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The Good and the Bad of Glutamate Receptor RNA Editing

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Abstract Glutamate receptors play a key role in excitatory synaptic transmission and plasticity in the central nervous system (CNS). Their channel properties are largely dictated by the subunit composition of tetrameric receptors. Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate channels are assembled from GluA1–4 AMPA or GluK1–5 kainate receptor subunits. However, their functional properties are highly modulated by a post-transcriptional mechanism called RNA editing. This process involves the enzymatic deamination of specific adenosines (A) into inosines (I) in pre-messenger RNA. This post-transcriptional modification leads to critical amino acid substitutions in the receptor subunits, which induce profound alterations of the channel properties. Three of the four AMPA and two of the five kainate receptor subunits are subjected to RNA editing. This study reviews the advances in understanding the importance of glutamate receptor RNA editing in finely tuning glutamatergic neurotransmission under physiological conditions and discusses the way in which the dis-regulation of RNA editing may be involved in neurological pathology.

Keywords RNA editing · Glutamate receptors · Kainate receptors · Q/R site · R/G site · Neurological disorders

In the mammalian central nervous system (CNS), fast excitatory neurotransmission is largely linked to a class of ligand-gated ion channels called ionotropic glutamate receptors. Glutamate receptor channels bind glutamate as their ligand, thereby triggering post-synaptic depolarisation and leading to the propagation of the neuronal stimulus [1]. Glutamate receptors, all of which are permeable to Na^+, Ca^{2+} and K^+ and are primarily located in the post-synaptic membrane, are divided into the following three groups based on their specific pharmacological properties: the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, the kainate receptors and the N-methyl-D-aspartate (NMDA) receptors. In addition, two delta subunits (GluD1 and GluD2) have also been described, but their function is still unresolved [1].

AMPA receptors are typically homo-heterotetramers that are composed of four different subunits of similar size (~900 amino acids) [2] and share 68–73 % amino acid sequence identity [3]. Each subunit, named GluA1–4, is composed of four transmembrane hydrophobic domains M1–M4; only the M2 domain does not completely cross the membrane and enters from and exits to the cytoplasm side of the membrane (Fig. 1).

Glutamate receptor subunit protein complexity is increased by alternative splicing. In particular, each subunit exists as two splicing isoforms called "flip" and "flop" [4], which are generated after the alternative splicing of two mutually exclusive 115-bp exons in the primary transcript. This event produces two protein isoforms with a different 38 amino acid domain in the extracellular loop. The two splicing isoforms show different kinetic properties. Specifically, the GluA1-4 flop variant subunits have a faster desensitisation rate than do the flip isoforms [5, 6] and show reduced current responses to glutamate than do the flip variants [4].

AMPA Receptor RNA Editing

In addition to alternative splicing, another post-transcriptional mechanism may contribute to the complexity of AMPA

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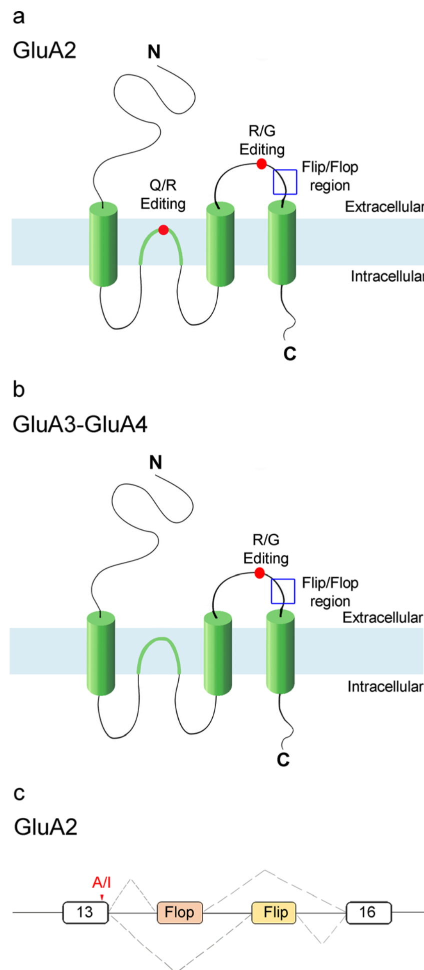

Fig. 1 Schematic representation of AMPA receptor subunits. **a** GluA2 subunit: the *red dots* show the Q/R and the R/G editing sites; the *blue square* indicates the flip/flop splicing cassette. **b** GluA3–4 AMPA receptor subunits with the R/G editing site and the splicing cassette. **c** GluA2 mRNA with the R/G editing site (marked in *red*) and the alternative flip/flop exons; the *dotted lines* indicate the splicing events

receptors: adenosine (A) to inosine (I) RNA editing. The term RNA editing was introduced in 1986 as the insertion of uridine residues in mRNA coding for the mitochondrial cytochrome oxidase (cox) subunit II in trypanosome species [7]. Then, in a later study of Powell et al. [8], the existence of this phenomenon was also confirmed in mammals. Since this important discovery, "RNA editing" has indicated modifications in RNA molecules that are not coded in the original DNA strand, leading to increased transcriptional variability in the cell.

In eukaryotic cells, RNA editing is mainly a post-transcriptional enzymatic deamination that converts adenosines (A) into inosines (I) or cytidines (C) into uridines (U) [9]. In mammals, the most common process is the (A) to (I) conversion [10, 11]. Typically, the inosine is read by ribosomes as a guanosine, changing the meaning of codon and, consequently, the amino acid in the protein if the edited nucleotide is located in a coding sequence. This editing reaction is catalysed by a class of enzymes called adenosine deaminase acting on RNA (ADAR), that recognise duplex RNA formed between the sequence containing the editing site and a complementary downstream sequence (Fig. 2). In mammals, three types of ADAR are present, ADAR1, ADAR2 and ADAR3, which are characterised by different subcellular and tissue distributions and activities [10, 12].

Concerning AMPA receptors, only GluA2-A3-A4 are subjected to RNA editing at different sites. The editing positions are named based on the amino acid substitution. In particular, GluA2 has two different editing sites: the Q/R site, where the RNA editing event implies the conversion of a CAG (glutamine) codon to a CGG (arginine) codon, and the arginine to glycine site (R/G). The first one is specifically edited by ADAR2 [13, 14], the second is edited by both ADAR1 and ADAR2 [15, 16].

The GluA2 Q/R site is located in the M2 of the subunit, inside the channel pore. At this site, RNA editing modifies the Ca^{2+} permeability of the channel because the arginine is a positively charged amino acid that prevents cation entry [17] (Fig. 3). In particular, only one edited GluA2 subunit in the Q/R site is sufficient to induce Ca^{2+} impermeability for the entire AMPA channel [18].

The Q/R site of GluA2 pre-mRNA is fully edited early in the brain development and under physiological conditions [18–20]; however, the step of brain development at which RNA editing arises remains controversial. Whitney et al. [21] found approximately 60 % of unedited GluA2 Q/R transcripts in human neuronal progenitor cells, indicating that GluA2 unedited subunits may be important for development. In contrast, the finding of Pachernegg et al. [22] supports the

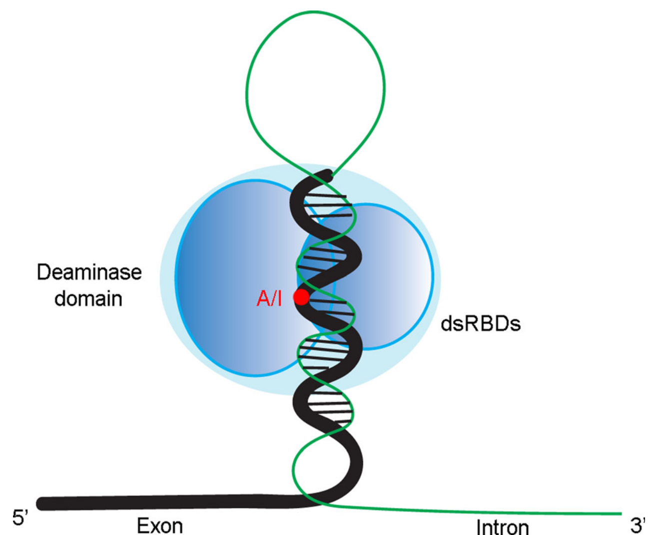

Fig. 2 Schematic representation of ADAR–RNA interaction. ADARs (*big light blue circle*) recognise duplex RNA formed between the sequence containing the editing site and a complementary sequence that is often located in a downstream intron. The enzymes bind to double-stranded (ds) RNA through their double-strand ribonuclear binding domains (dsRBDs) and deaminate a specific adenosine to inosine

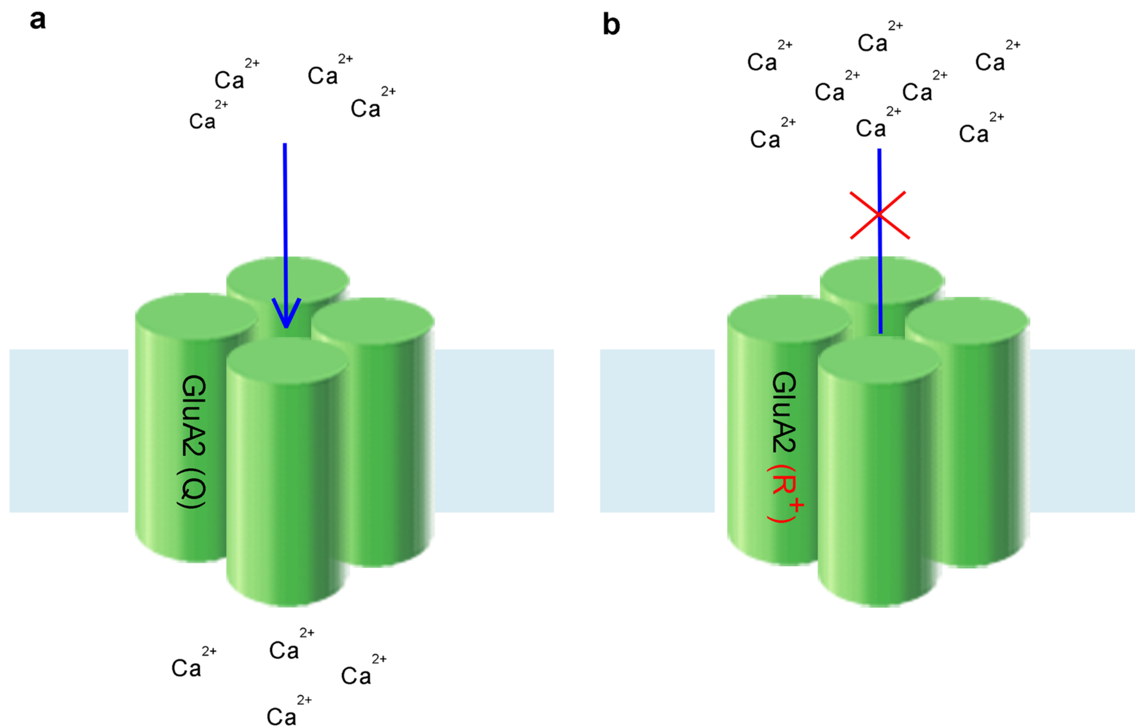

Fig. 3 Effect of GluA2 Q/R editing on channel Ca^{2+} permeability. **a** The unedited subunit allows Ca^{2+} entry through the GluA2-containing AMPA receptor. **b** The editing process converts the glutamine into arginine, a positively charged amino acid, preventing Ca^{2+} influx

hypothesis that the GluA2 Q/R unedited subunit is not significant for neuronal development because they found 100 % of GluA2 Q/R edited subunits in neuroepithelial precursor cells (NEPs). GluA2 Q/R editing in NEP after 4.5 days of 46C embryonic stem cell differentiation showed that only 10 % of GluA2 Q/R site subunits were unedited; however, 0.5 days later, the editing level reached 100 %. One possible explanation for the early onset of editing in GluA2 Q/R is that ADAR2, the only enzyme able to perform the reaction at this site, is expressed in NEPs before the beginning of GluA2 transcription [22].

This result confirms the data obtained by Kask et al. [23] in mice with normal development that completely lacked GluA2 Q/R editing, indicating that the GluA2 (Q) form does not play an important role during CNS differentiation. In contrast, in the study by Li et al. [24], a zebrafish model lacking GluA2 Q/R editing had abnormal development of the CNS and cranial neural crest cells; therefore, the significance of GluA2 Q/R editing during development is still a matter of debate.

The importance of GluA2 Q/R editing in adults has been clearly demonstrated by knockout studies. Brusa et al. [25] showed that mice lacking the editing complementary sequence (ECS) have approximately 25 % of unedited mRNA at the Q/R site, leading to seizures and premature death. Higuchi et al. [15] showed that ADAR2 knockout mice became prone to seizures and died young due to the excitotoxicity induced by excessive Ca^{2+} permeability. This lethal phenotype was rescued in transgenic mice with a genome-encoded arginine at the Q/R site [15]. All of these data support the idea that the unedited GluA2 in Q/R site is not compatible with normal life and may threaten CNS physiology.

Another important role for the GluA2 Q/R site lays in the regulation of endoplasmic reticulum (ER) trafficking of AMPA subunits. Greger et al. [26] demonstrated that the unedited subunit is rapidly released from the ER and inserted into neuronal membranes, whereas the edited form is retained in the ER. Trafficking to the cell surface may only be allowed for the fully assembled, hetero-tetrameric receptors in which the retention signal is masked by the presence of other GluA subunits. The Q/R editing site may also control the availability of the GluA2 subunit to assemble into AMPA channels.

GluA2, GluA3 and GluA4 subunits are also edited at the R/G site located in the extracellular domain close to the glutamate binding site, just before the flip/flop splicing cassette. Editing at this site, together with the alternative splicing of the flip/flop cassette, is important for the kinetic properties of AMPA receptors, especially in modulating desensitisation and the recovery time. Specifically, the G-edited subunits have an enhanced rate of recovery from desensitisation, generating channels that respond more rapidly to new glutamate stimuli [27].

RNA editing at the R/G site increases during neuronal cell maturation for all AMPA receptors, and the editing level can be modulated by neuronal activity in vitro [28]. In the work by Balik et al. [29], a fine regulation of AMPA R/G editing in the

hippocampus after activity modulation by TTX (sodium channel inhibitor) and BIC (GABA-A channel blocker) was reported. The editing level modifications are bi-directionally regulated, reversible and correlate with the ADAR2 levels. Moreover, these modifications are specific for the CA1 hippocampal subfield. The deep sequencing data presented by Sanjana et al. [30] reported RNA editing modulation after induced changes of neural activity. In particular, these modifications of the A-to-I RNA editing level in rat cortical neuron cultures are present after 6 h of acute high potassium depolarisation but not after 1 h, and they require calcium entry into neurons. Moreover, chronic treatment revealed a negative feedback phenomenon: the depolarisation increased the editing levels for several targets, whereas turning off the activity meant decreasing the RNA editing levels. All of these data confirm the possibility of modulating RNA editing through external stimuli, tuning protein properties and glutamatergic neurotransmission.

Kainate Receptor RNA Editing

Kainate receptors are tetrameric glutamate receptors composed of different combinations of GluK1–5 subunits. Among these, GluK1–3 may form functional homomeric or heteromeric receptors, but GluK4–5 can create functional receptors only when co-expressed with GluK1–3 [31, 32].

Kainate receptors regulate the activity of synaptic networks through diverse mechanisms that include post-synaptic depolarisation at a subset of excitatory synapses, pre-synaptic modulation of both excitatory and inhibitory transmission, refinement of synaptic strength during development and enhancement of neuronal excitability [33].

The Kainate receptor structural repertoire is extended via the RNA editing of two subunits. GluK1 can be edited only at the Q/R site, whereas GluK2 can be edited at two additional sites, the I/V and the Y/C located in the transmembrane domain I (TM1), where an isoleucine (ATT) is modified into a valine (ITT) and a tyrosine (TAC) into a cysteine (TIC), respectively (Fig. 4) [34–36].

In contrast to GluA2, the editing in the Q/R site of GluK1 and GluK2 mRNA occurs at very low levels in the embryonic brain and increases to 40 % (GluK1) and to 80 % (GluK2) of the mRNA within the first few days after birth in most regions of the brain [37–40]. The main function of Q/R editing is modulating the GluK Ca^{2+} permeability [34, 35], channel conductance [41, 42] and altering the current-voltage relationship during cell maturation [43, 44]. To investigate the importance of the GluK Q/R editing site, a knockout mouse was studied in which the GluK2 ECS was deleted, and the results showed that

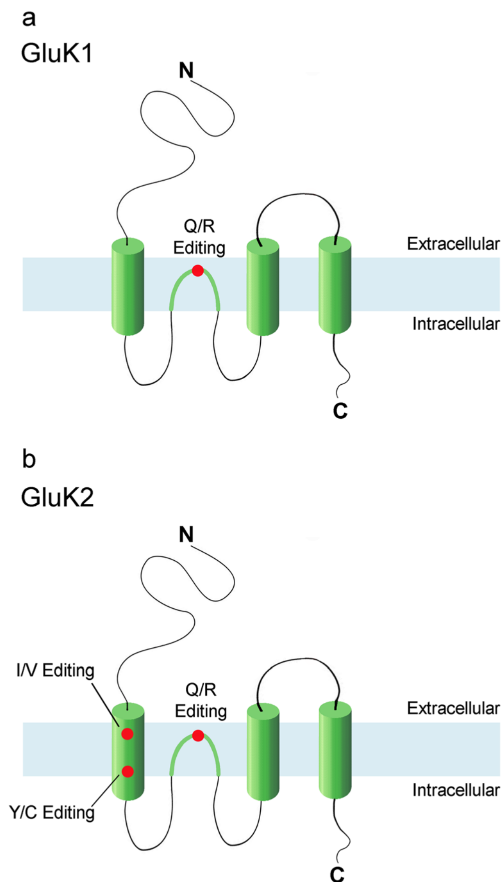

Fig. 4 Schematic representation of kainate receptor subunits. **a** GluK1 has just one Q/R editing site located in the M2 domain (*red spot*). **b** The GluK2 subunit has three editing sites (*red spots*): I/V and Y/C are both in the first transmembrane domain, and the Q/R site is in the M2 domain, similar to GluK1

the unedited GluK2 modulated synaptic plasticity and vulnerability to seizures [42]. In contrast, mice carrying constitutively edited GluK1 did not show developmental alterations or abnormal behaviour [45]. Another important feature of GluK editing in the Q/R site is linked to the membrane trafficking of the receptor: Q/R editing reduces oligomerisation, endoplasmic reticulum (ER) export, plasma membrane expression and stability of homomeric GluK2-containing Kainate receptors. These results indicate that the Q/R editing of GluK2 may influence the channel subunit composition during Kainate receptor assembly in the ER [46]. Moreover, the RNA editing of the Q/R site controls GluK susceptibility to inhibition by *cis*-unsaturated fatty acids and blockage by cytoplasmic polyamines [47].

The I/V and the Y/C editing sites are located in the first transmembrane domain and appear to be involved in the regulation of ion permeability in combination with the Q/R site [35, 48]; however, clear electrophysiological analysis remains to be conducted.

Coordination of Post-Transcriptional Events: RNA Editing, Splicing and Transport

The influence of editing and splicing on glutamate receptor-coding transcripts has been extensively evaluated. Editing at the GluA2 Q/R site and at an intronic editing hotspot has been shown to be a prerequisite for efficient splicing and processing of the pre-mRNA [15]. Conversely, the lack of editing in GluA2 Q/R inhibits nearby splicing [49, 50]. Moreover, concerning the R/G site, it is located two nucleotides upstream of a donor splicing site, which leads to the splicing of two mutually exclusive exons: flip and flop. R/G editing has been proposed to reduce splicing efficiency of the adjacent intron, influencing the alternative splicing events downstream of the R/G site [49, 51]. These data indicate that editing at different sites can both stimulate and repress splicing.

Furthermore, both RNA editing at the R/G site and the flip/flop splicing are dynamically and closely coordinated by neuronal activity in the rat hippocampus. In particular, a linear relationship links G editing and flip exon insertion [29]. Because editing occurs before splicing, R/G editing influences the inclusion of the downstream flip exon [29]. Established evidence has demonstrated mutual regulation mechanisms between editing and the alternative splicing process [52].

Glutamate receptor-coding transcripts are subject to another post-transcriptional regulation called RNA trafficking [53]. Several mRNAs are actively transported to the synapse and translated locally, allowing the synapse itself to answer independently to a sudden depolarising stimulus, which may require new proteins in the spine. The mRNA is usually localised to the synapse in a complex with RNA-binding proteins forming the so-called “RNA granules” that interact with the cellular cytoskeleton for dendritic targeting [54–56]. Among others, glutamate receptor-coding transcripts are actively transported to the synapses [57].

We have recently highlighted the relationship between RNA editing, trafficking and alternative splicing for AMPA receptor-coding transcripts [58]. After determining that all four GluA1–GluA4 coding transcripts are localised to the synaptic spine, we showed that dendritic AMPA mRNAs are present in the flip versions, whereas the flop splicing version is primarily restricted to the soma. Moreover, we reported that GluA2 transcripts carrying an unedited nucleotide at the R/G site, in combination with the flip exon, are more efficiently targeted to dendrites when compared with the edited-flip versions, perhaps contributing to attenuated post-synaptic activity. The data show that post-transcriptional regulation such as RNA splicing, editing and trafficking may be mutually coordinated and that the localisation of different AMPA receptor mRNAs in dendrites may play a functional role in the regulation of neuronal transmission [59].

Involvement of Glutamate Receptor Editing in Neurological Diseases

As described above, RNA editing is a very important process in the CNS, where it is one of the main strategies involved in modulating AMPA—kainate receptor activity in the synapse. Consequently, the deregulation of this process has huge consequences and has been linked to important pathological events (Table 1).

An important alteration of GluA2 Q/R editing and ADAR2 expression has been reported after forebrain ischemia in adult rats [60]. The reduced expression of the ADAR2 enzyme and, hence, a disruption of RNA Q/R site editing of the GluA2 subunit in vulnerable pyramidal neurons in the hippocampal region CA1 has been shown. The authors demonstrate the reduced expression of GluA2 mRNA due to the failure of Q/R editing. Additionally, a mechanism for the modulation of GluA2 editing was described. Specifically, the downregulation of ADAR2 expression was linked to the altered expression of the cAMP response element-binding protein (CREB), and the restoration of the CREB levels implies the proper expression of the enzyme and the proper level of GluA2 Q/R editing, thus preventing post-ischemic injury in the rat brain [60]. However, these data have not been confirmed in other independent studies.

An important alteration of RNA editing is found in spinal cord pathologies as sporadic amyotrophic lateral sclerosis (ALS). In a seminal study, Kawahara et al. [61] found the downregulation of GluA2 Q/R editing in the motor neurons of ALS patients, indicating that the abnormal generation of the Ca^{2+} permeable AMPA receptors damages motor neurons as a consequence of glutamate excitotoxicity. The downregulation of ADAR2, the only editing enzyme for the GluA2 Q/R site, leads to Q/R editing downregulation [62, 82]. In several studies on conditional ADAR2 knockout mice [63, 83], a clear link between ADAR2 and GluA2 Q/R editing is established as the onset reason of several forms of sporadic ALS. The authors discovered that the reduced ADAR2 activity causes a heavy downregulation of GluA2 Q/R editing levels with the subsequent increase of AMPA receptor Ca^{2+} permeability. This cation activates the cysteine protease calpain, which cleaves several targets and, in particular, the TAR-DNA binding protein 43 (TDP-43). This protein is then mis-localised to the cytoplasm where aggregation-prone fragments of the protein could be found, causing the so-called TDP-43 pathology [63].

The relationship between ALS and ADAR2 became stronger in a recent study in which the authors rescued the ALS phenotype in an ADAR2 conditional knockout mouse model by an intravenous injection of an adeno-associated virus serotype 9 (AAV9) vector that provides ADAR2 gene delivery [84]. Furthermore, a recent report indicates that a selective AMPA receptor antagonist rescued death of motor

Table 1 Pathologic conditions in which glutamate receptor RNA editing is involved

Pathologic conditions	Glutamate receptor subunit	Editing site	Reference
Forebrain ischemia	GluA2	Q/R	[60]
Amiotrophic lateral sclerosis	GluA2	Q/R	[61–63]
Spinal cord injury	GluA2, GluA3, GluA4	R/G	[64]
	GluK1	Q/R	[65]
	GluK2	Q/R	[65]
		Y/C	[65]
		I/V	[65]
Excitotoxicity	GluA2, GluA3, GluA4	R/G	[66]
Epilepsy	GluA2	R/G	[67, 68]
	GluK1	Q/R	[69]
	GluK2	Q/R	[42, 69]
Schizophrenia	GluA2	Q/R	[70]
		R/G (murine model)	[71]
	GluA3	R/G (murine model)	[71]
	GluK2	Q/R (murine model)	[71]
Bipolar disorders	GluK2	I/V	[72]
Antidepressant treatment	GluA2	Q/R (in vitro)	[73]
		R/G	[74, 75]
	GluA3	R/G	[74, 75]
	GluK2	Q/R, I/V, Y/C (astrocytes)	[76, 77]
		Q/R	[74]
Glioblastoma	GluA2	Q/R	[78]
Fear conditioning	GluK1	Q/R	[79]
Alzheimer's disease	GluA2, GluA3, GluA4	R/G	[80]
	GluA2	Q/R	[81]

neurons resulting from failure of GluA2 Q/R site RNA editing in mice [85].

The role of RNA editing in the pathophysiology of motor neurons has been shown in an animal model of spinal cord injury (SCI). We have shown that after the injury, a strong downregulation of AMPA receptor R/G editing could be observed without any effect on GluA2 Q/R sites and with a partial decrease of ADAR2 activity [64]. The neurons may reduce the excitatory response to glutamatergic stimulation, limiting death progression, by diminishing R/G editing. Kainate receptor editing is also modulated [65]. Specifically, the editing level of GluK1 and GluK2 Q/R sites is decreased after a lesion was induced in the spinal cord, with persistent effects at least until 30 days from injury. Moreover, the I/V and Y/C sites in GluK2 were affected by SCI [65].

With this type of lesion, the excitotoxicity linked to the abnormal glutamate release leads to the uncontrolled continuous depolarisation of neurons and plays an important role in triggering the influx of Ca^{2+} and causing cell death [86]. Recently, we attempted to evaluate the role of RNA editing in AMPA receptors and ADAR enzyme activity during glutamate overstimulation [66]. We used rat primary cortical cell cultures exposed to glutamate for 24 h, and we showed the downregulation of editing levels for the AMPA receptor subunits R/G site but not the GluA2 Q/R site. Glutamate treatment also downregulates both ADAR1 and ADAR2 enzyme protein levels through a pathway that is Ca^{2+} and calpain dependent. Given that AMPA receptors containing unedited subunits show a slower recovery rate from desensitisation compared with those containing edited forms, the reduced editing at the R/G site may, at least in part, compensate for glutamate overstimulation, perhaps through the reduced activation of post-synaptic receptors. In summary, our data provide direct evidence of the involvement of ADAR1 and ADAR2 activity as a possible compensatory mechanism for neuronal protection following glutamate overstimulation [66].

Glutamate overactivation and the consequent neuronal excitotoxicity have been identified as crucial factors in the status epilepticus (SE) [87]. In particular, in the study by Russo et al. [67], a downregulation of the R/G editing levels was shown for the flip splicing isoforms in AMPA receptor subunits after pilocarpine-induced SE. These data, together with modification in AMPA protein expression and phosphorylation, lead to an attenuation of AMPA post-synaptic

response to glutamate stimulation, protecting neurons against the SE excitatory conditions. In humans, Vollmar et al. [68] reported an increase in GluA2 R/G editing levels in the hippocampus of temporal lobe epilepsy patients; however, whether this finding is the cause or an adaptive mechanism in the epileptic seizures remains unclear.

The epileptic event appears to be linked not only to AMPA receptor editing but also to GluK2 Q/R editing. To investigate the functional role of this editing in vivo, Vissel and colleagues [42] engineered mice deficient in GluK2 Q/R site editing. In these mutant mice but not in wild-type mice, NMDA receptor-independent long-term potentiation (LTP) was induced at the medial perforant path–dentate gyrus synapse. This finding indicates that kainate receptors with unedited GluK2 subunits can mediate LTP, and a behavioural test showed that the engineered mice were vulnerable to kainate-induced epileptic seizures. Together, these results suggest that the GluK2 Q/R site RNA editing may modulate synaptic plasticity and seizure vulnerability [42]. In the same year, Kortenbruck and co-workers [69] evaluated the editing efficiencies of AMPA GluA2 and kainate GluK1–2 Q/R sites from the hippocampus and temporal cerebral cortex of patients with pharmacoresistant temporal lobe epilepsies. The editing efficiency for the kainate receptor subunits GluK1 and GluK2 was significantly higher in the temporal cortex of the patients with epilepsy than in the normal controls, leading to the hypothesis that alterations in GluK1 and GluK2 mRNA editing in the neocortical tissue may reflect an adaptive reaction of ongoing seizure activity to prevent excessive Ca^{2+} influx [69].

RNA editing of glutamate receptors has also been linked to psychiatric disorders such as schizophrenia and mood disorders. Akbarian et al. [70] found a slight decrease in the GluA2 Q/R editing levels in the post-mortem cerebral cortex samples from schizophrenic patients. However, two recent studies [88, 89] reported no AMPA or kainate receptor editing alterations in the pre-frontal cortex of patients affected by schizophrenia or bipolar disorders. In contrast, a downregulation of the GluK2 I/V site was reported in bipolar disorder (BPD) patients [72]. Using a murine model of the disease (phencyclidine-treated mice), we reported [71] a decrease in the GluA2–3 R/G editing levels with a significant increase in the GluK2 Q/R editing levels. The data indicated that phencyclidine treatment induces a specific and site-selective reduction of glutamatergic neurotransmission by modifying RNA editing levels; however, the link with human pathology remains unclear.

RNA editing of AMPA receptors may play a role in the pathogenesis of mood disorders and in the action of antidepressant drugs. We have shown that chronic treatment with fluoxetine and desipramine exerted moderate but selective effects on glutamate receptor expression and editing, mainly on GluA2 R/G site and GluK2 Q/R site [74]. More recently, it was reported [75] that 4 weeks of drug treatment may alter the GluA2 R/G site with time-dependent effects that are consistent with the onset of therapeutic effect of these drugs. Furthermore, the editing efficiency at the GluA2 Q/R site was significantly increased after treatment with seven antidepressants in a HeLa cell line that stably expresses half-edited GluA2 pre-mRNAs [73]. Fluoxetine has been shown to affect GluK2 editing, glutamate-evoked Ca^{2+} influx and extracellular signal-regulated kinase phosphorylation in mouse astrocytes but not in neurons [76, 77], indicating a cell-type specific effect for this molecule. Taken together, these data indicate that RNA editing is a potential target for antidepressant action.

Moreover, fear conditioning, a behavioural paradigm in which organisms learn to predict aversive events, leads to a decrease in RNA editing at the Q/R site of kainate GluK1 subunits in the amygdala [79]. However, acute foot shock stress does not alter glutamate RNA editing in the pre-frontal cortex or hippocampus [90]. Recently, another work has shown that in an ADAR2 +/- knockout mouse model, editing of the R/G sites of AMPA receptors was decreased, and these mice showed increased activity in the open-field test, resistance to immobility in the forced swimming test and enhanced amphetamine-induced hyperactivity. These findings collectively suggest a possible role of altered RNA editing efficiency of AMPA receptors due to ADAR2 downregulation in the pathophysiology of mental disorders [89]; however, human studies do not directly support the role of RNA editing modifications in mood disorders [72].

Alterations in RNA editing events have been recently reported in Alzheimer's disease (AD) by a massive sequencing approach [80]. Among others, the downregulation of RNA editing in several glutamate receptors such as GluA2 (in the temporal and frontal lobe), GluA4 (in the temporal lobe and hippocampus) and GluA3 (in the hippocampus) has been reported. A slight downregulation of GluA2 has already been reported in the hippocampus of AD patients [81]. These results may shed light on a possible association between the neurodegenerative processes typical for AD and deficient RNA editing.

Increasing evidence correlates modifications in RNA editing events and cancer progression [91]. Concerning glutamate receptor editing, its role has primarily been studied in astrocytoma, the most severe form of glioblastoma multiforme (GBM), which is usually fatal within 18 months [92]. The downregulation of GluA2 Q/R site editing levels in GBM samples has been reported compared with control samples [78]. These data have been linked to decreased ADAR2 activity correlated with increased malignancy, although ADAR2 expression was unchanged [93]. The authors also extended the investigation to astrocytoma cell lines, demonstrating the relationship between ADAR2 overexpression and reduced cell proliferation and migration [93]. Moreover, in GBM, the Ca^{2+} influx mediated by the unedited AMPA GluA2 Q/R site

activated the Akt pathway, promoting proliferation and mobility, and the upregulation of the Akt pathway was reversed when GluA2 Q/R was edited [94].

In conclusion, the editing of AMPA receptors may be a potential target for many pharmacological applications, but further investigations are needed to obtain a better understanding of all of the mechanisms involved in these processes.

Concluding Remarks

Glutamate receptor RNA editing is a fine molecular mechanism involved in response to excitatory stimuli. Most of the sites are not fully edited, indicating that edited and unedited receptor subunits are simultaneously present within the same cell, thus creating a heteromeric channel with distinct but specific properties. Moreover, the editing levels increase during development until a specific, conserved value is reached in a tissue-specific manner. The editing of glutamate receptor levels may also be cell specific and activity dependent [29], indicating that this important molecular mechanism allows single neurons to respond independently to a glutamatergic stimulus.

A growing list of other re-coding editing sites has been identified in neuronal targets other than glutamate receptor transcripts via bioinformatics and high throughput sequencing approaches [59]. These data show that in neurons, RNA editing helps generate a diverse and complex repertoire of proteins. The great variability of proteins produced by RNA editing allows neuronal cells to dynamically react to rapid changes and favours protection and fine tuning in the nervous system responses towards new sudden stimuli.

In addition, the discovery that many transcripts are localised at the synaptic level [95], where they are subjected to local protein synthesis, shows that the individual synaptic spine may regulate its morphology and function at the subcellular level. RNA editing deepens the complexity of transcript regulation at the synaptic level because this process influences the differential transport of AMPA receptor mRNAs to dendrites [58]. Future developments in single cell analysis will increase our understanding of how glutamate receptors and RNA editing may regulate neuronal function at the cellular and subcellular levels.

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