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[Review Article / *Neuropharmacology*]

Ca²⁺-permeable AMPA receptors: a new perspective on amyloid-beta mediated pathophysiology of Alzheimer's disease

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Abstract

α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA_Rs) are the primary conduits of excitatory synaptic transmission. AMPA_Rs are predominantly Ca²⁺-impermeable in the matured excitatory synapse, except under certain circumstances. Growing evidence implicates the Ca²⁺ permeability of AMPA_Rs in the regulation of long-term synaptic plasticity and in the pathophysiology of several neurological disorders. Therefore, the Ca²⁺ conductance of AMPA_Rs may have both physiological and pathological roles at synapses. However, our understanding of the role of Ca²⁺ permeable AMPA_Rs (CP-AMPA_Rs) in Alzheimer's disease is limited. Here we discuss insights into the potential CP-AMPA_R mediated pathophysiology of Alzheimer's disease, including: 1. Ca²⁺-mediated aberrant regulation of synapse weakening mechanisms, and 2. neuronal network dysfunction in the brain. Consideration of CP-AMPA_Rs as primary drivers of pathophysiology could help in understanding synaptopathologies, and highlights the potential of CP-AMPA_Rs as therapeutic targets in Alzheimer's disease.

It has become increasingly evident that in certain pathological states, AMPAR expression is compromised, resulting in alterations to synaptic function. CP-AMPARs in particular have well-established roles in epilepsy (Grooms et al., 2000, Rajasekaran et al., 2012, Malkin et al., 2016), ischaemia (Kwak and Weiss, 2006), traumatic brain injury (Spaethling et al., 2008), and illicit substance addiction and withdrawal (Pistillo et al., 2016, Wolf, 2016). Indeed, the contribution of CP-AMPARs to these disease etiologies has been thoroughly reviewed (Tanaka et al., 2000, Liu and Zukin, 2007, Henley and Wilkinson, 2016) and the potential for targeting AMPARs as a therapeutic strategy continues to be explored (Chang et al., 2012, Franco et al., 2013, Zaccara and Schmidt, 2016). In addition to these diseases, it has been postulated that CP-AMPARs might also contribute to progressive neurodegeneration (Weiss and Sensi, 2000, Kwak and Weiss, 2006). However, until recently, there has been limited evidence to support this claim. Thus, this review will discuss recent evidence implicating CP-AMPARs in Alzheimer's Disease (AD), and describe how targeting AMPARs may offer a potential therapeutic strategy in treating AD patients.

1. Ca²⁺-permeable AMPA receptors: structure, function and expression

α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are ionotropic receptors, formed by the tetrameric assembly of GluA1-4 subunits, and are widely expressed throughout the central nervous system (Hollmann and Heinemann, 1994). AMPARs are highly dynamic complexes, being able to transition between different subunit assemblies depending on the synaptic environment (Schwenk et al., 2014, Herguedas et al., 2016). In the adult hippocampus, AMPARs are typically composed of a combination of GluA1 and GluA2, or GluA2 and GluA3 subunits (Wenthold et al., 1996). The AMPAR subunits themselves have four distinct domains: an N-terminal extracellular domain; a ligand binding domain (composed of two extracellular polypeptide sections, termed S1 and S2 (Keinanen et al., 1990, Stern-Bach et al., 1994); a membrane-localised channel domain (formed by three transmembrane α -helices and a channel pore loop, termed M1, M2, M3 and M4); and an intracellular C-terminal domain (**Figure 1**).

The functional properties of AMPARs depend on the composition of its subunits. For instance, inclusion of the GluA2 subunit in a receptor confers Ca²⁺ impermeability and these are the major species of receptor found in glutamatergic neurons (Wenthold et al., 1996). The impermeability to Ca²⁺ is conferred by editing of the Q/R

site of GluA2 pre-mRNA. Here, a glutamine (Q) codon (which lies within the channel-forming M2 re-entrant membrane loop region) is modified into an arginine (R) codon (Sommer et al., 1991, Burnashev et al., 1992). However, AMPARs can be Ca^{2+} permeable in certain circumstances; (1) in the instances where they contain unedited GluA2(Q) subunits, or (2) when they are formed without the inclusion of the GluA2 subunit. GluA2-lacking AMPARs, which are often homomeric for the GluA1 subunit, are termed Ca^{2+} -permeable AMPARs (CP-AMPARs). CP-AMPARs are known to have greater single channel conductance than GluA2-containing AMPARs (Swanson et al., 1997), though less than N-methyl-D-aspartate receptors (NMDARs) (Dingledine et al., 1999). Additionally, CP-AMPARs have faster desensitization constants than GluA2-containing receptors (Traynelis et al., 2010) The majority of CP-AMPARs display a inwardly rectifying current-voltage relationship (though see Gilbertson et al., 1991), whereby the receptors do not permit the passage of current at depolarising membrane potentials, due to channel pore blockade by intracellular polyamines (Bowie and Mayer, 1995, Donevan and Rogawski, 1995, Guerra et al., 2016); **Figure 2A, B**). This change in rectification properties conferred by endogenous intracellular polyamines is, however, subject to regulation by the AMPAR auxiliary subunit stargazin (Soto et al., 2007). Stargazin reduces the sensitivity of CP-AMPARs to polyamine block, as well as increasing single-channel conductance and slowing deactivation of receptors, altogether increasing the influx of Ca^{2+} . This regulation of channel properties by stargazin may increase the functional diversity of CP-AMPARs, with populations of CP-AMPARs in regions where stargazin is not expressed displaying altered functional characteristics. The wide-ranging effects that external and internal polyamines have on AMPAR channel conductance, and contrasting data obtained from bi-polar retinal cells, has led some to question whether GluA2-containing AMPARs can actually display Ca^{2+} -permeable characteristics (Bowie, 2012). Thus, it is highly evident that further investigation is required to substantiate the exact composition of the different populations of AMPARs.

Expression of CP-AMPARs is evident during the early developmental stages of the hippocampus, compared to just a small fraction of CP-AMPARs present in mature hippocampal neurons (Wentholt et al., 1996, Rozov et al., 2012). This is in part due to the presence of unedited forms of GluA2 mRNA at embryonic stages, which later become almost entirely obsolete as the brain reaches maturity (Burnashev et al., 1992, Kawahara et al., 2003). Coupled with a higher ratio of GluA1, GluA3, and GluA4 to GluA2 subunits, CP-AMPARs are known to be relatively prevalent in the

hippocampus during the first few postnatal weeks (Pellegrini-Giampietro et al., 1992, Ho et al., 2007). However, a subsequent increase in edited GluA2 subunit expression can be seen after approximately 1-3 weeks of postnatal development (Pellegrini-Giampietro et al., 1992, Pickard et al., 2000, Ho et al., 2007, Blair et al., 2013). A similar profile is found in other brain regions, where low GluA2 abundance in early developmental stages results in CP-AMPA expression in neonatal neurons of the cortex, striatum and cerebellum, which gradually declines after a short developmental time window (Pellegrini-Giampietro et al., 1992, Kumar et al., 2002, Shin et al., 2007, Miyazaki et al., 2012). Other findings have shown that CP-AMPA receptors emerge at later time points in certain cell-types, replacing Ca^{2+} -impermeable AMPARs in fast spiking interneurons of the prefrontal cortex during adolescence (Wang and Gao, 2010). Thus, the expression of CP-AMPA is tightly regulated and linked to developmental stages, brain regions and distinct cell-types.

2. Physiological roles of Ca^{2+} -permeable AMPA receptors at the synapse

Though limited in their expression in the mature synapse, CP-AMPA receptors are nevertheless thought to play important roles in the physiological function of neurons. AMPARs are pivotal in both the induction and expression of plasticity events that occur during synaptic stimulation (Henley and Wilkinson, 2016). The insertion of AMPARs at the synapse is an underlying molecular mechanism of long-term potentiation (LTP), a form of synaptic plasticity widely considered to be a correlate of learning and memory at the molecular level (Bliss and Collingridge, 1993). Whilst it was initially thought that only heteromeric assemblies of AMPARs containing both GluA1 and GluA2 subunits were trafficked to the synaptic membrane of CA1 pyramidal neurons during synaptic stimulation, later studies have shown that expression of LTP requires the insertion of CP-AMPA receptors under certain circumstances, but that their expression is transient (< 25 min) in nature (Jia et al., 1996, Plant et al., 2006, Jaafari et al., 2012, Park et al., 2016). It is however, debatable whether CP-AMPA receptors are expressed during LTP induction (Adesnik and Nicoll, 2007, Gray et al., 2007). Whilst these two studies bring in to question the importance of CP-AMPA receptors in the induction of synaptic plasticity, a possible explanation for these contradictory results may be related to the age of animal and experimental protocol. This was observed in a recent study, where LTP was blocked by IEM-1460 - a voltage-dependent AMPAR open channel blocker selective for CP-AMPA receptors (Schlesinger et al., 2005) - in animals around 2 weeks of age (Sanderson et al., 2016). In contrast, LTP in animals closer to 3 weeks of age was insensitive to IEM-1460 treatment,

illustrating the small time frame in which CP-AMPARs may contribute to synaptic plasticity. Here, we will not cover this debate further since it is beyond scope of this review, however it is clear that further work is required to fully understand the specific circumstances where CP-AMPARs are pivotal for plasticity induction.

We have recently shown that in addition to possible roles in the induction of LTP *per se*, CP-AMPARs might also confer metaplastic properties to hippocampal neurons. We reported that acute stress or brief application of the GR agonist dexamethasone (DEX) results in a long-lasting increase in synaptic potentiation, which is mediated through the insertion of CP-AMPARs at the synaptic membrane (Whitehead et al., 2013) (**Figure 3**). We showed that, whilst this stress-induced increase in LTP was, in part, mediated through activation of NMDARs, a portion of synaptic potentiation was found to be sensitive to treatment with IEM-1460, indicating the involvement of CP-AMPARs. Moreover, acute stress resulted in an inwardly rectifying current/voltage (I/V) relationship, which is indicative of increased CP-AMPAR surface expression. We also found that the expression of CP-AMPARs required the protein kinase A (PKA)-mediated phosphorylation of the GluA1 serine 845 residue (S845), a known mechanism regulating CP-AMPAR synaptic expression (He et al., 2009). Consistent with our findings, a recent report has noted that acute footshock stress results in the rapid upregulation of S845 GluA1 phosphorylation, suggestive of the increased incorporation/stabilization of GluA1-containing AMPARs (Bonini et al., 2016). Further, phosphorylation of GluA1 at the serine 831 residue (S831) was found to occur under certain circumstances following acute swim stress (Fumagalli et al., 2012), which robustly increases single channel conductance (Kristensen et al., 2011). Taken together, these results suggest that CP-AMPARs can rapidly respond to environmental stimuli in order to regulate synaptic transmission and function.

Interestingly, whilst the findings of CP-AMPARs in acute stress might suggest a role in enhancing memory or learning, conversely, CP-AMPARs have also been shown to also be important in memory erasure (Clem and Huganir, 2010). During the consolidation period following fear memory conditioning, expression of CP-AMPARs in the amygdala was found to be increased, which resulted in a greater magnitude of the long-term depression (LTD) form of synaptic plasticity and increased chance of memory extinction. Thus, it appears that CP-AMPARs can regulate both forms of synaptic activity – LTP and LTD. For example, it was shown that CP-AMPARs are recruited to the synaptic membrane during LTD induction, through activation of PKA anchored to a kinase anchor protein 150 (AKAP150), and phosphorylation of S845

on the GluA1 subunit (Sanderson et al., 2016). Whilst LTD could be induced by NMDARs alone, the magnitude of LTD was smaller compared to when CP-AMPARs were expressed. Clearly then, CP-AMPARs can have a multitude of roles in normal physiological function of neurons. It is of interest therefore whether the molecular mechanisms that regulate CP-AMPARs are differentially regulated in pathological conditions in the brain.

3. Potential role of Ca²⁺-permeable AMPA receptors in Alzheimer's disease

In an examination of postsynaptic density-rich fractions of human AD patients' hippocampus, an increase in GluA1 levels was reported when compared with healthy control patients, whereas no changes to NMDAR subunit expression were observed (Marcello et al., 2012). This suggests a selective increase in GluA1-containing receptors at synapses in the AD hippocampus. Consistent with this, we have recently shown that direct infusion of oligomerised amyloid- β (A β) - thought to be a key driving force in AD pathogenesis (LaFerla et al., 2007) - into CA1 hippocampal neurons resulted in a rapid synaptic insertion of CP-AMPARs (Whitcomb et al., 2015). This effect enhances AMPAR-mediated excitatory postsynaptic current (EPSC_{AMPA}) and was absent in cells treated with IEM-1460 or in cells transfected with shRNA directed against the GluA1 AMPAR subunit. We also showed that these effects operate through PKA-mediated S845 GluA1 phosphorylation (see **Figure 4**) suggesting that A β utilises a canonical mechanism of CP-AMPAR expression. In addition, a recent study of an AD transgenic mouse model reported aberrant CP-AMPAR expression and increased GluA1 phosphorylation specifically in young mice, prior to any overt neuropathology (Megill et al., 2015). Together, these findings indicate that CP-AMPAR synaptic insertion may be an early-stage event in AD pathogenesis.

What is currently missing in our understanding of CP-AMPAR function in AD pathology is how the expression of the receptor might translate into pathological consequences for the neuron. A compelling hypothesis is that aberrant CP-AMPAR expression causes excessive intracellular Ca²⁺ influx that leads to synaptic dysfunction and neurodegeneration. Physiologically, CP-AMPARs appear to be only transiently expressed in response to synaptic activity (Plant et al., 2006, Sutton et al., 2006, Hou et al., 2008, Yang et al., 2010). If this is case, CP-AMPAR expression is tightly regulated as a physiological necessity, and this likely provides a mechanism that protects against aberrant and/or sustained Ca²⁺ flux through CP-AMPARs in excitatory synapses. Therefore, it is likely that aberrant activation of CP-AMPAR

function may elicit Ca^{2+} -mediated synaptic and neuronal degeneration. Indeed, alterations in Ca^{2+} homeostasis have been proposed to be crucial in the initial stages of AD development (LaFerla, 2002). Changes to Ca^{2+} signaling have been linked to dysregulation of amyloid precursor protein (APP) processing, responsible for $\text{A}\beta$ production, and may augment the formation of toxic $\text{A}\beta$ oligomers (Mattson, 1990, Mattson et al., 1993). Indeed, the increased production of $\text{A}\beta$ oligomers in AD patients has been attributed to the higher incidence of epileptic seizures, especially in patients in the early stages of disease (Amatniek et al., 2006). It is also worth considering the overt link between CP-AMPA expression and aberrant neuronal network activity that is prevalent in epilepsy (Rajasekaran et al., 2012), in the context of the seizure activity and cognitive impairments that are evident in APP transgenic mouse models and AD patients (Palop et al., 2007, Pandis and Scarmeas, 2012). These findings support the notion that dysregulated Ca^{2+} flux through sustained CP-AMPA expression in early phases of AD may accelerate the onset of neuronal network dysfunction and neuronal excitotoxicity, thus propagating cognitive decline (Palop and Mucke, 2009), though it remains to be seen whether CP-AMPA receptors are expressed solely at these initial stages of pathology, or again at a later point in the disease cycle.

Aberrant synapse weakening, which promotes the elimination of synaptic connections, also appears to be an underlying feature of several neuropathological conditions (Hasbani et al., 2000, Bradley et al., 2012, Sheng et al., 2012, Park and Biederer, 2013). Synapse weakening processes involve a number of specific catalyzing signals (Collingridge et al., 2010). We have recently identified the activation of caspase-3 and glycogen synthase kinase 3 β (GSK3 β), and phosphorylation of the microtubule associated protein tau (pTau), as being pivotal and necessary end-point signals in synapse weakening (Kimura et al., 2014, Regan et al., 2015, Regan et al., 2016). Critically, aberrantly enhanced pTau is a common factor to synapse dysregulation and weakening induced by a variety of factors, including $\text{A}\beta$, stress and neurotrophins (Sotiropoulos et al., 2011, Pooler et al., 2014, Kailainathan et al., 2016). Given the aforementioned importance of CP-AMPA expression to the initial synaptic alterations induced by stress and $\text{A}\beta$ (Whitehead et al., 2013, Whitcomb et al., 2015), one favourable hypothesis is that CP-AMPA expression leads to aberrant synapse weakening via the activation of signaling pathways culminating in tau phosphorylation. Interestingly, synaptic activity leading to accumulation of intracellular Ca^{2+} has been shown to increase phosphorylation of tau at serine residues 396/404 (S396/404), via Ca^{2+} -dependent activation of GSK3 β

(Pierrot et al., 2006). In addition, hyperphosphorylation of tau has been linked to abnormal Ca^{2+} signaling through excitotoxic levels of glutamate (Guo et al., 1999, Leissring et al., 2000), and this dysregulated Ca^{2+} could serve as the conduit between CP-AMPA expression and pTau. Further work is therefore required to fully determine the potential role of CP-AMPA receptors in synapse weakening pathways including pTau and other substrates.

4. Conclusion and translation

Neurodegenerative diseases such as AD are currently without effective treatments or cures (Casey et al., 2010). Given the growing evidence implicating CP-AMPA receptors in the onset of synaptic pathology (Grooms et al., 2000, Kwak and Weiss, 2006, Rajasekaran et al., 2012, Whitcomb et al., 2015), this form of AMPAR could well serve as a therapeutic target in the development of new treatments in AD and other neurodegenerative diseases. Indeed, targeting CP-AMPA receptors has been cited as a potential strategy in other neurological disorders (Henley and Wilkinson, 2016). However, in order to effectively develop novel methodologies to modulate CP-AMPA receptor function in disease, we first require an understanding of the mechanisms by which CP-AMPA receptors aberrantly function, and the downstream consequences. In doing so, meaningful approaches in the development of CP-AMPA receptor regulators can be undertaken. Two non-competitive inhibitors of AMPA receptors, talmpanel and peramppanel, have shown some efficacy in reducing seizure activity in clinical trials (Chappell et al., 2002, Kerling and Kasper, 2013) and have been shown to reduce neuronal Ca^{2+} elevations in cultured neurons (Hanada et al., 2011, Paizs et al., 2011). However, whether these antagonists might prove to be a useful therapeutic strategy for AD remains to be seen. A promising strategy for limiting the progression of the disease could involve the development of a highly selective, bioavailable CP-AMPA receptor antagonist administered at an early, pre-symptomatic stage of AD.

Figure Legend

Figure 1. Structure and binding partners of AMPAR subunits.

The structure of an AMPAR subunit, consisting of an extracellular N-terminal domain (NTD) and an intracellular C-terminal domain (CTD), three transmembrane domains (M1, M3, M4) and a channel pore loop (M2). The alternately spliced flip/flop site encodes a short amino-acid sequence within an extracellular domain of the AMPAR subunit and the Q/R editing site is shown within the channel pore loop. Depending on the AMPAR subunit, the CTD may be either short or long-tailed, which alters the trafficking properties and interacting partners of AMPARs. Shown are the AMPAR CTD binding proteins 4.1N, synapse-associated protein 97 (SAP97), post synaptic density protein (PSD95), Drosophila disc large tumor suppressor (Dlg1), and zonula occludens-1 protein (zo-1) (PDZ), N-ethylmaleimide-sensitive factor (NSF), Glutamate receptor-interacting protein (GRIP), and protein that interacts with protein C-kinase 1 (PICK1).

Figure 2. The role of CP-AMPA receptors in synaptic function.

(A and B) CP-AMPA receptors exhibit a characteristic inward rectification, a result of channel pore block by intracellular polyamines that limits current flow at positive membrane potentials. This is in contrast to GluA2-containing AMPARs, which are insensitive to polyamine blockade, and therefore demonstrate a linear current flow as a function of membrane potential. (C) The C-terminal domain (CTD) of GluA1-containing AMPARs is subject to several characterized phosphorylation events through a number of identified kinases, including Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII), protein kinase C (PKC), protein kinase A (PKA), and p21-activated kinase 3 (PAK3). Phosphorylation at specific residues has downstream effects upon synaptic AMPAR trafficking.

Figure 3. Stress-primed metaplasticity and CP-AMPA receptors.

Release of glucocorticoids (GCs) during an acute stressor primes synapses for subsequent plasticity inducing events. Transient activation of glucocorticoid receptors (GR) promotes CP-AMPA receptor insertion at the synapse via PKA-mediated phosphorylation of the GluA1 CTD. A consequence of this is the facilitation of LTP due to the addition of an NMDAR-independent, CP-AMPA receptor-mediated component of synaptic potentiation.

Figure 4. Intracellular amyloid- β mediated CP-AMPA receptors trafficking.

Intracellular amyloid- β ($A\beta$) oligomers promote CP-AMPA insertion at the synapse. Presynaptic glutamate release activates postsynaptic GluA2-containing AMPARs to elicit excitatory postsynaptic potentials (EPSCs). Infusion of $A\beta$ oligomers induces the PKA-mediated phosphorylation of S845 of GluA1, promoting the synaptic expression of CP-AMPA. The consequences of this in the short-term are a rapid enhancement of synaptic transmission and neuronal activity.

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