

REVIEW ARTICLE

Targeting Ionotropic Glutamate Receptors in the Treatment of Epilepsy

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Abstract: Background: A dysfunction in glutamate neurotransmission is critical for seizure. Glutamate is the major excitatory drive in the cerebral cortex, where seizures occur. Glutamate acts *via* (i) ionotropic (iGlu) receptors, which are ligand-gated ion channels mediating fast excitatory synaptic transmission; and (ii) G proteins coupled metabotropic (mGlu) receptors.

Objective: To overview the evidence on the role of iGlu receptors in the onset, duration, and severity of convulsive and non-convulsive seizures to lay the groundwork for novel strategies for drug-resistant epilepsy.

Methods: We used PubMed crossed-search for “glutamate receptor and epilepsy” (sorting 3,170 reports), searched for “ionotropic glutamate receptors”, “AMPA receptors”, “NMDA receptors”, “kainate receptors”, “convulsive seizures”, “absence epilepsy”, and selected those papers focusing this Review’s scope.

Results: iGlu receptor antagonists inhibit, whereas agonists worsen experimental seizures in various animal species. Clinical development of iGlu receptor antagonists has been limited by the occurrence of adverse effects caused by inhibition of fast excitatory synaptic transmission. To date, only one drug (perampanel) selectively targeting iGlu receptors is marketed for the treatment of focal epilepsy. However, other drugs, such as topiramate and felbamate, inhibit iGlu receptors in addition to other mechanisms.

Conclusion: This review is expected to help dissect those steps induced by iGlu receptors activation, which may be altered to provide antiepileptic efficacy without altering key physiological brain functions, thus improving the safety and tolerability of iGlu-receptor directed antiepileptic agents. This effort mostly applies to drug resistant seizures, which impact the quality of life and often lead to status epilepticus, which is a medical urgency.

Keywords: Ionotropic glutamate receptors, AMPA, NMDA, kainate, epilepsy, convulsive seizures, absence epilepsy.

1. INTRODUCTION

1.1. Glutamate, Excitotoxicity and Epileptic Seizures

The word “excitotoxicity” as introduced by Olney [1] meant the “excitation to death” produced by the acidic amino acids glutamate, aspartate and their analogs. These compounds, indeed, were known to damage neurons due to an over-depolarization since the early 1960s [2]. At present, the concept of excitotoxicity pervaded almost all fields in neuroscience research and mostly in neurological disorders [3-5]. This concept, which refers to the presence of endogenous neurotoxins was anticipated by the concept of exogenous neurotoxins-induced cell death. In both cases, it was most

struggling the outcome of a “selective neurotoxicity”, which suggested the presence of a sort of selective binding to limit the damage to a specific neuronal cluster. When applied in the field of epilepsy such a specificity was related to the selective regions being recruited by seizure spreading. On the other hand, this phenomenon needs the presence of specific receptors on post-synaptic neurons, which are able to selectively bind and transduce the input provided by glutamate neurotransmission. The fast post-synaptic alterations provided by the activation of ionotropic glutamate (iGlu) receptors offers the basis of such a selective and massive effect. In the present review, the anatomical and pharmacological basis for the selectivity produced by iGlu receptors activation in the course of epilepsy is provided. At the same time, we discuss the bias which may be induced when a systemic excitotoxin is administered. In fact, in these experimental conditions, the neuronal selectivity for excitotoxicity simply relies on the presence of ionotropic receptors. This condition produces an artifact since the selective pattern of the anatomical

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circuitry, which is indeed recruited, is lost. Thus, two conditions generate the selective excitotoxicity in seizures and epilepsy: (i) the presence of specific glutamate receptors; (ii) the brain sites selectively recruited during the natural seizure spreading.

The occurrence of excitotoxicity requires an altered status which may be simplified by a few items which lose their balance: (i) excessive and/or prolonged release of glutamate into the synaptic cleft, (ii) impaired clearance of glutamate from the extracellular space and (iii) impairment of surrounding GABAergic inhibition. This imbalance between glutamate and GABA seems to be critical. For instance, in a seminal paper, Sloviter *et al.* [6] showed the co-existence of GABA within glutamatergic hippocampal mossy fibers and demonstrated an activity-dependent (compensatory?) increase in GABA synthesis. The preferential zonal representations of glutamate receptors could be a critical factor for the selective vulnerability of different classes of neurons to different insults [7]. Interestingly, when acute insults are repeated, the neuronal loss progresses downstream to synaptically linked neurons. This trans-synaptic progression of neuronal death after repeated acute insults (*e.g.* epilepsy) resembles what slowly occurs in neurodegenerative diseases in which the “systemic degeneration” consists of spreading cell loss to neurons interconnected in functional circuits. This was postulated in 1997 by Fornai *et al.* [8], and clearly established by Freire [9], who reported the occurrence of primary traumatic events followed by secondary pathological events contributing to tissue damage where glutamate release plays a leading role, and recently by Kaur and Sharma [10] who posed the role of excitotoxicity in the course of events which sustain the natural course of neuronal damage following an acute traumatic event.

2. IONOTROPIC GLUTAMATE RECEPTORS AS TARGET IN EPILEPSY

An imbalance between excitatory and inhibitory neurotransmission lies at the core of the pathophysiology of epilepsies, independently of the specific syndrome and disease. This is expected to modulate seizure onset, spreading, spontaneous resolution, along with seizure-induced sensitization (kindling) and seizure-induced brain damage. Apart from the literature concerning the inhibitory effect played by GABA, when the excitatory over-activity is considered, most data refer to the excitatory role of glutamic acid, which represents the prevalent excitatory neurotransmitter in the mammalian brain (Fig. 1). This explains why drugs acting at glutamate receptors potentially alter all seizure-related events; similarly, drugs acting as agonists and (or) antagonists at specific glutamate receptors are strong candidates to treat epilepsies. Despite a plethora of findings and review articles on the role of glutamate receptors in seizures, the present review is an attempt to provide novel insights to finely dissect the role of iGlu receptors in the context of specific, still questionable, seizure-related events [11-16]. In keeping with this introductory statement, it is mandatory to distinguish three classic types of iGlu receptors: AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), NMDA (N-Methyl-

D-aspartic acid), and kainate receptors. All these receptor types are structured as ligand-gated ion channels; thus, upon binding with endogenous glutamate, specific inward cation currents are produced due to channel openings. This contrasts with metabotropic glutamate (mGlu) receptors, which, once binding extracellular glutamate, activate specific intracellular biochemical pathways through an intramembrane G protein. The role of mGlu receptors in the pathophysiology of convulsive and absence epilepsy has been extensively discussed in a number of review articles [12, 15, 17-24].

Glutamate is the principal excitatory neurotransmitter of the mammalian brain. The major source of glutamate in the brain is glutamine, which is converted in glutamate *via* glutaminase enzyme. The vesicular glutamate transporter, vGluT, mediates the increased concentration of glutamate in synaptic vesicles in the axon terminals. Glutamate acts *via* ionotropic receptors (NMDA, AMPA, and kainate) and metabotropic (mGlu) receptors. Astrocytes play a major role in glutamate reuptake through GLAST and GLT-1 transporters.

All iGlu receptors are heterotetramers, each subunit being formed by three trans-membrane (TM) domains (TM1, -3 and -4) and an incomplete TM2 domain, which does not cross the membrane but kinks back on itself within the membrane. This allows the intracellular C-terminus receptor domain to interact with a number of scaffolding and adaptor proteins. The incomplete TM2 domain contributes to build the wall of an ion channel, and its amino acid composition confers specific ion selectivity (*i.e.*, the Na^+ to Ca^{2+} ratio) to the three iGlu receptors. This feature considerably varies depending on the combination of receptor subunits that contribute to forming the whole iGlu receptor subtype. In fact, in spite of three classic receptor types, iGlu receptors may vary depending on specific subunit composition and assembly, which in turn may be altered by ongoing synaptic activity via epigenetic alterations. In most cases, AMPA receptors are impermeable to Ca^{2+} in most of the synapses due to the presence of a positively charged arginine residue in the TM2 of the GluA2 subunit (see paragraph 3) [25-28]. AMPA receptor permeability may vary depending on several conditions. Similarly, the overall impact of each iGlu receptors in the pathophysiology of epilepsy depends on a high number of variables, such as their surface expression, opening frequency and dissociation kinetics, cation selectivity, expression of interacting proteins, regulation of intracellular transduction mechanisms. For instance, S-palmitoylation of the receptor allows a reversible covalent link of the receptor protein to membrane lipids, which regulates a variety of iGlu receptors properties such as: synaptic and membrane expression, intracellular placement, and the type of scaffolding proteins. In general, it is reported that a defective iGlu receptor palmitoylation may cause neuronal hyperexcitability and fosters the onset of epileptic seizures [29].

Here, we will discuss the specific role of each iGlu receptors in the pathophysiology of seizures and the potential treatment of epilepsy.

In order to provide a vision “at a glance” of those concepts developed in the review, we built a summarizing table

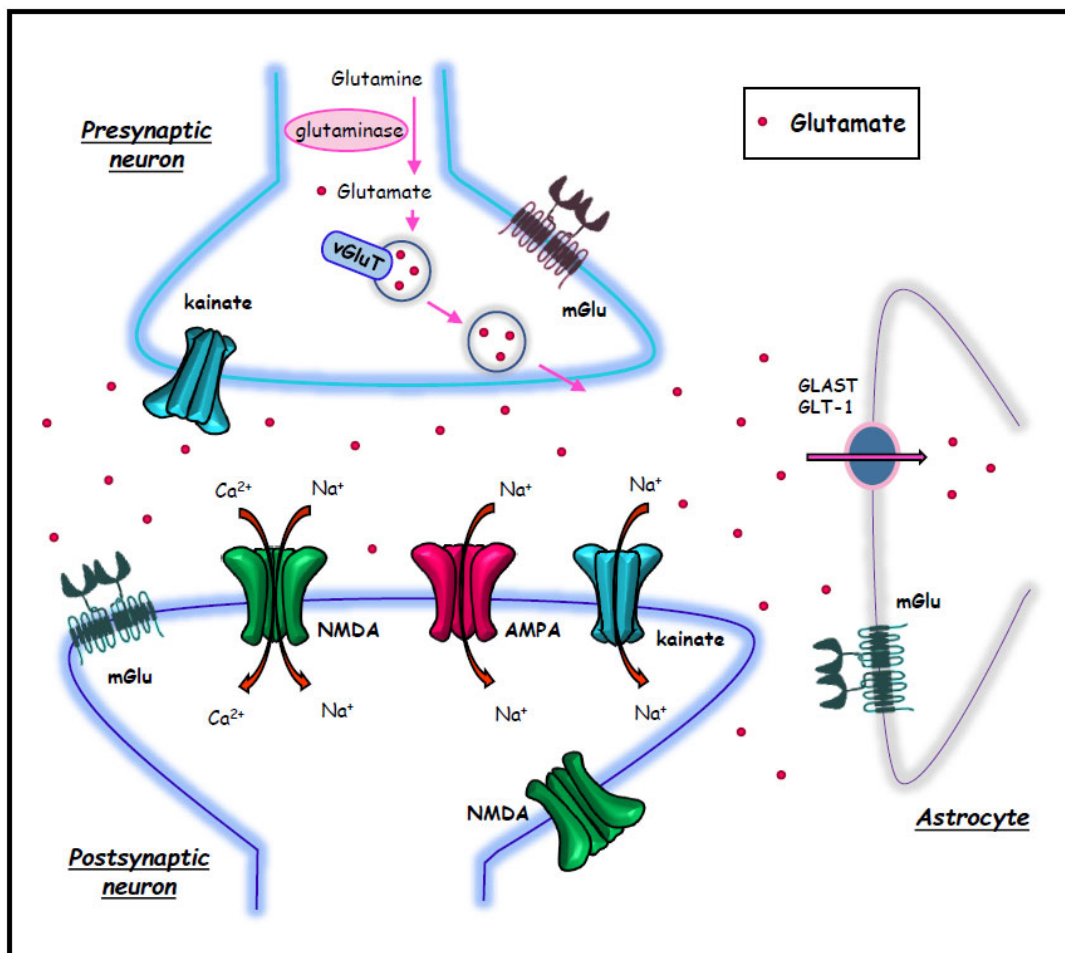


Fig. (1). Glutamate synapse components. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Table 1. Summary of specific ionotropic glutamate receptors, their ligands and mechanisms of action. AMPA receptors and convulsive seizures. Competitive antagonists of AMPA receptors.

Compound	Subject	Effect	Refs.
NBQX	DBA/2 mice	protects against sound-induced seizures	[60]
	rat amygdala-kindling model	decreases the duration of after discharge activity	[62]
	mouse model of mesial temporal lobe epilepsy	attenuates spontaneous seizures and occludes limbic seizure-induced brain damage	[64]
	Long-Evans rats	suppression of behavioral alterations and the onset of spontaneous secondary seizures	[65]
YM872	rat amygdala kindling model	suppressed fully kindled seizures	[68]
YM90K	DBA/2 mice	potent suppressive activity against audiogenic seizure	[69]
	rat amygdala-kindling model	suppressed fully kindled seizures	[70]
LY293558	mouse	protection <i>versus</i> maximal electroshock seizures and decreases in spontaneous motor activity	[73]
RPR117824	mouse or rat	blocker of convulsions induced by supramaximal electroshock or chemoconvulsive agents	[74]
NS1209	mouse	increased the seizure threshold for electroshock-induced tonic seizures	[76]
	rat	protects against status epilepticus induced by electrical stimulation of the amygdala	[77]

(Table 1) contd....

Negative allosteric modulators of AMPA receptors.

Compound	Subject	Effect	Refs.
GYKI52466	NIH Swiss mice	protective against seizures in maximal electroshock seizure test	[56]
	mouse	inhibition of seizure activity and recurrence in kainic acid-induced status epilepticus	[88]
Telampanel	rat	protective activity in the kainate-induced neonatal status epilepticus model	[89]
Topiramate	human	approved for the treatment of partial seizures, primarily generalized seizures, and seizures associated with Lennox-Gastaut syndrome	[90-91]
	mouse	protection against seizures induced by infusion of ATPA	[98]
	human	reduces seizures when administered as an add-on treatment for drug-resistant focal epilepsy	[101]
Perampanel	human	approved for the treatment of focal epilepsy and generalized tonic-clonic epilepsy; restrains myoclonic or absence seizures	[102-109]
	mouse	protection against PTZ-induced clonic seizures and psychomotor seizures in the 6-Hz stimulation protocol	[110]
	rat amygdala kindling model	shortens after-discharge activity and prolongs latency to onset of generalized seizures	[111, 112]
	rat	block of pilocarpine-induced status epilepticus	[113]
	human	good efficacy and tolerability in young children with intractable epilepsy	[116]

AMPA receptors in models of absence epilepsy.

Compound	Subject	Effect	Refs.
Topiramate	GAERS rats	dose-dependently reduces SWDs	[99]
GDEE	WAG/Rij rats	dose-dependently decreases absence seizures	[120]
CNQX	WAG/Rij rats	dose-dependently reduces the number of SWDs	[122]
CFM-2 THIQ-10c	WAG/Rij rats	dose-dependently reduce frequency and duration of SWDs	[124]
Telampanel	WAG/Rij rats	reduces the number of SWDs	[126]
Perampanel	WAG/Rij rats	reduces the number of SWDs	[127]

NMDA receptors and convulsive seizures.

Compound	Subject	Effect	Refs.
7-chlorokynurenic acid D-cycloserine	kindled rats	anticonvulsant effects in focal seizures	[156]
ketamine	human	seizure blockade in children with severe refractory epilepsy	[160]
MK-801	rat	dose-dependently prevents orphenadrine-induced status epilepticus	[161]
MNQX	DBA/2 mice	protective effects against kindling-induced status epilepticus	[163]
Remacemide	rat	anticonvulsant by blocking NMDA receptors	[173]
	human	efficacy in patients with two or more focal or generalized tonic-clonic seizures	[174]
	human	efficacy as adjunctive therapy in patients with refractory epilepsy	[175]
Felbamate	human	effective in a variety of pediatric seizure types including Lennox-Gastaut syndrome	[177]
	human	useful in the treatment of refractory epilepsy in children	[178, 179]

NMDA receptors in models of absence epilepsy.

Compound	Subject	Effect	Refs.
MK-801	WAG/Rij rats	reduces the number and mean duration of SWDs	[194]
	rat	attenuates the gamma-hydroxybutyrate-induced SWDs	[195, 196]
	GAERS rats	dose-dependently suppresses SWDs	[197]
Remacemide FPL 12495	GAERS and WAG/Rij rats	reduce the frequency of SWDs	[199]

(Table 1) contd....

Kainate receptors and epilepsy.

Compound	Subject	Effect	Refs.
NS1209	human	effective against refractory status epilepticus	[219]
CNQX	rat	prevents high-frequency oscillations associated with seizures in the kainic acid-induced status epilepticus	[220]
LY293558	rat	reduces soman-induced seizures	[221]

(Table 1- Summary of specific ionotropic glutamate receptors, their ligands and mechanisms of action).

3. AMPA RECEPTORS, SEIZURES AND EPILEPSY

AMPA receptors consist in the heterotetrameric combination of GluA1-4 subunits, encoded by the *GRIA1-4* genes [30, 31]. The incomplete TM2 domain of the GluA2 subunit contains an arginine residue in position 607, which restrains Ca^{2+} influx. Thus, AMPA receptors typically own a high Na^+ to Ca^{2+} ratio concerning channel permeability [32]. Remarkably, when AMPA receptors constitutively lack GluA2, Ca^{2+} permeability is present and a similar effect occurs within the context of activity-dependent synaptic plasticity that diminishes the expression of GluA2 [30]. This witnesses how iGlu receptor subunits composition may result from inherited constitutive structure or is the consequence of specific micro-environmental stimuli, which eventually alter subunit gene expression and synaptic plasticity [33]. This may explain why Ca^{2+} -permeable AMPA receptors are mainly expressed on the surface of inhibitory interneurons, which routinely receive a significant excitatory input [34, 35]. AMPA receptors are predominantly expressed at the core of postsynaptic targets, to produce fast excitatory postsynaptic events all over the central nervous system (CNS) [36]. Changes in membrane expression of AMPA receptor subunits are critical to produce long-term potentiation (LTP) and long-term depression (LTD), which represent plastic phenomena concerning excitatory synaptic transmission [37]. These changes are partly due to in-and-out movements of AMPA receptors, which are driven by nanoscale dynamics of receptor organization [36, 37]. GluA1, GluA2, and GluA3 are the most abundant subunits in the forebrain, with the exception of some thalamic nuclei, where GluA4 is also abundant [38].

AMPA receptors are intimately associated with numerous auxiliary proteins, like the transmembrane AMPA receptor regulatory proteins (TARPs), γ -2 (stargazin), γ -3, γ -4, γ -5, γ -7 and γ -8 [39]. TARPs may stabilize AMPA receptors on the cell surface of synaptic areas [40]. A loss of TARPs, reduces the stability and surface expression of AMPA receptors [41, 42]. TARPs also influence the kinetics of AMPA receptor currents and responses to receptor ligands [43-45]. Impairments in the regulation of AMPA receptor function, trafficking, and signalling may produce neuronal hyperexcitability and epileptogenesis, which suggests how AMPA receptors may represent a potential target for epilepsy treatment [46]. The critical role of AMPA receptors in the pathophysiology of epileptic seizures and anti-epileptic treatment is highlighted by elegant reviews [47, 48].

AMPA receptors play a key role in seizure generation and spreading, as demonstrated in human brain regions high-

ly involved in epilepsy, such as the isocortex [49, 50] and limbic regions, such as the entorhinal mesocortex [51].

Egbenya *et al.* [52] examined long-term changes in synaptic contents of AMPA receptor subunits, which could influence calcium regulation in chronic epilepsy. A relative increase in the expression of GluA2-lacking (Ca^{2+} -permeable) AMPA receptors was found in hippocampal synaptosomes prepared from rats treated with kainic acid, which model temporal lobe epilepsy (TLE, the most common form of refractory focal epilepsy).

3.1. AMPA Receptors and Convulsive Seizures

AMPA receptor antagonists have been developed for the treatment of convulsive epilepsy showing good efficacy in preclinical models [53, 54]. Negative allosteric modulators (NAMs) have a greater clinical potential compared with competitive antagonists due to high PK compatibility. However, a concern was raised by the occurrence of CNS depression with some of these drugs due to the key role played by AMPA receptors in fast excitatory synaptic transmission in the CNS [55]. Accordingly, AMPA receptor antagonists were found to induce neurological side effects at anticonvulsant doses in animal models, although this depends on specific seizure models and testing conditions [56, 57].

3.1.1. Preclinical Data with Competitive Antagonists of AMPA Receptors

Quinoxaline derivatives CNQX (6-cyano-7-nitroquinoxaline-2,3-dione) and NBQX (2,3-dihydroxy-6-nitro-7-sulfamoylbenzo (F) quinoxaline) represent the most common AMPA receptor antagonists [58-63].

NBQX is a competitive AMPA receptor antagonist that showed anti-seizure but not antiepileptogenic activity in the mouse model of mesial temporal lobe epilepsy induced by intrahippocampal injection of kainate [64]. Acute treatment with NBQX soon after hypoxia-induced postnatal seizures attenuates spontaneous seizures and occludes limbic seizure-induced brain damage, as evidenced by hippocampal mossy fiber sprouting [64]. Occlusion of such a pathological alteration, which is reminiscent of medial temporal lobe sclerosis and correlates with secondary epileptogenesis is confirmed by data showing suppression of behavioral alterations and the onset of spontaneous secondary seizures following NBQX in adult Long-Evans rats [65]. This suggests that persistent alterations of AMPA receptors play a role in maladaptive plasticity underlying epilepsy-induced secondary seizures and kindling. In humans, this may be relevant when considering how epileptic seizures in children may promote a later in life occurrence of epilepsy. As expected, NBQX

consistently reduces seizure-induced motor activity (convulsions) and, when tested in the experimental model of amygdala kindling, it decreases the duration of after discharge activity [62]. As a direct effect of the antagonism on AMPA receptors, NBQX powerfully occludes AMPA-induced seizures [60]. It is remarkable that NBQX also powerfully mitigates hindbrain seizures induced by sound in DBA/2 mice [60]. Despite being routinely considered as a specific AMPA receptor antagonist, NBQX indeed binds with a noticeable affinity to kainate receptors; thus, the data reported above cannot be considered as necessary due to the role of AMPA receptors, unless the role of kainate receptor is ruled out. This is a common problem with a number of non-NMDA receptor antagonists as it leaves unanswered the specific role of AMPA and kainate receptor as non-NMDA seizure determinants.

In fact the issue remains with additional quinoxalinediones with *in vivo* anticonvulsant activity, such as YM872 [66-68], YM90K [69, 70], ZK 200775 (MPQX, fanapanel) [71], AMP397 (becampanel) [63, 72], and LY293558 (tezampanel = (3S,4aR,6R,8aR)-6-[2-(1(2)H-Tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid) [73]. Some other competitive AMPA receptor antagonists with *in vivo* anticonvulsant activity were identified, including the pyrazine derivative RPR117824 [74, 75], and isatin oximes, such as NS1209 (SPD 502) [76, 77], which inhibits GluK1-containing kainate receptors. NS1209 was investigated as an intravenous agent for the treatment of status epilepticus because it is not orally active [78]. Pitkänen *et al.* [77] demonstrated that NS1209 potently protects against status epilepticus induced by electrical stimulation of the amygdala.

In spite of the promising preclinical findings, competitive antagonists have not advanced to clinical development because of their sub-optimal PK profile (water-soluble molecules, such as CNQX, poorly penetrate the blood-brain barrier, whereas lipophilic molecules, such as NBQX, precipitate in the kidney [79]).

3.1.2. Pharmacological Probing of AMPA vs. Kainate Selectivity in non-NMDA iGlu Receptor-induced Seizures

There are only a few pharmacological tools that can efficiently discriminate between AMPA and kainate receptors, and, therefore, the role played by AMPA or kainate receptors in several seizure models are either over- or underestimated. Within current literature, this mostly applies to AMPA receptors and it is the consequence of the early overestimation of NBQX as a potential selective AMPA receptor antagonist. This led to a number of reports, which attributed to AMPA receptors a number of effects in the field of epilepsies; in contrast, these effects were due to a combined activation of AMPA and kainate receptors [47, 48, 52, 80-82].

At the experimental level, such an issue was solved by using a class of compounds known as desensitization blockers, which allow to discriminate between AMPA and kainate receptors or the ratio of one receptor vs. the other. These probes were validated by patch clamp recording and they are fully disclosed in their molecular mechanisms. Thus, in or-

der to produce an overstimulation, which is purely due to AMPA receptors, we need to administer cyclothiazide, which is a selective blocker of AMPA desensitization. Conversely, when the kainate receptor needs to be overactivated, the kainate desensitization blocker Concanavalin A can be administered. These compounds were used in experimental models to assert and validate the role of AMPA receptor in seizures [83].

In particular, in order to avoid the bias due to systemic administration, the AMPA receptor desensitization blocker, cyclothiazide, was focally administered in the rat within the rostral piriform allocortex, alone or in combination with the GABA_A antagonist, bicuculline [83]. In these experimental conditions, the proconvulsant effects of focally administered bicuculline, induced by the relief from baseline GABAergic inhibition, were enhanced by the concomitant microinfusion of cyclothiazide [83].

Noteworthy, while the seizure produced by bicuculline could be suppressed by either D-2-amino-7-phosphonoheptanoic acid (AP7, an NMDA receptor antagonist,) or NBQX (a non-NMDA receptor antagonist), seizures induced by cyclothiazide *plus* bicuculline were refractory to AP7 and were either prevented or suppressed by NBQX administration [83]. This suggests that, while serial seizures induced by bicuculline were sustained by the combined activity of NMDA and non-NMDA receptors, seizures produced by cyclothiazide *plus* bicuculline fully depend on over-activation of non-NMDA receptors. Since cyclothiazide is a pure ligand for AMPA receptor subtypes, these seizures fully depend on over-activation of AMPA receptors. Remarkably, these seizures induced by combined drug administration were not merely an amplification phenomenon consisting of more robust seizures compared with that induced by bicuculline alone. In fact, in the presence of bicuculline, serial seizures starting around 5 min following microinjection progressively became more frequent up to a point in which a single seizing episode was no longer discernible, and a continuous persistent long-acting and self-sustaining status epilepticus developed [83]. The duration of such a status epilepticus far exceeded the persistence of bicuculline in the brain, showing that a self-sustaining phenomenon was taking place where the epileptic circuitry downstream the infusion site took a leading role as seizure pacemaker. This demonstrates that, while NBQX was effective to prevent seizure onset and still effective to suppress serial seizures, when limbic status epilepticus is manifest the drug is no longer effective when infused in the same site. Still, some anticonvulsant effect could be obtained by micro-infusing NBQX in brain areas placed downstream of the piriform allocortex in the limbic seizure circuitry [84-86]. Thus, a novel, important role of AMPA receptors in seizure consisted of switching serial seizure episodes (reminiscent of limbic seizures in humans) into self-sustaining status epilepticus (reminiscent of the most common form of status epilepticus in humans, which affects limbic regions associated with mesial temporal lobe sclerosis). This condition is often refractory to drug administration and is associated with brain damage, which may be implicated in secondary epileptogenesis leading to cognitive

impairment. The duration of such a status epilepticus may last for days, and while no convulsive activity is detected in response to diazepam administration, electroencephalography (EEG) abnormalities are not suppressed, as convulsions reappear when diazepam-induced sedation vanishes. AMPA receptors are critically involved in two phenomena that influence the clinical outcome of epilepsy, *i.e.*, drug resistance and the onset of status epilepticus. From a physiological perspective, AMPA receptors are likely to induce a spontaneously epileptic circuitry in which the ongoing epileptic activity increases synaptic strength as a consequence of maladaptive plasticity. Accordingly, GluA2 subunit-containing AMPA receptors show a transition to a higher conductance state in the presence of cyclothiazide, which stabilizes the open configuration of the receptor prolonging the depolarization phase [87].

3.1.3. Negative Allosteric Modulators of AMPA Receptors: From the Bench to the Clinic

In line with the previous data, administering GYKI 52466 (1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine), the prototypic compound of the 2,3-benzodiazepine family, a highly selective, non-competitive AMPA receptor antagonist produces similar evidence concerning the significance AMPA receptors and seizures. Fritsch *et al.* [88] evaluated the effect of GYKI 52466 on early and late kainate-induced SE, demonstrating that GYKI 52466 inhibited both seizure activity and recurrence.

Yamaguchi *et al.* [56] compared the anticonvulsant activities of GYKI 52466 and NBQX in the maximal electroshock seizure (MES) test, where both were found to be protective. GYKI 52466 was also able to protect against seizures and lethality induced by 4-aminopyridine, kainate and AMPA, whereas NBQX was ineffective [56]. Talampanel (GYKI 53773, LY300164 = 7-acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo(4,5H)-2,3-benzodiazepine), a selective non-competitive antagonist of AMPA receptors, showed protective activity in the kainate-induced neonatal status epilepticus model [89].

Topiramate is an antiepileptic drug approved for the treatment of partial seizures, primarily generalized seizures, and seizures associated with Lennox-Gastaut syndrome in children [90, 91]. Its mechanisms of action include blockade of voltage-sensitive sodium channels, enhancement of GABAergic transmission, and antagonism of AMPA/kainate receptors [92, 93]. Topiramate showed antiepileptic and neuroprotective properties inhibiting responses to kainate and AMPA in cultured neurons [94, 95]. Topiramate also reduced high basal concentrations of extracellular glutamate in the hippocampus of spontaneously epileptic rats [96]. The drug was found to selectively inhibit pharmacologically isolated GluK1 kainate receptor-mediated postsynaptic currents, whereas AMPA receptor-mediated currents were only modestly reduced [97]. Topiramate afforded protection against seizures induced by intravenous infusion of the selective GluK1-containing kainate receptor agonist, ATPA, but

was less effective on clonic seizures induced by AMPA or NMDA. This indicates that the selective interaction of topiramate with GluK1-containing kainate receptors is relevant to its anticonvulsant properties [98].

Consistently with the effects of AMPA receptors reported in paragraph 2, topiramate dose-dependently reduces spike-and-wave discharges (SWDs) in Wistar Audiogenic Sensitive (AS) rats, an audiogenic model of convulsive seizures [99].

There is evidence that topiramate can be clinically effective in treating different forms of status epilepticus [100]. A recent study showed that topiramate reduces seizures when administered as an add-on treatment for drug-resistant focal epilepsy [101].

Perampanel 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydro-3-yl)benzimidazole, a potent, selective, and orally-active AMPA receptor NAM, has been approved by FDA and EMA for the treatment of focal epilepsy and generalized tonic-clonic epilepsy [102-106]. Perampanel selectively inhibits AMPA receptors at concentrations falling within the therapeutic range, although it can also inhibit NMDA and kainate receptors at higher concentrations [107]. Interestingly, perampanel also restrains myoclonic or absence seizures [108, 109], and, in animals, shows protection against audiogenic seizures [47], pentylenetetrazole (PTZ)-induced clonic seizures and psychomotor seizures in the 6-Hz stimulation protocol [110].

Perampanel shortens after-discharge activity and prolongs latency to onset of generalized seizures in the amygdala kindling [111, 112], while blocking pilocarpine-induced status epilepticus [113]. Augustin *et al.* [114] demonstrated that the combined use of perampanel and dietary decanoic acid (also acting as a non-competitive AMPA receptor antagonist) act synergistically in restraining seizures in human brain slices.

Perampanel is well tolerated in children and adolescents with focal epilepsy [115]. Perampanel also showed good efficacy and tolerability in young children with intractable epilepsy [116].

Experience from clinical trials indicates that AMPA receptor antagonists show a good tolerability profile, although they may cause transient sedation, an effect that is also observed in animal models [56]. AMPA receptor antagonists were found to be safe and effective in patients with partial-onset seizures [105].

Clinical studies have also shown that AMPA antagonists can be effective in the acute treatment of benzodiazepine-resistant status epilepticus [77, 88]. This is consistent with what was reported previously about the powerful induction of status epilepticus, which follows the potentiation of AMPA receptors in the presence of baseline glutamate activity.

3.2. AMPA Receptors in Models of Absence Epilepsy

Mice with genetic deletion of stargazin (*stargazer* mice) show ataxia and absence-like seizure [117]. *Stargazer* mice

show a selective loss of AMPA receptors at synapses between cortical afferent fibers and GABAergic neurons of the reticular thalamic nucleus (nRT) [118]. Interestingly, these mice possess lower levels of GluA1, 3 and 4 subunits of AMPA receptors, which anticipate seizure onset. In contrast, after seizure activity, there is a reduced expression of GluA2-containing AMPA receptors. Therefore, one might argue that a loss of GluA4-containing AMPA receptors (likely GluA1/4 and GluA3/4 receptors) is linked to seizure induction, whereas a loss of GluA2-containing AMPA receptors contributes to seizure maintenance [82]. A specific loss in cortical-nRT excitation, leading to a reduced feed-forward inhibition of thalamic relay nuclei, characterizes the absence of epilepsy model of Gria4 knockout mice, which lack the GluA4 subunit [119].

Peeters *et al.* [120] have studied the involvement of AMPA receptors in WAG/Rij rats, which develop spontaneous absence seizures after 2/3 months of age [121]. In these rats, intracerebroventricular (i.c.v.) injection of AMPA increases SWDs (the EEG hallmark of absence epilepsy). In contrast, i.c.v. injection of glutamic acid diethyl ester (GDEE), a non-subtype selective kainate/AMPA receptor antagonist, decreases absence seizures dose-dependently [120]. The AMPA receptor antagonist, CNQX, also dose-dependently reduces the number of SWDs in WAG/Rij rats after i.c.v. injection [122].

Jakus *et al.* [123] examined the effect of GYKI 52466 in WAG/Rij rats, showing that i.p. administration fast increases in a dose-dependent manner, both number and duration of SWDs. Two non-competitive AMPA receptor antagonists, CFM-2 (1-(4-aminophenyl)-3,5-dihydro-7,8-dimethoxy-4H-2,3-benzodiazepin-4-one) and THIQ-10c (N-acetyl-1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) reduce dose-dependently both frequency and duration of SWDs, when locally injected within the peri-oral region of the primary somatosensory cortex (S1po) of WAG/Rij rats, whereas they were inactive when locally injected within thalamic nuclei [124].

Russo *et al.* [125] tested the potential effect of THIQ-10c alone or in combination with the anti-absence drug, ethosuximide in WAG/Rij rats. THIQ-10c did not affect the number and duration of SWDs when administered alone, but it was able to enhance the antiepileptic activity of ethosuximide [125].

Both perampanel and telampanel reduced the number of SWDs in WAG/Rij rats after systemic administration [126, 127]. Finally, topiramate dose-dependently reduced SWDs in GAERS (Genetic Absence Epilepsy Rat from Strasbourg), which are widely used as an experimental animal model of absence epilepsy [99].

4. NMDA RECEPTORS AND EPILEPSY

NMDA receptors are receptor-operated channels (ROC) consisting of non-specific cation channels with a high permeability to Ca^{2+} (as well as Na^{+} and K^{+}) [128, 129]. At neuronal resting membrane potential, the channel is blocked by

Mg^{2+} ions and this block is released by membrane depolarization [130, 131]. NMDA receptors mediate most of the slow excitatory postsynaptic potentials (EPSP) essential to global information processing [11]. NMDA receptor activation is important in signal transduction, as well as synapse formation and maintenance [132-138].

Functional NMDA receptors are tetramers composed of GluN1, GluN2A-D, and/or GluN3A-B [26]. The genes encoding NMDA receptor subunits are called *GRIN1*, *GRIN2A*, *GRIN2B*, *GRIN2C*, *GRIN2D*, *GRIN3A*, and *GRIN3B* [26]. NMDA is mainly postsynaptic, but they have also been found at pre-synaptic sites on axon terminals. The distribution of NMDA receptors surpasses neuronal membrane being abundant also in cortical astrocytes [139].

GRIN2D variations have been associated with drug-refractory epileptic encephalopathy (which does not improve following conventional antiepileptic drug treatment [140]).

In 2017, Gao *et al.* [141] identified a *de novo* missense mutation (D731N) of *GRIN2A* gene in a patient with childhood focal epilepsy and acquired epileptic aphasia. The mutation, which is located in a portion of the agonist binding domain of GluN2A, reduces the potency of glutamate in activating NMDA receptors by > 3,000-fold.

Marwick *et al.* [142] investigated a *de novo* genetic variant found in patients with epileptic encephalopathy, which changes a residue located in the ion channel pore of GluN2A-containing NMDA receptors. In cultured primary mouse cortical neurons, this variant (GluN2A, N615K) markedly reduces Mg^{2+} blockade and increases channel conductance even when expressed alongside wild-type subunits.

4.1. NMDA Receptors and Convulsive Seizures

Recent studies show that blockade of GluN2B-containing NMDA receptors reduces short-term brain damage induced early-in-life by status epilepticus [143].

Inhibition of brain-specific microRNA-134, which is involved in NMDA receptor-dependent spine remodeling [144], can prevent spontaneous recurrent seizures, which appear several months after status epilepticus in >90% of animals, suggesting a new strategy to prevent TLE [145]. It has been reported that microRNA-139-5p negatively regulates NR2A-containing NMDA receptors in the rat pilocarpine model and patients with TLE [146].

Hamamoto *et al.* [147] recently studied the modulation of NMDA receptors in the amygdala and hippocampus of patients with mesial TLE with hippocampal sclerosis (which represents the most frequent form of focal epilepsy in adults). The authors observed an inverse relationship between miR-219 (that target GluN1) [148] and NMDA receptor expression, suggesting the importance of the regulatory role of miR-219 in excitatory neurotransmission in patients with epilepsy.

It is well known that agonists acting on NMDA receptors can elicit seizures in animal or human subjects, while antagonists inhibit seizures in animal models, indicating that

NMDA receptors are candidate targets for antiepileptic drugs [16]. However, NMDA receptor antagonists are largely inactive against fully kindled seizures and may produce adverse effects in kindled animals, such as hyperlocomotion and stereotypies [149, 150]. In some rodent models of epilepsy, competitive and non-competitive NMDA receptor antagonists have demonstrated weak efficacy [151, 152].

Competitive NMDA receptor antagonists binding at the glutamate recognition site, such as D-2-amino-5-phosphonopen-tanoate (AP5) [153] and 3-[(±)-2-carboxypiperazin-4-yl]propyl-1-phosphonate (CPP) [154], have a poor brain penetration, and their action may be overcome by the high concentrations of synaptic and extra-synaptic glutamate during epileptic seizures. Slow NMDA channel blockers, such as dizocilpine (MK-801) and the dissociative anesthetics phencyclidine and ketamine, which act as non-competitive antagonists overcome these limitations [155], but their use is limited by psychotomimetic effects and other adverse effects.

Rundfeldt *et al.* [156] demonstrated that injection of drugs acting as antagonists (7-chlorokynurenic acid), or partial agonists (R(+)-3-amino-1-hydroxypyrrolid-2-one, D-cycloserine) at the glycine site of NMDA receptors elicit potent anticonvulsant effects in fully kindled rats, causing an increase in the threshold for after-discharge activity in focal seizures.

Long-lasting status epilepticus may produce glutamate-dependent synaptic plasticity. This phenomenon in turn is believed to foster secondary spontaneous epileptogenesis. In this way, we should consider that when administering NMDA receptors, apart from producing symptomatic seizure occlusion, an altered maturation in the epileptic circuitry is promoted. This may prevent the generation of a self-sustaining, self-propagating, drug-refractory seizure activity from producing a disease modifying event, preventing later seizures [157]. In addition, the occlusion of glutamate overactivity produced by these drugs is supposed to prevent from potential seizure-induced brain damage. In fact, MK-801 and ketamine suppress seizures while protecting neuronal damage induced by long-lasting status epilepticus [158, 159].

Therefore, these drugs may be useful to disrupt epileptic circuitries when they become refractory to classic antiepileptic activity due to maladaptive plasticity. In line with this, ketamine has been reported to produce beneficial effects (seizure blockade within 24-48 hours) in children with severe refractory epilepsy (Lennox-Gastaut Syndrome, myoclonic-astatic epilepsy, progressive myoclonic epilepsy and Pseudo-Lennox Syndrome) [160]. Similarly, clinical studies extended the use of these drugs to long-lasting status epilepticus [160], where the non-competitive antagonist MK-801 dose-dependently prevents orphenadrine-induced status epilepticus [161].

The use of these compounds eventually leads to the addition of non-epilepsy related events, which may sustain unbearable side effects. In fact, MK-801 apart from increasing

seizure-threshold impairs motor activity, and combined administration of D-cycloserine with MK-801 potentiates MK-801-induced motor impairments without improving anticonvulsant effects, suggesting a deleterious enhancement of side- vs. therapeutic effects [162].

When referring to the modulation of NMDA receptors in seizures, it is critical to consider the glycine B site. In detail, the relevance of the glycine B site was reported as follows: The glycine B site possesses a key role in the ionotropic mediated glutamate-induced epileptic activity. This might be relevant also to convert seizures into status epilepticus. For instance, in DBA/2 mice, the administration of the glycine B site antagonist MNQX exerts protective effects against kindling-induced status epilepticus [163]. In fact, it is a common belief that at least part of the anticonvulsant effects exerted by felbamate, remacemide and riluzole is mediated by their antagonism at glycine B site [164]. Conversely, glycine B partial antagonists gifted with a weak intrinsic activity may exert a pro-convulsant effect.

This is further confirmed by the use of a highly selective glycine B antagonist SM-31900 [165], which occludes seizures induced by systemic administration of NMDA.

A number of drugs owing to multiple actions behave as the ligand for the glycine B site [166-172].

For instance, remacemide ((+/-)-2-amino-N-(1-methyl-1,2-diphenylethyl)acetamide), a weak inhibitor of NMDA receptors, and its active des-glycine metabolite, (+/-)-1-methyl-1,2-diphenylethylamine, displayed anticonvulsant and neuroprotective activities by blocking NMDA receptors [173].

Remacemide shows greater efficacy than the sodium channel blocker, carbamazepine, in patients with two or more focal or generalized tonic-clonic seizures [174]; however, remacemide demonstrated efficacy as adjunctive therapy in patients with refractory epilepsy [175].

The antiepileptic activity of felbamate has been ascribed to the inhibition of NMDA receptors [176]. Felbamate is effective in a variety of pediatric seizure types, including seizures associated with Lennox-Gastaut syndrome [177]. This makes it useful in the treatment of refractory epilepsy in children [178, 179], although there is no indication for the use of felbamate as an add-on therapy in people with drug-resistant focal epilepsy [180].

What is not consistent with the anti-seizure activity of NMDA receptor antagonists in animal models [181-184] is the occurrence of epileptic seizures in patients with limbic autoimmune encephalopathy caused by anti-NMDA receptor antibodies [185]. These antibodies target both GluN1 and GluN2 subunits, causing the internalization of NMDA receptors from plasma membrane to the cytosol [185-188]. Although in most animal studies NMDA receptor antagonists did not elicit seizures [189, 190], the competitive NMDA receptor antagonist, D-CPP-ene, worsened seizures in 3/8 patients with epilepsy [191]. The difference between animal and clinical studies may reflect the different distribution of

NMDA receptors in cortical inhibitory interneurons and pyramidal neurons. Parvalbumin-positive neurons, which represent the largest population of cortical interneurons, are constitutively activated by NMDA receptors, and inhibition of these interneurons may cause seizures in patients with anti-NMDA receptor antibodies.

4.2. NMDA Receptors in Models of Absence Epilepsy

Lacey *et al.* [192] observed a trafficking defect in synaptic AMPA receptors in nRT cells of *stargazer* mice, which leads to a compensatory increase in synaptic NMDA receptors and enhanced thalamic excitability. In a more recent study, however, Barad *et al.* [193] found that the defective AMPA receptor trafficking in the thalamus of *stargazer* mice does not cause compensatory increases in total and synaptic NMDA receptor expression. Thus, the role played by NMDA receptors in the pathophysiology of SWDs in *stargazer* mice is controversial.

MK-801 reduces the number and mean duration of SWDs in WAG/Rij rats [194], and attenuates gamma-hydroxybutyrate (GHB)-induced SWDs [195, 196].

Intraperitoneal or i.c.v. injections or bilateral infusion of MK-801 in the thalamus of GAERS rats, dose-dependently suppress SWDs [197].

Remacemide and its active metabolite, FPL 12495, were tested in the GAERS and WAG/Rij rat models of absence epilepsy. Both drugs reduce the frequency of SWDs [198, 199], and, in WAG/Rij rats, FPL 12495 has greater potency compared with remacemide [199].

5. KAINATE RECEPTORS AND EPILEPSY

Kainate receptors are homo- or heterotetramers formed by GluK1-5 subunits encoded by the *GRIK1-5* genes [26, 200], and they are placed at pre- and post-synaptic membranes, where they contribute to excitatory synaptic transmission and modulate network excitability by regulating neurotransmitter release [201-203]. Kainate receptors are structurally related to AMPA receptors but functionally different [204] and exert metabotropic/non-canonical actions [205, 206].

High densities of kainate receptors were found in the hippocampus, a key structure in TLE. Kainate receptors are up-regulated in astrocytes in response to status epilepticus [207]. Most of the studies on kainate receptors in epilepsy models used the prototype non-specific non-NMDA agonist, kainic acid, to induce seizures [208-211]. For example, kainic acid is used to model human TLE and status epilepticus in animals [212]. However, it should be highlighted that kainic acid can also activate AMPA receptors without inducing receptor desensitization [213]. This is an important confounding element because, in some studies, the pro-convulsant action of kainic acid was maintained in mice with genetic deletion of GluK1 subunit-containing kainate receptors [211].

Nonetheless, kainate injection produces acute epileptogenesis, which at least in part is mediated by kainate receptor-

mediated suppression of pre-synaptic GABA release, combined with the activation of post-synaptic kainate receptors [208]. There is evidence that GluK2 represents a major target for kainate-induced seizures and status epilepticus [209]. Presynaptic GluK2-containing kainate receptors modulate glutamate release also *via* metabotropic activity [201, 214].

The epileptogenic effects of pre-synaptic kainate receptors may also be due to disinhibition since kainate, acting on interneurons, reduces hippocampal GABA release [204, 215, 216]. In fact, studies carried out in GluK2-over-expressing or knock-out mice suggest that hippocampal GluK2 is critical for seizure activity [215, 217].

Kainate receptors containing the GluK2 subunit are linked to limbic epilepsy due to a widespread distribution within CA3 pyramidal neurons [218]. Consistently, deletion of GluK2 reduces seizure developments after kainate injection in mice [209].

The AMPA/kainate receptor antagonist, NS1209, is effective against refractory status epilepticus in phase 2 clinical trials [219]. CNQX, another AMPA/kainate receptor antagonist, prevents high-frequency hippocampal oscillations associated with seizures [220].

Fritsch *et al.* [211] demonstrate that selective activation of GluK1 kainate receptors elicit seizures *in vivo*, and epileptiform discharges in the BLA (basolateral amygdala) *in vitro*; however, whether or not GluK1-containing kainate receptors can be targeted by therapeutic intervention is still a matter of debate.

Although LY293558 was originally believed to be a selective AMPA receptor antagonist, it inhibits GluK1 (formerly known as GluR5)-containing kainate receptors with even greater potency. This compound is effective in status epilepticus, even when administered after seizure onset [221]. LY293558 has been clinically tested and found to be safe and well tolerated [222, 223]. Inhibition of GluK1-containing kainate receptors could also represent one of the mechanisms underlying the anticonvulsant activity of topiramate [224].

The role of kainate receptors in the pathophysiology of TLE remains elusive. Some studies have focused on the role of heteromeric GluK2/GluK5 kainate receptors in the generation of recurrent seizures in TLE: the inter-ictal and ictal events were reduced in mice lacking the GluK2 subunit or in the presence of a GluK2/GluK5 antagonist [215]. In tissue from patients with refractory TLE, an increase in GluK4 and GluK5 subunits has been reported [225]. GluK1 and GluK5 are up-regulated chronically during post-ictal spontaneous seizures [207].

Subtype-selective GluK5 kainate receptor antagonism prevents pilocarpine-induced limbic seizures in rats and epileptiform activity induced by electrical stimulation, both *in vitro* and *in vivo* [210].

Recent studies reported that GluK2 undergoes post-translational modifications such as S-nitrosylation (SNO), which is involved in neuronal injury in epileptic rats by forming a

calcium-dependent GluK2-PSD95-nNOS cytosolic complex, which may represent a therapeutic target for epilepsy [226].

Orav *et al.* [227] described neuropilin tolloid-like protein 1 (NETO1) as a potential therapeutic target for the treatment of both adult and early life seizures: it acts as kainate receptor auxiliary protein necessary for dendritic delivery of kainate receptor subunits and formation of kainate receptor-containing synapses in cultured GABAergic neurons.

CONCLUSION

Despite being apparently well-known, the role of iGlu receptors in epilepsies and seizures bring a number of confounding issues. In the present review, apart from summarizing the classic knowledge about the key role of these glutamate receptors in seizure onset, severity and duration, we presented findings on the various role played by these receptors depending on the kind of epileptic seizures. Again, we tried to elucidate the confounding role of non-NMDA receptors based on the experimental tools used to study their role in seizure activity. With the aim to overview critically the plethora of reports about the role of iGlu receptors in epilepsies, we faced novel issues that may be considered in re-evaluating ionotropic ligands as useful therapeutic agents in epilepsy. This mainly applies to refractory epilepsy and life-threatening conditions such as self-sustaining long-lasting status epilepticus. The development of new antiepileptic drugs with a better profile of tolerability and safety is an urgent medical need. Thus, we aimed to highlight the necessity of further research on this topic that would be useful to unravel the mechanisms underlying the development of epilepsies and to promote the development of drugs targeting the iGlu receptors.

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