Chapter 11
AMPA Receptor Assembly: Atomic Determinants and Built-In Modulators

Madhav Sukumaran, Andrew C. Penn, and Ingo H. Greger

Abstract Glutamate-gated ion channels (iGluRs) predominantly operate as heterotetramers to mediate excitatory neurotransmission at glutamatergic synapses. The subunit composition of the receptors determines their targeting to synaptic sites and signalling properties and is therefore a fundamental parameter for neuronal computations. iGluRs assemble as obligatory or preferential heteromers; the mechanisms underlying this selective assembly are only starting to emerge. Here we review recent work in the field and provide an in-depth update on atomic determinants in the assembly domains, which have been facilitated by recent advances in iGluR structural biology. We also discuss the role of alternative RNA processing in the ligand-binding domain, which modulates a central subunit interface and has the capacity to modulate receptor formation in response to external cues. Finally, we review the emerging physiological significance of signalling via distinct iGluR heterotetramers and provide examples of how recruitment of functionally diverse receptors modulates excitatory neurotransmission under physiological and pathological conditions.

M. Sukumaran
Laboratory of Cellular and Synaptic MRC LMB and Neurophysiology, National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD 20892, USA

A.C. Penn
Univ. de Bordeaux, Interdisciplinary Institute for Neuroscience, UMR 5297, F-33000, Bordeaux, France

CNRS, Interdisciplinary Institute for Neuroscience, UMR 5297, F-33000 Bordeaux, France

I.H. Greger (✉)
Neurobiology Division, MRC Laboratory of Molecular Biology, Hills Road, CB2 0QH Cambridge, UK
e-mail: ig@mrc-lmb.cam.ac.uk

M.R. Kreutz and C. Sala (eds.), *Synaptic Plasticity*,
Advances in Experimental Medicine and Biology 970,
DOI 10.1007/978-3-7091-0932-8_11,

Keywords Alternative splicing • AMPA receptor biosynthesis • Endoplasmic reticulum • Ligand binding domain • N-(amino) terminal domain • RNA editing • Synaptic plasticity

11.1 From Polysome to Receptor Oligomer

Cell surface receptors, such as ion channels and G-protein-coupled receptors, prominently operate as hetero-oligomers. Assembly from a pool of different subunits increases the versatility and plasticity of signal transmission and is under complex cellular control. Ionotropic glutamate receptors (iGluRs) provide a dramatic example of how functionally diverse receptor stoichiometries shape an essential cellular process. iGluRs mediate excitatory neurotransmission in vertebrate nervous systems. This process involves three distinct iGluR subfamilies (AMPA-, NMDA- and kainate types), differentially expressed and regulated subunits within each subfamily, and a multitude of accessory subunits (Hollmann and Heinemann 1994; Traynelis et al. 2010). The result of this rich variety of assembly substituents is a combinatorial diversity of receptor expression, which impact such receptor properties as gating kinetics (which can operate on time scales spanning four orders of magnitude), ion conductance, pharmacology and synaptic trafficking; all of these properties are dependent upon the receptor's subunit stoichiometry, in both vertebrates (Cull-Candy et al. 2006; Greger et al. 2007; Traynelis et al. 2010) and invertebrates (Abuin et al. 2011; Rasse et al. 2005; Qin et al. 2005). The resulting diversity of possible receptor properties will ultimately shape synaptic transmission and in turn the operation of neuronal networks.

Like a multitude of other post-synaptic signalling components, iGluRs are embedded in the post-synaptic density (PSD), a sub-synaptic anchoring platform which concentrates and positions receptors directly opposite presynaptic release sites (discussed in Chap. 3) (Sheng and Hoogenraad 2007). In addition to synaptic trafficking, positioning and anchorage in the PSD can be determined by the subunit composition of the receptor. In the case of NMDA-type iGluRs, receptors containing the NR2B subunit locate to the edge of the PSD (i.e. extrasynaptically) whereas receptors harbouring NR2A are concentrated more centrally (Tovar and Westbrook 1999; Rumbaugh and Vicini 1999). This location dependence arises from sequence determinants within cytosolic carboxy-termini and will ultimately impact signal transmission (Steigerwald et al. 2000).

In the three main iGluR subfamilies, assembly into heteromers is either obligatory (NMDA-type and GluK4 and GluK5-containing kainate iGluRs) or preferential (AMPA-type and GluK1–3 kainate receptors). Due to the less stringent assembly rules, AMPA- and low-affinity kainate receptors (GluK1–3) can also exist as homotetramers. Signalling through AMPA receptor (AMPAR) homomers, which in the absence of the GluA2 subunit are Ca^{2+} permeable (CP) (Jia et al. 1996; Isaac et al. 2007), modulates synaptic physiology; recruitment of CP-AMPARs appears to be dynamically regulated in a number of neurons, rendering these synapses more plastic

(see below) (Cull-Candy et al. 2006; Kauer and Malenka 2007). Determinants underlying these different assembly routes are starting to emerge.

Assembly into heteromers unlikely occurs by default. As a result of translation from polyribosomes, identical subunits, synthesized from an individual mRNA molecule, will be spatially and temporally concentrated on a patch of endoplasmic reticulum (ER) membrane (Fig. 11.1a). For example, *GRIA2* mRNA, encoding the GluA2 AMPA receptor subunit, with a length of ~3,000 base pairs could be translated by up to 30 ribosomes (Staehlin et al. 1964), resulting in ~30 nascent GluA2 polypeptides in close proximity; this local concentration is expected to promote assembly into homomers, which are not commonly observed. Parameters such as (1) diffusion in the plane of the ER membrane, (2) relative affinities of inter-subunit contacts as well as (3) the concentration of assembly partners in the ER are expected to determine the rate and extent of heteromeric assembly (summarized in Fig. 11.1a). We shall discuss the latter two parameters and how they are expected to affect different stages of iGluR biogenesis. We will focus on AMPA-type receptors; however, emerging principles will be generally applicable to the other iGluR subfamilies.

11.2 Dimer Formation

AMPARs form in two steps – subunits first dimerize, followed by assembly of dimers into tetramers. The dimer-of-dimers assembly has been observed at various levels. The crystal structure of the isolated L-glutamate ligand-binding domain (LBD) of GluA2 revealed a twofold symmetrical homodimeric complex (Armstrong and Gouaux 2000). Similarly, the second extracellular portion, the N-terminal domain (NTD), crystallized as a dimer, in both AMPA and kainate receptors (Fig. 11.1b) (Clayton et al. 2009; Jin et al. 2009; Kumar et al. 2009; Karakas et al. 2009; Kumar and Mayer 2010; Sukumaran et al. 2011). This overall twofold symmetry of the extracellular portion is also observed at the level of the intact receptor, whereas the ion channel adopts fourfold symmetry (Sobolevsky et al. 2009). Secondly, dimers (together with monomers and tetramers but not trimers) were also apparent on native gels (Penn et al. 2008; Greger et al. 2003). Dimers form first and are readily isolated from GluA2-expressing HEK293 cells for subsequent structural analysis (Shanks et al. 2010). Monomers are barely detected, thus dimers are the first stable assembly intermediate (Greger et al. 2003; Shanks et al. 2010). Dimer formation will be driven by the NTD (see below). This domain at the extreme N-terminus encompasses ~50% of primary sequence and is expected to fold first once threaded through the translocon into the ER lumen (Netzer and Hartl 1997). It is conceivable that subunit contacts via the NTD take place co-translationally, i.e. prior to folding of the remaining nascent chain (Fig. 11.1a), which would explain the paucity of monomers in biochemical experiments (see above). Accordingly, the NTD will initiate receptor formation. Recent crystal structures have provided atomic resolution of this critical assembly interface.

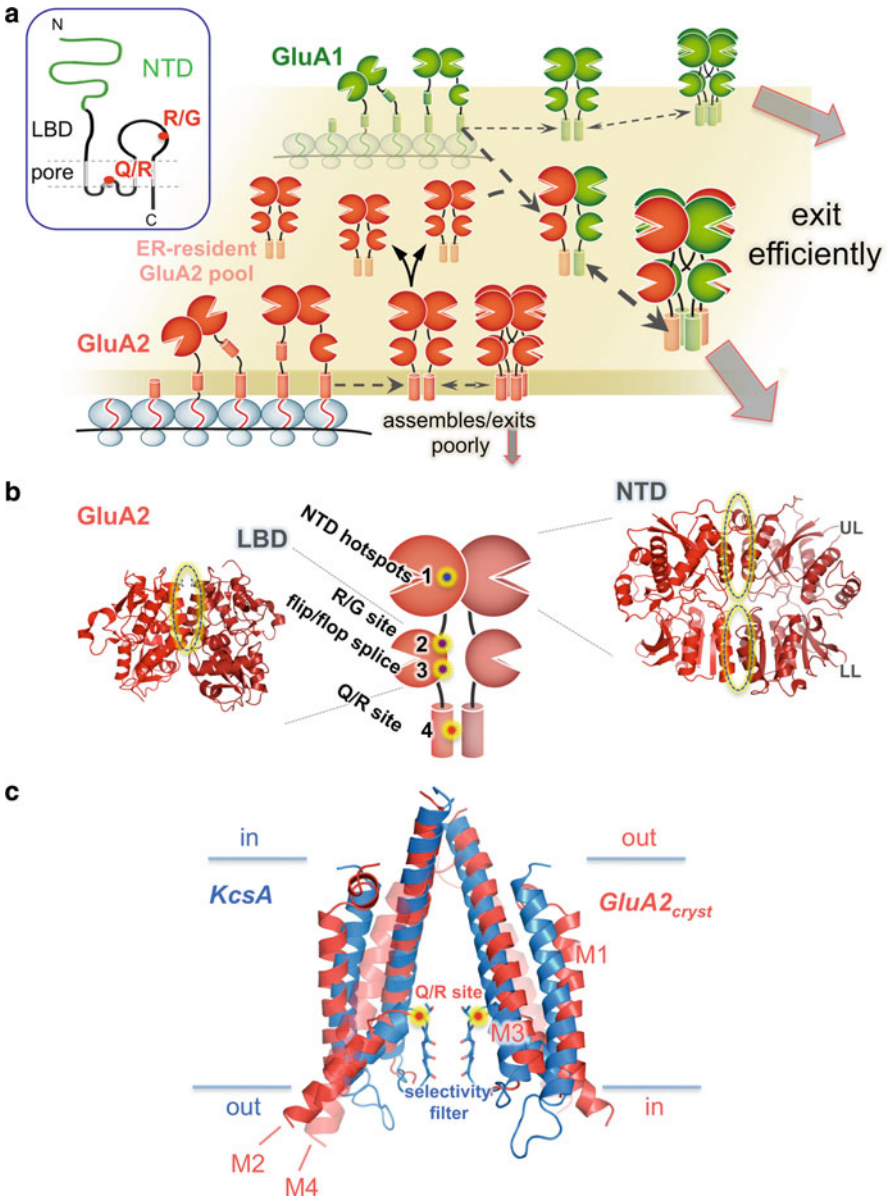

Fig. 11.1 AMPA receptors assemble into tetramers in the endoplasmic reticulum, with selective assembly modulated by domain-specific and subunit-specific determinants. (**a**) *Inset*: topology of an individual GluA2 AMPA receptor subunit. The extracellular N-terminal domain (NTD) and ligand-binding domain (LBD) are shown as *green* and *black* lines, respectively. Transmembrane helices that constitute the ion-channel pore are denoted as *grey* cylinders. Amino acid changes corresponding to RNA-editing sites are also denoted; the R/G site is conserved between GluA2, GluA3 and GluA4, whereas the Q/R site on a re-entrant pore loop is unique to GluA2. Note that the NTD is continuous in primary sequence, while the LBD is interrupted by multiple transmembrane segments.

11.2.1 The N-Terminal Domain Assembly Surface

The NTD is a hallmark of metazoan iGluRs but is absent in the prokaryotic GluR0-type channels (Chen et al. 1999) and in vertebrate kainate-binding proteins (Henley 1994). The function of this domain in non-NMDARs (AMPA and kainate receptors) has not been fully resolved. In NMDARs, powerful allosteric modulation of the channel via the NTD is well established, where channel open probability is reduced in response to binding of Zn^{2+} and other ligands (Mony et al. 2009). An allosteric role in the non-NMDAR NTD has not been described to date but cannot be ruled out (Sukumaran et al. 2011; Jensen et al. 2011). In all iGluRs, the NTD is implicated in subunit assembly (Hansen et al. 2010). Multiple iGluR genes are found in higher eukaryotes, which is not generally the case in prokaryotic genomes. Therefore, the need for a more sophisticated assembly determinant, orchestrating a fine balance of associations between homo- and heterotetramers *within* subfamilies in addition to preventing co-assembly *between* subfamilies, may explain the appearance of the NTD later in evolution concomitant with the radiation of iGluR paralogs by gene duplication and subsequent mutation. This distal segment appears to also play a role in synapse formation (Passafaro et al. 2003) and provides a binding site, both for presynaptic elements and for soluble factors released upon

Fig. 11.1 (continued) Main figure: A schematic of assembly in the endoplasmic reticulum (ER), highlighting different steps of AMPA receptor assembly. Nascent GluA2 (*red*) and GluA1 (*green*) polypeptides are shown emerging from polyribosomes (*grey*), translating into the ER lumen. NTD dimerization likely occurs co-translationally, due to its location at the extreme N-terminus. Because of the high local concentration of identical subunits, due to nearby ribosomes translating polypeptide in close proximity, homodimerization likely dominates at this stage. After folding is complete, dimeric subunits then subsequently assemble into tetramers. Due to its subunit-specific set of assembly determinants, native GluA2 assembles poorly into tetramers and inefficiently exits the ER; therefore, GluA2 likely forms a stable, ER-resident pool of dimers (*solid arrow*). This relatively higher concentration of dimers, concomitant with GluA2's favourable heteromerization capability, allows heterodimers to be formed efficiently upon translation of GluA1 subunits. Heterodimers assemble into heterotetramers and exit the ER efficiently; GluA1 is also capable of efficient homotetramerization and ER exit. (**b**) Sites of assembly determinants within a GluA2 subunit. A GluA2 dimer is depicted, with individual protomers coloured dark and light red, respectively. Homodimeric crystal structures of the isolated GluA2 domains are also shown (pdb codes 3hsy and 2uxa), with subunit dimer-interfaces depicted as ovals. Sites of assembly - specifying determinants are shown on the schematic: (*1*) hotspots in the NTD mediate homo- and heterodimerization, (*2*) the R/G site in GluA2–4 and (*3*) alternative splicing in GluA1-4 modulate overall heteromerization and ER-exit competence, and (*4*) the Q/R site in the GluA2 transmembrane domain renders GluA2 homotetramerization unfavourable versus heterotetramerization, leading to the stable ER-resident pool of dimers mentioned above. (**c**) The transmembrane domain of GluA2 is similar to potassium channels. A superposition of the transmembrane domains of the crystallized full-length GluA2 construct, $GluA_{cryst}$ (*red*; pdb code 3kg2), and the KcsA potassium channel (*blue*; pdb code 1r3j) shows that both are highly similar, albeit in opposite topological orientations. The assembly-critical Q/R site of GluA2 is shown, located on top of the selectivity filter. Transmembrane domains that make contacts in the tetrameric structure (*M1*, *M3* and *M4*) and the re-entrant pore loop (*M2*) are denoted

intense synaptic activity (O'Brien et al. 1999; Hansen et al. 2010). The latter functions will only be relevant in species with nervous systems, whereas in prokaryotes ion homeostasis is likely to be the main function of the NTD-lacking, homomeric GluR0 channel types.

Recent structural data on the intact GluA2 homomer together with high-resolution structures of isolated domains provide an overview of inter-subunit interactions along the major axis of the receptor (Sobolevsky et al. 2009). Dimeric contacts are prominent at the level of the NTD, whereas tetrameric packing is mediated by the transmembrane helices of the ion channel. A similar principle has been inferred for kainate receptors (Das et al. 2010). NTDs form extensive twofold symmetrical dimeric assemblies (Fig. 11.2) which, when isolated from the receptor, can also be measured in solution (Clayton et al. 2009; Jin et al. 2009; Kumar et al. 2009; Rossmann et al. 2011), in contrast to the LBDs, which are largely monomeric (in the case of RNA-edited GluA2-flop; Sun et al. 2002). Interestingly, in receptors assembling as obligatory heteromers, homodimeric NTD contacts are either absent (NR2B; Karakas et al. 2009) or severely reduced (GluK5; Kumar and Mayer 2010). A similar observation holds for the GluA3 subunit, which exhibits 'obligatory' heteromeric assembly behaviour within the AMPAR family (see below) (Rossmann et al. 2011). These observations underline the key role of the NTD in driving distinct assembly routes.

The NTD protomer adopts a fold analogous to prokaryotic type I periplasmic-binding proteins (PBPs; Quiocho and Ledvina 1996), where two globular lobes (the upper and lower lobes; Fig. 11.1b) are connected by three short hinges. Each lobe contributes to the bipartite NTD dimer interface (Fig. 11.2a). Contacts between the upper lobes are tight and evolutionarily conserved, thus bearing the hallmarks of a functionally relevant interface, whereas packing across the lower lobes is looser. This functional division is apparent in GluA2 and GluA3 (Sukumaran et al. 2011), with GluA3 providing the most striking example: in the most commonly observed dimeric form (Sukumaran et al. 2011) an unfavourable electrostatic potential between the lower lobes results in lobe separation (PDB 3O21; chains CD), to a degree seen in the analogous metabotropic GluR (mGluR) ligand-binding cores (Kunishima et al. 2000). In GluK2, the upper and lower lobes form similar interfaces that are both less compact than the upper lobe interface of the AMPAR subfamily.

Analytical ultracentrifugation with fluorescence detection (AU-FDS) provided a sensitive tool facilitating measurements of NTD associations at high resolution, in the sub-nanomolar range (MacGregor et al. 2004) and, more importantly, permits measurement of heteromeric assemblies (Rossmann et al. 2011). A surprising range of affinities among AMPAR NTDs, covering almost three orders of magnitude, could be discerned: GluA2 and GluA3 lie at the functional extremes with dimer dissociation constants (K_ds) of 1.8 and 1,200 nM, respectively; values for GluA1 and GluA4 NTD dimers were intermediate (Fig. 11.3a) (Rossmann et al. 2011). The relatively unstable homodimeric GluA3 contacts are most certainly a result of the 'unzipped' lower lobe interface (Fig. 11.2a), which underlies the 'obligatory' assembly behaviour of GluA3. First measurements of heteromeric assemblies revealed that AMPAR NTDs preferentially heterodimerize (Rossmann et al. 2011). Contrasting with the relatively poor homodimeric affinity, GluA3 produced tight heterodimers ($K_d \sim 1.3$ nM).

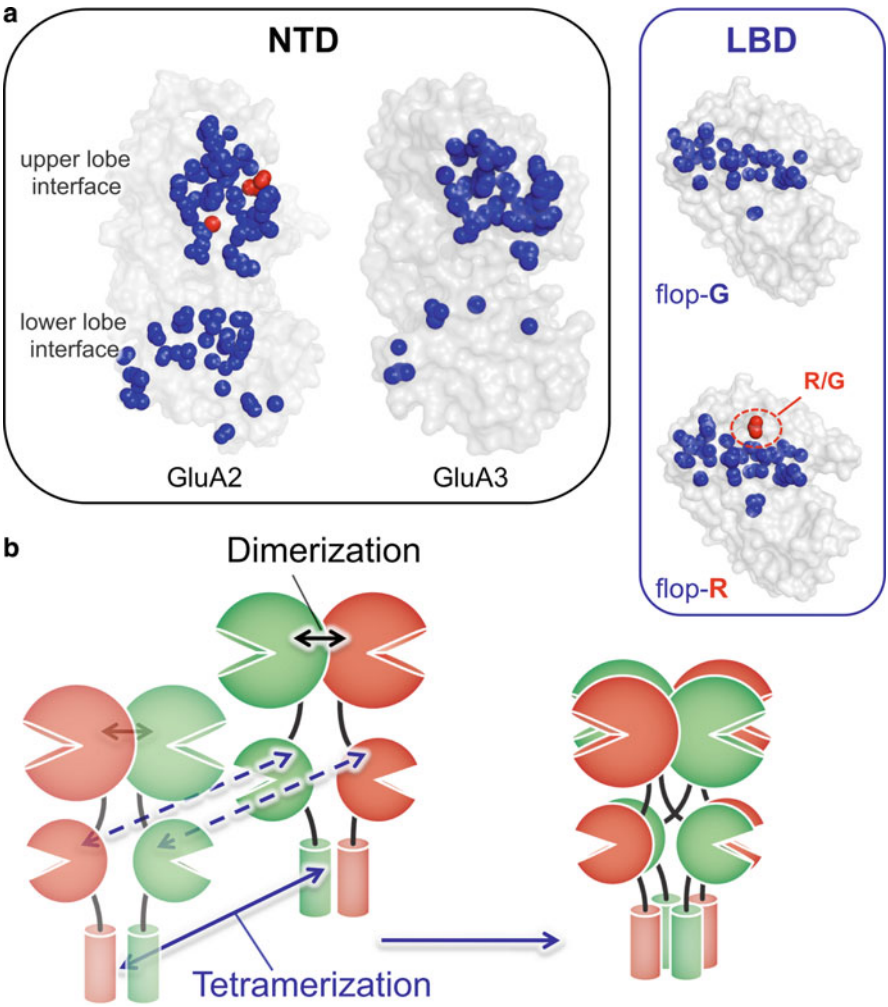

Fig. 11.2 Critical assembly determinants in the extracellular domains are located at subunit interfaces. (**a**) Assembly surfaces of the AMPAR extracellular domains. Atoms that make contacts across the dimer interfaces are shown as *blue* spheres, with specific assembly 'hotspots' and determinants highlighted in red. The GluA2 NTD (pdb code 3hsy) shows extensive dimerization contacts across both upper and lower lobe interfaces; however, GluA3 (pdb code 3o21) shows markedly less interface contacts in the lower lobe, suggesting differential, subunit-specific assembly behaviour for the NTD (Reproduced from (Sukumaran et al. 2011) with permission from Nature Publishing Group). In the case of the LBD (*flop-G*: pdb code 1ftj; *flop-R*: unpublished), interface contacts are largely uniform across subunits, but the interfaces are modulated at the level of RNA editing and alternative splicing; different interfaces for the edited G and unedited R forms are shown, with the Arg shown in *red*. Note a minor increase in subunit contacts with the unedited Arg, perhaps due to the favourable symmetrical arginine-arginine contacts across the homomer interface; therefore, editing to glycine reduces the homomeric LBD affinity and favours heteromerization. (**b**) The assembly steps from Fig. 11.1a, shown in detail. Dimerization (*black arrows*) is mediated co-translationally by the NTDs, whereas tetramerization (*blue arrows*) is mediated by determinants in the transmembrane domains. LBD 'dimerization' observed crystallographically for isolated LBDs only occurs upon tetramerization in the context of the full receptor

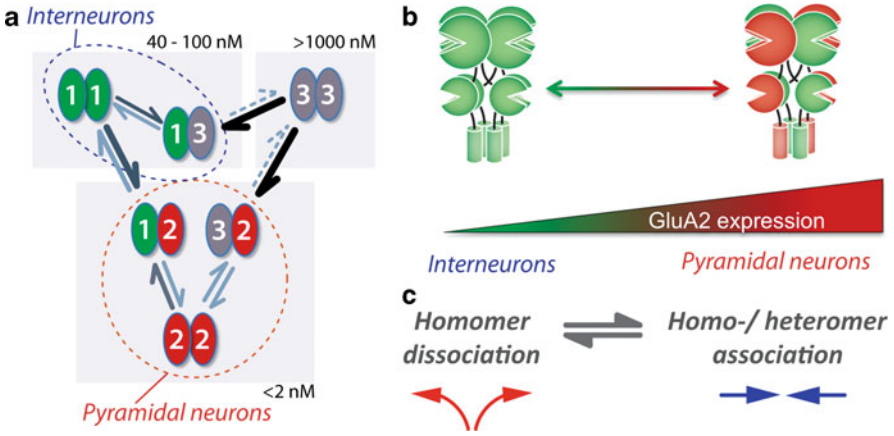

Fig. 11.3 Differential AMPA receptor assembly will be a balance between subunit affinities and subunit expression levels. (**a**) Measured association affinities between GluA1–3 NTDs define specific assembly regimes. Measured K_ds of homodimer and heterodimer dissociation by AU-FDS are shown for GluA1, GluA2 and GluA3 homomers and heteromers. These K_ds span three orders of magnitude, from very tight (<2 nM, *bottom*), for assembly driven by GluA2, to relatively loose, as in the case of GluA3 homomers (>1,000 nM, *top right*). The relationship between these homomeric and heteromeric affinities defines different 'regimes' dependent on cellular expression profile; example regimes are given for GluA2-expressing hippocampal neurons (*red outline*), which will efficiently incorporate GluA2 into receptors, versus GluA2-lacking hippocampal interneurons (*blue outline*), which will express GluA1/3 heteromers and GluA1 homomers but no GluA3 homomers. Due to its poor homomerization capability, GluA3 will 'obligatorily' form heteromers in the presence of the other subunits (Reproduced from (Rossmann et al. 2011 with permission from Nature Publishing Group). (**b**) Titration of subunit expression allows neurons to modulate channel properties. Despite GluA2's dominant assembly and functional phenotypes, neurons may be able to express functionally different receptors by modulating the ratio of expressed GluA2 versus GluA1. The example expression regimes outlined in panel A (hippocampal pyramidal neurons vs. interneurons) are denoted. (**c**) Heteromerization requires at least two steps: homomer dissociation and subsequent association of heteromers. For the second step, heteromerization will have to compete with re-association of homomers

Accordingly, GluA3 homomers are only expected to form under conditions of sub-stoichiometric expression of other assembly partners (Fig. 11.3a, b).

A number of concepts emerged from these results (Rossmann et al. 2011). First, AMPARs preferentially heteromerize at the level of the dimer. Preferential heterodimerization will bear upon subunit stoichiometry, spatial arrangement of subunits within tetramers, and will allow for formation of tri-heteromeric AMPARs. Secondly, GluA2, which restricts Ca^{2+} flux through AMPARs, is dominantly incorporated into heterodimers. This property of the GluA2 NTD together with assembly determinants in the LBD interface and the channel pore (see below) (Greger et al. 2007) likely explain the dominant expression of GluA2-containing heteromers throughout the brain (Isaac et al. 2007). Third, GluA1 and GluA4 exhibit a more 'balanced' assembly between homo- and heteromeric modes. This property likely underlies the existence of Ca^{2+}-permeable GluA1 homomers, which are detected in selected neurons under certain conditions (Cull-Candy et al. 2006; Carlezon and Nestler 2002). In sum, the

data imply the existence of two assembly routes for AMPAR heteromers, termed 'preferential' and 'obligatory' (Fig. 11.3a) (Rossmann et al. 2011). The affinity network shown in Fig. 11.3a together with relative expression levels of assembly partners in the ER (Fig. 11.3b) will ultimately determine the nature of receptor oligomer subpopulations in a given neuronal type.

These data support the previously recognized role of the NTD in assembly (Ayalon and Stern-Bach 2001; Leuschner and Hoch 1999) but reveal a dominant organizing function, which turns out to be more sophisticated. In fact, individual assembly determinants or 'hotspots' encoded in the highly conserved upper lobe dimer interface have been detected in GluA2 (Rossmann et al. 2011). These evolutionarily variable residues help explain how the tight GluA2 homodimeric contacts, which presumably will form co-translationally (Fig. 11.1a), allow formation of heteromers. A biophysical dissection of these 'hotspots' alluded to a principle whereby assembly is driven by two parameters: dissociation of homodimers prior to associations of heterodimers. If re-association is energetically favoured, the equilibrium will be shifted towards the newly formed heterodimer (Fig. 11.3c).

11.2.2 The Modulatory LBD Dimer Interface

The ligand-binding domain (LBD) overall resembles the bilobate fold of the NTD; however, its role in signal transmission and assembly is vastly different. Relatively loose dimer associations, mediated by the LBD upper lobes (Fig. 11.2), facilitate inter-subunit flexibility, a likely requirement for gating transitions (Mayer and Armstrong 2004). Like the NTD, the LBD has been crystallized as a twofold symmetrical dimer, which is evident for the isolated domain (for all iGluRs) and in the complete GluA2 AMPAR (Sobolevsky et al. 2009). LBD dimers are not detected in solution, except when stabilized by mutation or by allosteric modulators (Sun et al. 2002; Jin et al. 2005). Surprisingly, in the full-length receptor structure, LBDs swap to form '*trans*-dimers', i.e. the twofold symmetrical dimer observed for the isolated LBD is formed only upon tetramerization. Moreover, characterization of GluA2 dimers by single-particle electron microscopy revealed that the two LBDs are separated, and are 'held together' by the NTD contacts at the top and the transmembrane sector at the bottom (Shanks et al. 2010; Nakagawa 2010). These findings suggest that the LBD forms the crystallographically described twofold symmetrical dimer interface only in the tetrameric context, with LBDs associating between (rather than within) subunit dimers (Fig. 11.2b). Whether this represents the only accessible conformation remains to be seen. For example, heteromeric AMPARs or the AMPAR-TARP complex may give rise to '*cis*-dimers', featuring a closed LBD dimer interface within a subunit dimer analogous to the L483Y mutant dimer (Shanks et al. 2010). These may be energetically less favourable in the absence of a heteromeric or TARP partner and were, thus, not seen under the conditions used for crystallization and single-particle electron microscopy. Furthermore, a recent study has suggested that the LBD dimer interface is only formed upon ligand binding and channel opening, with individual LBDs decoupled

from each other in the resting (unliganded, closed channel) and desensitized (liganded, closed channel) states (Gonzalez et al. 2010). However, as this study was conducted in GluA4 constructs lacking the entire NTD, more work is required to fully understand the exact oligomeric conformation(s) of LBDs in the physiological context.

In stark contrast to the NTD, the LBD sequence is well conserved between AMPAR paralogs. Versatility is introduced post-transcriptionally by adenosine-to-inosine RNA editing and by alternative splicing (Seeburg 1996). All AMPAR subunits harbour the alternative flip/flop exons (Sommer et al. 1990), whereas RNA editing only targets GluA2–4 (Figs. 11.1a and 11.2a), resulting in a switch from a genomically encoded arginine (R) to a glycine (G) at the R/G site (Lomeli et al. 1994). These alternative RNA processing sites line the dimer interface (Fig. 11.2a) and alter assembly and secretory traffic (Greger et al. 2006; Greger et al. 2007; Coleman et al. 2006, 2010). This adds another facet to the assembly process: in addition to preferential heteromerization between subunit paralogs, different alternatively processed homologs (e.g. GluA1-flip + GluA1-flop) preferably co-assemble (Brorson et al. 2004). Whether these switches are affinity determinants or purely operate by altering the dwell time of assembly intermediates is not fully resolved. Clearly, the fact that editing at both the R/G and the Q/R site reduces secretory traffic of GluA2 will increase availability (i.e. the concentration) of this critical subunit in the ER (Greger et al. 2002, 2006), which will facilitate its uptake into heterodimers (Fig. 11.1a). The interplay between tight NTD- and looser LBD interactions in co-ordinating assembly are currently unclear.

Alternative splicing can be regulated by external cues resulting, for example, in changes of intracellular Ca^{2+} (Xie 2008; Stamm 2002). Similarly, editing by the editases ADAR1 and 2 can be reprogrammed (Schmauss 2005). Due to their strategic location at subunit interfaces (Fig. 11.2a), these 'built-in' modulators are primed to remodel assembly and secretory traffic of AMPARs, providing a homeostatic control hub for adjusting receptor type and number in response to altered neuronal activity (Penn et al. in review; Penn and Greger 2009).

11.3 Tetramer Formation

As discussed above, recent studies have indicated that AMPARs preferentially assemble as heterodimers (Rossmann et al. 2011), but whether there are similar mechanisms of preferential assembly at the tetramerization step is currently unclear. Earlier data indicate that tetramerization also follows specific pathways when bringing together different populations of homo- and heterodimers (Mansour et al. 2001). In the ion-channel sector, two major determinants will drive assembly: (1) packing between three transmembrane helices M1, M2 and M4 (Fig. 11.4a) and (2) the pore loop (M2), which forms a fourfold symmetrical contact point (Figs. 11.1c and 11.4a).

Helical packing in the transmembrane domain (TMD) of the AMPA receptor largely mirrors an inverted K^+ channel (Fig. 11.1c), which contains extensive contacts between transmembrane helices and provides the largest packing interface in the tetrameric context (Long et al. 2005), suggesting that the TMDs contribute

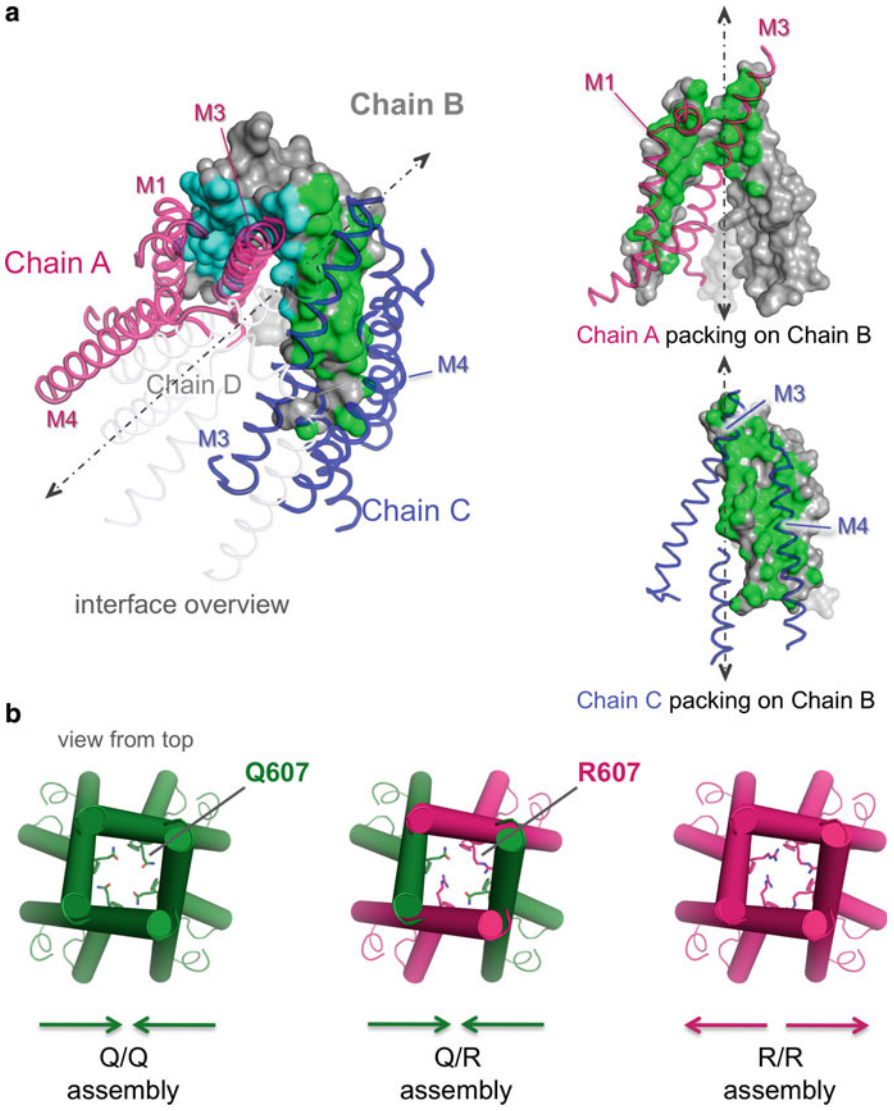

Fig. 11.4 Assembly determinants in the transmembrane domain. (**a**) Overview of the packing of the transmembrane domains (TMDs) of individual subunits against each other in the $GluA2_{cryst}$ homotetramer (pdb code 3kg2). In the interface overview, the tetrameric ion-channel domains of all four chains (A–D) are shown, with chain B (*grey*) shown as a molecular surface and chains A (*magenta*), C (*blue*) and D (*white*) shown in ribbon. Both chain A and chain C pack against chain B, forming two distinct assembly interfaces; the interface formed with chain A is shown in cyan on chain B, with the interface formed with chain C shown in green. Roughly, the M4 helix from each chain packs against a 'groove' formed by helices M1 and M3 from a partner chain; chain B forms the 'groove' for M4 from chain C, whereas the M4 from chain B packs against the M1/M3 groove from chain A. Views onto the individual A–B and B–C interfaces are also shown. (**b**) A key assembly determinant in the transmembrane domain is the Q/R site in GluA2. Q/R editing in

the major tetramerization drive. In further analogy, K^+ channels also exhibit a dimer-of-dimers assembly pattern (Tu and Deutsch 1999; Deutsch 2002).

In GluA2, the TMD contains an extensive packing interface (Sobolevsky et al. 2009). As outlined in Fig. 11.4, each protomer contributes three distinct contact points: the first interface is largely external to the aqueous ion-channel pore and consists of M4 packing against a 'groove' formed by M1 and M3 of the neighbouring subunit. The second, larger interface is the 'groove' provided by M1 and M3 of the other subunit in the dimer. As M4 is a novel insertion in eukaryotic iGluRs versus prokaryotic GluR0-type receptors and kainate-binding proteins, these two interfaces are expected to contribute additional assembly determinants in metazoa.

The third 'interface' contact is internal to the ion channel and is provided by residues in the re-entrant pore loop (M2) packing against copies of itself in the other protomers, as well as near a narrow constriction, where the four M3 helices from each subunit align with one another, putatively forming the channel gate (Fig. 11.1c). As the re-entrant pore loop is built incompletely in the currently available crystal structure (PDB: 3KG2), the packing of the pore loops is unknown at this point. As contacts in this region shape the aqueous vestibules of the pore upon channel assembly, regions around these interfaces will transition from lipid-exposed to solvent-exposed, and these transfer reactions could also contribute thermodynamically to channel assembly.

Sequence conservation among AMPAR paralogs in the transmembrane region is high; however, variability is introduced by RNA editing in the apex of the pore loop of GluA2 and GluK1 and GluK2 (Seeburg 1996). Recoding at the GluA2 Q/R site plays a critical role in the dimer-to-tetramer transition by destabilizing edited tetramers, thereby providing a strategically positioned assembly determinant (Greger et al. 2003) (Figs. 11.1c and 11.4b). An analogous case has been described recently for GluK2 (Ball et al. 2010) and most likely results from unfavourable electrostatics from the approximation of four arginines during pore formation (Fig. 11.4b). It is worth pointing out that Q/R-edited GluA2-R channels can form (Swanson et al. 1997), in particular when expressed with auxiliary factors (Yamazaki et al. 2004), albeit far less efficiently than unedited GluA2-Q (Greger et al. 2003). Therefore, in the presence of other subunit partners in the ER, the energetically preferred Q/R heteromers are likely to prevail over R-pore homomers. To draw another parallel between iGluRs and K^+ channels, an analogous position in the pore loop of the KCNQ3 potassium channel also slows channel transit from the ER relative to KCNQ2 (Gomez-Posada et al. 2010), suggesting that this site is critical to the general tetrameric channel fold.

Fig. 11.4 (continued) GluA2 results in a switch from Q607 (*green*), which allows efficient homomeric and heteromeric assembly, to R607 (*magenta*), which, due to charge repulsion of the arginines, allows heteromic assembly with Q but disfavours homomeric assembly and in turn ER export, giving rise to a stable pool of ER-resident GluA2 (Fig. 11.1a). Note that GluA1, GluA3 and GluA4 express Q at the analogous position, resulting in a favoured heteromeric Q/R pore stoichiometry in native AMPA receptors. Q607 and R607 TMD structures are homology models of the full-length pore modelled against the KcsA pore (Greger et al. 2003)

In addition to the pore sector, the extracellular domains also come into contact in the context of the crystallized $GluA2_{cryst}$ tetramer. The lower lobes of the NTD pack in the region of V209, and the LBDs form a small packing interface between two symmetrical helices (Sobolevsky et al. 2009). However, both of these inter-dimer contacts are only seen in one subunit pair. Also, different three-dimensional structures of the overexpressed GluA2 homotetramer and purified native AMPAR complexes reconstructed by electron microscopy show different inter-dimer arrangements and also show that the extracellular domains adopt different quaternary arrangements dependent on subunit inclusion and gating status (Midgett and Madden 2008; Nakagawa et al. 2005). Therefore, the inter-dimer interfaces in the extracellular domains might be transient and are unlikely the primary drivers of tetrameric assembly. Moreover, as discussed above, the LBD 'dimer' interface is putatively formed only upon channel tetramerization (Fig. 11.2b) (Nakagawa 2010). This suggests that variability in the LBD interface (flip/flop splicing and R/G editing) may also contribute to differential channel assembly at the level of tetramerization; as yet this question has not been explored experimentally and LBD dimer variability affecting tetrameric assembly is still speculative at this point.

AMPARs co-assemble with a variety of different auxiliary and modulatory subunits. At what stage these auxiliary factors, including TARPs (transmembrane AMPA receptor regulatory proteins), cornichons and CKAMP-44 (reviewed in Guzman and Jonas 2010; Jackson et al. 2011), complex with the core receptor is not fully resolved. TARPs, the best-studied auxiliary factors, do not co-purify stably with dimeric assembly intermediates, suggesting that they bind to already-assembled, tetrameric AMPARs (Shanks et al. 2010). Moreover, TARPs appear to associate in varying stoichiometries, depending on expression levels (Kim et al. 2010; Shi et al. 2009; Kato et al. 2010). Since TARP expression is not homogenous across neuronal populations, cell-type-specific receptor modulation by these cofactors can be expected (see below).

11.4 Why Heteromers?

The ability for receptors to assemble as heteromers imparts significant diversity and flexibility in the regulation of nervous system function. Much of what is inferred about the oligomeric state of native receptors comes from single-cell profiling of subunit mRNA expression, *in situ* localization of subunit mRNA or protein, and subunit-specific pharmacology or genetic manipulations. Overall, the findings reveal a predominance of heteromeric receptors, which vary in abundance during development and in a tissue- and neuron-specific manner. As discussed above, in the principal neurons of the vertebrate CNS, GluA2-containing AMPAR heteromers prevail, whereas interneurons often express a large population of GluA2-lacking receptors.

11.4.1 The Functional Dominance of Q/R-Edited GluA2

Heteromerization can have important consequences on AMPAR functional properties, trafficking and subcellular localization. Of particular significance, the incorporation of the Q/R-edited GluA2 subunit renders the channel pore impermeable to divalent cations, thus disarming them as an activator of calcium-dependent signalling cascades (Cull-Candy et al. 2006; Isaac et al. 2007). In addition, GluA2 inhibits the voltage-dependent block of the pore by intracellular polyamines, which can have consequences for short-term synaptic plasticity (Rozov and Burnashev 1999; Rozov et al. 1998) and redefine the rules for long-term changes in synaptic strength (Kullmann and Lamsa 2008). Furthermore, the attenuation of single-channel conductance and desensitization by GluA2 provides a means to regulate synaptic strength (Liu and Cull-Candy 2000) and shape synaptic transmission (Zhu 2009; Gardner et al. 2001a). Recently, it has also been suggested that incorporation of GluA2 can alter the capacity for regulation of receptor function by type II TARPs (Kato et al. 2008; Soto et al. 2009). These various means by which Q/R-edited GluA2 can have potent effects on receptor properties have prompted it to be referred to as the 'functionally dominant' subunit.

11.4.2 Subunit-Specific Accessory Factors

The formation of heteromeric receptors provides a means to expand the repertoire of interactions with scaffolding proteins and thus regulate AMPAR trafficking (Shepherd and Huganir 2007). GluA1 and GluA3 have long and short cytoplasmic carboxy-terminal domains (CTDs) respectively, whereas GluA2 and GluA4 can undergo alternative splicing to include either long or short CTDs (Bredt and Nicoll 2003). These AMPAR CTDs can participate in a variety of different protein interactions to regulate receptor trafficking. Long CTD subunit variants of GluA1 and GluA4 interact with band 4.1 protein, to could stabilize AMPAR surface expression via the spectrin-actin cytoskeleton (Coleman et al. 2003; Shen et al. 2000; Lin et al. 2009). In addition, GluA1 has a unique motif conforming to the general consensus for type I PDZ interactions to enable SAP97-mediated secretory trafficking (Sans et al. 2001). Short CTD subunits, on the other hand, have a clathrin-adaptor AP2 interaction site critical for clathrin-mediated endocytosis and central to the recycling of synaptic AMPARs (Sheng and Hoogenraad 2007). This site overlaps with the NSF-binding site in GluA2, which plays a critical role in the membrane fusion and synaptic expression of AMPA receptors (Steinberg et al. 2004; Luthi et al. 1999; Huang et al. 2005). In addition, the short CTD terminus has a type II PDZ ligand with phosphorylation-modulated PDZ interactions that are central to sorting of synaptic AMPA receptors and for synaptic plasticity in the cerebellum (Cull-Candy et al. 2006; Chung et al. 2000; Xia et al. 2000). Also of interest, it has recently been demonstrated that incorporation of subunits with short CTDs into heteromeric receptors blocks the

effects of a type II TARP auxiliary subunit (Soto et al. 2009). In general, factors controlling the subunit specificity or stoichiometry of auxiliary subunits to AMPARs could tune channel gating and potentially modify interactions with scaffolding proteins (Kim et al. 2010; Shi et al. 2009; Milstein and Nicoll 2008). Finally, multiple subunit-specific sites for post-translational modifications such as phosphorylation and palmitoylation further expand the repertoire of mechanisms regulating AMPA receptor function and trafficking (Bredt and Nicoll 2003; Shepherd and Huganir 2007). Therefore, combinatorial protein interactions resulting from the formation of heteromeric receptors is likely fundamental in tuning the regulation of AMPA receptors and the plasticity of synaptic transmission.

The same concepts for combinatorial CTD protein interactions likely also apply to the extracellular domain of the receptor. For example, the NTD of GluA2 (but not GluA1) directly interacts with the synaptic adhesion molecule N-cadherin to stimulate presynaptic development (Saglietti et al. 2007). In addition, AMPA receptor clustering and excitatory synaptogenesis is facilitated by trans-synaptic interactions of the secreted pentraxin NARP with the NTDs of GluA1–3 (but not GluA4) (O'Brien et al. 2002). In contrast, synaptic recruitment of GluA4 receptors is mediated by another pentraxin, NP1 (Sia et al. 2007). Together, combinatorial subunit-protein interactions might shed light on input-specific recruitment of AMPA receptors differing in oligomeric state (Zhu 2009; Good and Lupica 2010; Kielland et al. 2009; Soler-Llavina and Sabatini 2006; Harms et al. 2005; Gardner et al. 2001b; Toth and McBain 1998).

11.4.3 Differential Activity Patterns Result in Synapse-Specific Heteromer Recruitment

The recruitment of different AMPA receptor oligomers to synapses by activity or external cues has been demonstrated at various synapses in the nervous system. In the cerebellar cortex, stimulation of parallel fibre-derived stellate synapses induced a switch to GluA2-containing receptors and a concomitant decrease in the size of the synaptic current (Liu and Cull-Candy 2000), an effect more recently shown to be synapse specific (Soler-Llavina and Sabatini 2006). In a related *in vivo* study, noradrenaline release caused by fear-inducing stimulus was also shown to trigger a switch in AMPA receptor composition at these synapses by boosting expression of the GluA2 subunit (Liu et al. 2010). Plasticity at stellate cell synapses may provide a means to regulate this inhibitory network and optimize cerebellar learning (Jorntell et al. 2010). Strong emotional cues have also been shown to trigger changes in the AMPA receptor composition at synapses in the lateral amygdala. Here, fear conditioning has been shown to trigger both potentiation at thalamic inputs and a slow but transient incorporation of GluA2-lacking receptors, which impart the capacity for fear memory erasure by long-term depression (Clem and Huganir 2010).

Plasticity of the oligomeric state of AMPA receptors onto cortical pyramidal neurons has also been demonstrated. Whisker experience induced pathway-specific

strengthening of spared excitatory inputs onto layer 2/3 pyramidal cells of barrel cortex by recruitment of GluA2-lacking receptors (Clem and Barth 2006). In addition, dark-rearing rodents resulted in reversible incorporation of GluA2-lacking receptors and an increase in the size of synaptic currents of analogous connections in the visual cortex (Goel et al. 2006), a finding that is consistent with *in vitro* models of activity deprivation (Thiagarajan et al. 2005). Transient incorporation of GluA2-lacking receptors has also been detected by some groups at CA1 Schaffer collateral inputs in hippocampus, and that their calcium-permeability may be required for consolidating LTP of synaptic strength (Plant et al. 2006; but see Gray et al. 2007; Adesnik and Nicoll 2007).

In addition to these examples, a developmental switch from GluA2-lacking receptors to heteromers containing this subunit has been demonstrated throughout the nervous system including the retina (Osswald et al. 2007), neocortex (Kumar et al. 2002) and hippocampus (Ho et al. 2007; Stubblefield and Benke 2010), where the calcium-signalling capacity may play a role in juvenile forms of synaptic plasticity (Jensen et al. 2003). In summary, these are a few examples where heteromerization provides an important physiological means to regulate calcium signalling through AMPA receptors and synaptic transmission.

11.4.4 Failure to Heteromerize Is Associated with Neuropathology

There are also a number of conditions associated with insufficient heteromerization resulting in pathological synaptic expression of calcium-permeable AMPA receptors. Prolonged withdrawal from cocaine leads to the incorporation of GluA2-lacking receptors at excitatory inputs onto neurons of the nucleus accumbens (Conrad et al. 2008). In contrast, single cocaine administration caused a redistribution of GluA2-lacking receptors to synapses on dopaminergic cells of the ventral tegmental area (VTA); this effect was reversed by stimulating LTD with mGluR1 enhancers (Bellone and Luscher 2006). Interestingly, disruption of mGluR1 function reduced the level of cocaine exposure required to induce the switch in synaptic AMPA receptors in the nucleus accumbens (Mameli et al. 2009).

In the hippocampus, repeated morphine administration has been shown to increase synaptic expression of GluA2-lacking receptors and reduce the magnitude of LTD (Billa et al. 2010). Interestingly, recent findings show that the introduction of GluA2-lacking receptors at CA1 synaptic inputs adds the capacity for anti-Hebbian LTP and attenuation of NMDAR-dependent learning (Wiltgen et al. 2010). Finally, toxic expression of calcium-permeable AMPA receptors has been reported in a number of disease states including at CA1 neurons following ischemia and in motor neurons of patients with sporadic amyotrophic lateral sclerosis, where calcium-permeable AMPA receptor blockers or expression of the edited GluA2 subunit is neuroprotective (Liu and Zukin 2007; Peng et al. 2006; Hideyama et al.

2010; Noh et al. 2005). In summary, the plasticity of AMPA receptor expression and oligomerization is a key mediator in the pathology of various diseases.

Given the significance of forming AMPA receptor heteromers containing the GluA2 subunit in protecting certain neuronal types from pathological demise, modulation of AMPA receptor assembly may prove an appropriate therapeutic approach. Recently, it has become apparent that dimerization properties of the NTD impact the competence of subunits to heteromerize (Rossmann et al. 2011). Furthermore, clamshell movements of some NTDs may alter dimer affinities, thus making the putative capacity of these periplasmic binding protein homologs to bind ligand an attractive drug target (Sukumaran et al. 2011). The emerging structures of AMPA receptor NTDs and methods described to purify the soluble domain and quantify their dimer affinities provide a potential platform for drug discovery.

References

Abuin, L., Bargeton, B., Ulbrich, M. H., Isacoff, E. Y., Kellenberger, S., & Benton, R. (2011). Functional architecture of olfactory ionotropic glutamate receptors. *Neuron, 69*(1), 44–60. doi: S0896-6273(10)00984-0 [pii] 10.1016/j.neuron.2010.11.042.

Adesnik, H., & Nicoll, R. A. (2007). Conservation of glutamate receptor 2-containing AMPA receptors during long-term potentiation. *Journal of Neuroscience, 27*(17), 4598–4602. doi:27/17/4598 [pii] 10.1523/JNEUROSCI.0325-07.2007.

Armstrong, N., & Gouaux, E. (2000). Mechanisms for activation and antagonism of an AMPA-sensitive glutamate receptor: Crystal structures of the GluR2 ligand binding core. *Neuron, 28*, 165–181.

Ayalon, G., & Stern-Bach, Y. (2001). Functional assembly of AMPA and kainate receptors is mediated by several discrete protein–protein interactions. *Neuron, 31*, 103–113.

Ball, S. M., Atlason, P. T., Shittu-Balogun, O. O., & Molnar, E. (2010). Assembly and intracellular distribution of kainate receptors is determined by RNA editing and subunit composition. *Journal of Neurochemistry, 114*(6), 1805–1818. doi:JNC6895 [pii] 10.1111/j.1471-4159.2010.06895.x.

Bellone, C., & Luscher, C. (2006). Cocaine triggered AMPA receptor redistribution is reversed in vivo by mGluR-dependent long-term depression. *Nature Neuroscience, 9*(5), 636–641. doi: nn1682 [pii] 10.1038/nn1682.

Billa, S. K., Liu, J., Bjorklund, N. L., Sinha, N., Fu, Y., Shinnick-Gallagher, P., & Moron, J. A. (2010). Increased insertion of glutamate receptor 2-lacking alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors at hippocampal synapses upon repeated morphine administration. *Molecular Pharmacology, 77*(5), 874–883. doi:mol.109.060301 [pii] 10.1124/mol.109.060301.

Bredt, D. S., & Nicoll, R. A. (2003). AMPA receptor trafficking at excitatory synapses. *Neuron, 40*, 361–379.

Brorson, J. R., Li, D., & Suzuki, T. (2004). Selective expression of heteromeric AMPA receptors driven by flip-flop differences. *Journal of Neuroscience, 24*(14), 3461–3470.

Carlezon, W. A., Jr., & Nestler, E. J. (2002). Elevated levels of GluR1 in the midbrain: A trigger for sensitization to drugs of abuse? *Trends in Neurosciences, 25*(12), 610–615. doi: S0166223602022890 [pii].

Chen, G. Q., Cui, C., Mayer, M. L., & Gouaux, E. (1999). Functional characterization of a potassium-selective prokaryotic glutamate receptor. *Nature, 402*(6763), 817–821. doi:10.1038/45568.

Chung, H. J., Xia, J., Scannevin, R. H., Zhang, X., & Huganir, R. L. (2000). Phosphorylation of the AMPA receptor subunit GluR2 differentially regulates its interaction with PDZ domain-containing proteins. *Journal of Neuroscience, 20*(19), 7258–7267.

Clayton, A., Siebold, C., Gilbert, R. J., Sutton, G. C., Harlos, K., McIlhinney, R. A., Jones, E. Y., & Aricescu, A. R. (2009). Crystal structure of the GluR2 amino-terminal domain provides insights into the architecture and assembly of ionotropic glutamate receptors. *Journal of Molecular Biology, 392*(5), 1125–1132. doi:S0022-2836(09)00973-5 [pii] 10.1016/j.jmb.2009.07.082.

Clem, R. L., & Barth, A. (2006). Pathway-specific trafficking of native AMPARs by in vivo experience. *Neuron, 49*(5), 663–670. doi:S0896-6273(06)00072-9 [pii] 10.1016/j.neuron.2006.01.019.

Clem, R. L., & Huganir, R. L. (2010). Calcium-permeable AMPA receptor dynamics mediate fear memory erasure. *Science, 330*(6007), 1108–1112. doi:science.1195298 [pii] 10.1126/science.1195298.

Coleman, S. K., Cai, C., Mottershead, D. G., Haapalahti, J. P., & Keinanen, K. (2003). Surface expression of GluR-D AMPA receptor is dependent on an interaction between its C-terminal domain and a 4.1 Protein. *Journal of Neuroscience, 23*(3), 798–806. doi:23/3/798 [pii].

Coleman, S. K., Möykkynen, T., Cai, C., von Ossowski, L., Kuismanen, E., Korpi, E. R., & Keinänen, K. (2006). Isoform-specific early trafficking of AMPA receptor flip and flop variants. *Journal of Neuroscience, 26*, 11220–11229.

Coleman, S. K., Moykkynen, T., Hinkkuri, S., Vaahtera, L., Korpi, E. R., Pentikainen, O. T., & Keinanen, K. (2010). Ligand-binding domain determines endoplasmic reticulum exit of AMPA receptors. *Journal of Biological Chemistry, 285*(46), 36032–36039. doi:M110.156943 [pii] 10.1074/jbc.M110.156943.

Conrad, K. L., Tseng, K. Y., Uejima, J. L., Reimers, J. M., Heng, L. J., Shaham, Y., Marinelli, M., & Wolf, M. E. (2008). Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. *Nature, 454*(7200), 118–121. doi:nature06995 [pii] 10.1038/nature06995.

Cull-Candy, S., Kelly, L., & Farrant, M. (2006). Regulation of Ca^{2+}–permeable AMPA receptors: Synaptic plasticity and beyond. *Current Opinion in Neurobiology, 16*, 288–297.

Das, U., Kumar, J., Mayer, M. L., & Plested, A. J. (2010). Domain organization and function in GluK2 subtype kainate receptors. *Proceedings of the National Academy of Sciences of the United States of America, 107*(18), 8463–8468. doi:1000838107 [pii] 10.1073/pnas.1000838107.

Gardner, S. M., Trussell, L. O., & Oertel, D. (2001). Correlation of AMPA receptor subunit composition with synaptic input in the mammalian cochlear nuclei. *Journal of Neuroscience, 21*(18), 7428–7437. doi:21/18/7428 [pii].

Goel, A., Jiang, B., Xu, L. W., Song, L., Kirkwood, A., & Lee, H. K. (2006). Cross-modal regulation of synaptic AMPA receptors in primary sensory cortices by visual experience. *Nature Neuroscience, 9*(8), 1001–1003. doi:nn1725 [pii] 10.1038/nn1725.

Gomez-Posada, J. C., Etxeberria, A., Roura-Ferrer, M., Areso, P., Masin, M., Murrell-Lagnado, R. D., & Villarroel, A. (2010). A pore residue of the KCNQ3 potassium M-channel subunit controls surface expression. *Journal of Neuroscience, 30*(27), 9316–9323. doi:30/27/9316 [pii] 10.1523/JNEUROSCI.0851-10.2010.

Gonzalez, J., Du, M., Parameshwaran, K., Suppiramaniam, V., & Jayaraman, V. (2010). Role of dimer interface in activation and desensitization in AMPA receptors. *Proceedings of the National Academy of Sciences of the United States of America, 107*(21), 9891–9896. doi:0911854107 [pii] 10.1073/pnas.0911854107.

Good, C. H., & Lupica, C. R. (2010). Afferent-specific AMPA receptor subunit composition and regulation of synaptic plasticity in midbrain dopamine neurons by abused drugs. *Journal of Neuroscience, 30*(23), 7900–7909. doi:30/23/7900 [pii] 10.1523/JNEUROSCI.1507-10.2010.

Gray, E. E., Fink, A. E., Sarinana, J., Vissel, B., & O'Dell, T. J. (2007). Long-term potentiation in the hippocampal CA1 region does not require insertion and activation of GluR2-lacking AMPA receptors. *Journal of Neurophysiology, 98*(4), 2488–2492. doi:00473.2007 [pii] 10.1152/jn.00473.2007.

Greger, I. H., Akamine, P., Khatri, L., & Ziff, E. B. (2006). Developmentally regulated, combinatorial RNA processing modulates AMPA receptor biogenesis. *Neuron, 51*, 85–97.

Greger, I. H., Khatri, L., Kong, X., & Ziff, E. B. (2003). AMPA receptor tetramerization is mediated by Q/R editing. *Neuron, 40*, 763–774.

Greger, I. H., Khatri, L., & Ziff, E. B. (2002). RNA editing at Arg607 controls AMPA receptor exit from the endoplasmic reticulum. *Neuron, 34*, 759–772.

Greger, I. H., Ziff, E. B., & Penn, A. C. (2007). Molecular determinants of AMPA receptor subunit assembly. *Trends in Neurosciences, 30*, 407–416.

Guzman, S. J., & Jonas, P. (2010). Beyond TARPs: The growing list of auxiliary AMPAR subunits. *Neuron, 66*(1), 8–10. doi:S0896-6273(10)00243-6 [pii] 10.1016/j.neuron.2010.04.003.

Hansen, K. B., Furukawa, H., & Traynelis, S. F. (2010). Control of assembly and function of glutamate receptors by the amino-terminal domain. *Molecular Pharmacology, 78*(4), 535–549. doi:mol.110.067157 [pii] 10.1124/mol.110.067157.

Harms, K. J., Tovar, K. R., & Craig, A. M. (2005). Synapse-specific regulation of AMPA receptor subunit composition by activity. *Journal of Neuroscience, 25*(27), 6379–6388. doi:25/27/6379 [pii] 10.1523/JNEUROSCI.0302-05.2005.

Henley, J. M. (1994). Kainate-binding proteins: Phylogeny, structures and possible functions. *Trends in Pharmacological Sciences, 15*(6), 182–190.

Hideyama, T., Yamashita, T., Suzuki, T., Tsuji, S., Higuchi, M., Seeburg, P. H., Takahashi, R., Misawa, H., & Kwak, S. (2010). Induced loss of ADAR2 engenders slow death of motor neurons from Q/R site-unedited GluR2. *Journal of Neuroscience, 30*(36), 11917–11925. doi:30/36/11917 [pii] 10.1523/JNEUROSCI.2021-10.2010.

Ho, M. T., Pelkey, K. A., Topolnik, L., Petralia, R. S., Takamiya, K., Xia, J., Huganir, R. L., Lacaille, J. C., & McBain, C. J. (2007). Developmental expression of Ca^{2+}−permeable AMPA receptors underlies depolarization-induced long-term depression at mossy fiber CA3 pyramid synapses. *Journal of Neuroscience, 27*(43), 11651–11662. doi:27/43/11651 [pii] 10.1523/JNEUROSCI.2671-07.2007.

Hollmann, M., & Heinemann, S. (1994) Cloned glutamate receptors. *Annu. Rev. Neurosci. 17*, 31–108.

Huang, Y., Man, H. Y., Sekine-Aizawa, Y., Han, Y., Juluri, K., Luo, H., Cheah, J., Lowenstein, C., Huganir, R. L., & Snyder, S. H. (2005). S-nitrosylation of N-ethylmaleimide sensitive factor mediates surface expression of AMPA receptors. *Neuron, 46*(4), 533–540. doi:S0896-6273(05)00313-2 [pii] 10.1016/j.neuron.2005.03.028.

Isaac, J. T., Ashby, M., & McBain, C. J. (2007). The role of the GluR2 subunit in AMPA receptor function and synaptic plasticity. *Neuron, 54*, 859–871.

Jensen, V., Kaiser, K. M., Borchardt, T., Adelmann, G., Rozov, A., Burnashev, N., Brix, C., Frotscher, M., Andersen, P., Hvalby, O., Sakmann, B., Seeburg, P. H., & Sprengel, R. (2003). A juvenile form of postsynaptic hippocampal long-term potentiation in mice deficient for the AMPA receptor subunit GluR-a. *The Journal of Physiology, 553*(Pt 3), 843–856. doi:10.1113/jphysiol.2003.053637 jphysiol.2003.053637 [pii].

Jensen, M. H., Sukumaran, M., Johnson, C. M., Greger, I. H., & Neuweiler, H. (2011) Intrinsic motions in the N-terminal domain of an ionotropic glutamate receptor detected by fluorescence correlation spectroscopy. *J. Mol. Biol. 414*, 96–105.

Jia, Z., Agopyan, N., Miu, P., Xiong, Z., Henderson, J., Gerlai, R., Taverna, F. A., Velumian, A., MacDonald, J., Carlen, P., Abramow-Newerly, W., & Roder, J. (1996). Enhanced LTP in mice deficient in the AMPA receptor GluR2. *Neuron, 17*(5), 945–956. doi:S0896-6273(00)80225-1 [pii].

Jin, R., Clark, S., Weeks, A. M., Dudman, J. T., Gouaux, E., & Partin, K. M. (2005). Mechanism of positive allosteric modulators acting on AMPA receptors. *Journal of Neuroscience, 25*(39), 9027–9036. doi:25/39/9027 [pii] 10.1523/JNEUROSCI.2567-05.2005.

Jin, R., Singh, S. K., Gu, S., Furukawa, H., Sobolevsky, A. I., Zhou, J., Jin, Y., & Gouaux, E. (2009). Crystal structure and association behaviour of the GluR2 amino-terminal domain. *EMBO Journal, 28*(12), 1812–1823. doi:emboj2009140 [pii] 10.1038/emboj.2009.140.

Jorntell, H., Bengtsson, F., Schonewille, M., & De Zeeuw, C. I. (2010). Cerebellar molecular layer interneurons – Computational properties and roles in learning. *Trends in Neurosciences, 33*(11), 524–532. doi:S0166-2236(10)00119-0 [pii] 10.1016/j.tins.2010.08.004.

Karakas, E., Simorowski, N., & Furukawa, H. (2009). Structure of the zinc-bound amino-terminal domain of the NMDA receptor NR2B subunit. *EMBO Journal*. doi:emboj2009338 [pii] 10.1038/emboj.2009.338.

Kato, A. S., Siuda, E. R., Nisenbaum, E. S., & Bredt, D. S. (2008). AMPA receptor subunit-specific regulation by a distinct family of type II TARPs. *Neuron, 59*(6), 986–996. doi:S0896-6273(08)00633-8 [pii] 10.1016/j.neuron.2008.07.034.

Kauer, J. A., & Malenka, R. C. (2007). Synaptic plasticity and addiction. *Nature Reviews Neuroscience, 8*(11), 844–858. doi:nrn2234 [pii] 10.1038/nrn2234.

Kielland, A., Bochorishvili, G., Corson, J., Zhang, L., Rosin, D. L., Heggelund, P., & Zhu, J. J. (2009). Activity patterns govern synapse-specific AMPA receptor trafficking between deliverable and synaptic pools. *Neuron, 62*(1), 84–101. doi:S0896-6273(09)00198-6 [pii] 10.1016/j.neuron.2009.03.001.

Kim, K. S., Yan, D., & Tomita, S. (2010). Assembly and stoichiometry of the AMPA receptor and transmembrane AMPA receptor regulatory protein complex. *Journal of Neuroscience, 30*(3), 1064–1072. doi:30/3/1064 [pii] 10.1523/JNEUROSCI.3909-09.2010.

Kullmann, D. M., & Lamsa, K. (2008). Roles of distinct glutamate receptors in induction of anti-hebbian long-term potentiation. *The Journal of Physiology, 586*(6), 1481–1486. doi:jphysiol.2007.148064 [pii] 10.1113/jphysiol.2007.148064.

Kumar, S. S., Bacci, A., Kharazia, V., & Huguenard, J. R. (2002). A developmental switch of AMPA receptor subunits in neocortical pyramidal neurons. *Journal of Neuroscience, 22*(8), 3005–3015. doi:20026285 22/8/3005 [pii].

Kumar, J., & Mayer, M. L. (2010). Crystal structures of the glutamate receptor ion channel GluK3 and GluK5 amino-terminal domains. *Journal of Molecular Biology, 404*(4), 680–696. doi:S0022-2836(10)01103-4 [pii] 10.1016/j.jmb.2010.10.006.

Kumar, J., Schuck, P., Jin, R., & Mayer, M. L. (2009). The N-terminal domain of GluR6-subtype glutamate receptor ion channels. *Nature Structural & Molecular Biology, 16*(6), 631–638. doi:nsmb.1613 [pii] 10.1038/nsmb.1613.

Kunishima, N., Shimada, Y., Tsuji, Y., Sato, T., Yamamoto, M., Kumasaka, T., Nakanishi, S., Jingami, H., & Morikawa, K. (2000). Structural basis of glutamate recognition by a dimeric metabotropic glutamate receptor. *Nature, 407*(6807), 971–977. doi:10.1038/35039564.

Leuschner, W. D., & Hoch, W. (1999). Subtype-specific assembly of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor subunits is mediated by their n-terminal domains. *Journal of Biological Chemistry, 274*(24), 16907–16916.

Lin, D. T., Makino, Y., Sharma, K., Hayashi, T., Neve, R., Takamiya, K., & Huganir, R. L. (2009). Regulation of AMPA receptor extrasynaptic insertion by 4.1N, phosphorylation and palmitoylation. *Nature Neuroscience, 12*(7), 879–887. doi:nn.2351 [pii] 10.1038/nn.2351.

Liu, S. Q., & Cull-Candy, S. G. (2000). Synaptic activity at calcium-permeable AMPA receptors induces a switch in receptor subtype. *Nature, 405*(6785), 454–458. doi:10.1038/35013064.

Liu, Y., Formisano, L., Savtchouk, I., Takayasu, Y., Szabo, G., Zukin, R. S., & Liu, S. J. (2010). A single fear-inducing stimulus induces a transcription-dependent switch in synaptic AMPAR phenotype. *Nature Neuroscience, 13*(2), 223–231. doi:nn.2474 [pii] 10.1038/nn.2474.

Liu, S. J., & Zukin, R. S. (2007). Ca^{2+}−permeable AMPA receptors in synaptic plasticity and neuronal death. *Trends in Neurosciences, 30*, 126–134.

Lomeli, H., Mosbacher, J., Melcher, T., Hoger, T., Geiger, J. R., Kuner, T., Monyer, H., Higuchi, M., Bach, A., & Seeburg, P. H. (1994). Control of kinetic properties of AMPA receptor channels by nuclear RNA editing. *Science, 266*, 1709–1713.

Long, S. B., Campbell, E. B., & Mackinnon, R. (2005). Crystal structure of a mammalian voltage-dependent shaker family K+ channel. *Science, 309*(5736), 897–903. doi:1116269 [pii] 10.1126/science.1116269.

Luthi, A., Chittajallu, R., Duprat, F., Palmer, M. J., Benke, T. A., Kidd, F. L., Henley, J. M., Isaac, J. T., & Collingridge, G. L. (1999). Hippocampal LTD expression involves a pool of AMPARs regulated by the NSF-GluR2 interaction. *Neuron, 24*(2), 389–399. doi:S0896-6273(00)80852-1 [pii].

MacGregor, I. K., Anderson, A. L., & Laue, T. M. (2004). Fluorescence detection for the XLI analytical ultracentrifuge. *Biophysical Chemistry, 108*(1–3), 165–185. doi:10.1016/j.bpc.2003.10.018 S0301462203003041 [pii].

Mameli, M., Halbout, B., Creton, C., Engblom, D., Parkitna, J. R., Spanagel, R., & Luscher, C. (2009). Cocaine-evoked synaptic plasticity: Persistence in the VTA triggers adaptations in the NAc. *Nature Neuroscience, 12*(8), 1036–1041. doi:nn.2367 [pii] 10.1038/nn.2367.

Mansour, M., Nagarajan, N., Nehring, R. B., Clements, J. D., & Rosenmund, C. (2001). Heteromeric AMPA receptors assemble with a preferred subunit stoichiometry and spatial arrangement. *Neuron, 32*(5), 841–853. doi:S0896-6273(01)00520-7 [pii].

Mayer, M. L., & Armstrong, N. (2004). Structure and function of glutamate receptor ion channels. *Annual Review of Physiology, 66*, 161–181.

Midgett, C. R., & Madden, D. R. (2008). The quaternary structure of a calcium-permeable AMPA receptor: Conservation of shape and symmetry across functionally distinct subunit assemblies. *Journal of Molecular Biology, 382*(3), 578–584. doi:S0022-2836(08)00863-2 [pii] 10.1016/j.jmb.2008.07.021.

Milstein, A. D., & Nicoll, R. A. (2008). Regulation of AMPA receptor gating and pharmacology by TARP auxiliary subunits. *Trends in Pharmacological Sciences, 29*(7), 333–339. doi:S0165-6147(08)00109-0 [pii] 10.1016/j.tips.2008.04.004.

Mony, L., Kew, J. N., Gunthorpe, M. J., & Paoletti, P. (2009). Allosteric modulators of NR2B-containing NMDA receptors: Molecular mechanisms and therapeutic potential. *British Journal of Pharmacology, 157*(8), 1301–1317. doi:BPH304 [pii] 10.1111/j.1476-5381.2009.00304.x.

Nakagawa, T. (2010). The biochemistry, ultrastructure, and subunit assembly mechanism of AMPA receptors. *Molecular Neurobiology, 42*(3), 161–184. doi:10.1007/s12035-010-8149-x.

Nakagawa, T., Cheng, Y., Ramm, E., Sheng, M., & Walz, T. (2005). Structure and different conformational states of native AMPA receptor complexes. *Nature, 433*(7025), 545–549. doi:nature03328 [pii] 10.1038/nature03328.

Netzer, W. J., & Hartl, F. U. (1997). Recombination of protein domains facilitated by co-translational folding in eukaryotes. *Nature, 388*(6640), 343–349. doi:10.1038/41024.

Noh, K. M., Yokota, H., Mashiko, T., Castillo, P. E., Zukin, R. S., & Bennett, M. V. (2005). Blockade of calcium-permeable AMPA receptors protects hippocampal neurons against global ischemia-induced death. *Proceedings of the National Academy of Sciences of the United States of America, 102*(34), 12230–12235. doi:0505408102 [pii] 10.1073/pnas.0505408102.

O'Brien, R. J., Xu, D., Petralia, R. S., Steward, O., Huganir, R. L., & Worley, P. (1999) Synaptic clustering of AMPA receptors by the extracellular immediate-early gene product Narp. *Neuron 23*, 309–323.

O'Brien, R., Xu, D., Mi, R., Tang, X., Hopf, C., & Worley, P. (2002). Synaptically targeted narp plays an essential role in the aggregation of AMPA receptors at excitatory synapses in cultured spinal neurons. *Journal of Neuroscience, 22*(11), 4487–4498. doi:20026354 22/11/4487 [pii].

Osswald, I. K., Galan, A., & Bowie, D. (2007). Light triggers expression of philanthotoxin-insensitive Ca^{2+}−permeable AMPA receptors in the developing rat retina. *The Journal of Physiology, 582* (Pt 1), 95–111. doi:jphysiol.2007.127894 [pii] 10.1113/jphysiol.2007.127894.

Passafaro, M., Nakagawa, T., Sala, C., & Sheng, M. (2003). Induction of dendritic spines by an extracellular domain of AMPA receptor subunit GluR2. *Nature, 424*(6949), 677–681. doi:10.1038/nature01781 nature01781 [pii].

Peng, P. L., Zhong, X., Tu, W., Soundarapandian, M. M., Molner, P., Zhu, D., Lau, L., Liu, S., Liu, F., & Lu, Y. (2006). ADAR2-dependent RNA editing of AMPA receptor subunit GluR2 determines vulnerability of neurons in forebrain ischemia. *Neuron, 49*(5), 719–733. doi:S0896-6273(06)00079-1 [pii] 10.1016/j.neuron.2006.01.025.

Penn, A. C., & Greger, I. H. (2009). Sculpting AMPA receptor formation and function by alternative RNA processing. *RNA Biology, 6*(5), 517–522. doi:9552 [pii].

Penn, A. C., Williams, S. R., & Greger, I. H. (2008). Gating motions underlie AMPA receptor secretion from the endoplasmic reticulum. *EMBO Journal, 27*(22), 3056–3068. doi:emboj2008222 [pii] 10.1038/emboj.2008.222.

Plant, K., Pelkey, K. A., Bortolotto, Z. A., Morita, D., Terashima, A., McBain, C. J., Collingridge, G. L., & Isaac, J. T. (2006). Transient incorporation of native GluR2-lacking AMPA receptors during hippocampal long-term potentiation. *Nature Neuroscience, 9*(5), 602–604. doi:nn1678 [pii] 10.1038/nn1678.

Qin, G., Schwarz, T., Kittel, R. J., Schmid, A., Rasse, T. M., Kappei, D., Ponimaskin, E., Heckmann, M., & Sigrist, S. J. (2005). Four different subunits are essential for expressing the synaptic glutamate receptor at neuromuscular junctions of Drosophila. *Journal of Neuroscience, 25*(12), 3209–3218. doi:25/12/3209 [pii] 10.1523/JNEUROSCI.4194-04.2005.

Quiocho, F. A., & Ledvina, P. S. (1996). Atomic structure and specificity of bacterial periplasmic receptors for active transport and chemotaxis: Variation of common themes. *Molecular Microbiology, 20*, 17–25.

Rasse, T. M., Fouquet, W., Schmid, A., Kittel, R. J., Mertel, S., Sigrist, C. B., Schmidt, M., Guzman, A., Merino, C., Qin, G., Quentin, C., Madeo, F. F., Heckmann, M., & Sigrist, S. J. (2005). Glutamate receptor dynamics organizing synapse formation in vivo. *Nature Neuroscience, 8*(7), 898–905.

Rossmann, M., Sukumaran, M., Penn, A. C., Veprintsev, D. B., Babu, M. M., & Greger, I. H. (2011). Subunit-selective N-terminal domain associations organize the formation of AMPA receptor heteromers. *EMBO Journal*. doi:emboj2011.16.

Rozov, A., & Burnashev, N. (1999). Polyamine-dependent facilitation of postsynaptic AMPA receptors counteracts paired-pulse depression. *Nature, 401*(6753), 594–598. doi:10.1038/44151.

Rozov, A., Zilberter, Y., Wollmuth, L. P., & Burnashev, N. (1998). Facilitation of currents through rat Ca^{2+}−permeable AMPA receptor channels by activity-dependent relief from polyamine block. *The Journal of Physiology, 511*(Pt 2), 361–377.

Rumbaugh, G., & Vicini, S. (1999). Distinct synaptic and extrasynaptic NMDA receptors in developing cerebellar granule neurons. *Journal of Neuroscience, 19*(24), 10603–10610.

Saglietti, L., Dequidt, C., Kamieniarz, K., Rousset, M. C., Valnegri, P., Thoumine, O., Beretta, F., Fagni, L., Choquet, D., Sala, C., Sheng, M., & Passafaro, M. (2007). Extracellular interactions between GluR2 and N-cadherin in spine regulation. *Neuron, 54*(3), 461–477. doi:S0896-6273(07)00291-7 [pii] 10.1016/j.neuron.2007.04.012.

Sans, N., Racca, C., Petralia, R. S., Wang, Y. X., McCallum, J., & Wenthold, R. J. (2001). Synapse-associated protein 97 selectively associates with a subset of AMPA receptors early in their biosynthetic pathway. *Journal of Neuroscience, 21*(19), 7506–7516. doi:21/19/7506 [pii].

Schmauss, C. (2005). Regulation of serotonin 2C receptor pre-mRNA editing by serotonin. *International Review of Neurobiology, 63*, 83–100. doi:S0074774205630048 [pii] 10.1016/S0074-7742(05)63004-8.

Seeburg, P. H. (1996). The role of RNA editing in controlling glutamate receptor channel properties. *Journal of Neurochemistry, 66*, 1–5.

Shanks, N. F., Maruo, T., Farina, A. N., Ellisman, M. H., & Nakagawa, T. (2010). Contribution of the global subunit structure and stargazin on the maturation of AMPA receptors. *Journal of Neuroscience, 30*(7), 2728–2740. doi:30/7/2728 [pii] 10.1523/JNEUROSCI.5146-09.2010.

Shen, L., Liang, F., Walensky, L. D., & Huganir, R. L. (2000). Regulation of AMPA receptor GluR1 subunit surface expression by a 4. 1N-linked actin cytoskeletal association. *Journal of Neuroscience, 20*(21), 7932–7940. doi:20/21/7932 [pii].

Sheng, M., & Hoogenraad, C. C. (2007). The postsynaptic architecture of excitatory synapses: A more quantitative view. *Annual Review of Biochemistry, 76*, 823–847. doi:10.1146/annurev.biochem.76.060805.160029.

Shepherd, J.D., Huganir, R.L. (2007). The cell biology of synaptic plasticity: AMPA receptor trafficking. *Annu. Rev. Cell. Dev. Biol. 23*, 613–643.

Shi, Y., Lu, W., Milstein, A. D., & Nicoll, R. A. (2009). The stoichiometry of AMPA receptors and TARPs varies by neuronal cell type. *Neuron, 62*(5), 633–640. doi:S0896-6273(09)00391-2 [pii] 10.1016/j.neuron.2009.05.016.

Sia, G. M., Beique, J. C., Rumbaugh, G., Cho, R., Worley, P. F., & Huganir, R. L. (2007). Interaction of the N-terminal domain of the AMPA receptor GluR4 subunit with the neuronal pentraxin NP1 mediates GluR4 synaptic recruitment. *Neuron, 55*(1), 87–102. doi:S0896-6273(07)00453-9 [pii] 10.1016/j.neuron.2007.06.020.

Sobolevsky, A. I., Rosconi, M. P., & Gouaux, E. (2009). X-ray structure, symmetry and mechanism of an AMPA-subtype glutamate receptor. *Nature, 462*, 745–756. doi:nature08624 [pii] 10.1038/nature08624.

Soler-Llavina, G. J., & Sabatini, B. L. (2006). Synapse-specific plasticity and compartmentalized signaling in cerebellar stellate cells. *Nature Neuroscience, 9*(6), 798–806. doi:nn1698 [pii] 10.1038/nn1698.

Sommer, B., Keinanen, K., Verdoorn, T. A., Wisden, W., Burnashev, N., Herb, A., Kohler, M., Takagi, T., Sakmann, B., & Seeburg, P. H. (1990). Flip and flop: A cell-specific functional switch in glutamate-operated channels of the CNS. *Science, 249*, 1580–1585.

Soto, D., Coombs, I. D., Renzi, M., Zonouzi, M., Farrant, M., & Cull-Candy, S. G. (2009). Selective regulation of long-form calcium-permeable AMPA receptors by an atypical TARP, gamma-5. *Nature Neuroscience, 12*(3), 277–285. doi:nn.2266 [pii] 10.1038/nn.2266.

Staehlin, T., Wettstein, F. O., Oura, H., & Noll, H. (1964). Determination of the coding ratio based on molecular weight of messenger ribonucleic acid associated with ergosomes of different aggregate size. *Nature, 201*, 264–270.

Stamm, S. (2002). Signals and their transduction pathways regulating alternative splicing: A new dimension of the human genome. *Human Molecular Genetics, 11*(20), 2409–2416.

Steigerwald, F., Schulz, T. W., Schenker, L. T., Kennedy, M. B., Seeburg, P. H., & Kohr, G. (2000). C-terminal truncation of NR2A subunits impairs synaptic but not extrasynaptic localization of NMDA receptors. *Journal of Neuroscience, 20*(12), 4573–4581. doi:20/12/4573 [pii].

Steinberg, J. P., Huganir, R. L., & Linden, D. J. (2004). N-ethylmaleimide-sensitive factor is required for the synaptic incorporation and removal of AMPA receptors during cerebellar long-term depression. *Proceedings of the National Academy of Sciences of the United States of America, 101*(52), 18212–18216. doi:0408278102 [pii] 10.1073/pnas.0408278102.

Stubblefield, E. A., & Benke, T. A. (2010). Distinct AMPA-type glutamatergic synapses in developing rat CA1 hippocampus. *Journal of Neurophysiology, 104*(4), 1899–1912. doi: jn.00099.2010 [pii] 10.1152/jn.00099.2010.

Sukumaran, M., Rossmann, M., Shrivastava, I., Dutta, A., Bahar, I., & Greger, I. H. (2011). Dynamics and allosteric potential of the AMPA receptor N-terminal domain. *EMBO Journal*. doi:emboj2011.17.

Sun, Y., Olson, R., Horning, M., Armstrong, N., Mayer, M., & Gouaux, E. (2002). Mechanism of glutamate receptor desensitization. *Nature, 417*, 245–253.

Swanson, G. T., Kamboj, S. K., & Cull-Candy, S. G. (1997). Single-channel properties of recombinant AMPA receptors depend on RNA editing, splice variation, and subunit composition. *Journal of Neuroscience, 17*(1), 58–69.

Thiagarajan, T. C., Lindskog, M., & Tsien, R. W. (2005). Adaptation to synaptic inactivity in hippocampal neurons. *Neuron, 47*(5), 725–737. doi:S0896-6273(05)00647-1 [pii] 10.1016/j.neuron.2005.06.037.

Toth, K., & McBain, C. J. (1998). Afferent-specific innervation of two distinct AMPA receptor subtypes on single hippocampal interneurons. *Nature Neuroscience, 1*(7), 572–578. doi:10.1038/2807.

Tovar, K. R., & Westbrook, G. L. (1999). The incorporation of NMDA receptors with a distinct subunit composition at nascent hippocampal synapses in vitro. *Journal of Neuroscience, 19*(10), 4180–4188.

Traynelis, S. F., Wollmuth, L. P., McBain, C. J., Menniti, F. S., Vance, K. M., Ogden, K. K., Hansen, K. B., Yuan, H., Myers, S. J., Dingledine, R., & Sibley, D. (2010). Glutamate receptor ion channels: Structure, regulation, and function. *Pharmacological Reviews, 62*(3), 405–496. doi:62/3/405 [pii] 10.1124/pr.109.002451.

Tu, L., & Deutsch, C. (1999). Evidence for dimerization of dimers in K+ channel assembly. *Biophysical Journal, 76*(4), 2004–2017. doi:S0006-3495(99)77358-3 [pii] 10.1016/S0006-3495(99)77358-3.

Wiltgen, B. J., Royle, G. A., Gray, E. E., Abdipranoto, A., Thangthaeng, N., Jacobs, N., Saab, F., Tonegawa, S., Heinemann, S. F., O'Dell, T. J., Fanselow, M. S., & Vissel, B. (2010). A role for calcium-permeable AMPA receptors in synaptic plasticity and learning. *PloS One, 5*(9). doi:10.1371/journal.pone.0012818.

Xia, J., Chung, H. J., Wihler, C., Huganir, R. L., & Linden, D. J. (2000). Cerebellar long-term depression requires PKC-regulated interactions between GluR2/3 and PDZ domain-containing proteins. *Neuron, 28*(2), 499–510. doi:S0896-6273(00)00128-8 [pii].

Xie, J. (2008). Control of alternative pre-mRNA splicing by Ca(++) signals. *Biochimica et Biophysica Acta, 1779*(8), 438–452. doi:S1874-9399(08)00032-1 [pii] 10.1016/j.bbagrm.2008.01.003.

Yamazaki, M., Ohno-Shosaku, T., Fukaya, M., Kano, M., Watanabe, M., & Sakimura, K. (2004). A novel action of stargazin as an enhancer of AMPA receptor activity. *Neuroscience Research, 50*(4), 369–374. doi:S0168-0102(04)00258-5 [pii] 10.1016/j.neures.2004.10.002.

Zhu, J. J. (2009). Activity level-dependent synapse-specific AMPA receptor trafficking regulates transmission kinetics. *Journal of Neuroscience, 29*(19), 6320–6335. doi:29/19/6320 [pii] 10.1523/JNEUROSCI.4630-08.2009.