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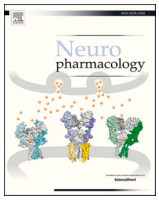

The many faces of the AMPA-type ionotropic glutamate receptor

A B S T R A C T

Knowledge of the biology of ionotropic glutamate receptors (iGluRs) is a prerequisite for any student of the neurosciences. But yet, half a century ago, the situation was quite different. There was fierce debate on whether simple amino acids, such as L-glutamic acid (L-Glu), should even be considered as putative neurotransmitter candidates that drive excitatory synaptic signaling in the vertebrate brain. Organic chemist, Jeff Watkins, and physiologist, Dick Evans, were amongst the pioneering scientists who shed light on these tribulations. By combining their technical expertise, they performed foundational work that explained that the actions of L-Glu were, in fact, mediated by a family of ion-channels that they named NMDA-, AMPA- and kainate-selective iGluRs. To celebrate and reflect upon their seminal work, *Neuropharmacology* has commissioned a series of issues that are dedicated to each member of the Glutamate receptor superfamily that includes both ionotropic and metabotropic classes. This issue brings together nine timely reviews from researchers whose work has brought renewed focus on AMPA receptors (AMPARs), the predominant neurotransmitter receptor at central synapses. Together with the larger collection of papers on other GluR family members, these issues highlight that the excitement, passion, and clarity that Watkins and Evans brought to the study of iGluRs is unlikely to fade as we move into a new era on this most interesting of ion-channel families.

It has been just over 40 years since Professors Jeff Watkins and Dick Evans from the University of Bristol first published their highly influential tome on the actions, biosynthetic origins and regional distribution of excitatory amino acid neurotransmitters in the vertebrate brain (Watkins and Evans, 1981). It was essential reading for anyone wishing to take a sneak peek into the brave New World of the brain's neurochemistry. Here, neurotransmitter candidate molecules were unexpectedly simple amino acids, such as L-glutamic acid (L-Glu), whose identity was more familiar to the biochemist as an intermediary in the metabolism of carbon and nitrogen, and depending on requirement, served either as a source of energy or reservoir of ammonia (Erecinska and Silver, 1990). But yet, L-Glu was known to be an important constituent of nervous tissue since the early 1900s (Abderhalden and Weil, 1913) and, with later work in the 1950s (Weil-Malherbe, 1950), Takashi Hayashi explains he was prompted to test and eventually demonstrate the convulsant effects of L-Glu by injecting relatively small volumes onto the cerebral cortex (Hayashi, 1954). These findings led David Curtis, John Phillis and a young, organic chemist, Jeff Watkins, to repeat these experiments but using the new techniques of intracellular recording and iontophoresis to show that L-Glu depolarised *individual* neurons of the cat spinal cord (Curtis et al., 1959, 1960) (see also (Evans and Watkins, 2021)). These observations were later extended by Kris Krnjevic and John Phillis in cats, rabbits and monkeys in the cerebral cortex and cerebellum (Krnjevic and Phillis, 1963) confirming the pervasiveness of L-Glu's actions.

The departure of Jeff Watkins from Canberra, Australia to Bristol, England in 1973 unwittingly sparked the next major discovery phase of the Glutamate Receptor story. Teaming up with physiologist, Dick Evans, who was already a faculty member at the University of Bristol, they published a series of landmark papers over the next decade that provided the pharmacological framework to allow everyone to understand the actions of L-Glu. By first identifying selective agonists, such as domoic acid and quisqualate (Biscoe et al., 1975) with the earlier discovery of N-methyl-D-aspartate (NMDA) (Curtis and Watkins, 1961, 1963), they were able to start to dissect out subtypes of receptors activated by L-Glu (Watkins and Jane, 2006). These findings were strengthened by their discovery of several selective antagonists, such as Mg^{2+} (Evans et al., 1977), which led them to propose that L-Glu acts on NMDA-, quisqualate/AMPA- and kainate-selective receptors (Watkins and Evans, 1981), which essentially forms the receptor classification that still holds today (Hansen et al., 2021). Little could they have known that their findings would spark 40 years of investigation that has attracted molecular biologists, electrophysiologists, biochemists, and more recently, structural biologists to shed light on this ever-expanding ion-channel family that dominates the neuronal circuits of the mammalian brain. It is fitting, therefore, that *Neuropharmacology* has commissioned several issues of the Journal to reflect upon the achievements and impact of team Watkins and Evans. This issue on the topic of AMPA receptors (AMPARs) highlights the intensity and importance of the ongoing research that is likely to proceed unabated into the future.

1. Structural and functional make-up of the AMPA receptor-auxiliary subunit complex

The review article by Drs. Ian Coombs and Stuart Cull-Candy from University College London provides a comprehensive treatise on the single channel properties of AMPARs (Coombs and Cull-Candy, 2021). The Cull-Candy lab has been at the forefront of this field of research for many decades starting with their observation that native ionotropic

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glutamate receptors activate ion-channels with multiple conductance states of differing amplitude (Cull-Candy and Usowicz, 1987) (see also (Jahr and Stevens, 1987)). The amplitude of these single channel events is markedly affected by RNA editing and alternate splicing of AMPARs, particularly by the presence of the arginine (Arg) pore residue at the Q/R site of the GluA2 subunit (Swanson et al., 1997) which also impacts divalent transport and polyamine block (Bowie, 2018). GluA2-lacking AMPARs (i.e. GluA1, A3 and A4), which possess a glutamine (Gln) residue at the Q/R site, exhibit single channel events which can be resolved as discrete sublevels in the range of 5–30 pS (Banke et al., 2000; Poon et al., 2010; Swanson et al., 1997) whereas the single channels elicited by homomeric GluA2 channels are in the femtosiemen range and can only be resolved by noise analysis (Swanson et al., 1997). This distinction in ion transport is thought to reflect the electrorepulsive effect of the positively-charged Arg at the Q/R site of GluA2-containing AMPARs which hampers the permeation of mono- and divalent ions through the pore. The myriad of auxiliary subunits that assemble with the pore-forming subunits of AMPARs also greatly affect the unitary conductance with both the TARP and cornichon families increasing channel conductance (Coombs et al., 2012; Tomita et al., 2005) whereas GSG1L lowers it (McGee et al., 2015). The authors conclude by focusing on how phosphorylation of the cytoplasmic tails (C-tails) of AMPARs influences their gating and channel properties. Phosphorylation is often triggered by periods of sustained patterned activity or altered homeostasis at central synapses which leads to changes in the responsiveness of synaptic AMPARs. For example, phosphorylation by CaMKII or protein kinase C increases the occurrence of larger subconductance states (Derkach et al., 1999) whereas protein kinase A, which phosphorylates different C-tail residues, primarily enhances the AMPAR response by increasing open channel probability (Banke et al., 2000). Over the decades, much has been learned of how the distinct conductance states adopted by pore regions of AMPARs contributes to their biology. The future awaits a better grasp of the role fulfilled by the C-tail that has until now eluded serious structural study, but yet, plays a pivotal role as the recipient of phosphorylation/dephosphorylation modification as well as the docking site for many auxiliary proteins.

Matthews and colleagues from the MRC Laboratory of Molecular in Cambridge, England provide a complementary perspective on AMPARs by documenting the life cycle of the many helper proteins that transport and stabilize AMPARs at central synapses as well as modifying their functional behavior (Matthews et al., 2021). First identified in Stargazer, an ataxic and epileptic mutant mouse that lacks surface AMPARs in cerebellar granule cells (Chen et al., 2000), the prototypical AMPAR auxiliary protein, stargazin or γ2, was later shown to be part of an extended family of interacting proteins that includes other transmembrane AMPA receptor regulatory proteins (TARPs), γ3, γ4, γ5, γ7, γ8 (Jackson and Nicoll, 2011) and the claudin homolog, Germ cell-specific gene 1-like protein (GSG1L) (Shanks et al., 2012). Other families of auxiliary proteins, such as the cornichons (Schwenk et al., 2009), the CKAMP/Shisha family (von Engelhardt, 2019; von Engelhardt et al., 2010) and the SynDIG/proline-rich transmembrane protein (PRRT) family (Diaz, 2021; Kalashnikova et al., 2010), were all shown to decorate synaptic AMPARs and fine tune their responsiveness (Hansen et al., 2021). The authors explain that other families of interacting proteins additionally act at various stages of the AMPAR life cycle including their biogenesis in the endoplasmic reticulum. For example, several chaperone proteins have emerged as being critical in AMPAR biogenesis including α/β-hydrolase domain-containing protein 6 (ABHD6) (Schwenk et al., 2019) and porcupine O-acetyltransferase (PORCN) (Schwenk et al., 2012), which interact with AMPAR monomers, most likely with their transmembrane domains, to stablize and protect them from ER-degradation (Schwenk and Fakler, 2021). The next step of AMPAR subunit dimerization is assisted by the ferruic-chelate reductase 1-like (FRRS1l or C9orf4) together with the ER-specific carnitine palmitoyl tranferase-1c (CPT1c), which promote dissociation of ABHD6 from the AMPAR complex enabling the formaiton of mature tetramers as dimer of dimers (Brechet et al., 2017; Schwenk et al., 2019). The authors note that like ABHD6 and PORCN, CPT1c only interacts with AMPARs in the ER and consequently, does not affect their gating properties but primarily promotes receptor surface trafficking. Once on the cell surface, the authors explain that the density and responsiveness of AMPAR complexes is then fine tuned through complex interactions exterted by the binding of the TARP, cornichon and CKAMP protein families. Surprisingly, AMPAR auxiliary proteins modulate AMPAR functional behavior through discrete interactions, such as the evolutionary-conserved KGK site on the lower lobe of agonist binding domain that is specific for TARP modulation of AMPARs (Dawe et al., 2016) where as several lipid-exposed residues in the transmembrane domain impact both TARP and cornichon interactions with AMPARs (Hawken et al., 2017). With most of our understanding of AMPAR interacting proteins gleaned from studies in the hippocampus and cerebellum, an important next step will be to determine whether these general rules that regulate the biogenesis and surface expression of mature AMPAR tetramers can be extended to all other neuron classes and brain regions.

2. The dynamic life of the glutamatergic synapse

Dr. Jelena Baranovic from the University of Edinburgh considers the very significant time and space constraints that shape the response of native AMPARs (Baranovic, 2021). Although it has been accepted for some time that L-glutamic acid is the main excitatory neurotransmitter in the vertebrate CNS, there has been debate over the years about the peak concentration achieved at central synapses and its duration. Early studies used concentration clamp experiments on patches excised from hippocampal neurons to argue that AMPAR deactivation/desensitization kinetics best matched miniexcitatory synaptic events if L-Glu was released into the cleft at near-saturating, millimolar levels but for only a few milliseconds (Colquhoun et al., 1992). Although there has been a general agreement on the brief time L-Glu resides at synapses (Jones and Westbrook, 1996), whether neurotransmitter concentrations are near saturating may not be the case in every instance (McAllister and Stevens, 2000). Dr. Baranovic extends these considerations by discussing interactions that AMPA receptors face in the synapse, with post- and presynaptic proteins, as well as secreted proteins with a focus on how spatial and temporal conditions impact and constrain AMPA receptor activation, including its conformational flexibility. With the elucidation of the full-length AMPAR tetrameric structure alone (Herguedas et al., 2016; Sobolevsky et al., 2009) or in complex with auxiliary proteins (Nakagawa, 2019; Twomey et al., 2017; Zhang et al., 2021; Zhao et al., 2019), it has been appreciated that they dominate the landscape of central synapses reaching heights of 100–120 Å. As noted by the author, this dominant position permits them to interact and form complexes with presynaptic proteins to sustain neurotransmission and permit synaptic plasticity (Diaz-Alonso and Nicoll, 2021; Fukata et al., 2021a; Sheng et al., 2018; Watson et al., 2017). A further complication is that high-resolution microscopy reveals that each AMPAR-auxiliary subunit signaling complex is arranged into nanodomains with central synapses averaging 1–2 nanodomains which are greater than 80 nm in size that contain 10-20 AMPARs (Choquet and Hosy, 2020). Furthermore, this crowded environment is on the move with cryo-EM studies suggesting significant displacement in the AMPAR structure following agonist binding and receptor desensitization (Durr et al., 2014; Meyerson et al., 2014), albeit under equilibrium conditions that Dr. Baranovic notes may not truly reflect the millisecond time scale of synaptic transmission. With recent atomic force microscopy studies revealing that even the apo state of the AMPAR undergoes nanoscale movement regulated by alternate splicing of the flip/flop cassette (Dawe et al., 2019), the stage is set for the next years to integrate all this information into a more complete picture of the glutamatergic synapse in both time and space.

The timely review by Fukata and colleagues from the National Institute for Physiological Sciences in Okazaki, Japan takes an even

deeper dive into the emerging and important role of *trans*-synaptic signaling complexes found at glutamatergic synapses (Fukata et al., 2021b). Drs. Masaki and Yuko Fukata lead a vibrant team of researchers that have championed the importance of the transsynaptic complex formed between Leucine-rich, glioma inactivated 1 (LGI1) and disintegrin and metalloproteinase domain-containing protein 22 (ADAM22) in health and disease of the vertebrate brain. Their dual role at glutamatergic synapses was first reported in a pivotal study that established that the postsynaptic, transmembrane protein, ADAM22, serves as a receptor for the secreted neuronal protein, LGI1 (Fukata et al., 2006). This intimate structural relationship explained earlier studies tying genetic mutations in both LGI1 and ADAM22 to the occurrence of epileptic seizures (Sagane et al., 2005; Steinlein, 2004). First appearing in the first week of the postnatal brain during synaptogenesis, LGI1 and ADAM22 form nanoscale clusters that are almost equidistant from postsynaptic PSD-95 and presynaptic Bassoon, placing ADAM22–LGI1 at the synaptic cleft, and forming a transsynaptic structure that is critical in preventing epileptic seizures (Fukata et al., 2021a). The authors propose that the LGI1–ADAM22 complex may have three distinct but not necessarily mutually exclusive roles to instruct membrane-associated guanylate kinase (MAGUK) family of scaffold proteins, such as PSD95, depending on the subcellular contexts: (a) to align pre- and postsynaptic MAGUKs as a hub of transsynaptic nanocolumns, (b) to locally condense MAGUKs as an extracellular scaffold, and (c) to activate the MAGUKs' scaffolding activity as a PDZ3 ligand. Although there is compelling evidence favouring the LGI1–ADAM22 complex as an extracellular master regulator that aligns pre- and postsynaptic MAGUKs, the authors also acknowledge that a similar role is shared by neurexin–neuroligin complexes, which also bind to pre- and postsynaptic MAGUKs (Sudhof, 2017). Whether these observations suggest that LGI1–ADAM22 and neurexin–neuroligin have redundant or distinct functions *in vivo* is still not clear, although, it is interesting that genetic mutations of neurexin–neuroligin are associated with autism (Sudhof, 2017; Tabuchi et al., 2007) and not epilepsy like the LGI1–ADAM22 complex. The authors conclude that autoantibodies against synaptic and cell-surface proteins, such LGI1, have given rise to a new disease called "autoimmune encephalitis or autoimmune synaptopathy" (Fukata et al., 2018; Pruss, 2021). LGI1 autoantibodies inhibit LGI1 and ADAM22/23 interactions and reversibly reduce the number of synaptic AMPAR clusters (Ohkawa et al., 2013) which presumably contribute to the occurrence of amnesia, seizures and cognitive dysfunction observed in anti-LGI1 limbic encephalitis (Spatola and Dalmau, 2017).

3. AMPA receptors and synaptic plasticity

The role of AMPARs in synaptic plasticity has been an area of intense investigation for the last three decades with the labs of Drs. Roger Nicoll, Yu Tian Wang and Zhengping Jia all making important contributions to our understanding.

The review article by Drs. Diaz-Alonso and Nicoll from the University of California San Francisco provide an updated mechanism by which AMPAR trafficking contributes to the plasticity mechanism of long-term potentiation (LTP) at glutamatergic synapses (Diaz-Alonso and Nicoll, 2021). Specifically, the authors aim to incorporate recent data highlighting how different domains of the AMPAR signaling complex, particularly the amino terminal (NTD) and cytoplasmic (CTD) domains, play key and distinct roles in the strengthening of excitatory synapses. Different forms of LTP have been identified across the vertebrate brain, however, the authors clarify that they will focus their considerations only to NMDAR-dependent strengthening of glutamatergic synapses found on the distal dendrites of CA1 hippocampal pyramidal cells which have been studied extensively (Nicoll, 2017). The CTD of the GluA1 AMPAR subunit has received a significant amount of attention from researchers who have focused on two specific properties, (i) the ability of the CTD to dock important signaling proteins alongside synaptic AMPARs through specific PDZ domain mediated protein-protein interactions and (ii) posttranslational modification of the CTD through its phosphorylation by different families of cytosolic kinases. The possible role of PDZ binding interactions in LTP has provided mixed results with early studies suggesting that these interactions may have key roles (e.g. (Hayashi et al., 2000)) whereas later studies that have deleted the entire CTD of the GluA1 subunit did not observe an effect on LTP (Diaz-Alonso et al., 2020; Granger et al., 2013). GluA1 AMPAR phosphorylation has also been studied extensively which has highlighted the phosphorylation sites of Ser831 and 845 residues of the CTD, in addition to the important role of abundantly expressed kinase, CaMKII. Despite this, the authors question whether GluA1 phosphorylation plays a necessary role in LTP given that mutation of either the Ser831 or 845 residues in knock-in studies has apparently little effect on LTP (though LTD is affected by the S845A mutant) (Lee et al., 2010). Despite this, an early study where mutation of both sites was performed blocked LTP, at least in the adult hippocampus (Lee et al., 2003). The authors acknowledge the phosphorylation of 831 and 845 residues of the GluA1 CTD *in vivo*, but question whether it is essential for LTP. The role of the GluA1 NTD in synaptic transmission and LTP is similarly controversial. More recent work, however, has been working towards consensus in understanding the role of the NTD in synaptic transmission and LTP. The authors note that some of the confusion may arise from previous experimental manipulations that have disrupted protein structures and interactions that are essential for LTP. As result, they propose any future enquiry should ensure that the extracellular NTD remains intact and that interactions formed between the GluA1 AMPAR subunit NTD with TARP auxiliary proteins and scaffolding proteins of the postsynaptic density also remain undisturbed. With the added complication that AMPARs may assemble as tri-heteromeric tetramers, as recently proposed from cryo-EM studies (Zhao et al., 2019), designing experiments to elucidate the precise roles of the ATD and/or CTD of the AMPAR subunit in LTP will require careful consideration.

Drs. Yuan Ge and Yu Tian Wang from the University of British Columbia, Vancouver, Canada focus on the role of homomeric GluA1 AMPARs in synaptic plasticity and neurological disease (Ge and Wang, 2021). Most native AMPARs in the CNS are thought to be heteromeric in nature composed of the GluA1/A2 or GluA2/A3 subunits (Bowie, 2012; Henley and Wilkinson, 2016). The authors note the ongoing controversy over the specific roles that individual GluA1 and GluA2 subunits play in plasticity mechanisms of LTP or LTD when assembled as GluA2-containing heteromeric receptors. They also point to the emerging evidence of the importance of GluA1 homomeric receptors which are distinct from other AMPARs in exhibiting high permeability to extracellular Ca^{2+} and sensitivity to voltage-dependent block by micromolar levels of cytoplasmic polyamines (Bowie, 2018). First identified in plasticity experiments performed in the basolateral amygdala, GluA2-lacking AMPARs were shown to be required for the induction of LTP (Mahanty and Sah, 1998) which is thought to give rise to the enhanced neuronal synchrony observed in response to fear conditioning (Quirk et al., 1995). In contrast, similar experiments on CA3 interneurons of the hippocampus induces LTD (Laezza et al., 1999), with the distinction being that the locus of the change in synaptic efficacy is thought to be presynaptic in origin (Lei and McBain, 2004). Long-lasting Ca^{2+}-permeable AMPAR-dependent synaptic plasticity is also involved in activity-dependent changes in the subunit composition of AMPARs, as noted in studies of the hippocampus (Ju et al., 2004), amygdala (Clem and Huganir, 2013) and cerebellum (Liu and Cull-Candy, 2000), where there is an exchange between GluA2-containing and -lacking AMPARs at glutamatergic synapses. Homomeric GluA1 AMPARs are also thought to play a role during early LTP observed at Schaffer collateral—CA1 synapses where their insertion is thought to transiently increase cytosolic Ca^{2+} that, in turn, promotes the full expression of LTP with GluA2-containing AMPARs (Plant et al., 2006) (though see (Adesnik and Nicoll, 2007)). The insertion of GluA1 homomeric AMPARs into synapses from perisynaptic sites (He et al., 2009) has been proposed to involve phosphorylation of the GluA1 Ser845 C-tail residue by protein

kinase A and anchoring by the scaffold protein, AKAP150, which together promote the transient increase in synaptic GluA1 homomeric AMPARs that add to NMDAR-dependent induction of LTD (Sanderson et al., 2016). A more recent study has identified a role for p97 that specifically interacts with and promotes the formation of GluA1 homomeric AMPARs. Specifically, p97 retains GluA1 homomers in the intracellular compartment under basal conditions, and its dissociation allows GluA1 AMPARs to be rapidly inserted into the postsynaptic membrane shortly after LTP induction (Ge et al., 2019). Drs. Ge and Wang conclude by discussing the role fulfilled by GluA1 AMPAR homomers in ischemia and drug addiction suggesting that further investigation into this unique class of AMPARs may be beneficial in the treatment of these most intractable CNS diseases.

The comprehensive review article by Drs. Radu Gugusteau and Zhengping Jia from the Hospital for Sick Children and University of Toronto in Canada concludes the theme of synaptic plasticity by recounting how genetic manipulations have uncovered multiple forms of LTP and LTD at the CA1 hippocampal synapse (Gugustea and Jia, 2021). Specifically, they have focused on both transgenic approaches and gene targeting and how they have tease apart the contributions different AMPAR subunits to basal synaptic transmission, LTP and LTD. The authors have painstakingly documented the many studies on global knockouts of AMPAR subunits as well as similar work on conditional knockout and knockin mice making this article a must read for anyone wishing a crash course on this topic. For brevity, I have kept my comments restricted to the early global knockout studies. Dr. Zhengping Jia has been at the forefront of this research generating the first genetic knockout of the GluA2 subunit just over 25 years ago (Jia et al., 1996). Interestingly, he and his colleagues were able to show the GluA2 KO mouse displayed no abnormalities in gross brain anatomy, neuronal morphology, or in major fiber tracts but had a reduced basal synaptic transmission and enhanced LTP consistent with the expression of GluA2-lacking AMPARs that would further contribute the enhancement of postsynaptic Ca^{2+} mediated by NMDARs (Jia et al., 1996). Unexpectedly, NMDAR-dependent LTD was not impaired in the GluA2 KO mouse, albeit in two-week old animals, suggesting that LTD mechanisms is fundamentally different between KO and WT mice. The requirement for GluA2 in NMDAR-dependent LTD may be age-dependent since NMDA-induced LTD was completely abolished in adult GluA2-KO mice (Cao et al., 2018). Global knockout of the GluA1 subunit was distinct from the GluA2 KO mice with a substantial redistribution of AMPARs within the hippocampal network. Despite this, glutamatergic synaptic currents were unaltered with evoked dendritic and spinous Ca^{2+} transients and hippocampal field potentials similar to WT mice. In contrast, however, LTP was absent at the CA3 to CA1 synapses but spatial learning in the water maze experiments was unimpaired (Zamanillo et al., 1999) revealing a dichotomy between LTP in CA1 and the acquisition of spatial memory. Interestingly, LTD was still observed at the CA1 synapse of GluA1 KO mice (Granger and Nicoll, 2014), although, there is a debate on whether the underlying mechanisms were altered under these conditions (Gugustea and Jia, 2021). GluA3 global KO mice show normal overall growth, brain anatomy, synapse number, morphology as well as basal synaptic transmission (Meng et al., 2003). There were, however, regional specific impairments such as LTP at the climbing fiber- Purkinje cell synapses in the cerebellum (Gutierrez-Castellanos et al., 2017). At the CA1 synapse, NMDAR-dependent LTP was normal or even enhanced in GluA3-KO (Meng et al., 2003) although the authors note that GluA3 may play a role in CA1 hippocampal LTP under certain conditions. Interestingly, amyloid beta-induced synaptic depression and spine loss (Reinders et al., 2016), a phenomenon similar to LTD, is impaired in GluA3-KO mice, indicating that perhaps the GluA3 subunit plays an unappreciated role in the synaptic deficits caused by Alzheimer's disease. Finally, global KO of the GluA4 subunit shows deficits in signaling by fast spiking parvalbumin positive interneurons (Fuchs et al., 2007) and, whilst having no effect on basal transmission and LTP of AMPAR synapses in adult CA1 neurons (Sagata et al., 2010), synapse maturation was delayed (Luchkina et al., 2014) reaffirming the importance role of neonatal expression of GluA4 for the adult brain (Zhu et al., 2000).

4. RNA aptamers and microRNA control of AMPA receptors

Dr. Jonathan Hanley from the University of Bristol reviews the important and emerging roles of microRNAs (miRNAs) in AMPAR trafficking and plasticity as well as explaining the critical roles they may fulfill in neurological disease (Hanley, 2021). Specifically, he focuses on the miRNAs that regulate physiological and pathological changes in AMPAR subunit expression at synapses. The miRNAs target messenger RNAs encoding AMPAR subunits and their accessory proteins. Dr. Hanley explains that miRNAs are small noncoding endogenous RNA molecules that repress the translation of target mRNAs fine-tuning protein synthesis in a wide range of cellular processes (Treiber et al., 2019). The first evidence linking miRNA control of AMPARs arose from a study examining the mechanisms underlying homeostatic plasticity of glutamatergic synapses. Blocking action potential firing and NMDAR signaling with TTX and APV respectively, the study identified miR-92a as a regulator of translation that binds to the 3′ untranslated region of GluA1 mRNA (Letellier et al., 2014). Under these conditions with neuronal circuit activity globally down-regulated, expression of miR-92a is reduced which, in turn, releases the translational repression of GluA1 mRNA enhancing AMPAR expression. Similarly, more recent studies have shown that other miRNAs, most notably miR-124 and miR-186-5p, can repress GluA2 protein synthesis to favour the expression of GluA2-lacking, Ca2+-permeable AMPARs (Hou et al., 2015; Silva et al., 2019). Metabotropic glutamate receptor (mGluR) mediated LTD has also been shown to rely on miRNAs with miR-137 expression upregulated in response to mGluR5 activation (Olde Loohuis et al., 2015). Mir-137 targets the Gria-UTR reducing the synthesis of GluA1 subunit leading to a reduction in synaptic strength. NMDAR dependent LTD has been linked to miRNAs, such as miR-501-3p, which are rapidly upregulated to control GluA1 expression in response to NMDAR activation, albeit after some delay (Hu et al., 2015). The delay, Dr. Hanley argues, suggests that miR-501–3p is unlikely to be involved in the early stages of LTD expression but rather in its maintenance. In terms of LTP mechanisms, miR-181-a has been shown to be downregulated in experiments using a chemical form of LTP which induced upregulation of GluA2 (Rodriguez-Ortiz et al., 2020), a known target for miR-181a from work performed in the nucleus accumbens (Saba et al., 2012). Accordingly, the downregulation of miR-181a promotes an increase in GluA2 protein synthesis with an increase in AMPAR expression. Dr. Hanley also notes that miRNAs also target proteins that regulate AMPAR trafficking such as complexin-1 and -2 whose expression is controlled by miR-135 (Hu et al., 2014) as well as SAP97 whose expression is regulated by miR-9-3p (Sim et al., 2016). In concluding, Dr. Hanley highlights ongoing research efforts linking distinct miRNAS to Alzheimer's disease, multiple sclerosis, schizophrenia and cerebral ischemia which suggest translational pathways that may be suitable for future investigation into CNS therapies.

Last but certainly not least, Drs. Zhen Huang and Li Niu from the State University of New York, Albany, USA extends this discussion of translation by considering the case for RNA aptamers targeted to AMPARs (Huang and Niu, 2021). RNA aptamers are single-stranded RNA molecules that, in principle, can bind to a specific target molecule for both basic research and clinical purposes (Keefe et al., 2010). The authors highlight the efforts of many researchers over the decades to develop small molecule therapies by targeting iGluRs and the challenge they face in identifying drug classes with a high degree of selectivity. The use of RNA aptamers bypasses some of the concerns of traditional drug discovery strategies in that lead compounds can be identified without, for example, a priori knowledge of the target's structure. As noted by the authors, the strategy to identify RNA aptamers was introduced independently by the Szostak and Gold labs (Stoltenburg et al., 2007; Tuerk and Gold, 1990), who coined the term systematic evolution

of ligands by exponential enrichment, or SELEX, to describe the recursive nature of the selection procedure. In keeping with this, the lab of Dr. Niu explored the use of SELEX to identify and isolate RNA aptamers targeted to AMPARs starting with NBQX and GluA2 AMPAR subunit to elute candidate RNAs with the aim of identifying competitive antagonists (Huang et al., 2007). Using this approach, they identified AN58, a 58 nucleotide RNA aptamer that competitively inhibits homomeric GluA2 AMPARs with an apparent affinity (IC50) of 30 nM, making it a highly potent blocker of AMPARs (Huang et al., 2007). A similar strategy was then used to identify RNA aptamers that were selective for the open- or closed-state of the GluA2 AMPAR (Huang et al., 2010; Park et al., 2011). The authors concluded by discussing the challenges but also the promises of using RNA aptamers as therapeutically relevant drugs. They note that RNA aptamers have been used to dirupt viral RNA-protein binding to oppose viral replication (Sullenger et al., 1990) with some recent studies of RNA aptamers being approved to treat macular degeneration of the eye (Nimjee et al., 2017; Zhou and Rossi, 2017). The promise of RNA aptamers as therapeutics to treat CNS disease linked to AMPARs or other families of iGluRs has yet to be realised. However, as we better understand how iGluR dysfunction contributes to neurological disease, strategies using RNA aptamers for treatment may then be within our reach.

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