AMPA Receptors

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Advanced article

Article Contents

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Neuronal communication relies on rapid signalling through chemical synapses. The majority of excitatory neurotransmission in the central nervous system is mediated by binding of glutamate to a family of postsynaptic glutamate receptors. Among these, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPARs) mediate fast excitatory synaptic transmission and play a critical role in the synaptic plasticity that underlies learning and memory. AMPAR function is influenced on multiple levels by a combination of transcriptional modifications, post-translational regulation, and association with a multitude of auxiliary subunits. These processes give rise to a diverse array of receptors with unique properties for their specific role in brain function. Due to their central role in neuronal signalling, malfunction in AMPAR production or regulation can cause severe neurological and neuropsychiatric diseases. Since their cloning in the 1990s, much has been learned about AMPAR structure, assembly and trafficking, demonstrating the molecular complexity that underlies brain function.

History

Studies in the 1950s and 1960s demonstrated that the amino acid glutamate is a potent excitant of nervous tissue, providing some of the first evidence that glutamate was an excitatory neurotransmitter in the brain. Subsequent pharmacological analyses showed a differential sensitivity of some classes of neurons to the glutamate analogues *N*-methyl-d-aspartate (NMDA) and kainate, revealing that the action of glutamate was mediated by multiple types of glutamate receptors. Elucidation of the role of the various classes of glutamate receptors in synaptic physiology began with the pioneering work of Davies and Watkins in the late 1970s and early 1980s (Watkins and Evans, 1981). These studies showed that the amino acid antagonist 2-amino-5-phosphonovaleric acid (APV) blocked the excitatory activity of the agonist NMDA but not of kainate, and some synaptic activity was resistant to APV but sensitive to other compounds. Using voltage clamp techniques, Mayer and Westbrook (1984) established that the majority of the glutamate sensitivity of neurons could be explained by a combination of two classes of receptors – NMDA and non-NMDA receptors. These receptors are now termed NMDA and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPARs), named after their selective agonists. A third class of ionotropic glutamate receptors (iGluRs), the kainate receptor, was identified on the basis of kainate-binding studies. **See also**: **Amino Acid Neurotransmitters**; **Glutamate as a Neurotransmitter**; **Glutamate Receptors**; **Metabotropic Glutamate Receptors**

In the late 1980s and early 1990s, the glutamate receptor field was propelled forward by the cloning of the glutamate receptor subunits (Hollmann and Heinemann, 1994), which clarified the pharmacological distinctions between classes of ionotropic glutamate receptors. Subunits were identified for AMPA (GluA1–4), NMDA (GluN1, GluN2A-D and GluN3A-B) and kainate (GluK1–5) receptors. The iGluR family also contains two 'orphan' receptors GluD1/2, which have substantial sequence conservation, but do not appear to be glutamate-gated ion channels. In addition, metabotropic glutamate receptors were cloned (mGluR1–8), belonging to the G-protein coupled receptor family. Importantly, the GluA1–4 subunits precisely matched the predicted pharmacology of the AMPA class of glutamate receptors, and are now recognised as mediating the fast, rapidly desensitising, currents that underlie most excitatory synaptic transmission in the central nervous system. **See also**: **Chemical Synapses**; **NMDA Receptors**

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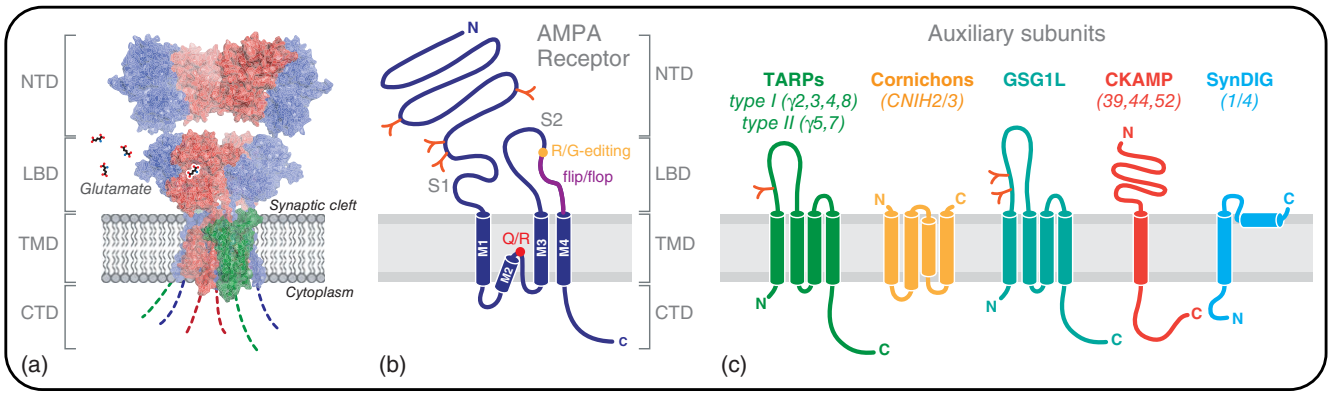

Figure 1 AMPAR and auxiliary subunit architectures. (a) Structure of the AMPAR-TARP complex (PDB:6KQZ), demonstrating the overall architecture and four domain layers (NTD, *N*-terminal domain; LBD, ligand-binding domain; TMD, transmembrane domain; CTD, *C*-terminal domain), and glutamate binding site. The GluA1 (blue) and GluA2 (red) subunits of the heteromeric assembly are located in distinct positions within the tetramer, and TARP γ8 (green) is associated with the TMD. The membrane (grey) is indicated. (b) A schematic of the receptor polypeptide depicting the membrane topology and arrangement of membrane helices (M1-4). The Q/R and R/G editing sites, and flip/flop splicing site are highlighted. The LBD is formed by two sequence regions (S1 & S2). Glycan positions (GluA2) are depicted as orange trees. (c) The arrangement and topology of currently known AMPAR auxiliary subunits, with glycans indicated.

AMPA Receptor Architecture

Following their cloning, the topology of the individual AMPAR subunits was initially proposed to be analogous to other ligand-gated ion channels, such as the nicotinic acetylcholine receptor and the γ-aminobutyric acid type A ($GABA_A$) receptor, which have four transmembrane domains (TMDs) with both *N*- and *C*- termini in the extracellular space. However, ionotropic glutamate receptors adopt a very different architecture. The transmembrane structure of AMPARs was clarified by studying native glycosylation patterns, and inserting glycosylation sites, epitope tags or protease sites into the primary sequence, allowing selective detection on either the intra- or extracellular sides of the membrane. Together, this work described the channel as having four membrane segments (M1-4), one of which (M2) does not span the membrane, but is a reentrant loop from the cytoplasmic side, akin to voltage-gated potassium channels, leaving the *N*-terminus on the extracellular and the *C*-terminus on the intracellular side of the membrane (Bennett and Dingledine, 1995). **See also**: **$GABA_A$ Receptors**

Extensive structural biology studies have since demonstrated the architecture of the AMPAR and other ionotropic glutamate receptor family members in greater and greater detail (Nakagawa *et al*., 2005; Sobolevsky *et al*., 2009). The tetrameric AMPAR is assembled as a dimer of dimers, with four distinct domain layers, arranged globally with approximate twofold symmetry (**Figure 1a**). These four domains include the extracellular *N*-terminal domain (NTD, or amino-terminal domain, ATD) and ligand-binding domain (LBD), followed by the TMD, forming the ion channel pore, and an intracellular *C*-terminal domain (CTD) (**Figure 1b**). Each of the domain layers is interconnected by polypeptide linkers, giving rise to a flexible receptor assembly. While the NTD and LBD form the twofold axis of symmetry, the ion channel pore has fourfold rotational symmetry. Interestingly, the dimer pairs in the NTD and LBD layers are formed by different subunits, causing a striking subunit crossover between domains, which will be of functional significance for receptor biogenesis and channel gating.

The LBD and TMD are the most evolutionarily conserved receptor portions and are highly akin to bacterial glutamate receptors, while the NTD and CTD are substantially sequence-diverse. The large NTD, comprising around 50% of the primary sequence, folds into a 'clamshell-like' structure; however, with no currently known ligands. This domain plays a role in receptor assembly, in the formation of tetrameric channels, and in particular of heteromeric assemblies (Greger *et al*., 2017). In addition, the domain is emerging as a crucial player in AMPAR localisation at the synapse.

The LBD is formed of two noncontiguous regions of the polypeptide (S1 and S2), which also fold into a clamshell-like domain, binding the channel agonist, glutamate, in its cleft. The four AMPAR subunits are further diversified by alternative splicing, introducing either the 'flip' or 'flop' exons, which alter the LBD sequence, uniquely influencing channel gating properties (Sommer *et al*., 1990). Ribonucleic acid (RNA) editing of the GluA2-4 subunits at the 'RG-site' also modifies gating. Adenosine to inosine editing produces an arginine (R) to glycine (G) exchange, speeding channel kinetics (**Figure 1b**) (Lomeli *et al*., 1994).

The pore of the AMPAR is built by sixteen α-helices from the four subunits of the tetramer, with the crossing of the M3 helices forming the channel gate and the re-entrant M2 helices creating the ion selectivity filter of the channel pore. Another RNA editing site, specific to the GluA2 transcript causes a glutamine to arginine (Q to R) single amino-acid transition at the Q/R site (position 607) at the apex of the M2 helix (Sommer *et al*., 1991), which is a major determinant of channel properties.

The CTD of the channel is an apparently unstructured polypeptide sequence (50–100 amino acids) following the M4 transmembrane helix, containing phosphorylation and protein interaction sites that have been extensively studied in the trafficking of receptors to synaptic sites (Shepherd and Huganir, 2007). Aside from

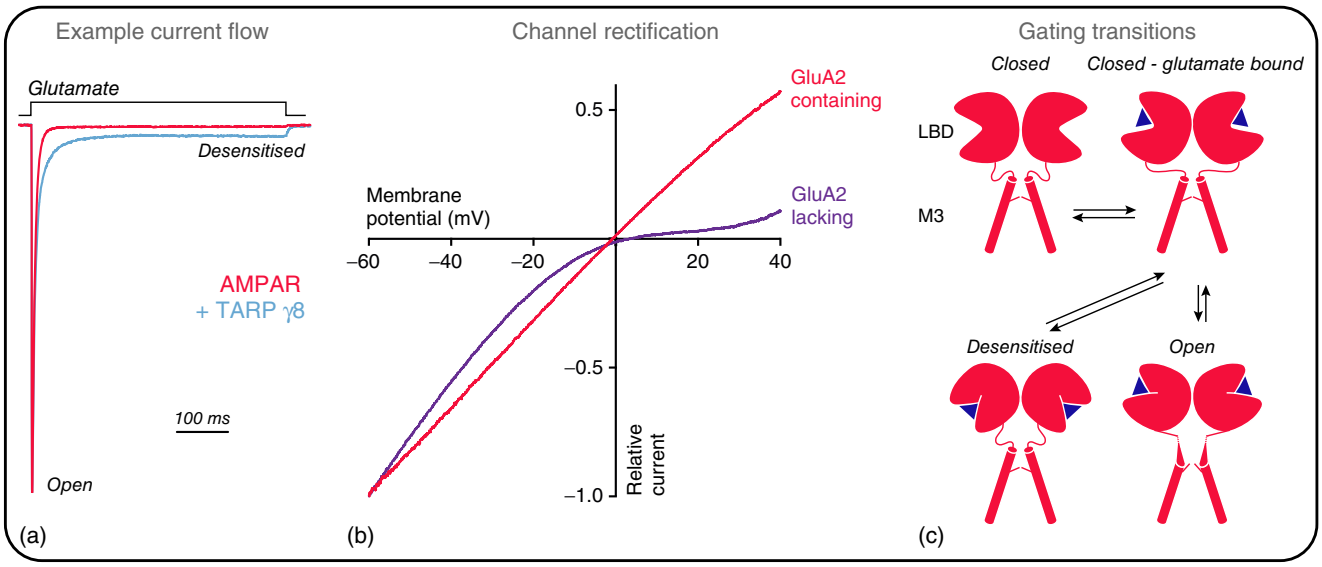

Figure 2 AMPAR gating. (a) An example recording of glutamate-gated AMPAR currents from GluA1/2 receptors with (blue) and without (red) association of the TARP γ8 auxiliary subunit, which slows desensitisation. (b) Current–voltage relationships for AMPARs are affected by inclusion of the GluA2 subunit. Polyamine molecules inhibit GluA2-lacking receptors (purple) at positive membrane potentials. (c) Schematic of AMPAR gating transitions within the ligand-binding domain (LBD), M3 helices and connecting linkers during receptor activation. The agonist, glutamate, is depicted in blue.

the flip/flop cassette, further RNA splicing of GluA1, 2 and 4 subunits occurs at the sequence encoding the CTD, producing alternative CTD variants of these subunits. As the CTD has multiple protein interactions, these will be differentially determined by splicing events.

Molecular Biology of the AMPAR

AMPARs are ligand-gated cation channels predominantly permeable to Na^+ and K^+ ions. The AMPAR subunits GluA1–4, encoded by the *GRIA1-4* genes, range from 102 to 108 kDa in size. AMPARs contain multiple glycosylation sites on the NTD, and the NTD-LBD interdomain linkers, modifications that appear to influence receptor trafficking and surface delivery.

The subunit composition of these assemblies can have profound effects on channel properties, principally on channel conductance and ionic permeability (Traynelis *et al.*, 2010). The great majority of native AMPARs are heteromers containing the GluA2 subunit. Incorporation of GluA2 confers calcium impermeability due to inclusion of a positively charged, arginine (R) residue at the Q/R editing site in the channel pore (**Figure 1b**). Channel assemblies lacking GluA2, are, therefore, permeable to calcium and appear to have unique roles in cellular signalling. Q/R editing of GluA2 also reduces the channel conductance and prevents inhibition by intracellular polyamines. Polyamine molecules, such as spermine, block GluA2-lacking receptors specifically at positive membrane potentials, giving rise to a 'rectifying' channel response (**Figure 2b**) (Traynelis *et al.*, 2010). RNA editing at the Q/R site of GluA2, enacted by a nuclear adenosine deaminase, ADAR2, is almost 100% complete in the postnatal brain and is essential for survival (Higuchi *et al.*, 2000).

Biogenesis of the receptor

Like most membrane proteins, AMPARs are translated at the ER where they first assemble into dimers, driven by NTD interactions, which then form the tetrameric channel as dimers of dimers (**Figure 3**). Heteromerisation is also driven by the NTD, as NTD dimerisation affinities largely favour formation of heteromers over homomers (Rossmann *et al.*, 2011). The final tetrameric receptor is stabilised by association of the transmembrane helices.
See also: **Membrane Proteins**

A consideration in the assembly of the AMPAR is subunit placement. Given this tetrameric channel has twofold symmetry, there are two nonequivalent subunit positions contributing differently to the gating machinery. As receptor subunits have diverse properties, such as glutamate affinities, the arrangement of subunits within one receptor has the potential to alter final receptor's functioning. Thus far, GluA2 appears to be preferentially located to a more dominant gating position within heteromeric assemblies (**Figure 1a**) (Herguedas *et al.*, 2019; Zhao *et al.*, 2019).

Several AMPAR interaction partners that facilitate the assembly process have been characterised (**Figure 3**). FRRS1L, ABDH6 and CPT1c are ER-localised proteins, which aid the production of functional surface AMPARs by stabilising assembly intermediates (Schwenk *et al.*, 2019). It is possible that auxiliary proteins may additionally support the trafficking and delivery of newly synthesised receptors to the cell surface, however, it is currently unclear at what point in their life cycle, these proteins associate with the receptor tetramer.

After leaving the ER, AMPARs will transit through the Golgi, for glycosyl processing, prior to delivery to the cell surface or synaptic areas by active transport. Local translation of AMPARs at dendrites has been reported, which may offer branch-specific AMPAR production. Finally, recycling of receptors from the cell

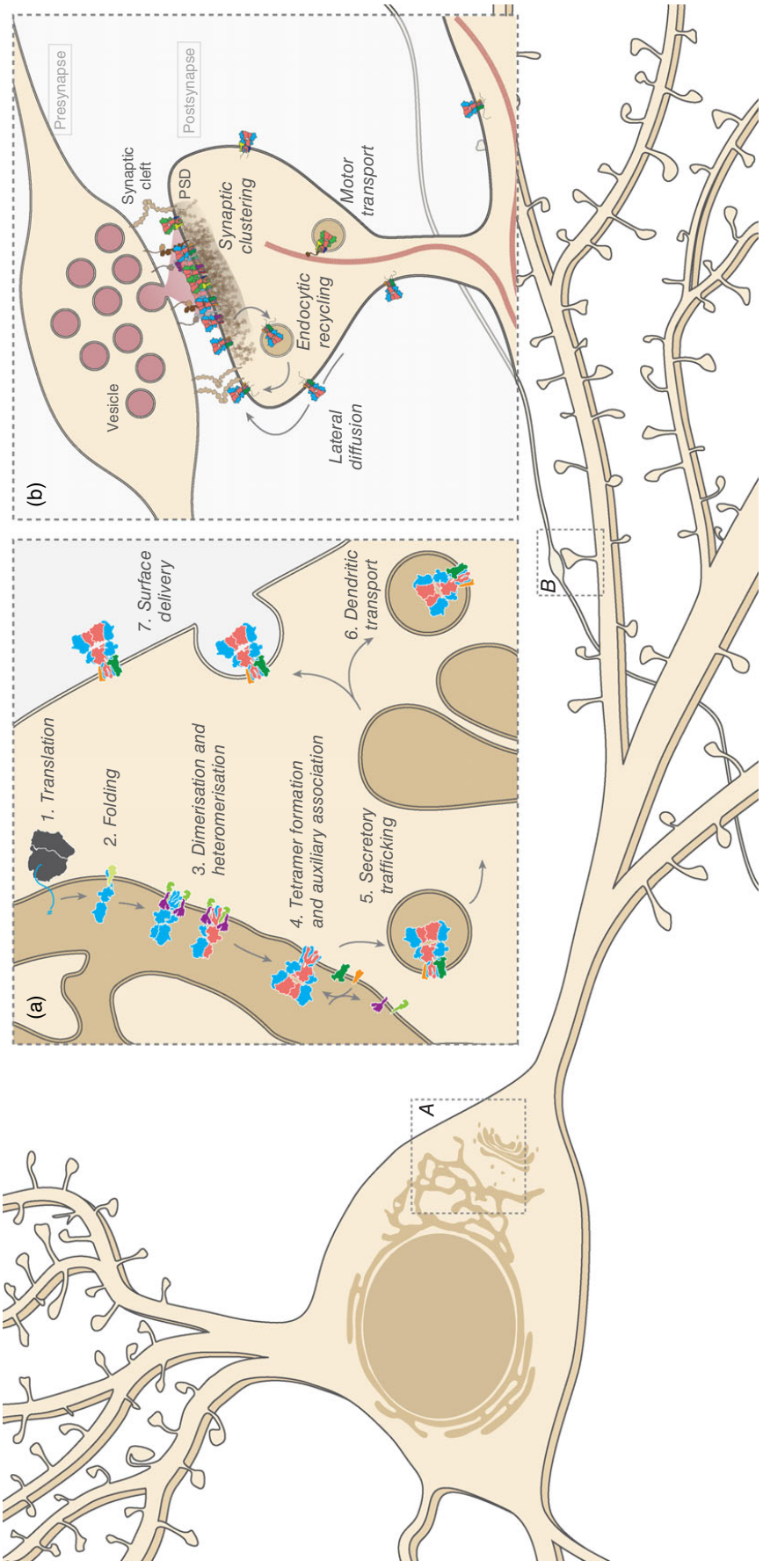

Figure 3 The life-cycle of an AMPAR. (a) AMPARs are translated (ribosome – black) at the endoplasmic reticulum, before assembling into a tetramer through specific protein association, followed by auxiliary subunit association and secretory trafficking. (b) Receptors are delivered to the synapse by lateral diffusion or intracellular transport, where they are clustered opposite the sites of vesicle release. Endocytic recycling can regulate the levels of synaptic receptors within a spine head.

surface is an important regulator of synaptic transmission, providing a mechanism for synaptic plasticity (Opazo and Choquet, 2011). **See also**: **Protein Synthesis in Neurons**

AMPA receptor gating

The AMPAR exhibits uniquely rapid kinetics to enable fast excitatory neurotransmission in the brain. Channel opening and closure, either by deactivation or following desensitisation, produce current responses on the millisecond time-scale and are, therefore, far faster than in other iGluR family members (**Figure 2a**).

Channel gating is initiated by glutamate binding in the cleft of the LBD, which induces clamshell closure around the ligand. These conformational changes pull on the linkers between the LBD and TMD, in particular those connected to the M3 gate helices. Unwinding of the M3 helices opens the channel pore to allow ion flow across the membrane. Desensitisation of the channel occurs by separation of LBD dimers from one another, releasing the tension on peptide linkers connected to the channel pore, and thus rapidly preventing ion flux (**Figure 2c**). The AMPAR has multiple sub-conductance levels (up to 4), corresponding to different numbers of agonist molecules binding at the four LBDs of the tetrameric channel. Maximal channel conductance is achieved through full agonist occupancy (Greger *et al*., 2017).

Receptor kinetics are finely tuned by a number of mechanisms, including RNA splicing and editing as previously mentioned, but also due to subunit composition. For example, incorporation of GluA2 into a heteromeric assembly with GluA1 confers slower desensitisation kinetics, and faster recovery from desensitisation compared to homomeric GluA1 alone (Traynelis *et al*., 2010). One further factor that influences the gating properties of the AMPAR is its association with auxiliary subunits, a plethora of which have been discovered and characterised.

Auxiliary Subunits

Native AMPARs were originally thought to exist simply as combinations of the core subunits; however, recent studies have identified auxiliary subunits with various roles in AMPAR stability, trafficking and function (**Figure 1c**) (Greger *et al*., 2017). The first auxiliary protein to be identified was 'stargazin', discovered through analysis of the *stargazer* mutant mouse, which shows deficits in brain function, such as ataxia (Chen *et al*., 2000). Subsequent work demonstrated that stargazin was just one of a family of six 'transmembrane AMPAR regulatory proteins' (TARPs), homologous to calcium channel γ subunits: γ2 (stargazin), γ3, γ4, γ5, γ7 and γ8 (Tomita *et al*., 2003).

TARPs interact with all AMPAR subunits but not with other glutamate receptors. This family of proteins have four transmembrane helices, with both *N*- and *C*-termini located intracellularly. TARPs interact with the TMD of the receptor, at up to four sites per tetramer, with long extracellular loops between transmembrane helices, that are able to interact with the LBDs to modulate receptor function (**Figure 1c**).

TARPs regulate AMPARs on multiple levels. Firstly, they alter channel properties, such as desensitisation and deactivation rates, pharmacology and conductance, but also trafficking and localisation of receptors within the neuron. TARPs appear to stabilise receptors on the cell surface, and an absence of this auxiliary subunit, for example at cerebellar granule cells in the *stargazer* mouse, leaves the cell membrane devoid of AMPARs. Synaptic localisation of AMPARs is also heavily dependent on this auxiliary subunit. Type I TARPs (γ2, γ3, γ4 and γ8) contain interaction sites at their extreme *C*-termini for PDZ (postsynaptic density (PSD)-95, discs large and zona-occludens-1) domain-containing proteins, such as PSD-95/93, which are important for synaptic anchoring of the receptors (Greger *et al*., 2017).

The second auxiliary protein family to be identified was the cornichon proteins (CNIH2/3), homologues of yeast ER chaperone proteins (Schwenk *et al*., 2009). CNIHs associate with the AMPAR TMD at the same site as TARP molecules (Nakagawa, 2019), and similarly have four transmembrane helices, however, with inverted topology: both protein termini are located extracellularly. CNIH proteins dramatically slow AMPAR channel closure, prolonging synaptic signalling where they are expressed in the brain. As CNIH proteins have minimal extracellular and intracellular regions, their mechanism of action for receptor modulation is expected to be very different from other auxiliary proteins.

Further AMPAR auxiliary proteins affecting channel trafficking and/or kinetics include cysteine-knot AMPAR modulatory proteins (CKAMP44/39/52), synapse differentiation induced genes (synDIG1/4) and germ-specific gene 1-like (GSG1L) (Von Engelhardt *et al*., 2010; Schwenk *et al*., 2012). These proteins vary greatly in their structure (**Figure 1c**), expression patterns and regulation of AMPARs, and contribute to the diversity of synaptic signalling properties of AMPAR complexes across the brain. CKAMP59 (also known as Shisa7) has been considered an AMPAR auxiliary subunit, but recent evidence has proposed that it also modulates $GABA_AR$ function (Han *et al*., 2019).

The essential role for auxiliary proteins in regulating AMPARs appears to be a general and evolutionarily conserved principle. The AMPAR homologue in the nematode worm *Caenorhabditis elegans,* GLR-1, has two auxiliary proteins so far identified; STG-1, a homologue of mammalian TARPs, and SOL-1, a C1r/C1s, Uegf, Bmp1 (CUB) domain-containing protein, which regulates ion channel gating (Zheng *et al*., 2006). Moreover, TARP-like proteins that are required for invertebrate AMPAR function have now been identified in other organisms, such as *Drosophila* and honey bees (Walker *et al*., 2006).

The diversity of AMPAR complexes

The number of core AMPAR subunits and auxiliary subunits allow vast combinations of unique AMPAR complexes, which will define the signalling properties of individual synaptic connections and, in turn, neuronal networks.

Firstly, the inclusion of GluA2 in a receptor defines its calcium permeability. Subpopulations of neurons in some brain areas express low levels of GluA2 and therefore employ GluA2-lacking, calcium-permeable AMPARs. Best described of these cells are hippocampal GABAergic interneurons, cerebellar stellate cells (another class of GABAergic interneurons) and midbrain dopaminergic neurons (Cull-Candy *et al*., 2006). There is also evidence that principal forebrain neurons (pyramidal

neurons) can express GluA2-lacking AMPARs that play a role in certain forms of synaptic plasticity (Cull-Candy *et al*., 2006). The kinetics of AMPAR subunits dictate the time-course of synaptic transmission, for example the particularly fast kinetics of GluA4 being employed for the temporal encoding of auditory information at the bushy cell synapse of the cochlear nucleus (Gardner *et al*., 1999).

In the hippocampus, the majority of AMPARs contain GluA2 in complex with either GluA1 or GluA3 subunits. A thorough single-cell genetic approach determined that approximately 80% of synaptic AMPARs in hippocampal CA1 pyramidal neurons are GluA1/A2 heteromers with a smaller subpopulation of GluA2/A3 heteromers (Lu *et al*., 2009).

Auxiliary subunits show unique expression patterns across the brain, and their role in defining the functional properties of neuronal circuits is only beginning to be recognised and understood. TARP expression is regionally distinct with γ2 primarily expressed in the cerebellum and γ8 present at high levels in the hippocampus. Multiple auxiliary proteins can co-assemble with one AMPAR, as TARP γ8 containing hippocampal receptors also associate with CNIH2 (Kato *et al*., 2010) in pyramidal neurons. This unique combination of proteins assembles a relatively slowly desensitising AMPAR complex, which would aid integration of signals from multiple synapses, as is required for pyramidal cell function.

AMPA Receptor Synaptic Localisation

The number of AMPARs at a synapse directly correlates with the strength of synaptic transmission. Receptor trafficking and synaptic targeting are therefore highly regulated through various mechanisms, including subunit-specific protein interactions, auxiliary subunit association and different post-translational modifications.

AMPARs are recruited to the synaptic area either by lateral diffusion from extra-synaptic sites or through exocytosis from intracellular stores. The receptors are in constant dynamic exchange between synapses and extra-synaptic sites, while the availability of extra-synaptic surface receptors is tightly regulated by endo- and exocytosis. To mediate synaptic transmission, AMPARs are accumulated and retained at postsynaptic sites, which is facilitated by specific protein interactions (Opazo and Choquet, 2011).

Within the postsynaptic area, AMPARs are concentrated into specific subsynaptic regions around 70–80 nm in diameter opposite to presynaptic neurotransmitter release sites. Given the relatively low glutamate affinity of AMPARs in comparison to other iGluRs, this arrangement appears to be important for high-fidelity neurotransmission. Individual synapses may contain multiple AMPAR clusters, each consisting of about 25 receptors (Biederer *et al*., 2017).

The association of AMPARs with TARP auxiliary subunits plays a major role in anchoring receptors at the synapse by virtue of the TARP's *C*-terminal PDZ interaction with intracellular scaffold proteins (**Figure 3**), such as PSD-95, a highly abundant component of the PSD (Opazo and Choquet, 2011).

Interactions with the intracellular CTDs of the pore-forming subunits further influence synaptic targeting of glutamate receptors. The GluA1 CTD contains a class-I PDZ domain ligand, which binds to SAP97, another postsynaptic scaffolding protein. Distinct SAP97 splice variants alter AMPAR surface expression and differentially regulate their subcellular localisation (Shepherd and Huganir, 2007). The intracellular *C*-termini of GluA2 and GluA3 instead associate with type II PDZ domain-containing proteins such as GRIP/ABP and PICK1. These protein interactions can be differentially modulated by GluA2 phosphorylation on Ser880, within the PDZ-binding motif, which disrupts association with GRIP/ABP and promotes PICK1 interaction (Shepherd and Huganir, 2007). Whereas binding to GRIP/ABP facilitates receptor anchoring to the PSD, interaction with PICK1 mediates receptor endocytosis (Diering and Huganir, 2018). GluA2 also associates with *N*-ethyl-maleimide-sensitive factor (NSF), an adenosine triphosphatase (ATPase) required for membrane fusion events, and AP-2, a clathrin adaptor protein, at a distinct region of its CTD. These interactions antagonistically influence receptor recycling to regulate AMPAR surface levels (Shepherd and Huganir, 2007).

Recent evidence points to an important role for the extracellular AMPAR NTD in synaptic receptor anchoring (Díaz-Alonso *et al*., 2017; Watson *et al*., 2017) potentially by engaging with components of the synaptic cleft, such as neuronal pentraxin 1, thus stabilising receptors at the synapse (Farhy-Tselnicker *et al*., 2017).

Mechanisms underlying subsynaptic AMPAR clustering are still not fully understood, but likely involve multiple intra- and extracellular receptor interactions, in order to position receptors at specific postsynaptic locations. A nonuniform subsynaptic distribution has been observed for a number of postsynaptic scaffolding proteins, including PSD-95, which likely provides the structural basis for AMPAR clusters. Recent findings suggest the formation of TARP-CTD, PSD-95 and other postsynaptic protein-aggregates *in vitro* through liquid–liquid phase separation, a process which creates distinct phases from a mixture of components with different solubilities (Chen *et al*., 2020). Such events may potentially contribute to the formation of the PSD and the nonuniform distribution of synaptic proteins, but their role in promoting protein clustering at the synapse needs further investigation. **See also**: **Glutamatergic Synapses: Molecular Organisation**

A final layer of regulating surface AMPARs is added by different posttranslational modifications such as palmitoylation, a reversible lipid modification whereby palmitic acid is attached to intracellular cysteine residues. These modifications can generally lead to changes in protein trafficking, stability, subcellular localisation and function. There are two conserved palmitoylation sites on AMPAR subunits – one in the channel pore domain between M1 and M2 (GluA1 – C585) and the other in the juxtamembrane region of the CTD (GluA1 C811). Palmitoylation at both sites reduces AMPAR surface levels involving different mechanisms. AMPAR palmitoylation is itself dynamically regulated by neuronal activity and receptor palmitoylation can be increased by activity blockade (Lu and Roche, 2012).

Considering the diversity of possible regulations, it is likely that neurons use a combination of these mechanisms to target AMPARs to synapses, with differences specific to cell types and

brain regions. Many of these processes are used to dynamically regulate AMPAR numbers during synaptic plasticity.

AMPA Receptors in Synaptic Plasticity

Changes in the strength of synaptic connections, termed plasticity, are thought to underlie experience-dependent behavioural adaptations, including learning and memory. The best-characterised forms of long-term synaptic plasticity in the mammalian brain are NMDA receptor-dependent long-term potentiation (LTP) of glutamatergic synaptic transmission and its counterpart long-term depression (LTD). Both forms of plasticity are expressed as a long-lasting change in the efficacy of AMPAR-mediated synaptic transmission triggered by specific patterns of activity at these synapses (Malenka and Bear, 2004). **See also**: **Long-term Potentiation**; **Long-term Depression and Depotentiation**

The expression of this form of LTP requires the rapid recruitment of additional AMPARs to synapses through lateral diffusion of extra-synaptic receptors and exocytosis of intracellular receptors from recycling endosomes (Granger *et al*., 2013; Penn *et al*., 2017). Conversely, the expression of LTD involves the removal of synaptic AMPARs via diffusion followed by clathrin and dynamin-dependent endocytosis (Malenka and Bear, 2004). Both processes involve a variety of post-translational modifications and protein interactions (Diering and Huganir, 2018). Recently, synaptic recruitment of AMPARs has been demonstrated *in vivo* in response to behavioural learning tasks (Roth *et al*., 2020).

While still a matter of debate (Hayashi *et al*., 2000; Granger *et al*., 2013; Zhou *et al*., 2018), many studies suggest a contribution of AMPAR CTD phosphorylation and protein interactions to LTP and LTD. These mechanisms involve phosphorylation by several protein kinases, including PKA (cyclic adenosine mono-phosphate (cAMP)-dependent protein kinase), CaMKII (calcium–calmodulin-dependent protein kinase II) and protein kinase C (PKC). The GluA1 CTD contains two phosphorylation sites important for LTP, S831 and S845, which are substrates for CaMKII and PKC or PKA, respectively. Phosphorylation at either site enhances AMPAR-mediated synaptic currents. S845 phosphorylation facilitates surface delivery of GluA1-containing receptors by limiting receptor endocytosis and increasing recycling from endosomes. Conversely, dephosphorylation of the same residue reduces surface AMPARs and has been implicated in LTD. An additional mechanism associated with LTD involves phosphorylation of Ser880 in the GluA2 CTD, whereby modification of this residue abolishes the interaction with GRIP/ABP which stabilises AMPARs at the synapse and instead promotes binding to PICK1, facilitating receptor endocytosis (Diering and Huganir, 2018).

CaMKII-mediated phosphorylation of TARPs γ2 and γ8 has also been linked to LTP, facilitating their interaction with PSD-95, thus retaining AMPARs at postsynaptic sites (Opazo and Choquet, 2011). While these findings are still a matter of debate, AMPAR anchoring through TARP – PDZ interactions seem to be important for the expression of LTP (Sheng *et al*., 2018). Recent studies also implicate the extracellular GluA1 NTD for LTP maintenance, possibly by mediating receptor anchoring through yet unidentified protein interactions (Díaz-Alonso *et al*., 2017; Watson *et al*., 2017).

While most of the studies performed so far describe a predominant role of GluA1-containing receptors in LTP, a distinct mechanism of potentiation involving GluA3-containing receptors has been reported to occur at both hippocampal synapses and the cerebellar parallel fibre to Purkinje cell synapse. This form of plasticity is not attributed to synaptic AMPAR recruitment but rather to a cAMP-dependent increase in the probability of channel opening, resulting in enhanced AMPAR-mediated transmission (Gutierrez-Castellanos *et al*., 2017; Renner *et al*., 2017). Together these findings suggest that multiple plasticity mechanisms can alter AMPAR-mediated synaptic transmission across the brain.

A distinct form of plasticity is the regulation of synaptic strength in response to chronic changes in activity, known as homeostatic scaling. Chronic reduction in neuronal activity results in the upregulation of synaptic AMPAR trafficking, whereas hyperexcitability reduces the synaptic receptor content (Diering and Huganir, 2018). In contrast to LTP and LTD, which are usually expressed within one hour, these adaptations require around 24–48 h, and therefore occur at much slower timescales. In addition, homeostatic scaling is less specific to individual synaptic connections.

Most mechanisms involved in homeostatic scaling enhance transmission by either strengthening synaptic AMPAR anchoring or shifting the balance between receptor exo- and endocytosis. For example, phosphorylation of GluA1 at Ser845, which regulates receptor recycling, can be bidirectionally modulated during homeostatic plasticity. Similarly, the surface expression of GluA2-containing receptors is regulated by GRIP/ABP and PICK1 interactions. This regulation may additionally involve GluA2 Tyr876 dephosphorylation by striatal-enriched protein tyrosine phosphatase ($STEP_{61}$), a protein that is itself is up- or downregulated during homeostatic scaling. A different mechanism for synaptic downscaling has been observed in cortical neurons whereby elevated neuronal activity promotes semaphoring 3F secretion, limiting the interaction of GluA1 with neuropilin-2 and thereby destabilising receptor surface levels by as yet unidentified mechanisms (Wang *et al*., 2017).

Interestingly, homeostatic scaling does not appear to affect the entire synaptic population to the same degree. Synapses with a high AMPARs content tend to be upregulated to a lesser extent in response to chronically reduced activity compared to those containing fewer receptors (Wang *et al*., 2019). These findings demonstrate the different layers of regulatory mechanisms underlying synapse-specific fine tuning of the synaptic AMPAR content.

AMPA Receptors in Disease

AMPARs have been implicated in a range of neurological and neurodevelopmental disorders. Several missense mutations and chromosomal aberrations (including deletions and copy number variations) affecting either AMPAR core subunits or auxiliary proteins such TARP γ2 and CNIH 2 have been linked

to intellectual disability and/or autism spectrum disorders (Soto *et al*., 2014; Davies *et al*., 2017; Geisheker *et al*., 2017; Salpietro *et al*., 2019). Changes in AMPAR composition, expression and other regulatory mechanisms are further linked to a number of pathological conditions. The selective loss of GluA2 containing receptors, resulting in an excessive level of calcium-permeable receptors, and the consequent calcium-dependent excitotoxicity, has been associated with cerebral ischaemia, amyotrophic lateral sclerosis, white matter damage, glioblastoma, chronic pain, epilepsy and addiction (Cull-Candy *et al*., 2006).

Autoantibodies against GluA1 or GluA2 subunits, inducing receptor internalisation and subsequently reducing AMPAR-mediated signalling, have been associated with cases of limbic encephalitis. This inflammatory disease is characterised by memory loss, behavioural abnormalities, epilepsy and in some cases dementia (Peng *et al*., 2015). In addition, antibodies against GluA3 were detected in a number of patients with different forms of epilepsy (Mantegazza *et al*., 2002) including Rasmussen encephalitis (Rogers *et al*., 1994). It remains, however, still unclear whether these antibodies initiate the disease or appear as a consequence of other pathological changes.

Finally, several neurological and neurodegenerative disorders affect AMPAR function secondarily. For example, amyloid β (Aβ), a secreted proteolytic derivative of the amyloid precursor protein (APP), is thought to initiate cognitive decline during early stage of Alzheimer disease, by inducing endocytosis of synaptic AMPARs. Subsequently, this results in NMDAR depletion and loss of synaptic spines, causing cognitive deficits. Interestingly, Aβ dependent AMPAR endocytosis requires the presence of GluA3 subunits which might be relevant for future therapeutic strategies (Jurado, 2018).

Given their essential function for excitatory neurotransmission and broad disease implication, AMPARs are appealing targets for therapeutic treatments. However, due to the widespread expression of AMPARs, compounds targeting the core pore-forming subunits, such as perampanel, an antagonist approved for epilepsy treatment, result in many off-target effects. More recent efforts instead focused on targeting specific AMPAR complexes through their auxiliary subunits, to enable brain-region specific modulation and thus minimising undesired side-effects. Compounds selectively targeting TARP γ8 containing AMPAR complexes represent an attractive strategy for epilepsy treatment by specifically binding to forebrain receptors without affecting cerebellar receptors, thus avoiding negative impacts on motor function (Kato *et al*., 2016; Maher *et al*., 2016).

Summary

The past three decades have seen dramatic advances in describing the functioning of the AMPAR, from its molecular architecture to its role in synaptic plasticity. Structural biology continues to provide views of the receptor and its associated auxiliary subunits across the spectrum of gating transitions. In addition, there has been substantial progress in understanding the trafficking of receptors from their assembly to accumulation at synaptic sites. Finally, pharmacological AMPAR-targeting has achieved great specificity that could dramatically improve therapeutic strategies. However, many questions still remain in understanding the regulation and functioning of specific AMPAR complexes in synaptic plasticity. These questions will continue to be addressed.

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Glossary

Channel gating Conformational changes underlying the opening (allowing ion flux) and closing of an ion channel. Channel closure can either occur directly by deactivation, resulting in structural rearrangements shutting the pore, initiating ligand unbinding and return to the resting state or secondly to the desensitised state.

Conductance The level of current flow at a particular potential difference. For ion channels, this property is the amount of ion flux, and therefore current, that can occur through the channel pore at a particular membrane potential (G (conductance) = I (current)/V (voltage).

Desensitisation A conformational state of the channel where agonist is bound, but the receptor is unable to strongly conduct ion flow.

PDZ-domain A structural domain of about 80–90 amino acids common to many signalling and scaffolding proteins. The name derives from the first three proteins discovered to contain the domain: PSD-95, *D*iscs large and *Z*ona-occludens-1. Interacting proteins contain so-called PDZ-ligands at their *C*-termini.

Posttranslational modifications Covalent linkage of other molecules to a protein, occurring after the initial protein formation. These modifications include glycosylation, phosphorylation and palmitoylation among many others.

Rectification Refers to the directionality of the current flow through an ion channel. Rectifying channels preferentially pass current into one direction, whereas channels conducting in- and outward currents to similar extents are termed nonrectifying. For example, an inwardly rectifying channel preferentially allows current flow into the cell.

RNA editing A post-transcriptional RNA modification involving changes, insertions or deletions of specific nucleotides. The most common form is the removal of an amino group from the nucleoside adenosine (A), changing it to inosine (I), and consequently altering the amino acid sequence of the encoded protein.

Synaptic plasticity Processes that change the strength of synaptic transmission.

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