HHS Public Access

Author manuscript

Sci Signal. Author manuscript; available in PMC 2020 April 22.

Published in final edited form as:

Sci Signal. ; 12(562): . doi:10.1126/scisignal.aar6889.

Mechanisms of postsynaptic localization of AMPA-type glutamate receptors and their regulation during long-term potentiation

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Abstract

L-glutamate is the main excitatory neurotransmitter in the brain, with postsynaptic responses to its release predominantly mediated by AMPA-type glutamate receptors (AMPARs). A critical component of synaptic plasticity involves changes in the number of responding postsynaptic receptors, which are dynamically recruited to and anchored at postsynaptic sites. Emerging findings continue to shed new light on molecular mechanisms that mediate AMPAR postsynaptic trafficking and localization. Accordingly, unconventional secretory trafficking of AMPARs occurs in dendrites, from the endoplasmic reticulum (ER) through the ER-Golgi intermediary compartment directly to recycling endosomes, independent of the Golgi apparatus. Upon exocytosis, AMPARs diffuse in the plasma membrane to reach the postsynaptic site, where they are trapped in order to contribute to transmission. This trapping occurs through a combination of both intracellular interactions, such as TARP (transmembrane AMPAR regulatory protein) binding to α-actinin-stabilized PSD-95, and extracellular interactions through the receptor N-terminal domain. These anchoring mechanisms may facilitate precise receptor positioning with respect to glutamate release sites to enable efficient synaptic transmission.

Introduction

The most prevalent neurotransmitter in the brain is glutamate (1), which predominantly activates AMPA-type glutamate receptors (AMPARs) (2). AMPARs consist of four homologous pore-forming subunits (GluA1–4), which mostly assemble into heteromers. For example, in the hippocampal CA1 area, GluA1/GluA2 and GluA2/GluA3 heteromers account for ~80 and ~20% of the postsynaptic AMPAR response under basal conditions, respectively (2). However, cAMP selectively increases the activity of GluA3-containing AMPARs in a PKA- and Ras-dependent manner (3). AMPAR organization is modular: their extracellular region consists of an N-terminal domain and a ligand binding domain, followed by the transmembrane, which forms the ion-conducting pore, and the cytosolic C-terminal domain (Figure 1) (4, 5).

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AMPARs are associated with various auxiliary subunits, which both influence receptor trafficking and modulate channel function (5). Among those, transmembrane AMPAR regulatory proteins (TARPs) are the most intensively studied. TARPs mediate postsynaptic receptor localization, which is best characterized for TARP γ2 (also known as stargazin) and γ8 due to their predominance in well studied brain areas, the cerebellum and hippocampus (6, 7). For this purpose, TARPs bind with their cytoplasmic C-termini to the first two PDZ domains of PSD-95, an abundant postsynaptic scaffolding protein. This TARP-mediated 'slotting' into the PSD scaffold has been recognized as a major AMPAR anchoring mechanism (6, 8–12) (Figure 1). Direct trapping of the receptor through its N-terminal domain, which protrudes into the synaptic cleft (Figure 1), has been described as an additional synaptic anchoring mechanism (13, 14). Here, we discuss such new mechanistic insights into AMPAR synaptic traffic and anchorage.

Secretory trafficking of AMPARs

AMPARs are synthesized in the endoplasmic reticulum (ER), where subunits assemble mainly into heterotetramers by first forming dimers and then dimers of dimers (15). The assembly of the initial dimers is driven by their N-terminal domains (16) (Figure 1), which have higher affinities for N-terminal domains of other subunits than their own (17). For instance, the GluA1 N-terminal domain has a more than 100-fold higher affinity for the GluA2 N-terminal domain than for another GluA1 N-terminal domain in a heterologous expression system, giving rise to predominantly heteromeric receptors. Quality control steps before AMPAR release from the ER are complex and poorly understood. These involve association with a select set of AMPAR-interacting proteins (18), sensing of Ca^{2+} release through ER-based IP_3 and ryanodine receptors (19) and sensing of conformations underlying gating functions (20). In the neuronal soma, AMPARs then traffic through the Golgi apparatus for maturation by posttranslational modifications, including a change from high mannosylation to complex glycosylation and ultimately the trans-Golgi network before being transported along microtubules into dendrites (21, 22). This AMPAR transport, at least in *Drosophila*, requires activity of the Ca^{2+}- and calmodulin-dependent protein kinase CaMKII (23, 24). This function is just one of various critical CaMKII functions, which, likely through additional molecular signaling mechanisms, plays a central role in the induction of long-term potentiation (LTP) (25, 26), which is thought to underlie learning and memory (27, 28).

AMPARs are also synthesized in dendrites, which appear to mostly lack the Golgi apparatus although a modified Golgi-related compartment, the Golgi outpost, has been described in dendrites for trafficking secretory cargo, which includes NMDA-type glutamate receptors (NMDARs) (29, 30). New work now reports that GluA1-containing AMPARs can traffic from dendritic ER through the ER-Golgi intermediary compartment directly to recycling endosomes, independently from the Golgi apparatus (31) (Figure 2). This secretory pathway contrasts with AMPAR trafficking in the soma, where AMPARs pass through the Golgi apparatus (31). In this work, the addition of an FK binding protein tag ($3xF_M$) retained GluA1 in the ER until a de-dimerizing compound was added. Upon release, GluA1 appeared in recycling endosomes before it was detectable at the dendritic surface. Furthermore, disruption of recycling endosomes by expression of a dominant negative form of Rab11

reduced surface expression of $3xF_M$/mCherry GluA1 2h and 4h after the addition of de-dimerizer. Expression of a dominant negative form of Rab8, which disrupts the Golgi apparatus, affected the surface expression of $3xF_M$/mCherry GluA1 at 4h but not at 2h. These findings imply that secretion of GluA1 through the dendritic ER – ER-Golgi intermediary compartment – recycling endosomes route is faster than through the somatic ER – ER-Golgi intermediary compartment – Golgi apparatus route. This secretory pathway was further supported by an elegant combination of blocking exit from the ER-Golgi intermediary compartment (but not exit from the ER) at 20°C and subsequently blocking Golgi apparatus function with brefeldin A. GluA1 reached the cell surface after the temperature was raised to 37°C even if brefeldin A was added to block Golgi apparatus-mediated secretion. Roughly half of GluA1 and GluA2 on the cell surface possessed a high mannose glycosylation pattern typical for proteins that have not been processed in the Golgi apparatus, which reflects the proteins bypassing the Golgi apparatus during secretory trafficking (31, 32). Strikingly, the auxiliary TARP subunit γ8 only shows complex glycosylation when at the cell surface. It is possible that in dendrites, other auxiliary subunits are synthesized alongside AMPAR core subunits to enable secretory trafficking to ER-Golgi intermediary compartment and recycling endosomes, such as cornichon proteins (33) or SynDIG4 (34). Alternatively, auxiliary and core subunits might be synthesized and travel independently to associate after glycosylation processing in a late secretory compartment (for example, recycling endosomes) or on the cell surface. These studies raise interesting questions about the essential requirement for TARPs in AMPAR forward trafficking, and the percentage of receptors that are TARP-associated throughout their life-cycle. Indeed, different populations of synapses, suggested to contain different levels of TARP-association, have been recorded in Purkinje neurons of the cerebellum (35); however, PDZ interactions of TARPs appear to be essential for all AMPAR postsynaptic anchoring in hippocampal CA1 cells (36).

The possibility of direct entry of AMPARs into recycling endosomes upon their synthesis in the ER without undergoing surface delivery and recycling has functional consequences because AMPAR trafficking through recycling endosomes is critical for LTP (37, 38). Accordingly, newly synthesized AMPARs can enter the LTP-supporting pool of AMPARs without prior surface insertion and endocytosis. That LTP requires stimulated exocytosis beyond basal surface delivery of plasma membrane proteins is also consistent with work demonstrating that LTP is prevented by clostridial toxins and other manipulations that interfere with the Ca^{2+}-triggered exocytosis machinery (39, 40). These findings have been extended to show that both receptor exocytosis and surface diffusion are differentially required for increasing the synaptic AMPAR content in LTP (41).

Regulation of surface delivery of AMPARs

Stimulation of the cAMP-dependent protein kinase PKA augments surface expression of AMPARs by increasing the rate of surface insertion or re-insertion (42–44) and decreasing endocytosis (42). Furthermore, weak (but not strong) paradigms of LTP induction require cAMP signaling and PKA (45–50). The PKA-dependency of LTP is also age-dependent. For instance, LTP induced by a single 1 s long tetanus of 100 Hz is blocked by inhibiting PKA in mice that are 7–12 weeks but not in mice that are 3–4 weeks old (46). PKA activation

through dopaminergic signaling can also convert the induction of spike timing-dependent synaptic depression into potentiation (51), which may be mechanistically underpinned by dopaminergic activation causing PKA-dependent AMPAR surface trafficking, as has been previously reported (44).

Stimulation of PKA renders AMPARs more readily available to contribute to and increase synaptic transmission, such as during LTP. This increase in AMPAR availability occurs because PKA stimulation promotes insertion of AMPARs into the neuronal surface (52, 53), particularly into the perisynaptic space (54–57) from where they can readily move to the actual postsynaptic site (Figure 3). The perisynaptic space is thought to be located somewhere on dendritic spines between the postsynaptic sites and the dendritic shaft although the precise localization is unclear and could also be on the shaft (but see below). It is functionally defined as containing AMPARs that become detectable during electrophysiological recording of postsynaptic responses to presynaptic electrical stimulation when glutamate reuptake is inhibited and thus a higher concentration of glutamate can reach the space surrounding the postsynaptic site upon presynaptic glutamate release. Given the arrangement of synaptic AMPARs opposite presynaptic release sites (58), and the non-saturation of synaptic AMPARs during transmission (59, 60), it is possible that this perisynaptic pool is localized at the postsynaptic density yet consists of receptors that are not aligned with vesicle release, and therefore do not contribute to synaptic transmission.

There is also an apparent connection between PKA-dependence of LTP and the requirement for Ca^{2+}-permeable AMPARs, because PKA promotes synaptic delivery of Ca^{2+}-permeable AMPARs during LTP (46, 61). Moreover, the dependence of potentiation on both PKA and Ca^{2+}-permeable AMPARs has been separated by two LTP induction protocols (62). When multiple weak, spaced stimulations are employed, LTP requires both PKA and Ca^{2+}-permeable AMPARs, whereas a single strong induction stimulus requires neither. Corresponding well with previous data (54–57), the authors suggest that PKA drives perisynaptic accumulation of Ca^{2+}-permeable AMPARs during spaced stimulation, which are then required for long-term stability of potentiation.

PKA-mediated accumulation of AMPARs at perisynaptic sites depends on phosphorylation of the AMPAR GluA1 subunit on Ser^{845} in its cytosolic C-terminus (54, 63), which is a phosphorylation site for PKA (64). How PKA augments AMPAR trafficking to the perisynaptic space is unclear but could be through intracellular activation of the β_2 adrenergic receptor– cAMP–PKA signaling cascade. The β_2 adrenergic receptor forms a complex with AMPARs by binding with its extreme C-terminus to the third PDZ domain of PSD-95 (65), which in turn binds with its first two PDZ domains to the extreme C-termini of TARPs, thereby anchoring AMPARs at postsynaptic sites (Figure 4). This complex also contains all the other elements of the β_2 adrenergic receptor– cAMP–PKA signaling cascade – namely, the trimeric stimulatory $G\alpha_s$ protein, adenylyl cyclase, and PKA – for efficient and localized regulation of AMPAR phosphorylation and surface expression (65). Only GluA1 associated with the β_2 adrenergic receptor becomes phosphorylated on Ser^{845} upon stimulation of the receptor. At the same time, β_2 adrenergic receptor stimulation increases the surface localization of GluA1 in dendritic shafts and spines within minutes, an effect that is inhibited when the β_2 adrenergic receptor is acutely displaced from AMPARs by peptides

that block the interaction (65). Collectively, these results indicate that β_2 adrenergic receptor stimulation mediates plasma membrane insertion of pre-existing β_2 adrenergic receptor–GluA1 complexes. Such findings raise the question how the endogenous β_2 adrenergic receptor agonist norepinephrine (NE) can reach these complexes inside neurons, given that NE typically acts upon its release from norepinephrinergic neurons on β adrenergic receptors at the cell surface. NE can enter the cell interior through the transporter OCT3 and stimulate β adrenergic receptors inside cells (66, 67). We hypothesize that NE accesses the lumen of recycling endosomes where it stimulates β_2 adrenergic receptors that form signaling complexes with AMPARs to trigger phosphorylation of Ser^{845}. This phosphorylation event then increases surface expression of AMPARs through unknown mechanisms (Figure 5).

Regulation of postsynaptic AMPAR content

PKA activity and the phosphorylation of GluA1 on its PKA site Ser^{845} are not always required for LTP (46, 68) and are not sufficient to increase postsynaptic AMPAR content. This increase also requires Ca^{2+} influx and activation and signaling by CaMKII (25, 44, 63, 69–73). CaMKII acts in part by phosphorylating the AMPAR auxiliary TARP subunits γ2 (74–76) and/or γ8 (77) on multiple sites. These phosphorylation events have been suggested to strengthen binding of γ2 and γ8 to PSD-95, which enhances trapping of AMPARs at postsynaptic sites (Figure 5) (6, 8, 10–12, 76). However conflicting reports have suggested a primary requirement for either phosphorylation or PDZ anchoring of γ8, with little influence of the other (7, 36, 77). These reports require reconciliation.

How is surface delivery of AMPARs stimulated in those forms of LTP that do not require PKA? Perhaps the high levels of Ca^{2+} influx that occur during strong stimulus paradigms drive acute AMPAR surface delivery through synapotagmin-1– and synapotagmin-7–mediated acute exocytosis (40). Alternatively, strong stimulation paradigms of LTP might activate CaMKII more so than weaker ones (for example, two compared to one 100 Hz tetanus) so that CaMKII can compensate for lack of PKA signaling by phosphorylating Ser^{831} in the C-terminal domain of GluA1 upon stronger stimulation. Ser^{831} is just 14 residues upstream of Ser^{845} and is a prominent phosphorylation site for CaMKII (64, 78). In support of this hypothesis, LTP is absent in GluA1 S831A/S845A double knock-in mice (79) but is not affected in mice with single S831A and S845A knock-ins (80). It appears that one site but not both sites are required for LTP. It is conceivable that surface delivery of GluA1-containing AMPARs to the perisynaptic space can be stimulated by phosphorylation of GluA1 on either Ser^{831} by CaMKII or Ser^{845} by PKA. In fact, a contributory role by CaMKII in surface insertion of GluA1 had been reported earlier (44). However, LTP can also be induced when GluA1, GluA2, and GluA3 are completely eliminated and are replaced by a GluA1 mutant lacking its C-terminal domain from residues 824–906 (and thus cannot be phosphorylated at Ser^{831} and Ser^{845}) (68). Furthermore, LTP can still be induced when Ser^{816} and Ser^{818} are replaced with Ala residues in the truncation mutant (68). Ser^{816} and Ser^{818} are phosphorylated by PKC and function as additional regulatory sites for surface expression and postsynaptic AMPAR targeting (81). These findings indicate that LTP and consequently an increase in postsynaptic glutamate receptor content can occur independently of these phosphorylation sites and that AMPARs can be anchored entirely by

TARP PDZ interactions (36). However, it is important to note that these findings do not show that phosphorylation of Ser^{831} and Ser^{845} would not contribute to the regulation of AMPAR trafficking and LTP under normal conditions, such as in wild type mice with all AMPARs subunits present. This notion is supported by the finding discussed above that LTP is impaired in S831A/S845A double knock-in mice (79). Similarly, LTP induced by a 5 Hz tetanus that lasts 180 s and requires co-stimulation of the β_2 adrenergic receptor is absent in single S845A knock-in mice (47). To clarify the confusion regarding the requirement for the GluA1 C-terminus in LTP, mice were engineered in which the GluA1 and GluA2 C-termini were exchanged, either individually, or simultaneously (82). In a GluA1-[GluA2 C-terminal domain] mouse, which lacks any GluA1 C-terminus, LTP is abolished but can be restored by knock-in of a form of GluA2 with the GluA1 C-terminal sequence (82). These data indicate that AMPAR trafficking in LTP requires the GluA1 C-terminal domain, likely through the aforementioned surface delivery mechanisms.

Knock-out of GluA1 (leaving GluA2 and GluA3 intact) impairs both surface expression of AMPARs and LTP (68, 83). Both AMPAR surface expression and LTP are impaired upon expression of C-terminal domain-lacking GluA1 or GluA2 on an AMPAR null background (68). Because of this coincidence of impaired surface expression and impaired LTP, the authors conclude that LTP requires an extrasynaptic pool of AMPARs at the cell surface (68). It is important to note that a role of extrasynaptic surface AMPARs does not exclude an equally important role of the pool of AMPARs in recycling endosomes (which could also be affected by these truncations). In fact, evidence for the requirement of both exocytosis and subsequent lateral diffusion to support the increase in postsynaptic AMPARs accumulation during LTP has been obtained with forms of GluA1 or GluA2 tagged on their extracellular N-termini by biotinylation in the ER (41). Cross-linking with tetrameric biotin binding proteins at the neuronal surface prevents short-term potentiation and impairs LTP in hippocampal slices. Accordingly, lateral diffusion of AMPARs present at the cell surface is required for LTP. A slowly developing potentiation that remains upon cross-linking is blocked by co-application of tetanus toxin, which inhibits exocytosis that is triggered by Ca^{2+} influx. In contrast, tetanus toxin does not block the short-term potentiation. Thus, the late phase of potentiation is driven by acute exocytosis, whereas the early phase within the first 2–3 min after the induction of LTP depends on lateral diffusion and not acute exocytosis.

The importance of precise postsynaptic localization of AMPARs

Because the affinity of AMPARs for glutamate is relatively low (high μM range), it had been predicted that only AMPARs that are precisely juxtaposed to presynaptic release sites are effectively activated (84, 85). Indeed, AMPARs are enriched in clusters that are ~80 nm in diameter (86, 87) and those clusters appear to be aligned with presynaptic release sites for fast and efficient synaptic transmission (58, 88). This arrangement has interesting consequences when considering synaptic potentiation. Does LTP involve enlargement of this trans-synaptic ‘nanocolumn’, addition of multiple aligned columns (89), or increased AMPAR clustering within a nanodomain? Enrichment of PSD-95 within nanodomains has been observed using chemical LTP induction (58). Functional evidence for activation of a subset of AMPARs within individual dendritic spines and perhaps within postsynaptic sites

has so far been lacking, but is in line with data demonstrating that postsynaptic AMPARs are not saturated by glutamate release (59, 60).

To address this question, the light-induced dimerization of the plant photoreceptor cryptochrome with its binding partner CIB1 has been harnessed to enable the optogenetic recruitment of cryptochrome-tagged GluA1 to synapses through binding to CIB1-tagged PSD-95 or Homer 1c (90). This approach leads to an increase in frequency but not the average amplitude of mini-EPSCs occurring through spontaneous transmission (90), whereas uncaging of glutamate, which activates all receptors in an individual dendritic spine, results in an increase in AMPAR response amplitudes at nearly all spines upon light exposure. These data have been interpreted as showing 'functional' delivery of AMPARs only at weak or silent synapses, with little effect on established connections, despite 'physical' delivery of AMPARs to all synapses. Although this is an exciting interpretation that supports the 'functionally clustered' arrangement of the synapse (58), interpretation of mEPSC data requires more detailed analysis due to the number of events hidden below the noise level, which may contribute to the observed effects.

Postsynaptic anchoring of AMPARs by α-actinin

Knock-down and knock-out of PSD-95 reduces postsynaptic AMPAR responses by ~40%, suggesting that PSD-95 mediates postsynaptic localization of ~40% of the AMPARs in pyramidal cells of the hippocampal CA1 region (8, 10–12). Another ~40% of AMPAR postsynaptic localization depends on PSD-93 and most of the rest on SAP102 (10, 11). How PSD-95 itself docks onto postsynaptic sites has been unclear. Ephrin B3 has been previously implicated in this process (91), although it is unclear if it would be present at high enough levels to mediate postsynaptic anchoring of the highly abundant PSD-95. Instead, postsynaptic anchoring of PSD-95 and consequently of AMPARs has been shown to require α-actinin, which is highly enriched in spines and binds to the N-terminal 13 residues of PSD-95 (92). Knock down of all three α-actinin isoforms that are present in neurons reduces the density of synapses by ~40% but AMPAR content in the remaining synapses is comparable to control conditions, which phenocopies PSD-95 knock down. Those AMPARs not affected by loss of postsynaptic PSD-95 through knock-down of α-actinin are presumably anchored by PSD-93 and SAP102, which do not show any detectable binding to α-actinin (92).

Ca^{2+} influx through NMDARs leads to diffusion of a portion of PSD-95 out of spines (93, 94). This displacement of PSD-95 is mediated by calmodulin (CaM), which binds in the presence of Ca^{2+} to the extreme N-terminus of PSD-95 (95, 96). Ca^{2+}/CaM promotes the depalmitoylation of the N-terminus of PSD-95 (95, 96), a posttranslational modification that is required for postsynaptic PSD-95 targeting (97, 98), and displaces α-actinin from PSD-95 (92), both of which contribute to the loss of PSD-95 from spines. During LTP, this PSD-95 displacement appears transient and to have a role in synaptic rearrangements that accompany stabilization of spine growth, which poses interesting questions about the role of PSD-95 in the initial potentiation of AMPAR currents. Ca^{2+}/CaM binding to the PSD-95 N-terminus is also required for homeostatic synaptic downscaling upon a chronic increase in network activity in dissociated hippocampal cultures (96) because mutating Glu^{17} in the PSD-95 N-

terminus to Arg (E17R) prevents Ca^{2+}/CaM binding and downscaling. Furthermore, both effects can be rescued by a form of CaM with mutation of the positively charged Arg^{126}, which forms an electrostatic interaction with the negatively charged Glu^{17}, to Glu (96). The same E17R mutation in PSD-95 also prevents LTD (99), indicating that NMDAR-dependent LTD is also driven by Ca^{2+}/CaM binding to the N-terminus of PSD-95 and its displacement from α-actinin and thereby from spines.

The role of N-terminal domains in postsynaptic anchoring of AMPARs

Synaptic anchoring of AMPARs does not depend only on the interaction of TARP PDZ-binding motif interactions with PSD-95, but also requires the PDZ-ligand in the C-terminal domain in the AMPAR GluA1 subunit (71, 100). Although such C-terminal domain interactions appear to not be essential for AMPAR clustering (86, 101) and their true influence on receptor anchoring are unclear (68, 102, 103), their predominant role may lie in the delivery of AMPARs to the surface, rather than stabilization at the synapse. Consistent with this notion, SAP97 recruits the A-kinase anchoring protein AKAP5 and with it PKA and adenylyl cyclase to GluA1 through binding to its C-terminal PDZ ligand motif (Figure 4) (104, 105), which is important for phosphorylation of Ser^{845} (105, 106), which in turn promotes surface expression of GluA1 as discussed above.

The influence of the N-terminal domains of AMPAR subunits in organizing functional synapses has been described in several reports. For instance, the N-terminal domain of GluA2 has been suggested to induce spine formation (107, 108), although other studies did not observe an effect of GluA2 on spine density (2, 13, 108) or even directly refuted this finding (109). The N-terminal domains of GluA2 has been reported to exert retrograde effects on presynaptic stabilization (108, 110). Moreover, the N-terminal domains of GluA subunits mediate the assembly of heterotetrameric AMPARs as discussed above (16, 17). Interactions of the N-terminal domains of GluA1 and GluA2 have been now reported to control the anchoring of AMPARs at postsynaptic sites (13). Utilizing the electrophysiological tagging method introduced by Malinow and his co-workers (71), Watson *et al.* ectopically expressed GluA2 in its unedited ‘R586Q’ form (‘GluA2Q’), which leads to the formation of homomeric AMPARs whose pores can be blocked by intracellular polyamines when the membrane potential is positive inside the cell (100,111). Using this indicator, GluA2Q expression was detected at synapses and contributed to transmission (13). However, removal of the N-terminal domain (ΔNTD) did not affect the rectification seen upon expression of GluA2Q, indicating that GluA2QΔNTD can accumulate at postsynaptic sites (13). However, expression of GluA2QΔNTD substantially reduced EPSC amplitudes and increased receptor mobility, causing an apparent reduction in the number of postsynaptic AMPARs. Thus, the N-terminal domain aids in the accumulation of AMPARs at postsynaptic sites presumably by fostering interactions with other synaptic proteins, which are abundant in the synaptic cleft (112).

Similar to GluA2Q expression, expression of full length GluA1 also results in inwardly rectifying AMPAR currents (100,111) and inwardly rectifying postsynaptic AMPAR responses (13). However, expression of N-terminally deleted ‘GluA1ΔNTD’ did not have these effects (13). Accordingly, postsynaptic accumulation of GluA1 strictly requires its N-

terminal domain whereas the N-terminal domain of GluA2 only augments its postsynaptic localization. LTP is impaired in cells expressing a form of GluA1 lacking the N-terminal domain indicating that AMPAR anchoring during LTP also depends on this domain (100) (14).

The N-terminal domains of GluA1 and GluA2 facilitate postsynaptic AMPAR localization presumably by mediating or augmenting interactions with other synaptic proteins, which will need to be identified in future studies. Although TARPs interact with the N-terminal domain and would be at first glance candidates for this critical interaction (113), N-terminal deletion does not appear to alter TARP association (13).

The reduction of EPSC amplitude by ectopic expression of GluA2QΔNTD (see above) is most parsimoniously explained by GluA2QΔNTD acting in a dominant negative manner by competing with endogenous AMPARs for other proteins that are important for postsynaptic targeting. The C-terminus of GluA2 interacts with various proteins (114–116) and is a prime contender of mediating such interactions that are also important for postsynaptic targeting in addition to the presumed N-terminal domain interactions. In support of this notion, replacement of the GluA2 C-terminal domain with that of GluA1 alleviates the dominant negative effect of GluA2QΔNTD. Such a role for the GluA2 C-terminal domain in basal transmission fits well with a previous model (100), and likely reflects the role of the domain in receptor recycling with intracellular pools (115, 116).

What are potential interaction partners for the N-terminal domains of GluA1 and GluA2? N-cadherin has been implicated in the spine-inducing effect of the N-terminal 92 residues of GluA2 mentioned above (107). At the same time, glycosylation of the N-terminus of GluA2 on residue Asn^{370} is important for secretory trafficking (117). The neuronal pentraxin family of proteins interacts with the AMPAR N-terminal domain (118), with critical roles in maintaining synaptic AMPAR content in inhibitory interneurons (119) and retinal ganglion cells (120), but not CA1 pyramidal neurons (121). Neuropilin-2 binds to the extracellular N-terminus of GluA1 through its two CUB domains (122), which is noteworthy because two different CUB domain-containing proteins, SOL-1 and SOL-2, have been identified as critical for functional surface expression of AMPARs in *Caenorhabditis elegans* (123, 124). Moreover, two other CUB domain-containing proteins, NETO-1 and NETO-2, are auxiliary subunits of kainate receptors, which constitute another group of ionotropic glutamate receptors homologous AMPARs (125, 126). The neuropilin-2–GluA1 interaction is disrupted upon increased neuronal network activity in hippocampal cultures due to the activity-induced secretion of the neuropilin-2 agonist Semaphorin 3F (122). This reduction in postsynaptic response depends on the Ras GTPase activating protein (GAP) activity of the cytosolic C-terminus of PlexinA3, which dimerizes with neuropilin-2 in the AMPAR complex.

The PlexinA3-related PlexinA4 can directly interact with GluA2 (127) largely through the immunoglobulin-like transcription factor (IPT) domain of PlexinA4, which is extracellular and thus likely interacts with the N-terminus of GluA2. This interaction is induced by Semaphorin 3A, an endogenous ligand for PlexinA4 that causes retrograde transport of

PlexinA4 from axons to the neuronal cell body where it binds GluA2 and stimulates its anterograde transport to distal dendrites.

Conclusions and Perspectives

Much has been learned about how AMPARs are trafficked and anchored at postsynaptic sites. This is a critical issue because synaptic strength is mostly determined by the number and functional availability of AMPARs, which is essential for normal learning of, for instance, declarative content, as well as pathological forms of learning such as drug addiction and posttraumatic stress disorder. Much more remains to be discovered about postsynaptic AMPAR localization in order to understand various forms of learning, which will inform strategies for the development of treatments for the pathological forms.

Acknowledgments

Funding: Work in the laboratories of the authors was supported by NIH R01 MH097887, R01 NS078792, R01 AG055357 (to JWH) and the MRC MC_U105174197 and the BBSRC BB/N002113/1 (to IHG).

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Gloss

Learning and memory are thought to be supported by experience-dependent neuronal plasticity, which on a cellular level is expressed as long-term changes (such as potentiation or depression) of synaptic responses. Glutamate-gated ion channels known as AMPA receptors mediate basal neurotransmission. Their postsynaptic functional availability can be selectively modulated in correlation with a given stimulus. This review discusses the molecular basis of AMPA receptor trafficking to and anchoring at excitatory postsynaptic sites and their regulation by protein kinases.

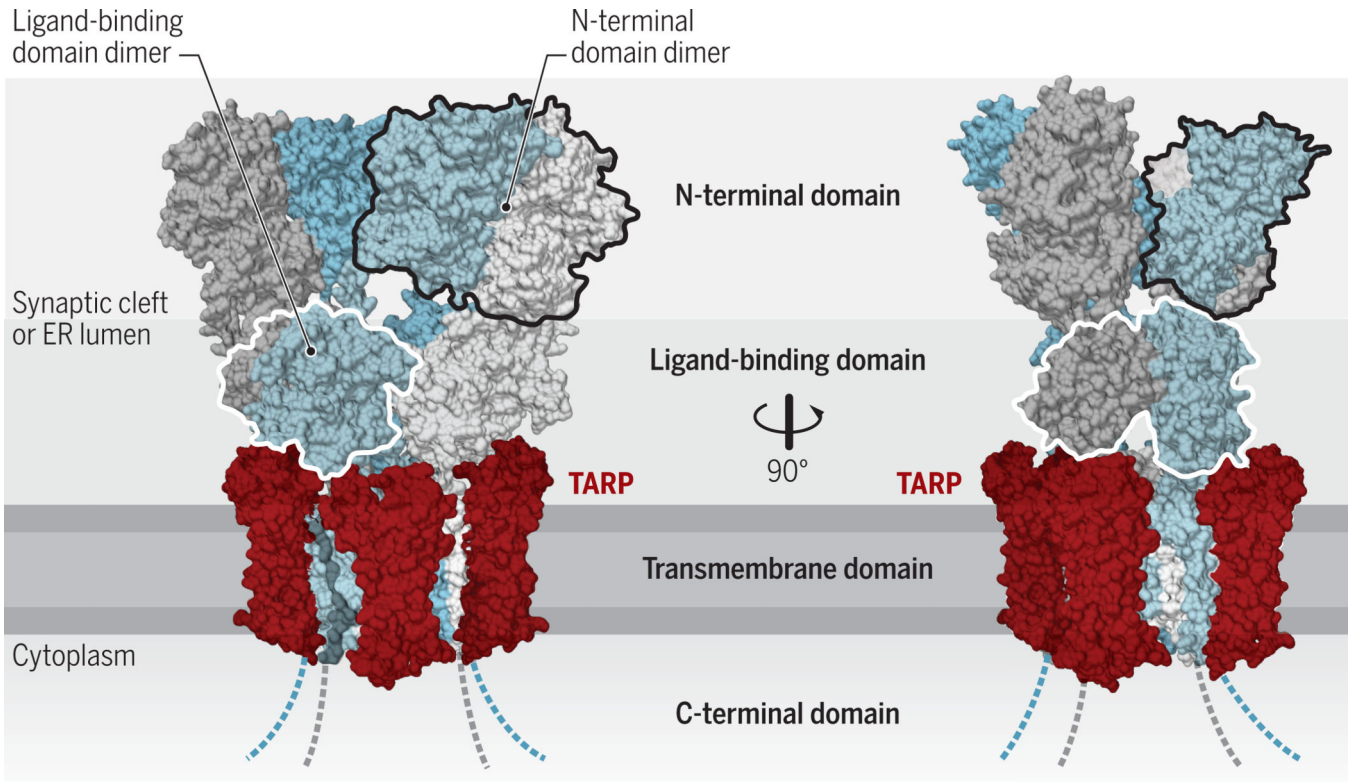

Figure 1. Structural architecture of AMPARs.

AMPARs are formed by four subunits, which are conformationally (and functionally) distinct (‘pore-proximal’ subunits are in grey and ‘pore-distal subunits’ in blue). These subunits consist of an extracellular N-terminal domain, the ligand binding domain, an integral membrane domain, and an intracellular C-terminus domain, and form tetrameric receptors (chains A-D). The large extracellular region faces the ER-lumen during receptor biogenesis and ultimately projects into the synaptic cleft. The transmembrane AMPAR regulatory proteins (TARPs) interact with the receptor at up to four positions around the transmembrane domain (two non-equivalent positions indicated in red; structure reproduced from PDB:5WEO). Credit: Adapted by A. Kitterman/*Science Signaling*

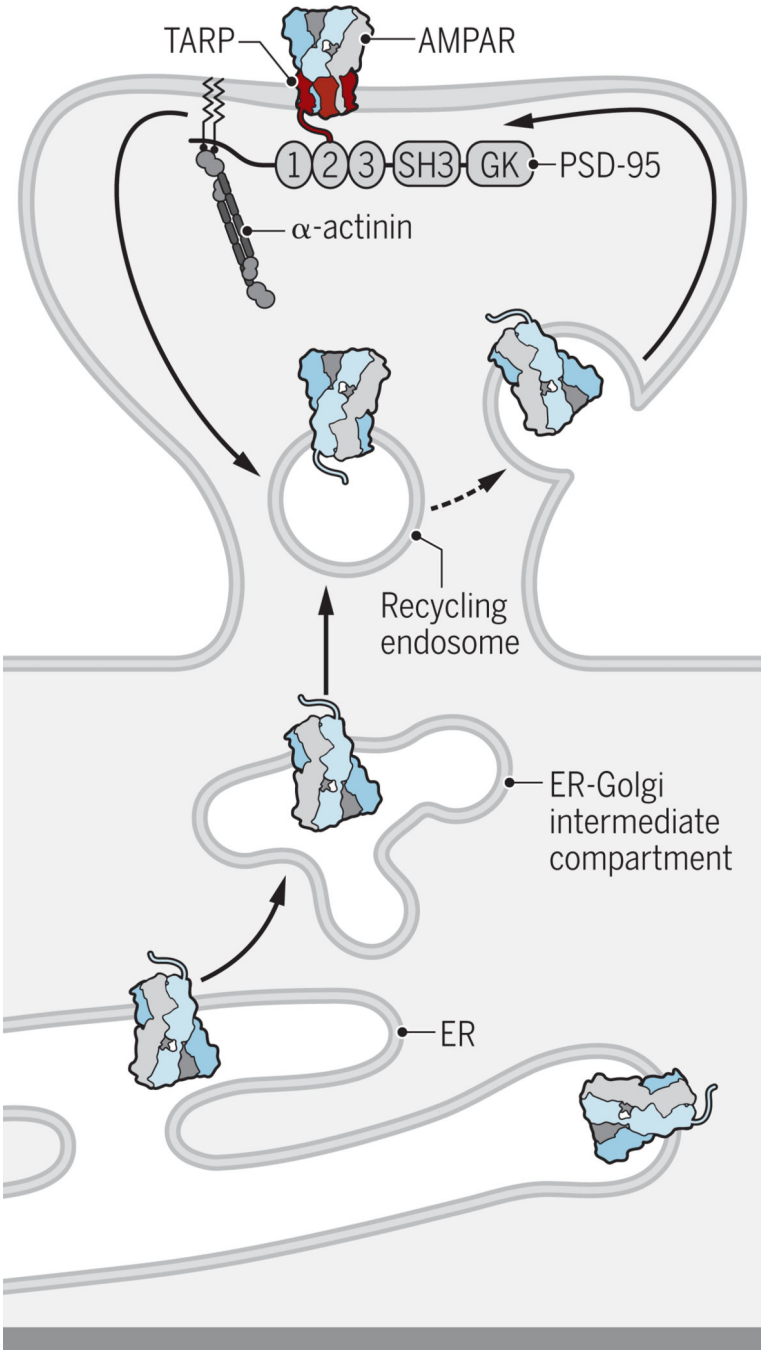

Figure 2. Dendritic AMPAR trafficking.

AMPARs are synthesized either in the soma (not depicted) or dendritic shaft in the endoplasmic reticulum (ER). From the dendritic ER AMPARs traffic through the ER–Golgi intermediate compartment to recycling endosomes, which mediate surface insertion of AMPARs (31). It is unclear where exactly exocytosis occurs but it is likely either in the dendritic shaft near dendritic spines or in dendritic spines outside the postsynaptic density (PSD). AMPARs then move through lateral diffusion to the PSD, where they are trapped by PSD-95 and its homologues through their binding to the C-termini of TARPs. PSD-95 is

anchored at postsynaptic sites by α-actinin. When and where TARPs, which are mostly if not exclusively translated in the soma (31), associate with AMPARs and especially those synthesized in dendrites is unknown. Credit: Kellie Holoski/*Science Signaling*

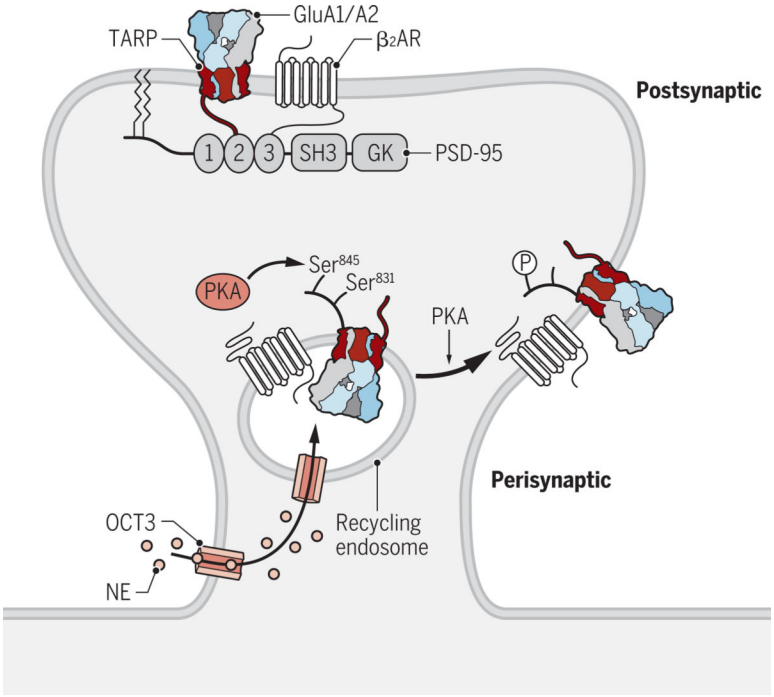

Figure 3. Regulation of perisynaptic AMPAR trafficking.

We propose that norepinephrine (NE) is shuttled by the amino acid transporter OCT3 localized in the plasma membrane from the cell exterior into the cytosol and then by OCT3 localized in recycling endosomes into their lumen. Here, NE stimulates the β_2 adrenergic receptor (β_2AR) associated with GluA1, which induces PKA activation and phosphorylation of Ser^{845} in GluA1. This phosphorylation event increases surface delivery of AMPARs from recycling endosomes. Lateral diffusion allows AMPARs to reach the PSD, where they are trapped by binding of the C_termini of TARPs to PSD-95. Credit: Kellie Holoski/*Science Signaling*

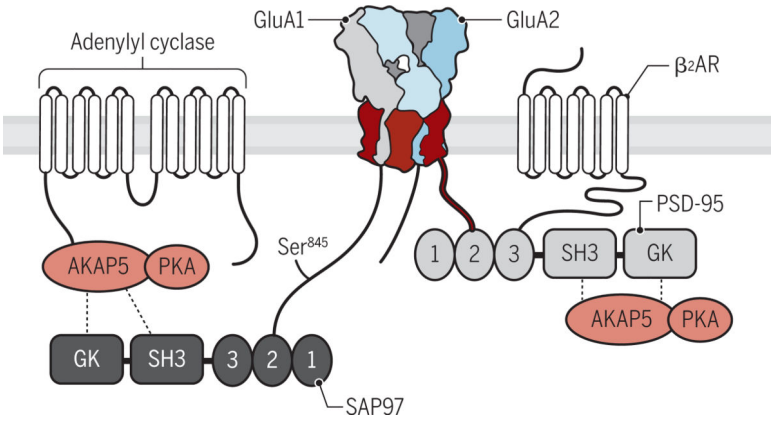

Figure 4. The AMPAR–β_2 adrenergic receptor signaling complex.

The β_2 adrenergic receptor binds through its extreme C-terminus to the third PDZ domain of PSD-95. In turn, the first two PDZ domains of PSD-95 bind to the C-termini of TARPs (red) including γ_2 and γ_8. Adenylyl cyclase binds through its N-terminus to the N-terminus of AKAP5 (also known as AKAP79 in humans, AKAP75 in cow, and AKAP150 in rodents), which binds through its C-terminus to PKA. AKAP5 is connected to AMPARs through SAP97, which binds to the C-terminus of GluA1, and potentially also through PSD-95. How G_s is linked to the β_2 adrenergic receptor (β_2AR) –AMPAR complex is unknown but could be through pre-association with the β_2 adrenergic receptor. Credit: Kellie Holoski/*Science Signaling*

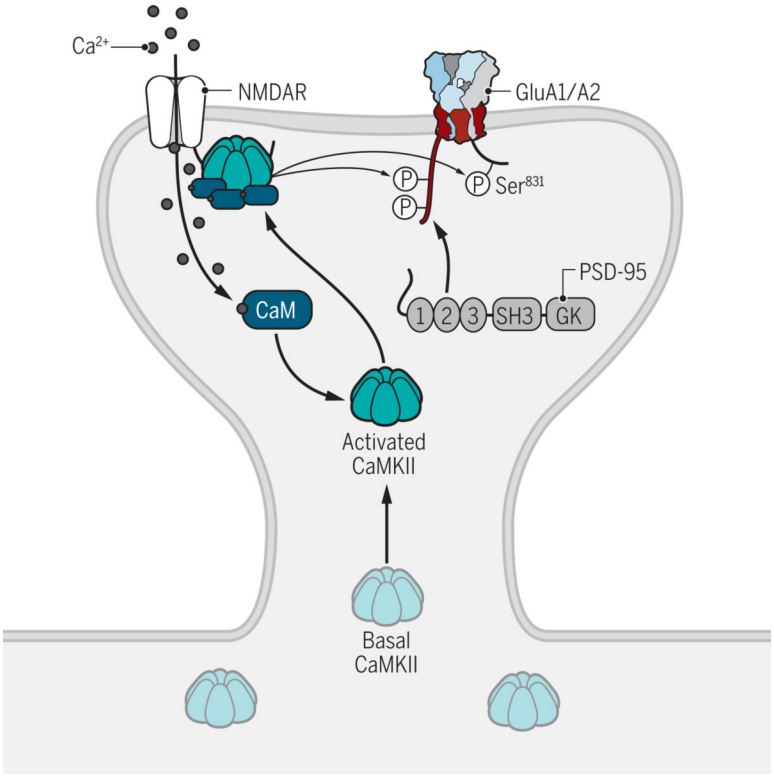

Figure 5. Regulation of postsynaptic AMPAR trafficking.

LTP-inducing stimuli trigger the influx of Ca^{2+} through NMDARs. Ca^{2+} binds to CaM and stimulates the activity of CaMKII. CaMKII is then recruited to the NMDAR complex by binding to the C-terminus of the GluN2B subunit. It subsequently phosphorylates the C-termini of TARPs including γ_2 and γ_8, which may lead to AMPAR trapping at the PSD. Phosphorylation of GluA1 on Ser^{831} by CaMKII also augments its channel activity. Credit: Kellie Holoski/*Science Signaling*