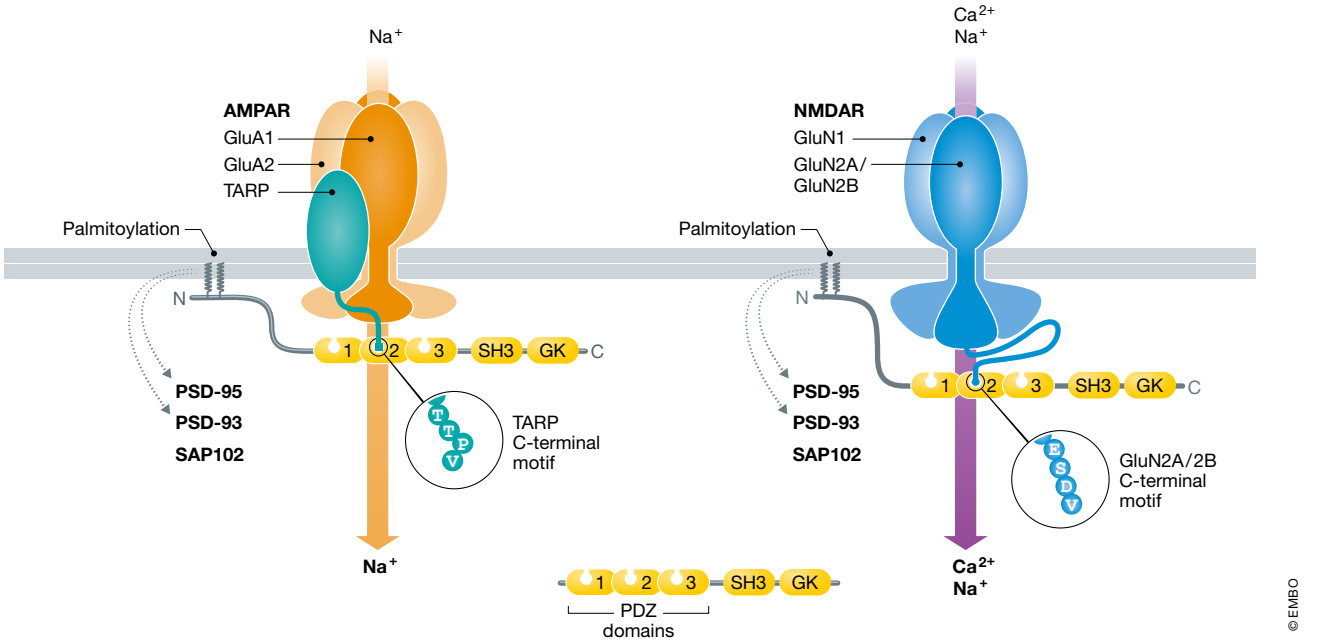

Figure 1. Postsynaptic AMPARs, NMDARs, and PSD-95.
AMPARs mostly consist of two GluA1 and two GluA2 subunits (blue) plus one or more TARP subunits (green). TARPs mediate postsynaptic localization by binding to PSD-95 (yellow) and its homologues, PSD-93, and SAP102, which contain three PDZ domains followed by an SH3 and a GK domain. NMDARs mostly consist of two GluN1 and two GluN2A/2B subunits (purple); GluN2A/2B directly bind to PSD-93/PSD-95/SAP102. AMPARs are mainly Na^+- and K^+-permeable, whereas NMDARs also conduct Ca^{2+}. Postsynaptic anchoring of PSD-95 and some PSD-93 isoforms but not of SAP102 requires palmitoylation of their N-termini (depicted in zigzag), which fosters their interactions with AMPARs and NMDARs. The C-terminal ESDV motif of GluN2A/2B has a higher affinity for PDZ1 and PDZ2 than the TTPV motif of TARPs.

AMPARs are ~24–27 nm and NMDARs ~30-32 nm apart when measured center to center (Chen *et al,* 2008, 2015; Fig 2). NMDARs tend to localize toward the PSD center when AMPAR density seems to be skewed toward the periphery (Matsubara *et al,* 1996; Kharazia & Weinberg, 1997; Petralia *et al,* 1998; Somogyi *et al,* 1998; Chen *et al,* 2008, 2015) although some other work suggests a more uniform distribution of AMPARs within the PSD (Nusser *et al,* 1994). AMPARs are concentrated in clusters of ~100 nm diameter, together with PSD-95 and its binding partners GKAP, Shank, and Homer (Fukata *et al,* 2013; MacGillavry *et al,* 2013; Nair *et al,* 2013; Sinnen *et al,* 2017). Localization of AMPARs in those nanoclusters is thought to be functionally important because affinity of AMPARs for glutamate is fairly low and only AMPARs that are exactly juxtaposed to presynaptic release sites might be effectively activated (Franks *et al,* 2003; Lisman & Raghavachari, 2006). In fact, those nanoclusters appear to be closely aligned with presynaptic release sites for fast and efficient synaptic transmission (Tang *et al,* 2016; Biederer *et al,* 2017; Hruska *et al,* 2018). New functional evidence for this hypothesis has recently been provided by optogenetically induced binding of GluA1 to postsynaptic proteins (Sinnen *et al,* 2017). Accordingly, optogenetic AMPAR recruitment to spines did not augment the mEPSC amplitude in synapses that already contained functional AMPAR (although it did induce AMPAR responses in so-called silent synapses in which no AMPAR activity was detected before light exposure). Glutamate uncaging, which stimulates AMPARs over the whole surface of dendritic spines, demonstrated that AMPARs were clearly increased on the spine surface of synapses that did contain AMPAR before light application, yet responses to presynaptic glutamate release were not. Furthermore, stochastic optical reconstruction microscopy (STORM) imaging showed that light-induced recruitment occurred into the postsynaptic density, the postsynaptic site of glutamatergic synapses. These results indicate that augmenting AMPAR content on the spine surface is not sufficient for augmenting postsynaptic response, thereby supporting the hypothesis that AMPARs must be present near the presynaptic glutamate release sites for their effective activation (MacGillavry *et al,* 2013; Nair *et al,* 2013; Tang *et al,* 2016; Hruska *et al,* 2018). However, it still remains unclear whether only AMPARs in those nanoclusters or AMPARs inside the PSD in general are activated during regular synaptic transmission.

However, the PSD is not static. Some AMPARs in PSDs are basically immobile on a minute timescale and apparently fairly stably anchored within PSDs (Tardin *et al,* 2003) especially when PSD-95 is overexpressed (Kerr & Blanpied, 2012). Other AMPARs show modest mobility within postsynaptic sites (Tardin *et al,* 2003). Extrasynaptic AMPARs are highly mobile and can diffuse right through synaptic sites (Tardin *et al,* 2003), but PDZ interactions between PSD-95 and AMPAR complexes (see below) can trap AMPARs at postsynaptic sites (Bats *et al,* 2007). More recent superresolution microscopy shows that AMPARs are either confined to the nanodomains described in the preceding paragraph with very low diffusion (presumably because they are anchored through protein interactions with PSD-95 and its homologues) or diffuse seemingly freely in and out of the nanodomains, apparently untethered (Nair *et al,* 2013). Some

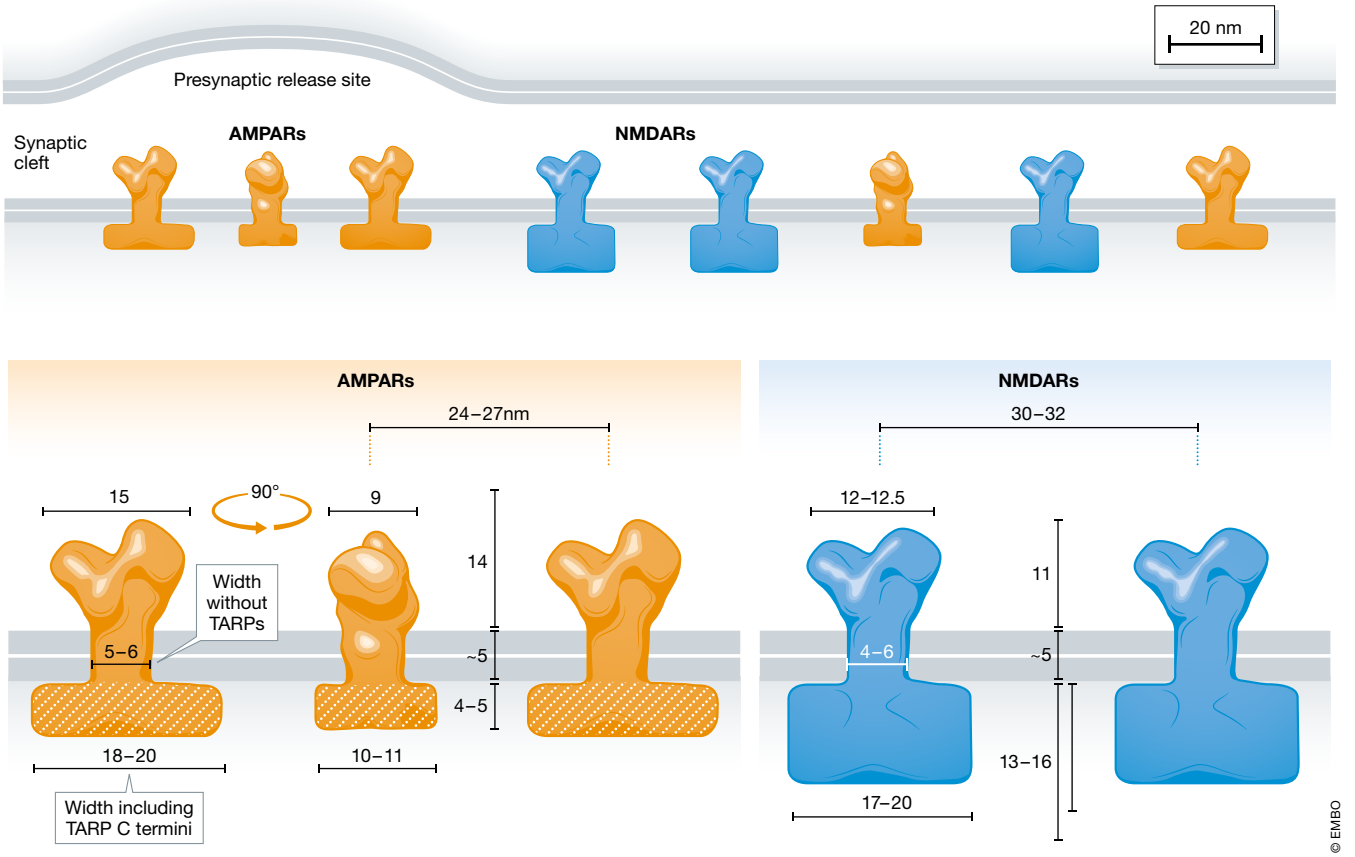

Figure 2. AMPAR and NMDAR dimensions and distribution at the postsynaptic site.
The extracellular N-termini of inactive AMPARs are V-shaped dimers of dimers and 14 nm high and 9 nm × 15 nm wide at the tip (Nakagawa *et al*, 2005; Sobolevsky *et al*, 2009). The transmembrane segment is ~5 nm long and 5–6 nm in diameter without TARPs (Nakagawa *et al*, 2006; Sobolevsky *et al*, 2009) and significantly wider with TARPs (Nakagawa *et al*, 2005). The intracellular AMPAR C-termini in conjunction with C-termini of associated TARPs are 18–20 nm × 10–11 nm wide and 4–5 nm high (Chen *et al*, 2008, 2015). The extracellular N-termini of NMDARs are 11 nm high and 12 nm × 12.5 nm wide at the tip (Lee *et al*, 2014). The transmembrane segment is ~5 nm long and 4–6 nm wide (Lee *et al*, 2014). The C-termini of NMDARs are 17–20 nm × 13–14 nm wide and 13–16 nm high (Chen *et al*, 2008, 2015). The center-to-center distance is on average 24 nm for AMPARs and 32 nm for NMDARs (Chen *et al*, 2008, 2015). The models are based on Nakagawa *et al* (2006).

AMPARs can diffuse in and out of a nanodomain but become temporarily confined inside the nanodomain (Nair *et al*, 2013). Nevertheless, the majority of postsynaptic AMPARs can turn over within minutes (Ashby *et al*, 2006) if not faster in hippocampal cultures (Groc *et al*, 2004) as well as acute slices (Heine *et al*, 2008) by lateral diffusion (Makino & Malinow, 2009), endocytosis, and insertion into the plasma membrane via exocytosis (Lissin *et al*, 1999; Ehlers, 2000; Passafaro *et al*, 2001; Petrini *et al*, 2009). In fact, in 40% of spines imaged by Nair *et al* (2013) showed nanodomains that were not stable for more than 5 min.

Postsynaptic NMDARs turn over much more slowly, on the hour-to-day timescale (Lissin *et al*, 1999; Tovar & Westbrook, 2002; Groc *et al*, 2004). NMDAR clusters are 100–200 nm in diameter (Chen *et al*, 2015; Hanamura *et al*, 2017; Ladepeche *et al*, 2018).

With respect to the overall dimensions of a synapse, it is noteworthy that spine volume and PSD size are strongly correlated with each other (Harris & Stevens, 1989), with presynaptic volume, vesicle content, and active zone size (Harris & Stevens, 1989; Schikorski & Stevens, 1997), and with AMPAR content (Nusser *et al*, 1998; Kharazia & Weinberg, 1999; Takumi *et al*, 1999). Spine size is also well correlated with postsynaptic response strength as determined by glutamate uncaging (Matsuzaki *et al*, 2001; Asrican *et al*, 2007; Araya *et al*, 2014). During LTP, AMPAR content increases within 1–2 min in parallel with spine size (Matsuzaki *et al*, 2004; Steiner *et al*, 2008; Zhang *et al*, 2008; Bosch *et al*, 2014) (see also Yang *et al*, 2008b) and F-actin (Fukazawa *et al*, 2003; Honkura *et al*, 2008; Bosch *et al*, 2014) mediating a lasting increase in synaptic strength (Collingridge *et al*, 2004; Lisman & Hell *et al*, 2008; Sudhof & Malenka, 2008; Kessels & Malinow, 2009; Huganir & Nicoll, 2013). Similarly, NMDAR-dependent LTD correlates with a decrease in spine size and F-actin (Okamoto *et al*, 2004; Zhou *et al*, 2004) and requires actin depolymerization (Wang *et al*, 2007).

Over time, F-actin defines not only spine size but also PSD size and AMPAR content although it is unclear how F-actin does so, a critical question for understanding synaptic strength and plasticity. However, LTD but not spine shrinkage depends on the protein phosphatase PP1 and spine shrinkage but not LTD on slingshot or a related phosphatase (Zhou *et al*, 2004; Wang *et al*, 2007),

separating the two events and thereby potentially uncoupling synaptic strength and spine size though this uncoupling lasts likely only for a limited time.

Postsynaptic AMPAR and NMDAR targeting by PSD-95

PSD-95 and its homologues PSD-93 and SAP102 are important for postsynaptic AMPAR targeting (El-Husseini *et al,* 2000; Schnell *et al,* 2002; Beique *et al,* 2006; Elias *et al,* 2006; Schluter *et al,* 2006; Bats *et al,* 2007). There are roughly 300 PSD-95, 60 PSD-93, and 40 SAP102 in an average PSD (Sheng & Hoogenraad, 2007). The abundance of SAP97, a fourth PSD-95 homologue linking PKA to GluA1 (see below), in PSD fractions is less certain as it is easily extracted with Triton X-100 (Leonard *et al,* 1998), which is required for purifying PSDs. SAP97 is likely not more abundant than PSD-93 or SAP102 given its relatively low apparent synaptic enrichment by immunofluorescence microscopy (Valtschanoff *et al,* 2000). PSD-95 in turn is localized to the synapse by α-actinin binding to the N-terminus of PSD-95 (Matt *et al,* 2018a). Postsynaptic targeting of PSD-95 also requires its palmitoylation of Cys3 and Cys5 near its N-terminus (Craven *et al,* 1999; El-Husseini Ael *et al,* 2002). α-Actinin binding to PSD-95 is not only important for the localization of PSD-95 but also of a substantial fraction (~40%) of AMPARs. Postsynaptic localization of most of the remaining AMPARs depends on PSD-93 and SAP102 (Elias *et al,* 2006, 2008), which do not bind to α-actinin and are anchored at postsynaptic sites independent of α-actinin (Matt *et al,* 2018a). The estimated presence of ~400 molecules PSD-95 and its homologues fits remarkably well with affinity determinations for PDZ interactions specifically for the interaction of the first two PDZ domains of PSD-95 with GluN2 subunits and TARPs. The average spine volume is $0.062 \pm 0.08\ \mu m^3$ (Harris & Stevens, 1989). If 400 PSD-95 homologues are even distributed throughout the spine, the concentration would be ~10 μM. Consistently, K_d values for the higher affinity GluN2 subunits are ~1 μM, whereas those for TARPs are in the range of 3–12 μM (Lim *et al,* 2002; Dakoji *et al,* 2003; Hafner *et al,* 2015; Pedersen *et al,* 2017).

Based on EM tomography, PSD-95 family members adopt an extended conformation to form vertical filaments (~5 nm diameter) that protrude from the PSD into the cytosol with their C-termini being 20–30 nm away from the PSD (Chen *et al,* 2008, 2011, 2015; Jeyifous *et al,* 2016) in agreement with immunogold EM localization of GKAP (~25 nm) and Shank (~30 nm) (Valtschanoff & Weinberg, 2001), with GKAP binding to the C-terminal GK domain of PSD-95 and Shank to GKAP. Notably, isolated PSD-95 family members show a C-shaped structure suggesting that its conformation can be regulated to expand (Nakagawa *et al,* 2004). In fact, palmitoylation induces an elongated shape of PSD-95, which is required for its binding to AMPARs and NMDARs (Jeyifous *et al,* 2016). The PSD-95 filaments are 13 nm apart (Chen *et al,* 2008, 2011) when distances between AMPARs are ~27 nm and NMDARs ~30 nm (Chen *et al,* 2015). Accordingly, the density of PSD-95 is higher than that of AMPARs and NMDARs. This finding is in agreement with the estimated PSD content of ~400 PSD-95 family members. If one assumes that an average PSD contains 100 glutamate receptors and one receptor associates with 2–4 PSD-95 family members, there would likely be some surplus of PSD-95. Accordingly, PSD-95 might associate with a limited number of postsynaptic protein complexes that do not contain AMPARs or NMDARs. One prominent binding partner is neuroligin, which augments synaptogenesis and functional availability of postsynaptic AMPARs, although its PDZ interaction does not appear relevant for this function (Shipman *et al,* 2011).

Postsynaptic targeting of AMPARs depends on auxiliary subunits known as TARPs with γ_2 (stargazin), γ_3, γ_4, and γ_8 being the main isoforms (Chen *et al,* 2000; Jackson & Nicoll, 2011). CNIH2/3 (Schwenk *et al,* 2009; Herring *et al,* 2013), SynDIG1 (Kalashnikova *et al,* 2010; Chenaux *et al,* 2016), and SynDIG4 (Prrt1) (Matt *et al,* 2018b) also promote synaptic AMPAR targeting, but their function is not as well defined and could be limited to augmenting AMPAR availability at extrasynaptic sites in the case of SynDIG4 (Matt *et al,* 2018b). TARPs bind with their very C-terminal ends to the first two PDZ domains of PSD-95 and its homologues PSD-93 and SAP102 for postsynaptic localization of AMPARs (Fig 1; El-Husseini *et al,* 2000; Schnell *et al,* 2002; Beique *et al,* 2006; Elias *et al,* 2006; Schluter *et al,* 2006; Bats *et al,* 2007). GluN2A and 2B bind directly with their C-termini to these PDZ domains (Kornau *et al,* 1995) and removal of PSD-95 and its homologues reduces excitatory postsynaptic currents (EPSCs) by NMDARs, suggesting that these scaffolds contribute channel functional availability (Elias *et al,* 2006, 2008; Ehrlich *et al,* 2007; Fig 1). However, PDZ interactions appear less critical for postsynaptic availability of NMDARs than of AMPARs as NMDAR EPSCs are less sensitive to a reduction in PSD-93/95 (Elias *et al,* 2006, 2008; Schluter *et al,* 2006; Ehrlich *et al,* 2007; Matt *et al,* 2018a) or mutations that affect PDZ binding (Schnell *et al,* 2002; Prybylowski *et al,* 2005). Nevertheless, acute disruption of PDZ binding does strongly increase lateral mobility of synaptic NMDARs (Bard *et al,* 2010), as it does increase diffusion of AMPARs (Sainlos *et al,* 2011). Furthermore, under conditions under which the PSD-93/PSD-95/SAP102 levels are more strongly reduced than by combined knockdown of PSD-93/PSD-95, a decrease in postsynaptic NMDAR function becomes obvious (Elias *et al,* 2006; Levy *et al,* 2015). Notably, GluN2A and 2B have much higher affinities for PDZ1 and PDZ2 than TARPs (Lim *et al,* 2002). The ESDV sequence at the C-termini of GluN2A and 2B subunits constitutes a nearly optimal binding motif for those PDZ domains with Q or E being desirable at the −3 position and D or E the −1 position in addition to the previously established requirement of S/T at the −2 and V the 0 position (Lim *et al,* 2002; Zhu *et al,* 2016). The C-terminal TTPV sequence of $\gamma_{2/3/4/8}$ is much less optimal; peptides mimicking the last 11 residues of GluN2A and 2B, which contain the C-terminal ESDV sequence, possess a K_d of ~1 μM for PDZ2 of PSD-95, whereas peptides mimicking the last 10 residues of γ_2, which contain the C-terminal TTPV sequence, have a K_d of ~12 μM (Lim *et al,* 2002; Dakoji *et al,* 2003; Pedersen *et al,* 2017) although extending the length of the γ_2 peptide decreases the K_d to 3.4 μM (Hafner *et al,* 2015). Thus, NMDARs will tie up available PSD-93/PSD-95/SAP102 before AMPARs have access. In other words, when the concentration of PSD-93/PSD-95/SAP102 is limited, a loss of postsynaptic AMPAR function will first be observed before a loss of NMDAR function.

In addition to potentially contributing to the direct anchoring of NMDARs at postsynaptic sites, PSD-95 might more indirectly foster postsynaptic content or functional availability of NMDARs by recruiting regulatory proteins, as abrogating PSD-95 binding of GluN2A decreases current density in HEK293 cells by more than

10-fold without significantly affecting surface expression (Lin *et al,* 2004). For instance, Pyk2 binds to PSD-95 to augment postsynaptic NMDAR function via Src during LTP (Huang *et al,* 2001; Bartos *et al,* 2010; Fig 3). Pyk2/Src might act in part by promoting phosphorylation of GluN2B on Y1472 (Yang *et al,* 2013), which impairs AP2 binding to this site and thereby NMDAR endocytosis (Roche *et al,* 2001; Prybylowski *et al,* 2005). As GluN2A does not share this endocytic motif, its regulation by PSD-95 must utilize a different mechanism that could potentially directly affect the channel activity of the NMDAR (Lin *et al,* 2004). A role of PSD-95 in promoting AMPAR trafficking to the postsynaptic site via β_2 AR–PKA signaling in addition to AMPAR anchoring is discussed below.

Induction of LTP by multiple glutamate uncaging pulses, which activate Ca^{2+} influx through NMDARs, increases spine size and spine content of GluA1, F-actin (Matsuzaki *et al,* 2004; Honkura *et al,* 2008), and especially its regulator cofilin within 1 min, but total PSD-95 content of spines and PSD size do not start to significantly increase before 1 h postinduction (Bosch *et al,* 2014; Meyer *et al,* 2014). Thus, PSD expansion and recruitment of PSD-95 trail far behind the recruitment of AMPARs. Either PSD-95 is not mediating the increase in postsynaptic AMPARs in the early phases of LTP, or spare PSD-95 in the PSD (see above) does so by an increase in its affinity for TARPs. Such an increase could translate into more pre-existing PSD-95 molecules binding incoming AMPARs. In fact, phosphorylation of stargazin/γ_2 at its C-terminus by CaMKII at multiple sites, which had been implicated earlier by Tomita *et al* (2005) in LTP, detaches the otherwise positively charged C-terminus from the plasma membrane for increased binding to PSD-95 and postsynaptic AMPAR localization (Opazo *et al,* 2010; Sumioka *et al,* 2010; Hafner *et al,* 2015). However, more recent work by Tomita and co-workers suggests a role of CaMKII-mediated phosphorylation of γ_8 and not of γ_2 in LTP, leaving open the question of whether and which TARPs are truly the relevant CaMKII targets (Sumioka *et al,* 2011; Park *et al,* 2016; Sheng *et al,* 2018).

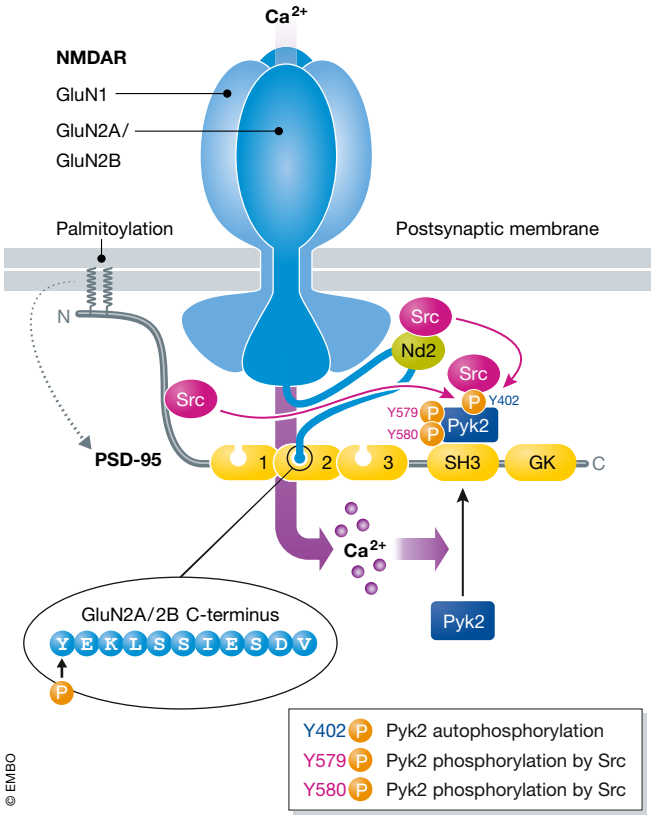

Figure 3. Role of PSD-95-anchored Pyk2 in NMDAR function.
Ca^{2+} influx induces Pyk2 relocation to postsynaptic sites via Ca^{2+}/CaM-stimulated binding to the SH3 domain of PSD-95 (Bartos *et al,* 2010). At the same time, Pyk2 trans-autophosphorylates on Y402 (Bartos *et al,* 2010), which creates a binding site for the SH2 domain of Src. Src might be recruited to pY402 from the N-terminus of PSD-95, which binds Src and modestly suppresses Src activity (Kalia *et al,* 2006), or from NADH dehydrogenase 2 (ND2), a Src-anchoring protein in the NMDAR complex in addition to PSD-95 (Gingrich *et al,* 2004). Binding to pY402 activates Src, which in turn phosphorylates Pyk2 on Y579 and Y580 located in its activation loop to strongly augment Pyk2 activity (Park *et al,* 2004; Yang *et al,* 2013). Src binding obviously protects pY402 from dephosphorylation, which is mediated by STEP (Xu *et al,* 2012). In addition, Y402 phosphorylation can likely be more effectively renewed by Pyk2 when phosphorylated by Src on Y579/Y580 for self-perpetuating activation of this Pyk2/Src complex as a form of molecular memory (Bartos *et al,* 2010).

Why does glutamate uncaging not increase postsynaptic PSD-95 content when spine size does go up? It appears that the glutamate-induced Ca^{2+} influx triggers two antagonistic events. One leads to actual net loss of PSD-95 from spines and the other to its accumulation in spines. The net loss of PSD-95 upon Ca^{2+} influx is well established; it is augmented by phosphorylation of PSD-95 on S73 within its first PDZ domain by CaMKII (Steiner *et al,* 2008) and on T19 by GSK3β (Nelson *et al,* 2013). In addition, the loss depends on Ca^{2+} influx-induced binding of Ca^{2+}/CaM to the very N-terminus of PSD-95 (Fig 4; Zhang *et al,* 2014). This interaction antagonizes palmitoylation of PSD-95 on Cys3 and Cys5, which is required for its postsynaptic localization and reversed upon NMDAR activation (El-Husseini Ael *et al,* 2002; Zhang *et al,* 2014). Ca^{2+}/CaM recruitment to the PSD-95 N-terminus also displaces α-actinin (Matt *et al,* 2018a), which anchors PSD-95 at the postsynaptic site (Matt *et al,* 2018a). Mutating Tyr12 near the N-terminus of PSD-95 to Glu not only abrogates Ca^{2+}/CaM binding and with it loss of PSD-95(Y12E) from spines but actually causes a substantial increase in postsynaptic accumulation of this PSD-95 mutant in spines upon Ca^{2+} influx. This latter finding is remarkable as it shows that Ca^{2+} influx can engage a mechanism that augments postsynaptic localization of PSD-95, but for endogenous PSD-95, this mechanism is overridden by the Ca^{2+}/CaM-driven displacement of PSD-95 from spines. We propose that the absence of postsynaptic PSD-95 accumulation during the first hour following glutamate-induced spine LTP is at least in part due to the Ca^{2+}/CaM-mediated loss of PSD-95 from spines, which curbs and effectively antagonizes the mechanism that would otherwise lead to immediate increase in postsynaptic PSD-95. Ca^{2+}/CaM-induced displacement of PSD-95 from spines is also relevant in homeostatic scaling down of the strength of all synapses in a neuron in response to a chronic increase in its excitatory input (Chowdhury *et al,* 2018).

Although the reason for the delay in the increased size of PSDs and their PSD-95 content following LTP is unclear, this delay does correlate with the finding that 1–2 h after saturating LTP by multiple trains of stimuli, further LTP can be induced by additional stimuli (e.g., Cao & Harris, 2014, and ref. therein). Perhaps delayed PSD-95 recruitment sets the stage for further LTP.

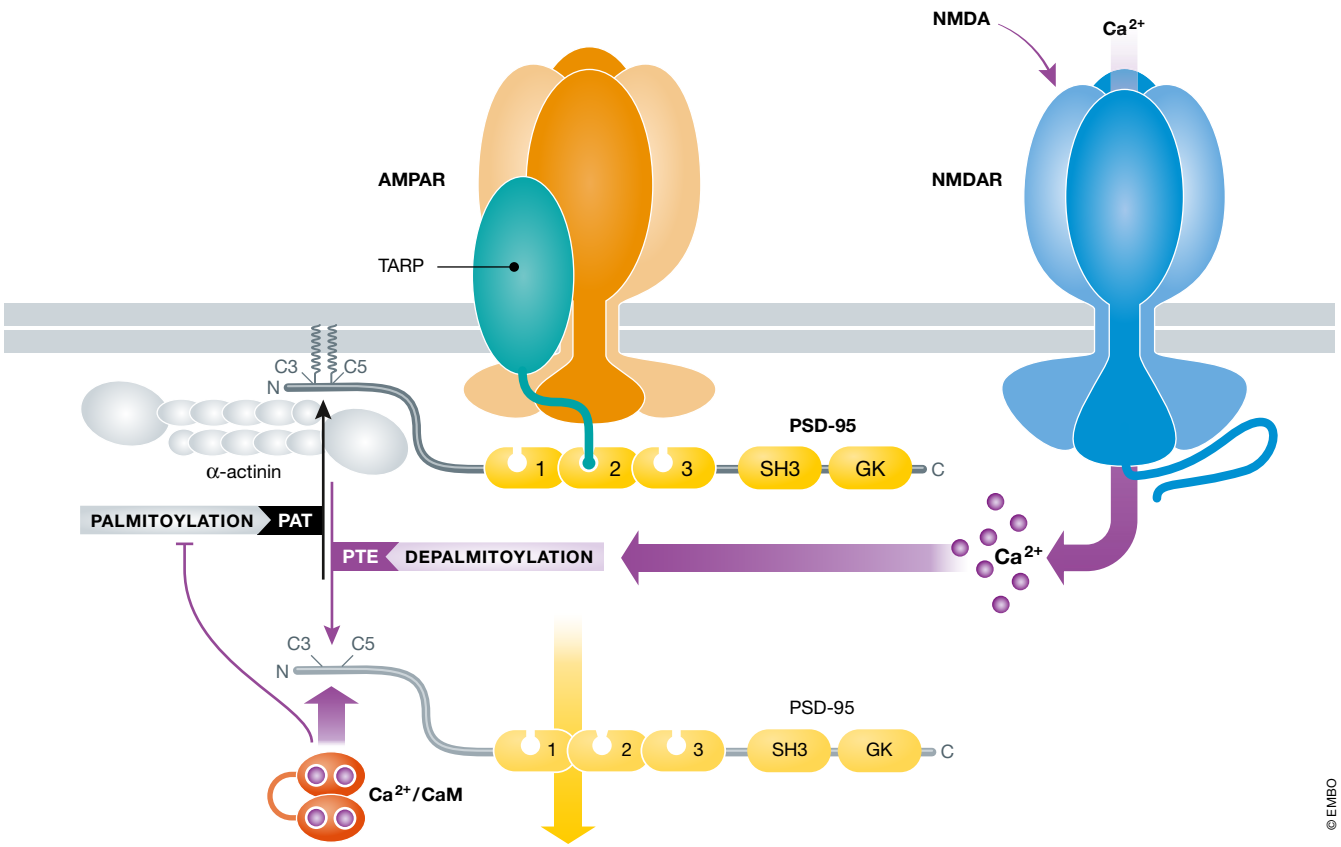

Figure 4. Displacement of PSD-95 from postsynaptic sites by Ca^{2+}/CaM.
Ca^{2+} influx via NMDARs likely stimulates depalmitoylation of PSD-95 by a hypothetical palmitoyl thioesterase (PTE). Binding of Ca^{2+}/CaM to depalmitoylated PSD-95 will prevent re-palmitoylation by a palmitoyl transferase (PAT). Lack of palmitoylation will reduce postsynaptic PSD-95 anchoring, leading to a loss of PSD-95 from postsynaptic sites (Zhang *et al*, 2014). Ca^{2+}/CaM also disrupts binding of PSD-95 to α-actinin, which anchors otherwise PSD-95 at postsynaptic sites (Matt *et al*, 2018a).

Complex signaling within spines

PSDs harbor at least 50 kinases (Collins *et al,* 2006), and hundreds of signaling mechanisms likely regulate postsynaptic functions (Coba *et al,* 2009). For instance, at least 15 different Rho family GEFs have been implicated in regulating spine size and morphology by controlling F-actin (Penzes *et al,* 2008; Kiraly *et al,* 2010; Kim *et al,* 2011). Such complexity enhances reliability of signaling as paradigmatically shown for TNF–NFκB signaling in fibroblasts (Cheong *et al,* 2011). It can explain why manipulations often lead to effects that are small or difficult to reproduce as alternative mechanisms can compensate. The best studied and perhaps most prevalent postsynaptic kinase signaling is by PKA and CaMKII, the focus of the remainder of this article.

PKA: structure, regulation, and localization by AKAPs

PKA is a tetramer formed by two regulatory (R) and two catalytic (C) subunits (Fig 5). Four genes encode RIα,β and RIIα,β and three genes Cα,β,γ (Taylor *et al,* 2012). R subunits homo-dimerize via their N-terminal dimerization domains forming a four-helix crossing bundle (Beene & Scott, 2007). C subunit activity is suppressed by a pseudosubstrate segment on R, which binds to the catalytic site on C and is released by cAMP (Brandon *et al,* 1997), although C does not have to be fully released from R in order to catalyze phosphorylation as indicated by correlating full dissociation of C from R or better a lack thereof with full enzymatic activity (Johnson *et al,* 1993; Yang *et al,* 1995). A recent publication seems to confirm these earlier studies as both R and C co-immunoprecipitate with the A kinase anchor protein AKAP5 from cell lysate prepared after strong β-adrenergic stimulation of the cells (Smith *et al,* 2017). Yet, follow-up work suggests that the co-immunoprecipitation is due to re-association of C with R upon cell lysis as cAMP becomes diluted (Walker-Gray *et al,* 2017).

Phosphotransfer and substrate release is modestly fast for most kinases (~500/s) (Zhou & Adams, 1997; Shaffer & Adams, 1999). However, ADP release is very slow for PKA (~20/s) (Zhou & Adams, 1997). The consequent low turnover number (<20/s) confers special importance to association of PKA with substrate proteins for effective phosphorylation of key targets and at the same time helps avoid phosphorylation of unintended targets. RII and to a lesser degree RI dimers are recruited to a number of substrates by AKAPs (Beene & Scott, 2007; Dai *et al,* 2009). AKAPs are a group of diverse and typically multifunctional scaffolding proteins, which share an amphipathic helix that interacts with the

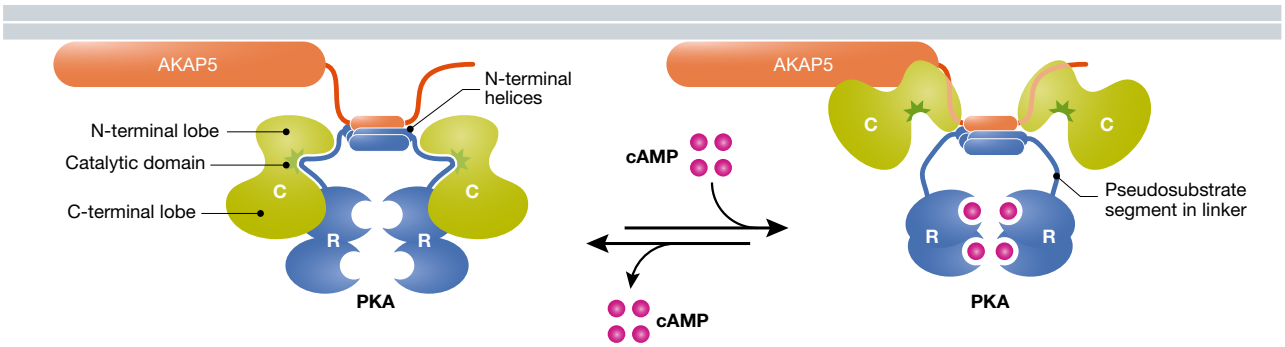

Figure 5. Overall structure and regulation of PKA.
The holoenzyme consists of two R and two C subunits. The catalytic center of the C subunit resides in the cleft between its N and C lobe. The N-termini of the R subunits homodimerize by forming a four-helix bundle, which are followed by flexible linkers. The pseudosubstrate segment in each linker binds to the catalytic site of the C subunit to suppress activity. cAMP binds with high cooperativity to two sites, CNBA and CNBB, on each R subunit to release the pseudosubstrate segment from the catalytic site. AKAP5 binds with an amphipathic α-helix to the four-helix bundle formed by the R subunits.

four-helix bundle formed by the N-terminal dimerization regions of two R subunits (Fig 5; Newlon *et al,* 2001).

Regulation of AMPARs by AKAP5-anchored PKA and PP2B during various forms of synaptic plasticity

AKAP5 is the most prevalent AKAP at postsynaptic sites (Smith *et al,* 2006; Lu *et al,* 2007; Tunquist *et al,* 2008; Weisenhaus *et al,* 2010). AKAP5 refers to human AKAP79 and rodent AKAP150, which is much larger than AKAP79 due to the insert of 36 imperfect octapeptide repeats of unknown function. A segment near the very C-terminus of AKAP5 is the docking site for PKA RII subunits (Fig 5; Carr *et al,* 1992; Murphy *et al,* 2014b). AKAP5 also anchors the Ca^{2+}/CaM-activated phosphatase calcineurin (PP2B). PP2B binds to the PIAIIIT motif in the central AKAP5 region, a modification of the PXIXIT motif used by other proteins to bind PP2B (Li *et al,* 2012). The three N-terminal polybasic segments of AKAP5 can bind PKC, Ca^{2+}/CaM, F-actin, cadherin, and PIP_2 and augment targeting of AKAP5 to spines (Klauck *et al,* 1996; Dell'Acqua *et al,* 1998; Gomez *et al,* 2002; Gorski *et al,* 2005; Tavalin, 2008; Patel *et al,* 2017; Woolfrey *et al,* 2018). Further postsynaptic targeting occurs via binding of the middle region of AKAP5 to the SH3 and GK domains of PSD-95 and SAP97 (Colledge *et al,* 2000; Bhattacharyya *et al,* 2009; Nikandrova *et al,* 2010; Fig 6).

Like PSD-95 (see above; El-Husseini *et al,* 2000), AKAP5 is a positive regulator of spine size and AMPAR content (Robertson *et al,* 2009); this effect depends on AKAP5's central domain, which binds to PSD-95 (Robertson *et al,* 2009). Perhaps AKAP5 works in conjunction with PSD-95 as part of a structural framework that determines synaptic size and strength, possibly including GKAP, Shank, and Homer (Sala *et al,* 2001; Baron *et al,* 2006). Consistent with this notion, the increase in postsynaptic strengthen by PSD-95 expression requires its SH3-GK region (Xu *et al,* 2008) perhaps for AKAP5 association (Robertson *et al,* 2009) although the SH3-GK region binds other proteins such as GKAP and Pyk2, which could be involved in spine enlargement (Sala *et al,* 2001; Bartos *et al,* 2010).

AKAP5 is linked to GluA1 via SAP97 (Colledge *et al,* 2000; Tavalin *et al,* 2002; Bhattacharyya *et al,* 2009), which binds with its first or second PDZ domain to the C-terminus of GluA1 (Fig 6; Leonard *et al,* 1998; Cai *et al,* 2002). Additional, more indirect association of AKAP5 with GluA1 could be via TARP-associated PSD-95 and via the β_2 AR (Dai *et al,* 2009), which directly binds to AKAP5 and indirectly to GluA1 via PSD-95/TARP (6; Joiner *et al,* 2010).

SAP97-anchored AKAP5 recruits PKA and the antagonistic PP2B to GluA1 for dynamic phosphorylation and dephosphorylation of S845 in the cytosolic C-terminus of GluA1 (Tavalin *et al,* 2002; Hoshi *et al,* 2005; Sanderson *et al,* 2012; Diering *et al,* 2014). S845 phosphorylation augments channel opening (Banke

Figure 6. Schematic structure of AKAP5 and its complexes with AMPARs and $Ca_v1.2$.
(A) Overview of AKAP5 binding partners and their binding sites. Residue numbering refers to human AKAP79. The N-terminus is formed by three segments designated A, B, and C. These segments are polybasic regions, each of which can bind to Ca^{2+}/CaM and PIP_2. In addition, PKC binds to A and adenylyl cyclases 5 and 6 (AC5/6) bind via their N-termini to B. PP2B binds to a PIXIT-like motif near the center of AKAP5 and PKA to a motif that is about 20 residues upstream of the very C-terminus. Immediately downstream of the PKA site is a leucine zipper-like motif that binds to a leucine zipper-like motif near the C-terminus of the $Ca_v1.2$ $\alpha_1 1.2$ subunit. PSD-95 and SAP97 interact through their SH3 and GK domains with a broad region in the center of AKAP5, which also binds to $K_V4.2$. Other binding sites are less clearly defined. The two palmitoylation sites are identified by red squares and the two known CaMKII phosphorylation sites by blue squares. (B) The β_2 AR–AMPAR complex. AC binds to the N-terminus, PP2B to the middle region, and PKA to the C-terminus of AKAP5, which is connected with AMPARs via SAP97, which binds to the very C-terminus of GluA1 (Leonard *et al,* 1998; Tavalin *et al,* 2002; Zhang *et al,* 2013). The β_2 AR binds to the third PDZ domain of PSD-95, which is linked to AMPARs via TARPs (γ), which bind with their very C-termini to the second and, with lower affinity, also first and third PDZ domains of PSD-95 (Hafner *et al,* 2015). PSD-95 might recruit a second AKAP5/PKA/PP2B complex. PKA and PP2B mediate phosphorylation and dephosphorylation of S845 on GluA1, respectively. (C) The β_2 AR directly binds to the C-terminus of $\alpha_1 1.2$. AKAP5 binds to three different regions as depicted (red arrows); the leucine zipper-like segment near C-terminus of $\alpha_1 1.2$ also binds alternatively AKAP7. AKAP5 recruits PKA, PP2B, and likely ACs to the $Ca_v1.2$ complex.

et al, 2000) and surface expression of GluA1 (Fig 7) (Sun *et al,* 2005; Gao *et al,* 2006; Oh *et al,* 2006; Man *et al,* 2007; Joiner *et al,* 2010) especially in the perisynaptic space (Oh *et al,* 2006; Yang *et al,* 2008a,b, 2010; He *et al,* 2009; Diering *et al,* 2014). The perisynaptic space is functionally defined as containing AMPARs that are activated upon presynaptic stimulation when glutamate reuptake is inhibited so that a higher concentration of glutamate can reach the space surrounding the postsynaptic site upon presynaptic glutamate release. Recruitment of AMPARs to this space provides a readily available reserve pool of AMPARs for postsynaptic insertion during LTP and constitutes a form of synaptic metaplasticity that fosters LTP (Esteban *et al,* 2003; Sun

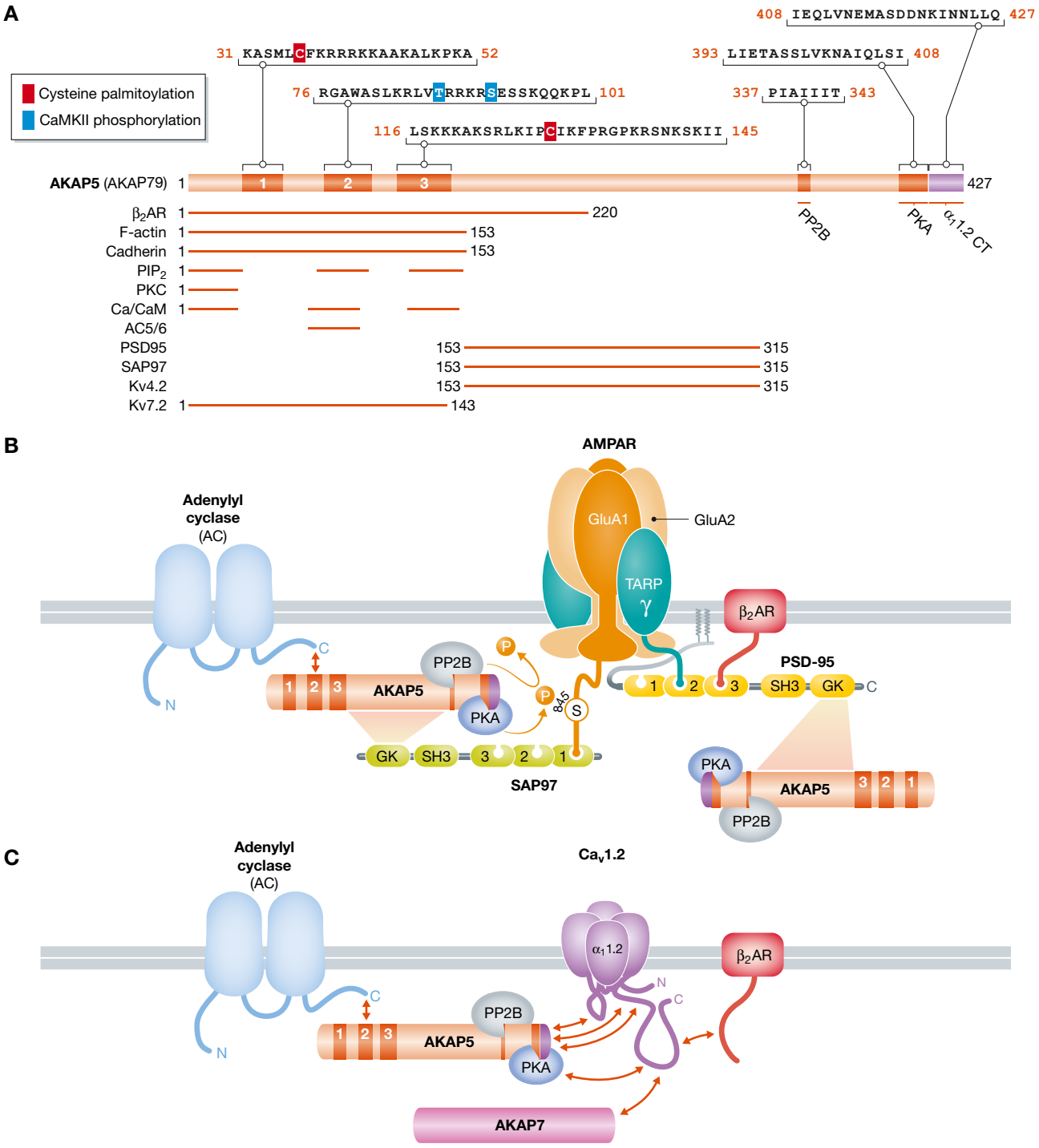

Figure 6.

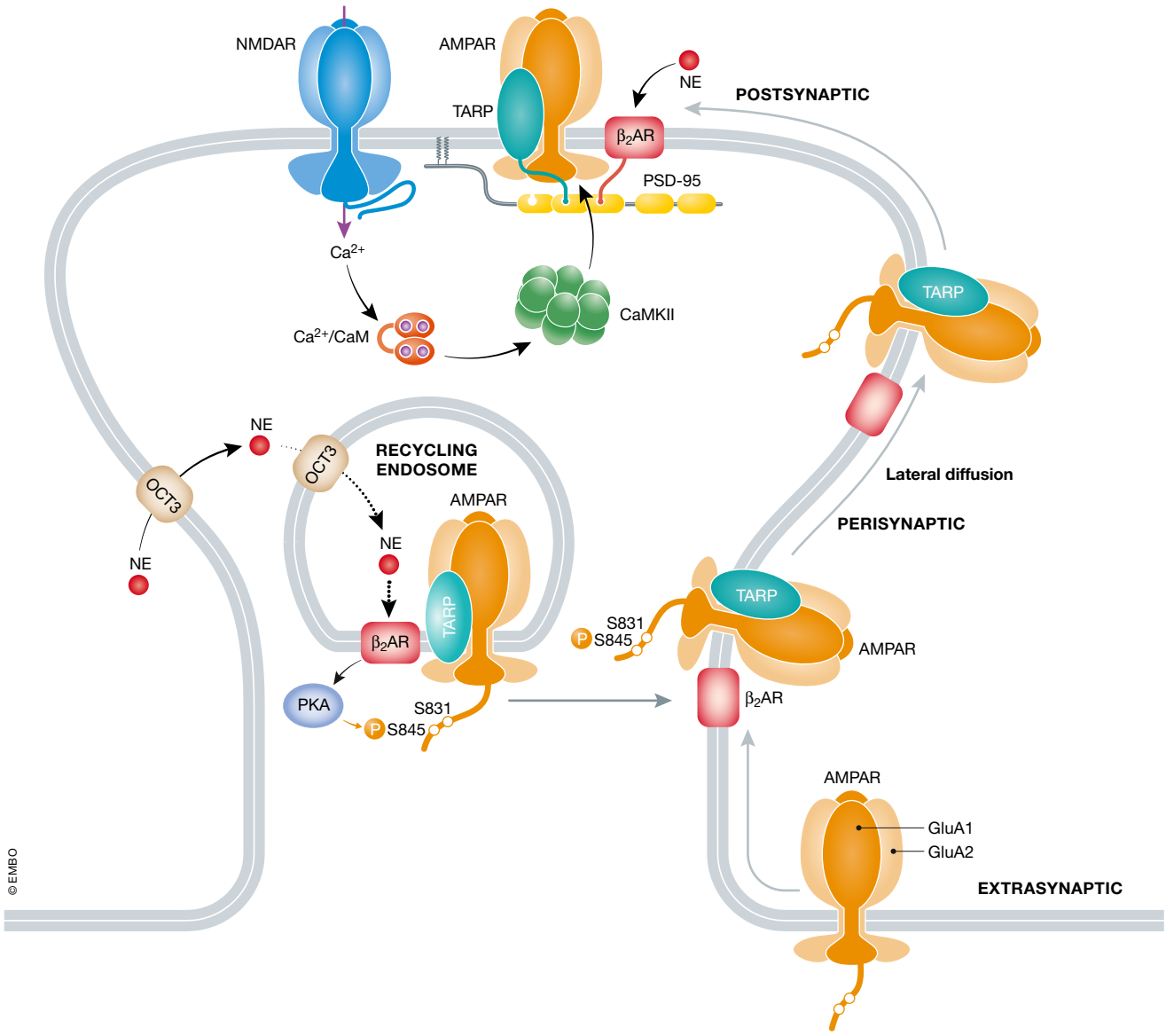

Figure 7. Two-step model of AMPAR surface trafficking and lateral diffusion to the postsynaptic site.
A significant portion of AMPARs are synthesized in the endoplasmic reticulum (ER) in dendrites possibly without TARPs, which might associate with the AMPAR core in a later secretory compartment (e.g., recycling endosomes (REs)) or the plasma membrane (Bowen *et al*, 2017). Surface insertion via REs is promoted by intracellular norepinephrine (NE) signaling, which is transported from the extracellular space via the OCT3 transporter first into the cytosol and then, as proposed here, into the lumen of REs, analogous to NE transport into the Golgi apparatus (Irannejad *et al*, 2017). This NE transport enables intracellular stimulation of β_2 ARs that are associated with GluA1 in RE analogous stimulation of β_2 ARs in endosomes (Tsvetanova & von Zastrow, 2014). The resulting S845 phosphorylation by PKA induces insertion of AMPARs into the perisynaptic membrane via unknown mechanisms. From there, AMPARs laterally diffuse into the postsynaptic density, where they are trapped especially upon activation of CaMKII by Ca^{2+} influx via NMDARs.

et al, 2005; Oh *et al*, 2006; Man *et al*, 2007; Yang *et al*, 2008a; Qian *et al*, 2012; Diering *et al*, 2014). In fact, an extrasynaptic surface pool of AMPARs is the only specific requirement for LTP in replacement experiments in which endogenous GluA1, GluA2, and GluA3 are all knocked out in individual neurons (Granger *et al*, 2013). Accordingly, the abundance of receptors in this reserve pool will determine, which receptors become incorporated into the PSD during LTP. When all subunits are present, S845 phosphorylation appears to afford an advantage that might become a necessity under certain conditions for activity-driven insertion of GluA1 homomeric AMPARs as formed when GFP-GluA1 is ectopically expressed (Esteban *et al*, 2003). However, LTP is normal in S845A knock-in mice (Lee *et al*, 2010). The discrepancy between these two papers can be explained by recent findings that implicate the N-terminal domain of GluA1 as important for its postsynaptic targeting and show that adding a tag such as GFP as in Esteban *et al* (2003) impairs this targeting (Diaz-Alonso *et al*, 2017; Watson *et al*, 2017). Accordingly, GFP-GluA1

requires S845 to augment postsynaptic targeting when this targeting is impaired, while S845 is less important for postsynaptic targeting of endogenous untagged GluA1.

In 2-week-old mice, GluA2-lacking CP-AMPARs (presumably GluA1 homomers) are transiently postsynaptically inserted right after induction of LTP (Plant *et al,* 2006) in a PKA- and AKAP5-dependent manner (Lu *et al,* 2007; Sanderson *et al,* 2016). This process is necessary for stabilization of LTP at 2 weeks of age (Plant *et al,* 2006) especially when induced by minimal stimulation (Lu *et al,* 2007; Sanderson *et al,* 2016). This process is not necessary for LTP in 3- to 4-week-old mice (Lu *et al,* 2007; Sanderson *et al,* 2016) but becomes necessary again at 8 weeks and older (Lu *et al,* 2007). The presence of four versus two S845 residues in GluA1 homomers versus GluA1/A2 diheteromers might be important for the temporary postsynaptic insertion of GluA1 homomers. In support of this notion, the increase in postsynaptic AMPARs during homeostatic synaptic plasticity upon chronic inhibition of neuronal activity or specifically L-type Ca^{2+} channels or NMDARs is often (but not always; see below) due to postsynaptic insertion of GluA1 homomeric CP-AMPARs (Thiagarajan *et al,* 2005; Sutton *et al,* 2006; Soares *et al,* 2013; Kim & Ziff, 2014; Sanderson *et al,* 2018) and requires S845 phosphorylation (Diering *et al,* 2014; Kim & Ziff, 2014) and anchoring of PKA by AKAP5, which is important for phosphorylation of S845 (Sanderson *et al,* 2018). Because GluA2-lacking CP-AMPARs including GluA1 homomers have a higher ion channel conductance than GluA2-containing CI-AMPARs, their insertion will immediately augment postsynaptic strength and also mediate Ca^{2+} influx, which promotes synaptic homeostasis (Kim & Ziff, 2014) and LTP under certain conditions (Plant *et al,* 2006; Lu *et al,* 2007; Sanderson *et al,* 2016). In fact, recent work indicates that blocking CP-AMPAR during the silencing phase also prevents upscaling suggesting that this Ca^{2+} influx during this phase is important in this process (Sanderson *et al,* 2018). However, other work indicates that homeostatic synaptic upscaling depends on GluA2 rather than GluA1 (Gainey *et al,* 2009, 2015; Goold & Nicoll, 2010; Tan *et al,* 2015; Ancona Esselmann *et al,* 2017) or does not specifically require either GluA1 or GluA2 (Altimimi & Stellwagen, 2013), possibly reflecting differences in the precise neuronal systems and signaling states within neurons between different laboratories.

In contrast to Plant *et al* (2006), who described postsynaptic insertion of CP-AMPARs right after LTP induction and their need for LTP maintenance, Adesnik and Nicoll (2007) did not find such evidence. Although both groups state that they used 2- to 3-week-old mice, this discrepancy could be explained if the mice used by Plant *et al* were actually closer to 2 weeks and those by Adesnik *et al* closer to 3 weeks in their development as systematic comparisons of 12- to 14-day and 20- to 22-day old mice find that in the younger but not older mice, CP-AMPARs are required for single tetanus LTP (Lu *et al,* 2007; Sanderson *et al,* 2016).

Long-term depression, the flip side of LTP, can be induced by two different mechanisms, prolonged Ca^{2+} influx via NMDARs (Dudek & Bear, 1992) and activation of mGluR1/5 receptors (Bolshakov & Siegelbaum, 1994; Oliet *et al,* 1997). NMDAR- but not mGluR1/5-dependent LTD requires anchoring of PP2B by SAP97/AKAP5 (Jurado *et al,* 2010; Sanderson *et al,* 2012, 2016). Elimination of PP2B binding to AKAP5 or of AKAP5 to the SH3 domain of PSD-95 abrogates removal of AMPARs and PSD-95 from spines during chemical LTD (Jurado *et al,* 2010; Sanderson *et al,* 2012). Furthermore, AKAP5-anchored PKA is required for transient recruitment of CP-AMPARs during LTD and AKAP5-anchored PP2B for subsequent removal of those CP-AMPARs (Sanderson *et al,* 2016). Abrogating PKA binding to AKAP5 by deletion of the PKA binding site on AKAP5 prevents the transient recruitment of CP-AMPAR during the 1-Hz/15-min stimulation (Sanderson *et al,* 2016), and little to no change in synaptic strength occurs upon this 1-Hz/15-min stimulation when the PKA binding site is deleted from AKAP5 (Lu *et al,* 2008; Sanderson *et al,* 2016). In fact, PKA has to be active during induction for LTD to occur (Lu *et al,* 2008). Abrogating PP2B binding to AKAP5 by deletion of the PP2B binding site on AKAP5 does not affect the initial recruitment of CP-AMPARs to the postsynaptic site but prevents the subsequent removal of these CP-AMPARs presumably by impairing dephosphorylation of S845 in GluA1, which is important for LTD (Lee *et al,* 2010). Due to the recruitment of CP-AMPARs during the early phases of LTD induction and the failure of their removal, LTP rather than LTD is observed in mice that lack the PP2B binding site in AKAP5 (Sanderson *et al,* 2016). Divergent findings that suggest PKA anchoring by AKAP5 is not necessary for LTD (Jurado *et al,* 2010) are likely explained by differences in the developmental stages of the two systems with LTD requiring PKA anchoring by AKAP5 at one stage as in Lu *et al* (2008) but not the other stage as in Jurado *et al* (2010), analogous to the age dependence of LTP on AKAP5-anchored PKA (Lu *et al,* 2007; Sanderson *et al,* 2016). Finally, although deletion of the PKA binding site in AKAP5 abrogated LTD, a full knockout of AKAP5 did not overtly affect LTD at 2 weeks of age (Weisenhaus *et al,* 2010). Perhaps complete removal of AKAP5 by knockout allowed compensation by another AKAP such as AKAP12 (see below) though the situation appears different at other ages where AKAP5 KD and KO did abolish LTD (Tunquist *et al,* 2008; Jurado *et al,* 2010).

Role of AKAP12 in postsynaptic signaling

AKAP12 (gravin, AKAP250, SSeCKS) is also required for several forms of LTP (Havekes *et al,* 2012). These forms include theta burst stimulation, which the authors find to depend on β_2 AR signaling, and LTP induced by a prolonged theta tetanus (PTT-LTP induced by a 3-min-long 5-Hz tetanus, with a β AR agonist present; Havekes *et al,* 2012), which also requires β_2 AR signaling (Qian *et al,* 2012), anchoring of AC and PKA by AKAP5 (Zhang *et al,* 2013), and S845 phosphorylation (Qian *et al,* 2012). The overall structural elements of AKAP12 exhibit remarkable similarities to AKAP5: It binds with N-terminal motifs to PKC and negatively charged phospholipids, which is inhibited by CaM binding to this very region, with central motifs to the β_2 AR and PP2B, and with a C-terminal motif PKA (Nauert *et al,* 1996; Shih *et al,* 1999; Tao *et al,* 2003; Dai *et al,* 2009; Havekes *et al,* 2012). Why both AKAP12 and AKAP5 are required for PTT-LTP (Havekes *et al,* 2012; Zhang *et al,* 2013) and what kinds of non-redundant roles these two AKAPs play in PTT-LTP are unclear.

Loss of AKAP12 impairs several forms of learning including spatial learning (Morris Water Maze), in contrast to the minimal effect on the Morris Water Maze task from loss of AKAP5

(Weisenhaus *et al,* 2010), and fear conditioning (M. Zhang & J.W. Hell, unpublished results). Tunquist *et al* (2008) report impaired Morris Water Maze learning in a different strain of AKAP5 KO mice. However, the AKAP5 KO mice still showed a tendency toward an increase in the time spent in the target quadrant during test runs of their memory. Although this increase was statistically not significantly at the $P = 0.05$ level compared to other areas in the Morris Water Maze, it is unclear whether the difference in the time spent in the target quadrant was actually statistically different from the time WT mice spent in the target quadrant. Whether memory retention is affected in one of the two AKAP5 KO mouse strains in this test thus remains unclear. Perhaps AKAP12 can compensate for loss of AKAP5 but not vice versa in these tests pointing toward a unique function of AKAP12 that remains to be revealed.

Binding of AKAP12 to the β_2 AR is strongly increased upon PKA-mediated phosphorylation of AKAP12 within its central, β_2 AR binding motif (Tao *et al,* 2003), which is important for de- and re-sensitization of the β_2 AR (Lin *et al,* 2000). This finding suggests that recruitment of PKA by AKAP12 to the β_2 AR could be activity driven rather than a more static anchoring mechanism as seen for other AKAPs. However, PKA binding to AKAP12 is required for phosphorylation of AKAP12 itself and the consequent increase in β_2 AR. Perhaps AKAP12 is an AKAP to stably anchor PKA for its own phosphorylation and PKA-driven binding of AKAP12 to the β_2 AR serves to recruit other binding partners such as PKC for β_2 AR de- and re-sensitization.

Potential role of the AKAP MAP2B in postsynaptic signaling

The microtubule binding protein MAP2B also anchors PKA, constituting a bona fide AKAP. Work with a mutant mouse in which the N-terminus of MAP2B, which anchors PKA, was deleted to prevent PKA anchoring suggested that PKA anchored at microtubules in the dendritic shaft is required for LTP (Zhong *et al,* 2009). Accordingly, during LTP induction the catalytic subunit is released from MAP2B to relocate into spines to support LTP, which is impaired in these mice. However, it is possible that effects other than the loss of PKA anchoring at microtubules are responsible for the loss of LTP as the MAP2B deletion mouse has a dramatically altered cytoarchitecture especially for apical dendritic arborization (Khuchua *et al,* 2003). Thus, this mutation has a widespread pleiotropic effect that will likely affect numerous neuronal functions, and conclusions about any specific molecular effect or mechanism cannot readily be drawn.

Localized signaling from the β_2 AR to AMPARs

Although cAMP is a readily diffusible second messenger, signaling downstream of GsPCRs, which act by stimulating adenylate cyclase (AC) through Gs, such as β ARs, can have different effects for different GsPCR even within the same cell (Steinberg & Brunton, 2001; Dai *et al,* 2009). Such differential effects require spatially restricted signaling by cAMP (Steinberg & Brunton, 2001; Dai *et al,* 2009). The discoveries of signaling complexes formed between the β_2 AR and two of its most prominent targets in the brain, the L-type Ca^{2+} channel $Ca_v1.2$ (Davare *et al,* 2001) and GluA1 subunit (Joiner *et al,* 2010) (see also Wang *et al,* 2010), that also contain Gs, AC, and PKA thus constitute true milestones in defining cAMP signaling. In detail, AKAP5 is linked together with AC, PKA, and the antagonistic phosphatase PP2B via SAP97 to GluA1 (Fig 6B; Leonard *et al,* 1998; Tavalin *et al,* 2002; Sanderson & Dell'Acqua, 2011; Zhang *et al,* 2013). The β_2 AR is recruited to the AMPAR complex via its binding to the third PDZ domain of PSD-95 (Joiner *et al,* 2010), which is linked to AMPARs by binding with its second and potentially also first and, possibly in AMPAR complexes not containing the β_2 AR, third PDZ domains to TARPs (Schnell *et al,* 2002; Hafner *et al,* 2015). The formation of this remarkable protein complex allows for highly localized cAMP signaling within nanodomains, as illustrated by the finding that only those GluA1 subunits that are part of β_2 AR-associated AMPARs become phosphorylated upon β AR stimulation, with β_2 AR-associated AMPARs accounting for likely much less than 20% of all AMPAR complexes (Joiner *et al,* 2010). Furthermore, the increase in surface expression in cultured hippocampal neurons and in postsynaptic AMPAR response in pyramidal neurons in the prefrontal cortex upon β_2 AR stimulation is blocked by disrupting the β_2 AR–AMPAR complex by two different peptides that interfere with the β_2 AR–PSD-95 and PSD-95–TARP interactions (Joiner *et al,* 2010). Accordingly, the β_2 AR has to be associated with AMPARs for their regulation.

A remarkable flip side to the localized stimulatory signaling from the β_2 AR to GluA1 is the localized inhibitory signaling at individual synapses by the α_2 AR and GABA B receptor, which are coupled to the AC-inhibitory Gi protein (Lur & Higley, 2015). In layer 5 pyramidal neurons in prefrontal cortex (PFC), activation of the α_2 AR and GABA B receptor specifically reduces synaptic transmission by AMPARs and NMDARs, respectively, but not vice versa. This selectivity within single postsynaptic sites is likely due to co-localization of the α_2 AR and GABA B receptor with the AMPAR and NMDAR, respectively, such that Gi activated by the α_2 AR or GABA B receptor has only immediate access to the respective glutamate receptor complexes. However, the cellular and molecular basis of this selectivity is unclear except it requires the regulator of G protein signaling RGS4, which limits the duration of Gi activation by promoting their GTPase activity (Lur & Higley, 2015).

Regulation of synaptic AMPAR trafficking by β_2 AR signaling

As detailed above, PKA drives AMPARs into the plasma membrane and especially into the perisynaptic space through phosphorylation of GluA1 on S845 to foster LTP (Fig 7) (Ehlers, 2000; Esteban *et al,* 2003; Sun *et al,* 2005; Gao *et al,* 2006; Oh *et al,* 2006; Man *et al,* 2007; Yang *et al,* 2008a,b, 2010; He *et al,* 2009; Joiner *et al,* 2010; Diering *et al,* 2014). Consistently, several forms of LTP, and especially those mediated by weak stimulation paradigms, require cAMP signaling and PKA for induction (Blitzer *et al,* 1995; Thomas *et al,* 1996; Gelinas & Nguyen, 2005; Lu *et al,* 2007; Qian *et al,* 2012, 2017). For instance, PTT-LTP is induced by a prolonged theta tetanus (5 Hz, 3 min) but only when the β_2 AR is stimulated (Qian *et al,* 2012). Furthermore, PTT-LTP also requires anchoring of AC and PKA by AKAP5 (Zhang *et al,* 2013), and S845 phosphorylation (Qian *et al,* 2012).

Precisely how PKA-mediated S845 phosphorylation augments surface trafficking of AMPARs is still unclear. One important question is how norepinephrine (NE), the main endogenous β AR agonist in the brain, can control trafficking of AMPAR–β_2 AR complexes from inside neurons to the surface. Recent work shows that NE is transported into the cell and from the cytosol into the lumen of intracellular vesicles via the transporter OCT3, which allows stimulation of β ARs inside cells (Tsvetanova & von Zastrow, 2014; Irannejad *et al,* 2017). We propose that NE accesses the lumen of recycling endosomes (REs), which contain recycled as well as newly synthesized AMPARs (Bowen *et al,* 2017), where it stimulates the β_2 ARs associated with AMPARs to trigger S845 phosphorylation (Fig 7). This phosphorylation then enhances insertion of AMPARs into the cell surface through mechanisms that are currently unknown. Consistent with this model, AKAP5 is targeted to RE via its palmitoylation on Cys36 and Cys129 and disruption of this palmitoylation interferes with trafficking of REs and AMPARs (Keith *et al,* 2012; Woolfrey *et al,* 2015).

Analogous considerations apply to signaling by dopamine via the Gs-coupled D1 and D5 receptors ($D_{1/5}R$), which increase GluA1 surface expression in cultured PFC and hippocampal neurons (Sun *et al,* 2005; Gao *et al,* 2006). Induction of chemical LTP with a subthreshold concentration of glycine leads to synaptic AMPAR incorporation if $D_{1/5}R$ activation with SKF81297 precedes the glycine treatment (Sun *et al,* 2005; Gao *et al,* 2006). In the hippocampal CA1 region, $D_{1/5}R$ stimulation also converts the induction of spike timing-dependent synaptic depression into potentiation at certain time points (Brzosko *et al,* 2015).

Localized and dynamic signaling from the β_2 AR to $Ca_v1.2$

Like AMPARs, $Ca_v1.2$ forms a complex that contains the β_2 AR, Gs, AC, and PKA for highly localized regulation via cAMP (Davare *et al,* 1999, 2001; Balijepalli *et al,* 2006) as well as the antagonistic phosphatases PP2A (Davare *et al,* 2000; Hall *et al,* 2006; Xu *et al,* 2010) and PP2B, the latter anchored via AKAP5 (Oliveria *et al,* 2007; Fig 6C). In cell-attached single-channel recordings, application of the β_2 AR-selective agonist albuterol results in a remarkably strong, more than twofold increase in channel open probability when applied inside the patch electrode but no increase at all when applied to the outside of the electrode. Although in the latter case > 99% of the cell surface and thereby the β_2 ARs are agonist accessible, β_2 AR stimulation does not allow the resulting cAMP, which is produced throughout the cell except the small patch that is physically occluded by the electrode, to effectively reach the channels under the patch (Chen-Izu *et al,* 2000; Davare *et al,* 2001). These results suggest that cAMP signaling is limited to less than 200 nm.

The C-terminus of β_2 AR directly binds to a small region of the $\alpha_1$1.2 C-terminus encompassing S1928 (Patriarchi *et al,* 2016; Fig 6C). S1928 is the main phosphorylation site for PKA (De Jongh *et al,* 1996), and its phosphorylation is increased in the brain in vivo upon β AR stimulation in WT but not AKAP5 KO mice (Hall *et al,* 2007). Nevertheless, S1928A KI mice have perfectly normal β AR regulation of $Ca_v1.2$ in the heart (Lemke *et al,* 2008). As it turns out, phosphorylation of S1928 serves two different functions: It increases channel activity in neurons (Patriarchi *et al,* 2016) and vascular smooth muscle cells (Lemke *et al,* 2008; Patriarchi *et al,* 2016; Nystoriak *et al,* 2017); at the same time, it displaces the β_2 AR from $Ca_v1.2$, which creates a refractory period of about 5 min during which $Ca_v1.2$ cannot be re-phosphorylated upon its dephosphorylation and also not re-stimulated by β AR agonist application (Patriarchi *et al,* 2016). A peptide that mimics the interaction site and disrupts the β_2 AR–$Ca_v1.2$ interaction prevents β AR stimulation of $Ca_v1.2$ (Patriarchi *et al,* 2016), which is further evidence not only for the requirement of β_2 AR binding to $Ca_v1.2$ for channel regulation but also for localized signaling by this cAMP-mediated mechanism.

Stimulation of the β_2 AR induces its phosphorylation by GPCR kinases (GRKs), leading to recruitment of β-arrestin and endocytosis of the β_2 AR (Shenoy & Lefkowitz, 2011; Staus *et al,* 2018). Does the $Ca_v1.2$-associated β_2 AR also undergo endocytosis? Obviously, displacement of the β_2 AR from $Ca_v1.2$ would create a situation during which the β_2 AR could easily be endocytosed although endocytosis does not contribute to the refractory period of $Ca_v1.2$

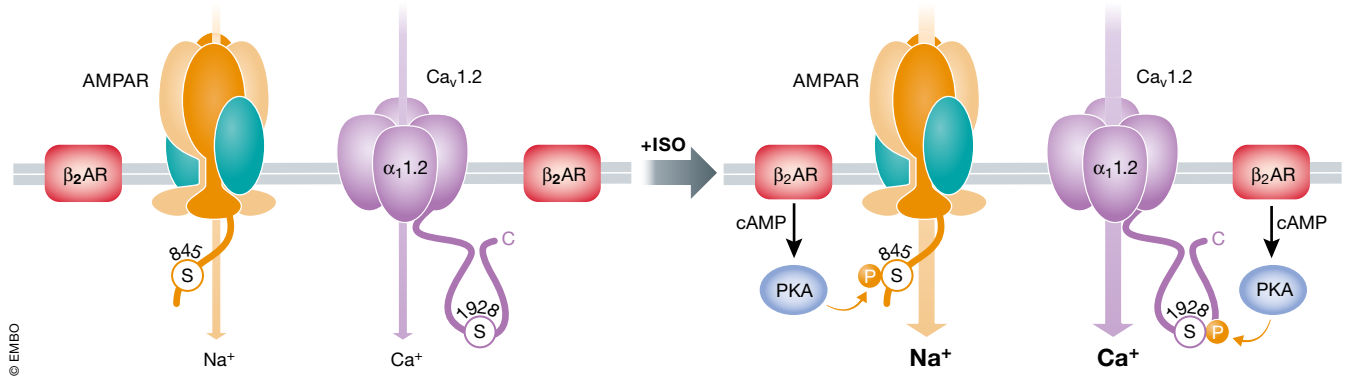

Figure 8. Role of upregulation of AMPAR and $Ca_v1.2$ activity by β_2 AR–PKA signaling during PTT-LTP.
Basal phosphorylation of GluA1 on S845 and of S1928 in the $Ca_v1.2$ $\alpha_1$1.2 subunit by PKA is low. β_2 AR stimulation activates PKA via G_s, AC (not depicted), and cAMP. The consequent phosphorylation of S845 increases P_o of the AMPAR and AMPAR postsynaptic accumulation and thereby Na^+ influx and depolarization during synaptic transmission. S1928 phosphorylation renders $Ca_v1.2$ more sensitive to depolarization and increases P_o of $Ca_v1.2$. The resulting increase in Ca^{2+} influx triggers via yet-to-be-defined signaling pathways the potentiation in PTT-LTP.

regulation by β_2 AR stimulation (Patriarchi *et al,* 2016). Furthermore, most recent work now shows that GRKs phosphorylate only β_2 AR monomers while the β_2 ARs in $Ca_v1.2$ complexes are dimers and those dimers are only phosphorylated by PKA (Shen *et al,* 2018). The PKA phosphorylation sites are different from the GRK sites. Only GRK- but not PKA-phosphorylated β_2 ARs undergo endocytosis (Shen *et al,* 2018) (see also Staus *et al,* 2018), suggesting that $Ca_v1.2$-associated β_2 ARs are not destined for endocytosis. Finally, phosphorylation of not only $Ca_v1.2$ itself on S1928 but also the β_2 ARs on its PKA sites S261/S262 is required for upregulation of $Ca_v1.2$ activity by β_2 AR signaling (Shen *et al,* 2018).

Role of regulation of $Ca_v1.2$ by β_2 AR signaling in PTT-LTP

As described above, LTP induced by a 3-min-long 5-Hz tetanus requires the β_2 AR and phosphorylation of the AMPAR subunit GluA1 on S845 by PKA (Qian *et al,* 2012). That $Ca_v1.2$ also forms a complex with β_2 AR, which makes it a prime target for NE signaling, raises the possibility that $Ca_v1.2$ stimulation by the β_2 AR is also required for PTT-LTP especially as $Ca_v1.2$ is co-localized with the β_2 AR at postsynaptic sites (Davare *et al,* 2001). In fact, PTT-LTP was only mildly if at all affected by NMDAR antagonists but completely blocked by dihydropyridines (DHPs) that inhibit L-type channel (Qian *et al,* 2017). Hippocampal slices from KI mice with a point mutation that renders $Ca_v1.2$ insensitive to DHPs showed PTT-LTP that was not affected by DHPs (Qian *et al,* 2017). Accordingly, $Ca_v1.2$ is absolutely required for PTT-LTP. In fact, PTT-LTP was completely absent in slices from S1928A KI mice (but not affected in slices from S1700A KI mice) (Qian *et al,* 2017) and blocked by the peptide that displaces the β_2 AR from $Ca_v1.2$ (Patriarchi *et al,* 2016). These results indicate that upregulation of both AMPAR and $Ca_v1.2$ activity by β_2 AR–PKA signaling is essential for PTT-LTP (Fig 8). PKA augments not only postsynaptic AMPAR recruitment (see above) but also open probability of AMPARs (Banke *et al,* 2000), which will amplify depolarization of postsynaptic sites. PKA will not only increase open probability and thereby activity of $Ca_v1.2$ (Patriarchi *et al,* 2016) but also make $Ca_v1.2$ more sensitive to depolarization; i.e., $Ca_v1.2$ will open more readily for the same level of depolarization upon its stimulation by PKA (Gray & Johnston, 1987; Sculptoreanu *et al,* 1993). These multiple effects will most likely act in a highly synergistic manner to drive the Ca^{2+} influx that is necessary for PTT-LTP (Fig 8).

Role of CaMKII in regulation of postsynaptic AMPAR localization

Activation of PKA and the phosphorylation of GluA1 on its PKA site S845 is not always required for LTP (Lee *et al,* 2003, 2010; Lu *et al,* 2007; Granger *et al,* 2013) nor is it sufficient by itself to increase postsynaptic AMPAR content in the hippocampal CA1 region (Esteban *et al,* 2003; Oh *et al,* 2006; Joiner *et al,* 2010) although PKA activation does increase postsynaptic AMPAR strength in cultured hippocampal neurons (Diering *et al,* 2014) and in PFC slices (Joiner *et al,* 2010). LTP also requires Ca^{2+} influx and activation and signaling by the Ca^{2+}- and calmodulin-dependent protein kinase CaMKII (Malenka *et al,* 1989; Malinow *et al,* 1989; Hayashi *et al,*

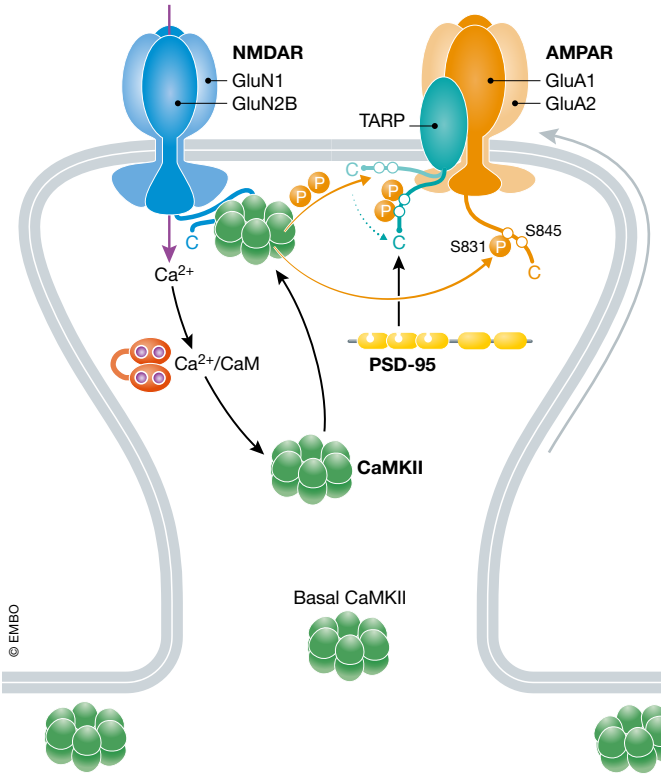

Figure 9. Hypothetical postsynaptic AMPAR regulation and trapping by CaMKII.
AMPARs reach the postsynaptic density by lateral diffusion. Ca^{2+} influx via the NMDA receptor will lead to activation of CaMKII by Ca^{2+}/CaM. The immediate autophosphorylation on T286 causes binding of CaMKII to the GluN2B C-terminus, which is important for phosphorylation of postsynaptic proteins (Halt *et al,* 2012). Phosphorylation of GluA1 on S831 increases channel activity. The Ca^{2+} influx also augments detachment of the TARP C-termini from the cytosolic face of the plasma membrane, which are then phosphorylated by CaMKII. Phosphorylation of either γ_2 or γ_8 will increase their binding to PSD-95 to trap AMPARs. Recruitment of CaMKII to postsynaptic sites that are activated during LTP is likely part of the mechanism that ensures synapse specificity of LTP (Hell, 2014).

2000; Esteban *et al,* 2003; Gao *et al,* 2006; Halt *et al,* 2012; Huganir & Nicoll, 2013; Hell, 2014; Herring & Nicoll, 2016). The role of PKA in promoting surface expression of AMPARs paired with the requirement of CaMKII for LTP is best explained by a two-step model (Fig 7) (Penn *et al,* 2017) (see also Opazo & Choquet, 2011, for a similar three-step model): AMPARs are first targeted to perisynaptic sites, and then, CaMKII induces trapping of AMPARs at the PSD proper. Accordingly, postsynaptic AMPAR accumulation during LTP requires exocytosis and subsequent lateral diffusion (Penn *et al,* 2017). Cross-linking of biotin-tagged AMPAR subunits at the cell surface impaired LTP indicating that lateral diffusion of AMPARs in the plasma membrane is required for LTP. A slowly developing potentiation that was not blocked by cross-linking was prevented by inhibition of Ca^{2+}-triggered exocytosis. The central role of CaMKII in governing postsynaptic AMPAR activity, presumably mostly through promoting postsynaptic AMPAR accumulation, is also illustrated by the surprising recent finding that single-cell KO of

CaMKIIα, the most prevalent CaMKII in forebrain, or double KO of CaMKIIα plus CaMKIIβ reduces AMPAR EPSCs under otherwise basal conditions by 50% and also NMDAR EPSCs by 30% and abrogated pairing-induced LTP (Incontro *et al,* 2018). Remarkably, rescue of AMPAR EPSCs as well as LTP required not only CaMKIIα that is catalytically active but also its binding to the NMDAR GluN2B subunit (see the next paragraph).

A key difference between signaling by NE–β_2 ARs–cAMP–PKA and by CaMKII is that the former is based on predetermined co-localization and co-assembly of all components except for NE, which is widely and diffusely released whereas CaMKII is evenly distributed throughout the dendritic shaft (Strack & Hell *et al,* 2008). However, stimulation of Ca^{2+} influx through postsynaptic NMDARs will lead to recruitment of CaMKII to the stimulated spines as seen with ectopically expressed GFP-CaMKII (Shen & Meyer, 1999; Otmakhov *et al,* 2004; Rose *et al,* 2009) as well as endogenous CaMKII (Merrill *et al,* 2005; Strack & Hell *et al,* 2008). This recruitment depends on CaMKII binding to residues 1290-1310 in the C-terminus of GluN2B (Strack & Colbran, 1998; Leonard *et al,* 1999; Bayer *et al,* 2001; Halt *et al,* 2012).

LTP induced by multiple 1-s/100-Hz tetani does not require PKA. It is possible that strong Ca^{2+} influx triggers AMPAR surface insertion via synaptotagmin-1- and synaptotagmin-7-mediated acute exocytosis (Wu *et al,* 2017). Alternatively, strong LTP induction paradigms could activate CaMKII more so than weaker ones (e.g., two versus one 100-Hz tetanus in 8-week-old mice; Lu *et al,* 2007). In this way, CaMKII could compensate for a lack of PKA signaling by phosphorylating S831 in the C-terminus of GluA1. S831 is close to S845 and is a prominent phosphorylation site for CaMKII (Roche *et al,* 1996). Consistent with this hypothesis, LTP is lost in GluA1 S831A/S845A double KI mice (Lee *et al,* 2003) while it is normal in single S831A and S845A KI mice (Lee *et al,* 2010). Hence, one site is both sufficient and required for LTP. Perhaps trafficking of GluA1 to the perisynaptic space can be stimulated by phosphorylation of GluA1 on either S831 by CaMKII or S845 by PKA. In fact, CaMKII can foster surface delivery of GluA1 (Gao *et al,* 2006).

Phosphorylation of TARPs by CaMKII

At the postsynaptic site, NMDAR-associated CaMKII acts locally to phosphorylate AMPARs on S831 (Halt *et al,* 2012), which will increase single-channel conductance of AMPARs (Kristensen *et al,* 2011) and might contribute to an increase in postsynaptic response during LTP as LTP has been associated with an increase in single-channel conductance (Benke *et al,* 1998) (Fig 9). Alternatively, this increase could also be due to recruitment of GluA1 homomeric AMPARs (Plant *et al,* 2006; Sanderson *et al,* 2016), which have a higher conductance than GluA2-containing AMPARs (Traynelis *et al,* 2010). However, no deficit in LTP has been found so far in S831A KI mice indicating that S831 phosphorylation is not strictly required (Lee *et al,* 2010). Rather, the main mechanism of LTP is a persistent increase in postsynaptic AMPAR number, which could be mediated by phosphorylation of the cytosolic C-termini of the AMPAR auxiliary TARP subunits γ2 (Tomita *et al,* 2005; Sumioka *et al,* 2010; Hafner *et al,* 2015) or γ8 (Park *et al,* 2016). These phosphorylations strengthen binding of γ2 and γ8 to PSD-95, thereby trapping of AMPARs at postsynaptic sites (Chen *et al,* 2000; Schnell *et al,* 2002; Elias *et al,* 2006, 2008; Schluter *et al,* 2006; Opazo *et al,* 2010; Hafner *et al,* 2015) (Fig 9). However, the apparent contradictions between findings that specifically implicate CaMKII-mediated phosphorylation of γ2 (Tomita *et al,* 2005) versus γ8 (Park *et al,* 2016) in LTP have to be addressed. There is also a disagreement between recent studies that suggest either phosphorylation of γ8 on S277 and S281 but not PDZ anchoring (Park *et al,* 2016) or PDZ anchoring of γ8 but not S277 and S281 phosphorylation (Sheng *et al,* 2018) is critical for LTP. The work by Park *et al* (2016) is based on KI mice in which the CaMKII phosphorylation sites had been eliminated and the work by Sheng *et al* (2018) on replacement of all endogenous AMPARs with a GluA1–γ8 fusion protein. Perhaps fusing γ8 to GluA1 leads to a conformation of the γ8 C-terminus that augments PSD-95 binding similar to the conformation that is induced by CaMKII-mediated phosphorylation as shown for γ2 (Sumioka *et al,* 2010; Hafner *et al,* 2015).

Phosphorylation of Kalirin and Trio by CaMKII

A second, increasingly prominent CaMKII target that is relevant for LTP is Kalirin 7, a splice isoform of Kalirin (also called Duo). Kalirin 7 is a guanine nucleotide exchange factor (GEF) for the small G protein Rac (Penzes *et al,* 2008). Activation of Rac by Kalirin 7 augments formation of F-actin via p21-activated kinase PAK and thereby spine enragement as well as postsynaptic AMPAR accumulation (Penzes *et al,* 2008). Ca^{2+} influx through NMDARs induces phosphorylation of Kalirin 7 on S95 by CaMKII, which leads to activation of PAK, spine enlargement, and an increase in postsynaptic AMPAR content (Xie *et al,* 2007). More recent work shows that Kalirin 7 as well as the closely related Trio fulfills overlapping functions with respect to synaptic maturation and LTP (Herring & Nicoll, 2016). The increase in postsynaptic AMPAR responses upon overexpression of either Kalirin 7 or Trio depended on basal spontaneous synaptic activity; it was prevented by concurrent inhibition of AMPARs and NMDARs. Knockdown (KD) of both proteins resulted in an ~80% loss of spines and of synaptic transmission by both AMPARs and NMDARs. These and earlier results indicate that these two proteins together mediate spine and synapse maturation under basal conditions (Xie *et al,* 2007; Herring & Nicoll, 2016). However, KD of Kalirin was insufficient to impair LTP and KD of Trio had only a modest effect. KD of both proteins abrogated synapse formation, but synapse formation can be rescued by KD-resistant Kalirin 7, which also rescued LTP. Importantly, rescue of LTP was not achieved if the CaMKII phosphorylation site S95 had been mutated to alanine. An analogous phosphorylation site is present in Trio, and LTP was rescued by KD-resistant WT Trio but not phosphorylation-deficient T66A Trio (Herring & Nicoll, 2016). Thus, phosphorylation of one of these two Rac GEFs by CaMKII is a critical step in LTP. Finally, mutations in the Rac GEF domain of Trio that have been linked to autism spectrum disorders affect AMPAR function (Sadybekov *et al,* 2017).

Emerging CaMKII targets in LTP: SynGAP and neuroligin-1

SynGAP is a Ras GTPase-activating protein; i.e., it terminates Ras signaling by stimulating its hydrolysis of GTP to GDP (Carlisle

et al, 2008). Ras in turn promotes postsynaptic delivery of AMPARs (Zhu *et al,* 2002). Recent work now finds that CaMKII phosphorylation of SynGAP leads to displacement of SynGAP from the postsynaptic site, thereby fostering LTP (Araki *et al,* 2015; Walkup *et al,* 2016).

Finally, the postsynaptic cell adhesion protein neuroligin-1 is important for synapse formation by interacting with presynaptic neurexin (Scheiffele *et al,* 2000). More recent work indicates that phosphorylation of neuroligin-1 on T739 promotes synapse stabilization and strength (Bemben *et al,* 2014).

Where PKA and CaMKII intersect

Given the prominence of PKA and CaMKII signaling at the postsynaptic site, it can be expected that signaling pathways by these two kinases interconnect. In fact, PKA-mediated phosphorylation of the NMDAR subunit GluN2B on S1166, which can be induced by β_2 AR stimulation, selectively increases Ca^{2+} permeability of NMDARs (Skeberdis *et al,* 2006; Murphy *et al,* 2014a). This phosphorylation is important for induction of CaMKII-dependent LTP by augmenting Ca^{2+} influx, which in turn is required for CaMKII activation.

On the other hand, CaMKII might antagonize PKA signaling in spines by phosphorylating AKAP5 on multiple serine and threonine residues in its polybasic regions, including T87 and S92 in region B (Fig 6A; Woolfrey *et al,* 2018). Interestingly, this phosphorylation is inhibited by Ca^{2+}/CaM binding to the polybasic regions and could only proceed after CaMKII becomes constitutively active through its autophosphorylation of T286 (Woolfrey *et al,* 2018). T286 phosphorylation results in Ca^{2+}/CaM-independent so-called autonomous CaMKII activity due to impaired rebinding of the autoinhibitory domain to the catalytic domain upon removal of Ca^{2+}/CaM from this autoinhibitory domain (Hell, 2014). In addition, Ca^{2+}/CaM had to be removed from the polybasic AKAP5 regions before autonomously active CaMKII could phosphorylate this region. Functionally, phosphorylation of AKAP5 by CaMKII proved to be important for removal of AKAP5 from spines (Woolfrey *et al,* 2018). This removal required in addition depalmitoylation of AKAP5, which in turn needed CaMKII activity. This complex mechanism is critical for LTD induction during which cytosolic Ca^{2+} levels remain elevated for some time before falling to resting levels. It is presumably during this phase of Ca^{2+} removal and with it of Ca^{2+}/CaM from AKAP5 that autonomously active CaMKII phosphorylates AKAP5. Although the molecular consequences remain to be determined, the loss of AKAP5 from spines upon this CaMKII-dependent phosphorylation and depalmitoylation likely translates into a reduction of PKA and thereby of PKA-mediated signaling in spines. The situation might be more complicated as loss of AKAP5 would also translate into loss of the phosphatase PP2B, which antagonizes postsynaptic PKA signaling.

Conclusion

The intricacy of signaling mechanisms at the postsynaptic site and of the underlying protein interactions we have unveiled so far is truly mind-boggling. One wonders how much more complex the whole postsynaptic signaling network will turn out to be. Postsynaptic signaling as it regulates postsynaptic AMPAR content and thereby synaptic strength is functionally highly relevant because changes in synaptic strength underly many forms of physiological as well as pathological learning. If we are to truly understand postsynaptic signaling and how it relates to synaptic strength in health and disease, an important long-term goal, we need to keep digging for years to come.

Acknowledgements

We thank Dr. T. Nakagawa, Vanderbilt University, Nashville, TN, for discussion and help with modeling of glutamate receptor structure and Dr. Lucas Matt, University of Tübingen, Germany, for help with figures.

Conflict of interest

All authors declare that they have no conflict of interest.

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