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GluA3-containing AMPA receptors: From physiology to synaptic dysfunction in brain disorders

Maria Italia, Elena Ferrari, Monica Di Luca, Fabrizio Gardoni *

Department of Pharmacological and Biomolecular Sciences (DiSFeB), University of Milan, 20133 Milan, Italy

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ABSTRACT

In the mammalian brain, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors (AMPARs) play a fundamental role in the activation of excitatory synaptic transmission and the induction of different forms of synaptic plasticity. The modulation of the AMPAR tetramer subunit composition at synapses defines the functional properties of the receptor. During the last twenty years, several studies have evaluated the roles played by each subunit, from GluA1 to GluA4, in both physiological and pathological conditions. Here, we have focused our attention on GluA3-containing AMPARs, addressing their functional role in synaptic transmission and synaptic plasticity and their involvement in a variety of brain disorders.

Although several aspects remain to be fully understood, GluA3 is a widely expressed and functionally relevant subunit in AMPARs involved in several brain circuits, and its pharmacological modulation could represent a novel approach for the rescue of altered glutamatergic synapses associated with neurodegenerative and neurodevelopmental disorders.

1. Introduction

Identifying the molecular and cellular mechanisms underlying long-lasting modifications of synaptic circuits, defining how these mechanisms drive cognition, and understanding how alterations in these mechanisms lead to the development of brain disorders represent key aims in the field of neuroscience. Decades of research have indicated that activity-dependent changes in synaptic efficacy, particularly synaptic plasticity events, serve as the cellular correlates for learning and memory.

In the central nervous system (CNS), excitatory neurotransmission is primarily mediated by glutamate and its ionotropic receptors, including the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPARs) that mediate rapid transmission (Hollmann and Heinemann, 1994; Malinow and Malenka, 2002; Diering and Huganir, 2018) and the *N*-methyl-D-aspartate (NMDA) receptors (NMDARs) that sustain the induction of long-term synaptic plasticity (Hunt and Castillo, 2012; Paoletti et al., 2013). NMDARs have been implicated in transcription-dependent forms of plasticity because NMDAR activation regulates gene transcription, affecting global protein synthesis (Hardingham and Bading, 2010; Gardoni and Di Luca, 2021). In the mammalian brain, AMPARs are cation-permeable, tetrameric receptors composed of various combinations of the pore-forming subunits GluA1–GluA4 (see Table 1). Although homotetrameric AMPARs have been described, most AMPARs are heteromeric (Wenthold et al., 1996; Lu et al., 2009). The subunit composition of AMPARs has been widely investigated, and the various subunit combinations have been suggested to regulate the biophysical properties of AMPARs (Isaac et al., 2007; Jonas, 2000), allowing different AMPAR heteromers to regulate receptor trafficking at synapses and mediate the fine modulation of synaptic strength and synaptic plasticity (Bredt and Nicoll, 2003; Shi et al., 2001). AMPAR subunits have been shown to differ in Ca^{2+} permeability: the presence of a positively charged arginine lining in the channel pore makes AMPARs containing GluA2 impermeable to Ca^{2+}, whereas GluA1, −3, and − 4 feature neutral glutamine residues on the pore face rather than arginine, allowing Ca^{2+} passage upon activation (Burnashev

Abbreviations: AD, Alzheimer's Disease; ALS, amyotrophic lateral sclerosis; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPARs, AMPA receptors; Aβ, beta-amyloid; CNS, central nervous system; cAMP, cyclic adenosine monophosphate; FTD, Frontotemporal Dementia; ID, intellectual disability; KO, knockout; LTD, long-term depression; LTP, long-term potentiation; mEPSC, miniature excitatory postsynaptic currents; NDD, neurodevelopmental disorders; NMDA, *N*-methyl-D-aspartate; NMDARs, NMDA receptors; NREM, non-rapid eye movement; PAM, positive allosteric modulator; PSD, postsynaptic density; PKA, protein kinase A; WT, wild-type..

* Corresponding author at: DiSFeB, Via Balzaretti 9, 20133 Milano, Italy.
E-mail address: fabrizio.gardoni@unimi.it (F. Gardoni).

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et al., 1992; Geiger et al., 1995; Jonas et al., 1994) (see Table 1).

AMPARs are widely distributed throughout the CNS, representing key factors in the activation of glutamatergic synapses; however, the relative abundance and subunit composition of AMPARs varies across brain areas (Petralia and Wenthold, 1992; Schwenk et al., 2014). Both proteomic and genetic analyses have demonstrated that in hippocampal neurons, GluA1 and GluA2 are the most abundant pore-forming subunits, comprising 80% of the entire pool of AMPARs (Lu et al., 2009; Schwenk et al., 2014). In other regions, such as the cortex and the striatum, GluA2 is the predominant subunit, whereas GluA1 and GluA3 are expressed at similar levels (Gold et al., 1996; Kessels and Malinow, 2009; Schwenk et al., 2014; Jacob and Weinberg, 2015). Although the majority of AMPAR research over the last two decades has focused on understanding the physiopathological roles played by GluA1/GluA2 AMPARs, attention must also be directed toward the GluA3 subunit, which is found in a number of AMPARs in the brain. GluA4 is mainly expressed in neurons early in life and provides plasticity events relevant for synapse maturation (Zhu et al., 2000).

Differences have been reported in the subcellular localization and synaptic trafficking of AMPARs containing GluA2/GluA3 compared with those comprising GluA1/GluA2. First, GluA3-containing AMPARs are uniformly enriched at synaptic sites and are only rarely distributed perisynaptically (Jacob and Weinberg, 2015). A proteomics study observed that the GluA3 subunit is the most enriched subunit within the excitatory postsynaptic density (PSD) under basal conditions (Pandya et al., 2017). Conversely, although GluA1/GluA2 AMPARs are enriched at synapses, they can also be located at extrasynaptic domains (He et al., 2009; Lu et al., 2009). Currently, scarce knowledge is available to explain these differences and demonstrate their associated functional outcomes. A large number of studies published in the past twenty years have demonstrated the existence of specific trafficking mechanisms that regulate the localization of different AMPAR pools. GluA1/GluA2 AMPARs are primarily inserted in the postsynaptic membrane following induction of synaptic plasticity (Shi et al., 2001), whereas GluA2/GluA3-containing AMPARs undergo constitutive recycling and replace GluA1/GluA2 AMPARs in synapses at rest (Shi et al., 2001). Within this framework, the functional role of GluA3-containing AMPARs at excitatory synapses has long been debated. Although the requirement for GluA1/GluA2 AMPARs to induce synaptic plasticity has been fully addressed, the relevance of GluA3 in these processes has remained unclear. Several hypotheses have been proposed, ranging from a key role for GluA3 subunits in the maintenance and stabilization of synaptic strength to the involvement of GluA3 subunits in the consolidation of long-term memories. In addition, and of utmost importance, the contribution of GluA3-containing AMPARs to the development of brain disorders has only recently begun to be explored, and several issues remain to be investigated.

Here, we review the current knowledge regarding the physiological role of GluA3-containing AMPARs and their contributions to synaptic dysfunction associated with various brain disorders.

2. GluA3-containing AMPARs: physiological roles

2.1. Involvement of GluA3-containing AMPARs in synaptic transmission and synaptic plasticity

The most extensively studied forms of long-term synaptic plasticity at excitatory synapses are long-term potentiation (LTP) and long-term depression (LTD), which are widely considered to be key processes for learning and memory (Cheyne and Montgomery, 2020). Alterations in the induction of LTP and LTD have been correlated with several brain disorders associated with both neurodevelopmental and neurogenerative states (Nathan et al., 2011).

The molecular mechanisms that govern the induction and long-term maintenance of synaptic plasticity have been intensively investigated, and seminal studies have identified that modifications in the functional properties, synaptic expression levels, and subunit compositions of AMPARs play fundamental roles in the expression of physiological forms of LTP and LTD in the mammalian brain (Malinow and Malenka, 2002; Anggono and Huganir, 2012). Each subunit within the AMPAR is proposed to play a distinct role at excitatory synapses during the regulation of synaptic plasticity. However, although a large number of studies have clearly addressed the specific roles played by GluA1- and GluA2-containing AMPARs in LTP and LTD, limited publications are currently available examining the role of GluA3-containing AMPARs in synaptic plasticity (Diering and Huganir, 2018).

The use of genetic approaches demonstrated that GluA2/GluA3 double-knockout (KO) mice are characterized by a dramatic decrease in the amplitude of basal synaptic transmission in the hippocampus, indicating that GluA2/GluA3 AMPARs are essential for *in vivo* physiological synaptic transmission. However, GluA2/GluA3 double-KO mice correctly display several forms of long-lasting hippocampal synaptic plasticity, including LTP and LTD (Meng et al., 2003).

GluA3 single-KO mice exhibit physiological hippocampal synaptic transmission, showing only a small reduction in synaptic currents and little changes in extrasynaptic currents (Meng et al., 2003; Humeau et al., 2007; Lu et al., 2009). However, analysis of the AMPA/NMDA ratio and the frequency of miniature excitatory postsynaptic currents (mEPSC) in CA1 hippocampal neurons in GluA3-deficient organotypic slices showed significant reductions compared with wild-type (WT) neurons (Reinders et al., 2016). Importantly, no alterations in LTD and enhanced or unchanged LTP were found in GluA3 KO mice (Meng et al., 2003; Humeau et al., 2007). Similarly, the use of a theta-burst stimulation at CA3–CA1 synapses resulted in an unchanged physiological LTP magnitude in GluA3-deficient slices (Reinders et al., 2016), which suggested that the GluA3 subunit is not involved in the expression of these primary forms of synaptic plasticity.

Renner et al. (2017) showed that GluA2/GluA3 AMPARs contribute little to glutamatergic transmission at CA1 hippocampal synapses at rest due to a low-conductance state but become functional following increased postsynaptic cyclic adenosine monophosphate (cAMP) concentrations, leading to augmented glutamate-gated channel opening and

Table 1
Summary of the main properties of each AMPAR subunit.

	GluA1	GluA2	GluA3	GluA4	References
Temporal expression	Early and late development, mature brain	Late development, mature brain	Early and late development, mature brain	Mainly during early development	Pellegrini-Giampietro et al., 1992
Regional predominance	Hippocampus	Hippocampus	Cortex	Cerebellum	Schwenk et al., 2014
Calcium permeability	yes	no	yes	yes	Burnashev et al., 1992
Synaptic targeting	Upon neuronal activity	Constitutively and upon neuronal activity	Constitutively	Upon neuronal activity	Shi et al., 2001;Hayashi et al., 2000
C-terminal Phosphosites	S818, S831, T840, S845, S863	S863, Y876, S880	Y881, S885	S842	Diering and Huganir, 2018
Intracellular C-terminal tail	Long (aa 809–889)	Short (aa 834–883)	Short (aa 839–888)	Long (aa 815–882)	Diering and Huganir, 2018

synaptic potentiation. These intracellular events require the activation of protein kinase A (PKA), the GTPase Ras, and the activation of β-adrenergic receptors (Renner et al., 2017); however, the specific contributions of these molecular mechanisms in the induction of hippocampal LTP remain to be fully addressed.

Importantly, studies have also addressed the role of GluA3-containing AMPARs in other brain circuits, beyond those in the hippocampus, that are relevant for learning and memory, motor, and social behavior. At thalamo- and cortico-lateral amygdala synapses, GluA3 deletion did not modify AMPAR-mediated synaptic transmission, although significant reductions in the amplitude and frequency of mEPSCs were observed (Humeau et al., 2007). Moreover, the amplitude of LTP at thalamo-amygdala synapses was not altered in GluA3 KO mice (Humeau et al., 2007). Conversely, LTP was absent in the cortico-amygdala pathway in GluA3 KO mice, suggesting the specific involvement of GluA3 at cortico-amygdala synapses (Humeau et al., 2007).

At synapses involving cerebellar Purkinje neurons, LTP was strictly dependent on the presence of GluA3- but not GluA1-containing AMPARs (Gutierrez-Castellanos et al., 2017). Interestingly, similar to the mechanism described at hippocampal synapses, GluA3-dependent LTP at cerebellar synapses does not involve GluA3 trafficking but correlates to a cAMP-dependent increase in the AMPAR channel open-probability (Gutierrez-Castellanos et al., 2017). Analysis of GluA3 KO mice also showed a fundamental role for this subunit in synaptic transmission and activity-dependent plasticity in endbulb–bushy cell synapses in the anteroventral cochlear nucleus of the auditory system (Antunes et al., 2020). At these synapses, the GluA3 subunit plays a relevant role in ultrastructural modifications (Rubio et al., 2017), activity-dependent plasticity, and normal auditory processing (García-Hernández et al., 2017; Antunes et al., 2020). In particular, GluA3 drives the ultrafast kinetics of endbulb synapse glutamatergic currents and is necessary for the function and maturation of the presynaptic terminal, modulating short-term plasticity (Antunes et al., 2020).

2.2. Role of GluA3-containing AMPARs in mouse behavior

The availability of GluA3-deficient mice has allowed for the detailed characterization of the role of GluA3 in various displays of animal behavior, providing an *in vivo* correlation with the function of the subunit in synaptic transmission and synaptic plasticity in different brain areas (see Table 2). GluA3 KO mice did not show gross behavioral abnormalities and were similar to WT mice in a wide array of behavioral assays evaluating exploration, anxiety, motor, and memory behaviors (Sanchis-Segura et al., 2006; Adamczyk et al., 2012). However, mild impairments in motor coordination and locomotor activity were observed in GluA3 KO mice compared with control mice (Sanchis-Segura et al., 2006; Adamczyk et al., 2012). The reduced performance of GluA3-deficient mice in motor tests, such as the accelerated rotarod assay, was not associated with any significant impairments in grip strength performance (Adamczyk et al., 2012). In support of the identified role for GluA3 in cerebellar Purkinje neurons, GluA3-deficient mice showed significant impairments in cerebellum-dependent learning involving the adaptation of compensatory eye movements (Gutierrez-Castellanos et al., 2017).

Importantly, GluA3-deficient mice did not display deficits relative to WT mice in the cognitive functions evaluated by the Morris water maze or Y-maze tests (Adamczyk et al., 2012; Humeau et al., 2007), indicating that GluA3-containing AMPARs do not play key roles in plasticity mechanisms associated with memory formation.

In a free behavior setting, GluA3 KO mice show an almost total absence of electroencephalographic signatures of non-rapid eye movement (NREM) sleep, and seizure activity was detected both during wakefulness and sleep, suggesting that GluA3 deficiency may predispose mice to seizures (Steenland et al., 2008). GluA3 KO mice also show a selective reduction in breathing rate during behavioral inactivity (Steenland et al., 2008). Overall, these *in vivo* data indicate that the GluA3 subunit plays a major role in neurophysiology.

Table 2
Summary of GluA3 KO mentioned effects in mice.

	Effect of GluA3 KO	References
Synaptic transmission and plasticity		
Short term depression at endbulb–bushy cell synapses	Enhanced	Antunes et al., 2020
LTD at cerebellar Purkinje neurons	Not affected	Gutierrez-Castellanos et al., 2017
LTP at thalamo-amygdala synapses	Not affected	Humeau et al., 2007
LTD at hippocampal synapses	Not affected	Meng et al., 2003 Humeau et al., 2007
AMPAR currents at thalamo- and cortico-lateral amygdala synapses	Not affected	Humeau et al., 2007
Hippocampal synaptic and extra-synaptic currents	Mildly reduced	Meng et al., 2003 Humeau et al., 2007 Lu et al., 2009
LTP at cortico-amygdala synapses	Reduced	Humeau et al., 2007
LTP at hippocampal synapses	Reduced[a]	Meng et al., 2003 Humeau et al., 2007 Reinders et al., 2016
AMPA/NMDA ratio at CA1 synapses	Reduced	Reinders et al., 2016
mEPSC at CA1 synapses	Reduced	Reinders et al., 2016
mEPSCs at thalamo- and cortico-lateral amygdala synapses	Reduced	Humeau et al., 2007
LTP at cerebellar Purkinje neurons	Reduced[a]	Gutierrez-Castellanos et al., 2017
Ultrafast kinetics of endbulb-bushy cell synapses glutamatergic currents	Reduced	Antunes et al., 2020
Animal behavior		
Aggressive and social behaviors	Enhanced	Adamczyk et al., 2012
Seizure activity	Enhanced	Steenland et al., 2008
Alcohol-seeking and relapse behavior	Not affected	Li et al., 2017
Grip strength performance	Not affected	Adamczyk et al., 2012
Morris maze and Y-maze	Not affected	Adamczyk et al., 2012 Humeau et al., 2007
Motor coordination and locomotor activity	Mildly reduced	Sanchis-Segura et al., 2006 Adamczyk et al., 2012
Conditioned freezing behavior	Delayed acquisition	Humeau et al., 2007
Cerebellum-dependent learning	Reduced	Gutierrez-Castellanos et al., 2017
Breathing rate during inactivity	Reduced	Steenland et al., 2008
Non-rapid eye movement sleep	Reduced	Steenland et al., 2008

Upper rows: effects on synaptic transmission and plasticity. Lower rows: effects on animal behavior.
[a] Effect correlated to a cAMP-dependent increase.

GluA3 KO mice have a delayed acquisition of conditioned freezing behavior. However, they show physiological freezing behavior after the third conditioned stimulus, during an aversive unconditioned stimulus pairing, and during conditioned stimulus and context memory tests (Humeau et al., 2007). As described above, LTP is absent in the cortico-amygdala synapses of GluA3 KO mice, suggesting the limited involvement of GluA3-containing AMPARs in conditioned freezing. Conversely, GluA3-deficient mice show altered aggressive and social behaviors, ranging from an increase in isolation-induced male aggression during the home cage resident-intruder test to an increase in sociality and male-male social interactions in a neutral arena (Adamczyk et al., 2012). In agreement with the observed increase in aggressive behavior, the *GRIA3* gene encoding the GluA3 subunit was identified as a quantitative trait locus for aggression (Brodkin et al., 2002).

Analysis of alcohol-seeking and relapse behavior, which are known to be associated with AMPAR function (Li et al., 2017), showed no alterations in ethanol self-administration behavior under operant or home cage drinking conditions in GluA3 KO mice. However, these animals

showed a blunted cue-induced reinstatement response and an alcohol deprivation effect compared with WT animals, suggesting a role for GluA3 in alcohol relapse (Sanchis-Segura et al., 2006).

Overall, the use of KO mice allowed for a deeper understanding of the role of GluA3 in synaptic transmission, synaptic plasticity and mouse behavior. However, it is worth mentioning that the absence of GluA3 might trigger compensatory mechanisms in the mouse brain that, in turn, could in part hide and minimize the effects that result from the loss of the receptor subunit. In this regard, it would be useful to develop a mouse model in which GluA3 is just temporary and locally turned off with a genetic or a pharmacological approach.

3. GluA3-containing AMPARs: role in synaptic dysfunction associated with brain disorders

3.1. Neurodegenerative disorders

Alterations in the glutamatergic system have been described in many neurodegenerative diseases, and a substantial body of evidence has identified excitotoxicity as a mechanism underlying cell death in several pathological conditions. Coherently, compounds that interfere with NMDAR and AMPAR activities have been proposed to counteract neurodegenerative disease onset and progression (Stone and Addae, 2002; Jayakar and Dikshit, 2004).

In this section, we describe the role played by GluA3-containing AMPARs in two different neurodegenerative disorders, Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS). In these two pathological conditions, the GluA3 subunit contributes to neurodegeneration through different and – at least in part – opposite mechanisms. In AD, the increased endocytosis of the GluA3 subunit is required for beta-amyloid (Aβ)-mediated synaptic and cognitive deficits (Reinders et al., 2016), whereas, in ALS, the increased expression of GluA3-containing AMPARs in motor neurons promotes excitotoxicity and neuronal death (Rembach et al., 2004; Spalloni et al., 2004) (see Fig. 1). Regardless of the mechanism, GluA3 plays a role in these pathological conditions and might represent a potential target for therapeutic strategies.

3.1.1. Alzheimer's disease

AD is the most common form of senile dementia, accounting for approximately 60%–80% of all dementia cases. The initial stages of AD are characterized by deficits in the process of encoding and storing new memories, followed by changes in cognition and behavior, which appear in later stages. These dramatic symptoms result from a diffuse neurodegenerative process throughout the brain (Soria Lopez et al., 2019).

Two primary pathological events are thought to be responsible for AD: alterations in the cleavage of amyloid precursor protein, followed by the subsequent production and oligomerization of the Aβ peptide, and the aggregation of hyperphosphorylated tau protein (Selkoe and Hardy, 2016). The production and oligomerization of Aβ result in the formation of extracellular senile plaques, whereas tau hyperphosphorylation results in the accumulation of intracellular neurofibrillary tangles. The accumulation of Aβ appears to play a prevalent role in neurodegeneration. According to the "amyloid cascade hypothesis," the pathological extracellular secretion of Aβ triggers multiple, detrimental, downstream effects, such as the formation of phospho-tau-based neurofibrillary tangles, excitotoxicity, inflammation, and oxidative stress (Selkoe, 2004; Querfurth and Laferla, 2010).

Senile plaques and neurofibrillary tangles, combined with metabolic, vascular, and inflammatory changes, reduce synaptic strength, leading to synaptic loss and neurodegeneration. Many pieces of evidence indicate that AD can be categorized primarily as a synaptopathy, in which the progressive loss of synaptic plasticity and synapses parallels the observed cognitive decline and other AD symptoms (Shankar et al., 2008; Talantova et al., 2013).

Importantly, the loss of synapses and dendritic spines, which

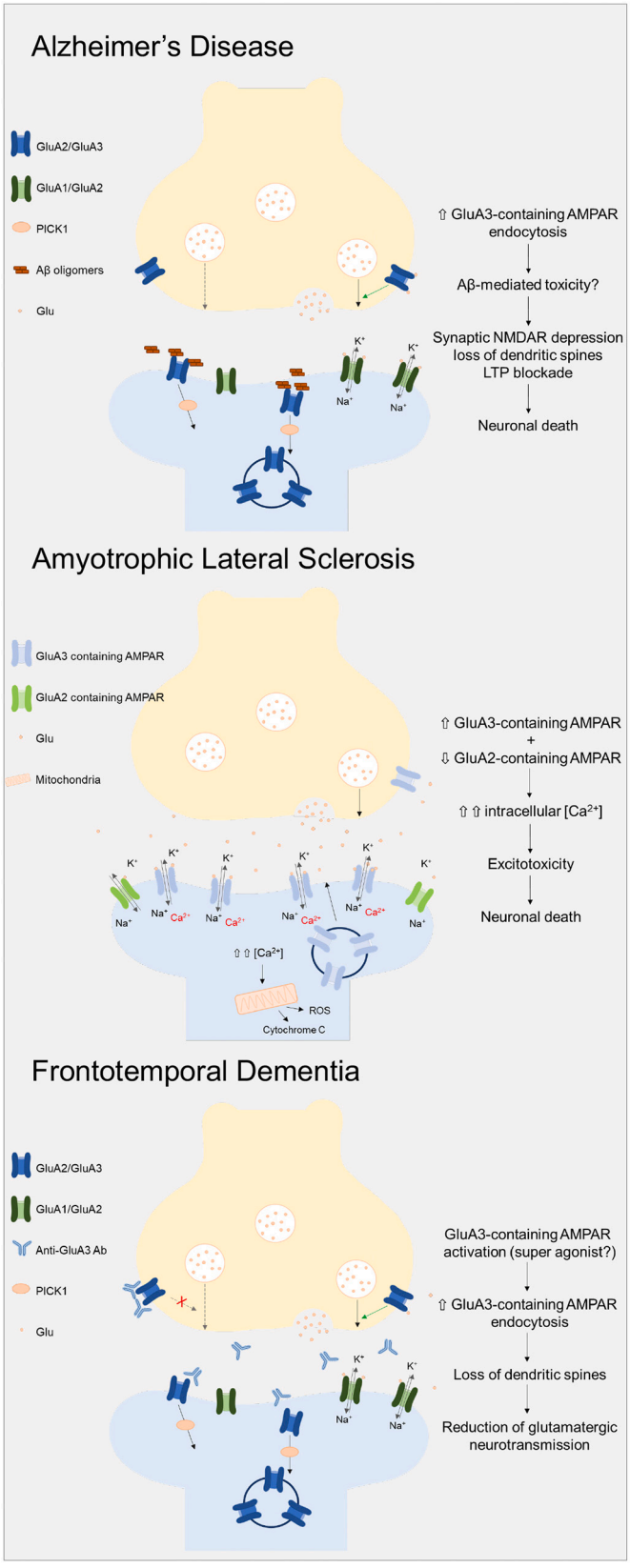

Fig. 1. Schematic representation of GluA3 subunit involvement in Alzheimer's disease, amyotrophic lateral sclerosis and frontotemporal dementia.

characterize the early phases of AD, are associated with the active Aβ-mediated removal of postsynaptic receptors. Specifically, Aβ generates structural and synaptic abnormalities *via* the endocytosis of AMPARs, suggesting that AMPARs downregulation underlies the observed Aβ-induced synaptic depression and dendritic spine loss (Baglietto-Vargas et al., 2018; Miyamoto et al., 2016; Hsieh et al., 2006; Minano-Molina et al., 2011; Alfonso et al., 2014; Henley and Wilkinson, 2016; Zhang et al., 2017). These observations are coherent with the general hypothesis that perturbations in glutamatergic signaling, specifically in the glutamate tripartite synapse, contribute to the pathogenic mechanisms of AD (Rudy et al., 2015; Findley et al., 2019). Intriguingly, Reinders et al. (2016) demonstrated that the GluA3 AMPAR subunit plays a prominent role in Aβ-dependent toxicity. Hippocampal neurons that did not express GluA3 were protected against Aβ-mediated synaptic depression and spine loss, and Aβ only disrupted long-term synaptic potentiation in neurons that expressed GluA3. Aβ-overproducing mouse (APP/PS1 transgenic mouse) crossed with GluA3 deficient one (male GluA3−/Y and female GluA3−/−) showed increased resistance against Aβ-induced memory impairments compared with animals expressing normal levels of GluA3 (Makino and Malinow, 2011). These experiments demonstrated that the presence of GluA3-containing AMPARs is critical for Aβ-mediated synaptic and cognitive deficits, and the active removal of GluA3-containing AMPARs is necessary to trigger the subsequent synaptic pathogenic events. Importantly, the GluA3 subunit has been described to play a role in the homeostatic scaling of synaptic strength (Makino and Malinow, 2011). We can, thus, speculate that the Aβ-induced removal of synaptic GluA3 may also impact homeostatic plasticity, which has been shown to be altered in AD (Jang and Chung, 2016). Coherently, protein interacting with C kinase 1 (PICK1), which is known to be involved in GluA3 endocytosis (Diering and Huganir, 2018), is also required for the synaptic-depressive effects of Aβ (Alfonso et al., 2014).

Another mechanism has been identified that might link GluA3 to AD development: GluA3 is modified by site-specific limited proteolysis, including cleavage by γ-secretase (Meyer et al., 2003). Alterations in the γ-secretase proteolytic system are associated with AD pathogenesis through the generation of the toxic Aβ peptide but they may also directly affect AMPAR function by modifying its physiological cleavage.

These preclinical studies are further supported by a recent study showing altered GluA3 levels in the biological fluids of AD patients. Enache et al. (2020) reported increased GluA3 levels in the cerebrospinal fluid (CSF) of AD patients compared with those from cognitively normal subjective cognitive decline (SCD) patients. Although the aim of this study was to identify synaptic proteins capable of marking differences between SCD and clinical dementia, the reported increase in GluA3 concentrations in the CSF from AD patients further indicates the involvement of this receptor subunit in AD.

Overall, these data demonstrate the increasing attention being paid to AMPARs in the AD field. Coherently, a treatment with an AMPAR positive allosteric modulator (PAM) was shown to ameliorate cognitive and memory deficits in a non-transgenic murine model of Aβ oligomer injection, reducing the accumulation of soluble tau in the hippocampus and resulting in decreased excitotoxic synaptic signaling (Monteiro-Fernandes et al., 2020). These findings suggest that the specific potentiation of AMPAR signaling can inhibit the effects of Aβ during the early disease stage. We can also speculate that the interference with the effects of Aβ on the GluA3 AMPAR subunit might represent a potential new strategy for counteracting early-stage AD progression. If Aβ requires GluA3 to exerts its detrimental effects on synapses (through an increased AMPAR endocytosis), as suggested by Reinders et al. (2016), preventing this interaction may represent an opportunity to counter-act the negative effects of Aβ even at earlier stages. In other words, Monteiro-Fernandes and colleagues showed that potentiating AMPAR ameliorate AD pathological phenotype but, possibly, preventing Aβ-mediated GluA3 endocytosis and all the pathological events that follows (including synapses loss and reduced AMPA/NMDA ratio) may contribute to tackle the problem from the root.

3.1.2. Amyotrophic lateral sclerosis

ALS is a neurodegenerative disease characterized by muscle atrophy and weakness, fasciculations, and spasticity, which result from the selective death of lower motor neurons in the brainstem and spinal cord and upper motor neurons in the motor cortex. In some cases, neurodegeneration also involves neurons in the prefrontal and temporal cortices, possibly leading to frontal executive dysfunctions and the concomitant appearance of frontotemporal dementia (FTD) symptoms (Robberecht and Philips, 2013).

A variety of mechanisms have been proposed to serve as triggers or enhancing factors that contribute to ALS pathogenesis, such as interference with normal proteasomal or autophagic protein degradation and the disturbance of normal RNA processing. Most of the genes associated with familial forms of ALS (FALS) are involved in these pathways, and the resulting alterations progressively lead to cellular failure. Other factors might contribute to the vulnerability of motor neurons, including the increased susceptibility to glutamate excitotoxicity, which appears to play a prevalent role (Robberecht and Philips, 2013). Only a few drugs have been approved for ALS treatment, including riluzole, a drug that exerts neuroprotective effects by attenuating glutamatergic neurotransmission (Bryson et al., 1996; Doble, 1996; Geevasinga et al., 2016).

Glutamate excitotoxicity results from glutamate-mediated neuronal overstimulation, which induces increased Ca^{2+} influx and triggers the subsequent aberrant activation of downstream pathways (Heath and Shaw, 2002). Multiple factors can contribute to excessive Ca^{2+} ion influx, such as pathologically high glutamate levels and changes in the AMPAR composition. For its being impermeable to Ca^{2+}, GluA2 plays a crucial role in counteracting glutamate excitotoxicity. Many pieces of evidence show that AMPAR-mediated Ca^{2+} influx contributes to selective motor neuron death (Shaw, 1994; Takuma et al., 1999). Reports show that motor neurons are physiologically GluA2-deficient, increasing their susceptibility to Ca^{2+}-mediated excitotoxicity (Petralia et al., 1997; Williams et al., 1997; Shaw and Ince, 1997; Heath et al., 2002; Van Damme et al., 2002; Kawahara et al., 2003).

A role for AMPARs, especially the GluA3 and GluA2 subunits, in ALS pathogenesis has been speculated. Multiple groups identified alterations in GluA3 expression in a well-validated transgenic mouse model of FALS, which overexpresses the mutant human superoxide dismutase (*SOD1*) gene, containing a glycine ➔ alanine (G93A) substitution ($SOD1^{G93A}$ mice; Gurney et al., 1994). Increased levels of GluA3 protein and mRNA expression were identified in spinal cords of $SOD1^{G93A}$ mice (Rembach et al., 2004) and cultured motor neurons derived from $SOD1^{G93A}$ mice (Spalloni et al., 2004). In the motor neurons of $SOD1^{G93A}$ mice, GluA3 mRNA and protein overexpression are accompanied by GluA2 protein downregulation (Tortarolo et al., 2006). Consistent with these alterations in AMPAR composition, $SOD1^{G93A}$ cultured motor neurons showed an increased vulnerability to AMPAR-mediated excitotoxicity (Spalloni et al., 2004).

Together, these independent results support the idea that the altered expression of Ca^{2+} permeable (GluA2-lacking) and impermeable (GluA2-containing) AMPARs contributes to disease onset and progression. Compared with WT motor neurons, the presence of higher numbers of Ca^{2+}-permeable AMPARs in motor neurons with *SOD1* mutations predisposes them to injury due to AMPAR-mediated glutamate stimulation.

Two different therapeutic strategies for ALS have been tested, targeting the AMPAR system. Rembach et al. (2004) proposed a rescue strategy using an antisense peptide nucleic acid that directly targets GluA3 and that demonstrated substantial reductions in *in vitro* GluA3 expression. Surprisingly, the administration of this compound to $SOD1^{G96A}$ mice extended the animal survival and delayed disease onset and progression, possibly due to the prevention of AMPAR-mediated excitotoxicity (as was demonstrated in the *in vitro* model). Similarly, the treatment of $SOD1^{G96A}$ mice with a non-competitive AMPAR

antagonist (ZK 187638) partially protected motor neurons, improved motor function, and prolonged animal survival (Tortarolo et al., 2006).

In summary, although historically the GluA2 subunit has been investigated for its role in ALS motor neurons excitotoxicity, the data reported above suggest that neuronal damage might be the result of the overall dysregulation of AMPAR composition that ultimately disrupts physiological calcium influx. In this view, GluA3 observed alterations could be considered an additional event that worsen the excitotoxic scenario. Coherently, these studies support the need of further investigating the timing of GluA3 dysregulation and the interactions between AMPARs and ALS-causing mutations. In conclusion, the interference with both GluA2 and GluA3 may represent a strategy for counteracting glutamate-mediated excitotoxicity in the motor neurons of ALS patients, which might ameliorate disease progression.

3.2. Neurodevelopmental disorders and intellectual disability

Imbalances in glutamatergic signaling have emerged as playing an important role in the pathogenesis of several neurodevelopmental disorders (NDDs), including intellectual disability (ID). Chromosomal rearrangements and gene mutations involving glutamate receptors and related synaptic scaffolding proteins have been linked to NDDs for several years (Moretto et al., 2018; Soto et al., 2014). Enormous advances in DNA sequencing technology have enabled the performance of whole-genome studies on large cohorts of patients, allowing for the better characterization of the roles and prevalence of various genes in the complex genetic landscapes of NDD and ID (Koboldt et al., 2013). Several clinical studies have identified alterations in the GluA3-encoding *GRIA3* gene in families with X-linked ID and mental retardation (Yuan et al., 2015). However, the identification of dysfunctions involving GluA3 activity in NDD and ID is insufficient to support any claims of common pathogenic mechanisms, and clinical presentations often vary from patient to patient, even within the same family. Functional studies of chromosomal rearrangements and gene variants identified in clinical cases have highlighted interesting pathogenic mechanisms.

3.2.1. Chromosomal rearrangements involving GRIA3

In 1999 the first evidence of *GRIA3* as a causative gene for ID was identified in a female patient carrying a balanced translocation involving the X-chromosome (Gécz et al., 1999). The patient presented with bipolar affective disorder, mental retardation, and epilepsy, which is a clinical presentation compatible with alterations in glutamatergic neurotransmission. Data collected on this clinical case did not allow for a detailed description of the specific pathogenic mechanism. However, the clinical presentation strongly supports the possible contribution of GluA3 alterations to at least some of the observed clinical manifestations.

A causative role for GluA3 in the pathogenesis of epilepsy was proposed in 1994. In particular, a study by Rogers et al. (1994) described patients with Rasmussen encephalitis bearing circulating GluA3 antibodies, the blockade of which improved neurological symptoms and epileptic manifestations. Subsequently, several other studies reported the involvement of *GRIA3* rearrangements in the etiology of different types of ID. Interestingly, whole-genome array comparative genomic hybridization studies performed in 2006 and 2013 correlated a genomic duplication containing *GRIA3* to syndromic autism spectrum disorder (Jacquemont et al., 2006) and syndromic ID (Philippe et al., 2013) in two different families. In addition to the link between whole-gene *GRIA3* duplications and ID, partial *GRIA3* duplications have been associated with X-linked mental retardation. Bonnet et al., in 2009, discovered a family bearing a partial tandem duplication of *GRIA3*, extending from exon 1 to exon 12. This work not only described the clinical and genomic alterations identified in affected individuals but also provided mechanistic insights on the underlying pathogenic process. Through expression analyses, they identified three aberrant transcripts originating from the partial duplication, which resulted in premature termination codons, leading to the loss of AMPAR function due to an imbalance in subunit composition. The working hypothesis is that the aberrant truncated transcripts produce truncated proteins that are either non-functional or undergo premature degradation (Bonnet et al., 2009).

3.2.2. Pathogenetic insights from GRIA3 deletions and mutations

Functional studies examining the effects of *GRIA3* deletions and missense mutations were performed, based on the sequencing results of 400 males with X-linked mental retardation (Wu et al., 2007). A complete gene deletion and four different *GRIA3* variants (G833R, M706T, R631S, and R450Q) were identified, all of which fall within important functional domains of the AMPAR subunit. *In vitro* functional studies were used to analyze the mRNA stability, protein levels, channel assembly, and AMPAR electrophysiological properties in the presence of the four missense variants. In particular, the G833R mutation resulted in a dramatic 78% reduction in the receptor protein level, and no or minimal channel currents were recorded in the presence of the M706T or R631S mutation. These results demonstrated, from both genetic and functional perspectives, that mutations in the GluA3 subunit have consequences on AMPAR-complex kinetics and functionality. Interestingly, these alterations were not only observed for GluA3 homomeric receptors but were also observed in GluA2-GluA3 heteromers. Despite being limited to an *in vitro* approach, this study suggested that specific neurological signs and mental retardation in human patients can be ascribed to decreased GluA3 channel activity (Wu et al., 2007).

The impact of single nucleotide variants and mutations in *GRIA3* on female subjects is still not clear, since in the majority of cases females carrying gene alterations are unaffected. So far, among 20 pathological *GRIA3* variants that have been described, only two patients were females (Trivisano et al., 2020; Gécz et al., 1999; Allen et al., 2016). Mothers bearing gene aberrations are usually healthy carriers, so, the mechanisms responsible for disease manifestations are largely unknown. Very recently a third female case has been reported, providing new insights into molecular pathogenic mechanisms (Sun et al., 2021). In details, a mutation in *GRIA3* has been discovered in a 1-year-old female with a severe neurologic clinical presentation comprising developmental delay and neonatal-onset epileptic encephalopathy. The R660T *de novo* variant falls within the extracellular region that links the transmembrane domain M3 and the ligand binding domain S2 of the subunit. This variant revealed to slow the deactivation and desensitization kinetics of both homomeric GluA3 and heteromeric GluA2/GluA3 AMPAR. In support of this mechanism, the importance of the linker domain was already highlighted by a work published in 2004. Mutations in the same region of GluA1, GluA2 and GluK2 subunits of glutamate receptors provoked as well a slowing of the channel kinetics (Yelshansky et al., 2004). Overall, the functional analyses conducted by Sun and colleagues point out a gain of function mechanism of this variant able to extend the duration of AMPAR activity, probably contributing to the epileptic manifestations (Sun et al., 2021).

Several lines of evidence have reported a role for glutamate in the regulation of sleep patterns and circadian rhythms (Ebling, 1996; Vyazovskiy et al., 2008), but the specific involvement of the GluA3 subunit had not been described. A large sequencing project in 2017 associated a GluA3 mutation with a presentation of ID accompanied by severe sleep disturbances (Davies et al., 2017). The identified single nucleotide variant (A653T) falls within the transmembrane domain of GluA3, which is highly conserved among species and among ionotropic glutamate receptors. This amino acid substitution affects the structure of the ion conduction pore, resulting in stabilization of the channel closed state, as demonstrated by *in vitro* functional and electrophysiological experiments. Moreover, gene editing using the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated 9 (Cas9)-mediated technique allowed for the study of this mutation in an *in vivo* mouse model. Similar to the findings reported for the GluA3 KO mouse model, the results of A653T variant expression in mice were

cryptic and did not phenocopy the human clinical presentation (Davies et al., 2017). However, mice exhibit more subtle alterations in activity and sleep than humans, in addition to an aberrant sensitivity to constant light. Therefore, the results of this study indicated that GluA3 activity might serve as a determinant of the sleep–wake cycle.

3.3. Roles of autoantibodies targeting the GluA3 AMPAR subunit in brain disorders: the case of frontotemporal dementia

Frontotemporal dementia (FTD) is a common type of presenile dementia that presents as a clinically and neuropathologically heterogeneous disorder. FTD is characterized by progressive deficits in behavior, executive functions, and language (Hodges and Piguet, 2018) that result from neuronal loss, predominantly involving the frontal and temporal lobes. The neuropathological substrate of FTD is heterogeneous; hyperphosphorylated tau and transactive response DNA-binding protein 43 (TDP-43) are the most frequently identified underlying proteinopathies, responsible for frontotemporal lobar degeneration (FTLD)-tau and FTLD-TDP43, respectively (Mackenzie et al., 2009).

Many pieces of evidence have suggested that immune system dysregulation plays a role in FTD pathogenesis. Epidemiological data and clinical studies have indicated a significantly increased risk of autoimmune disorders (Miller et al., 2013; Miller et al., 2016; Katisko et al., 2018) and autoimmune system alterations in FTD patients (Cavazzana et al., 2018; Borroni et al., 2017). In addition, genetic research has identified correlations between immune-associated loci and increased FTD risk (Ferrari et al., 2014; Broce et al., 2018).

Different experimental approaches including neurophysiological techniques have demonstrated that glutamatergic circuits are deficient both in sporadic and genetic FTD patients compared with healthy controls (Benussi et al., 2017; Murley and Rowe, 2018). Notably, autoantibodies directed against the GluA3 subunit of AMPARs have been identified in approximately 20% to 25% of FTD patients (Borroni et al., 2017). Data from *in vitro/ex vivo* studies indicate that the presence of GluA3 autoantibodies negatively affects glutamatergic neurotransmission at both pre- and postsynaptic sites, decreasing glutamate release and altering GluA3-containing AMPA receptor levels, leading to a significant reduction in dendritic spine density (Borroni et al., 2017; Palese et al., 2020) (see Fig. 1). The detrimental effects of GluA3 autoantibodies on glutamatergic neurotransmission have been verified in FTD patients: a neurophysiological approach showed a more pronounced deficit in glutamatergic circuits among FTD patients positive for GluA3 autoantibodies than in patients negative for autoantibodies (Palese et al., 2020). Altogether, these findings suggest that GluA3 autoantibodies not only affect GluA3-containing AMPARs but can trigger more profound morphological alterations in neuronal function that, in turn, might affect cognition and behavior. Scheggia et al. (2021) demonstrated that the acute administration of purified GluA3 autoantibodies to WT mice caused both molecular and morphological modifications (as suggested by *in vitro* studies) and behavioral and cognitive impairments.

The presence of anti-GluA3 autoantibodies in FTD patients may represent a point of contact between immune system dysregulation and glutamatergic neurotransmission, two features that have been independently observed in FTD pathogenesis. The initial failure of the immune system might lead to the production of toxic autoantibodies that have a detrimental effect on glutamatergic synapses, as suggested by preclinical data (Borroni et al., 2017; Palese et al., 2020, Gardoni et al., 2021), contributing to behavioral and cognitive alterations (Scheggia et al., 2021).

In this complex scenario, the mechanisms through which GluA3 autoantibodies lead to the observed pathological effects are not fully understood. Autoantibodies directed against the GluA3 subunit, which were identified in a few patients affected by epilepsy, have been shown to act as super-agonists for GluA3-containing AMPAR (Cohen-Kashi Malina et al., 2006), leading to increased GluA3 endocytosis (Palese et al., 2020). We hypothesize that, at a certain timing, the system reacts to the super-agonistic effect of autoantibodies, which might result in excitotoxicity, by de-potentiating glutamatergic synapses.

Given the negative effects of acute GluA3 autoantibody administration on synapses, behavior, and cognition (Scheggia et al., 2021), whether and how the chronic presence of autoantibodies triggers a neurodegenerative process and the association between this process and the appearance of FTD pathogenic biomarkers (*i.e.*, pTau or pTDP43 accumulation) should be further investigated. Answering these questions could shed light on whether GluA3 autoantibodies exacerbate an existing neurodegenerative process or, conversely, play an active role in triggering neurodegeneration. Importantly, differentiated neurons obtained from human-induced pluripotent stem cells incubated with human CSF positive for GluA3 autoantibodies demonstrated increased levels of intracellular tau expression (Borroni et al., 2017). Data from the literature have indicated the existence of cross-talk between AMPAR activity and tau pathology (Pooler et al., 2013; Kobayashi et al., 2017), and positive allosteric modulators of AMPARs have recently been shown to counteract tau-related excitotoxic synaptic signaling (Monteiro-Fernandes et al., 2020).

Although many open questions remain, and the underlying mechanisms have yet to be fully elucidated, GluA3 autoantibodies appear to play a role in FTD pathogenesis. We can, thus, imagine that both the potentiation of glutamatergic neurotransmission and interference in the aberrant immune system activation may represent possible strategies for ameliorating disease progression.

4. Conclusions

AMPARs are widely distributed throughout the brain and represent key players in synaptic transmission and synaptic plasticity at glutamatergic synapses. The relative abundance of GluA3-containing AMPARs varies across brain regions, and various experimental approaches have identified the GluA3 subunit as a fundamental contributor to AMPAR-mediated transmission in a high percentage of glutamatergic synapses. A growing number of published studies have focused on understanding the role played by GluA3-containing AMPARs in the brain, allowing for a deeper knowledge of the contributions of this subunit to basal synaptic transmission, synaptic plasticity, and different types of animal behaviors. Overall, these studies demonstrated the existence of several differences in the functional and trafficking properties of GluA2/GluA3 AMPARs compared with GluA1/GluA2 AMPARs.

Alterations in the function or expression levels of GluA3 appear to contribute to a vast array of pathological brain conditions, ranging from neurodevelopmental to neurodegenerative disorders. Based on these observations, the identification and characterization of novel tools and pharmacological approaches able to selectively target and modulate the GluA3 subunit represent currently unmet needs that might counteract brain disorders characterized by AMPAR alterations at the glutamatergic synapse. Additionally, the development of experimental strategies that selectively target GluA3 subunit may also provide new insights into GluA3 physiological role and function, addressing all aspects related to GluA3 role in brain physiology that are still not fully understood. In conclusion, deepening our knowledge of GluA3 subunit would contribute to a more complete view of glutamatergic system, unravelling new mechanisms and, possibly, opening to new strategies to counteract pathological conditions.

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Declaration of Competing Interest

None.

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