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Review Article

AMPA RECEPTOR: A REVIEW

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ABSTRACT

α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors (AMPARs) are of fundamental importance in the brain. They are responsible for the majority of fast excitatory synaptic transmission, and their overactivation is potently excitotoxic. Recent findings have implicated AMPA receptors in synapse formation and stabilization, and regulation of functional AMPA receptors is the principal mechanism underlying synaptic plasticity. Changes in AMPA receptor activity have been described in the pathology of numerous diseases, such as Alzheimer's disease, stroke, and epilepsy. Unsurprisingly, the developmental and activity-dependent changes in the functional synaptic expression of these receptors are under tight cellular regulation. The molecular and cellular mechanisms that control the postsynaptic insertion, arrangement, and lifetime of surface-expressed AMPARs are the subject of intense and widespread investigation. For example, there has been an explosion of information about proteins that interact with AMPA receptor subunits, and these interactors are beginning to provide real insight into the molecular and cellular mechanisms underlying the cell biology of AMPA receptors. As a result, there has been considerable progress in this field. The aim of this review is to provide an account of the current state of knowledge about AMPA receptors.

Keywords: AMPA receptors, Alzheimer's disease.

INTRODUCTION

Receptors are protein molecules, embedded in either the plasma membrane (cell surface receptors) or the cytoplasm (nuclear receptors) of a cell, to which one or more specific kinds of signaling molecules may attach. Molecule which binds (attaches) to a receptor is called a ligand, and may be a peptide (short protein) or other small molecule, such as a neurotransmitter, a hormone, a pharmaceutical drug, or a toxin. Each kind of receptor can bind only certain ligand shapes. Each cell typically has many receptors, of many different kinds. Ligand binding stabilizes a certain receptor conformation (the three-dimensional shape of the receptor protein, with no change in sequence). This is often associated with gain of or loss of protein activity, ordinarily leading to some sort of cellular response. However, some ligands (e.g. antagonists) merely block receptors without inducing any response. Ligand-induced changes in receptors result in cellular changes which constitute the biological activity of the ligands.[1]

Amino acid glutamate is the major excitatory neurotransmitter in the mammalian central nervous System (CNS1) and it exerts its physiological effects by binding to a number of different types of glutamate receptors (GluRs). Glutamate receptors can be divided into two functionally distinct categories: those that mediate their effects via coupling to G-protein second messenger systems, the metabotropic glutamate receptors (mGluRs) and ionotropic ligand-gated ion channels.[2]

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA receptor) is a non-NMDA-type ionotropic transmembrane receptor for glutamate that mediates fast synaptic transmission in the central nervous system (CNS).AMPA receptor is also called as quisqualate receptor. Its name is derived from its ability to be activated by the artificial glutamate analog AMPA.[3] we are here reviewing the importance and medicinal chemistry approach for AMPA receptors as new therapeutic drug target.

DISCOVERY

The receptor was discovered by Tage Honore and colleagues at the School of Pharmacy in Copenhagen, and published in 1982 in the Journal of Neurochemistry.

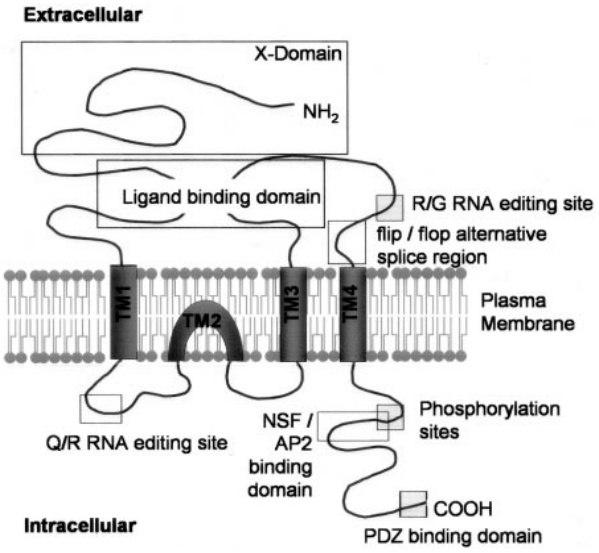


Fig. 1: It shows the topology of an AMPA receptor subunit

STRUCTURE OF AMPA RECEPTORS

Ionotropic glutamated receptor are composed of four subunits and each protomer consist of four discrete region.[4] Each subunit consist of three regions an extracellular N-terminal domain, four hydrophobic regions (TM1–4), and an intracellular C-terminal domain. The intracellular C terminus contains phosphorylation sites and conserved sequences that have been shown in schematic drawing to interact with a number of intracellular proteins, for example, PDZ domain-containing proteins and ATPase & NSF.

(PDZ is postsynaptic density 95-discs large-zona occludes 1 domain)

(NSF is *N*-ethylmaleimide-sensitive factor)

1) **N Terminus:** In eukaryotes, the N terminus contains the N-terminal domain of 400 amino acids and a 150 amino acid ligand-binding core. The N-terminal domain is also known as the X-domain because of its unknown function.[5] Suggestions for X-domain functions include receptor assembly, allosteric modulation of the ion channel, and binding of a second ligand. The X-domains of GluR4 form dimers in solution and confer specificity for AMPARs, as opposed to KARs upon coassembly with other subunits.[6] However, deletion of the entire X-domain of GluR4 did not alter the function of homomers expressed in human embryonic kidney 293 cells, indicating that it is not involved in homomeric assembly of this subunit.[7] The structure of this part of AMPARs is suggestive of a ligand-binding site, but no endogenous ligands have been found to bind here, although Zn^{2+} modulates at a similar site on NMDARs.[8] Intriguingly, the N terminus of GluR2 is involved in dendritic spine morphogenesis, perhaps through a receptor-ligand complex.[9]

The ligand-binding core of AMPARs confers pharmacological specificity to the receptors; indeed, swapping the domains of AMPA and KARs swapped both their affinity for the ligand and desensitization properties and proved that this is the glutamate binding site.[10] The structures of the ligand binding cores of GluR2 and GluR4 have been studied intensively [11] and this is the only part of any AMPAR to be crystallized so far.[12] For GluR2, the ligand-binding core has been crystallized with various pharmacological agents.[13] This approach gives an insight into the mode of action of some AMPAR agonists and antagonists and promises to be a valuable tool for the rational design of future drugs.

2) Hydrophobic Region: The transmembrane orientation of the AMPAR subunits was initially elucidated by the use of specific antibodies, N-glycosylation pattern, and proteolytic sites.[14]

Together, these studies demonstrated that the mature N terminus is expressed on the exterior surface of the neuron, and subsequent work showed that the TM1, TM3, and TM4 regions are all transmembrane spanning domains, whereas TM2 forms a hairpin loop on the intracellular side of the cell membrane. Similar to K^+ channels, the re-entrant loop contributes to the cation pore channel, although the specificity of AMPARs differ in that they gate Na^+ and Ca^{2+}in preference to K^+, perhaps because of a comparatively larger pore size.[15]

3*)* Intracellular C Terminus: The intracellular C terminus of eukaryotic AMPARs has been shown to be the interaction site for a range of different proteins, many of which are involved in the receptor trafficking and synaptic plasticity.[16]

Plasma Membrane Distribution of AMPA Receptors

1. Postsynaptic Membrane: It is well established that AMPARs reside in the postsynaptic compartment. GluR2/3 and GluR4 subunits colocalize throughout the postsynaptic density in the rat organ of Corti, with higher concentrations of receptors located around the periphery of the PSD (Postsynaptic domain). These subunits were not detected at extrasynaptic membranes, but some GluR4 subunits appeared to be presynaptic.[17]

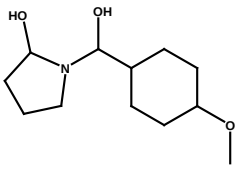
2. Extrasynaptic AMPA Receptors: Electrophysiological experiments indicate that AMPARs are widely distributed throughout the cell surface plasma membrane.

3. Presynaptic Terminal: AMPARs are present on presynaptic terminals and that they may play a role in the regulation of neurotransmitter release.[18]

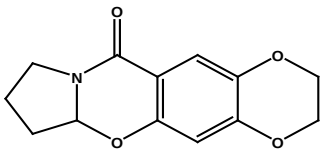
LIGANDS OF AMPA RECEPTOR

Positive allosteric modulators

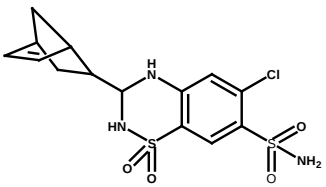
Positive allosteric modulators slows deactivation of AMPA receptors improve short-term memory in humans and may also prove useful for the treatment of depression and other disorders and diseases of the nervous system (O'Neill et al., 2004).[19] Studies using recombinant receptors and rapid perfusion, patch-clamp electrophysiology experiments, positive allosteric modulators such as **Aniracetam** [1-(4-methoxybenzoyl)-2-pyrrolidinone] (Ani) and **CX614** (pyrrolidino-1,3-oxazino benzo-1,4-dioxan-10-one) (CX) slow deactivation of AMPA receptors, or the rate at which the ion channel closes after the removal of glutamate.[20]



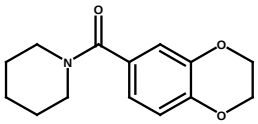
Aniracetm



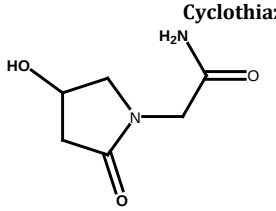
CX614



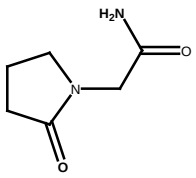
Cyclothiazide



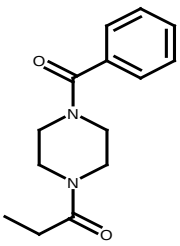
CX546



OXIRACETAM



PIRACETAM



SUNIFIRAM

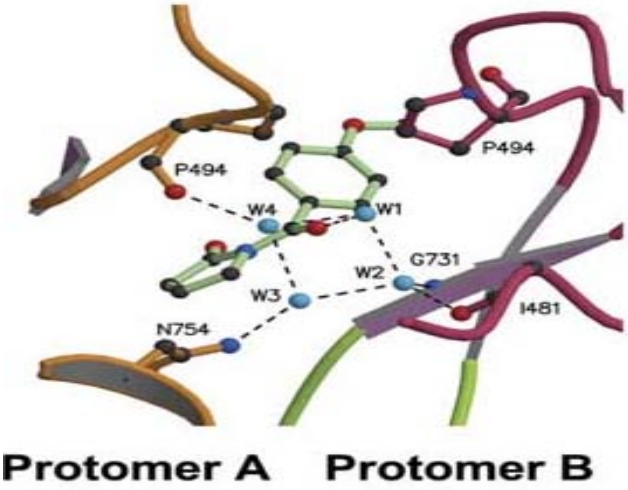


Fig. 2: It shows Hydrogen bonding interactions and binding modes of Aniracetam and CX614.

Top view of hydrogen bonding (dashed lines) between Aniracetam, protein residues, and water molecules (blue spheres), in which the domains are color coded.[21]

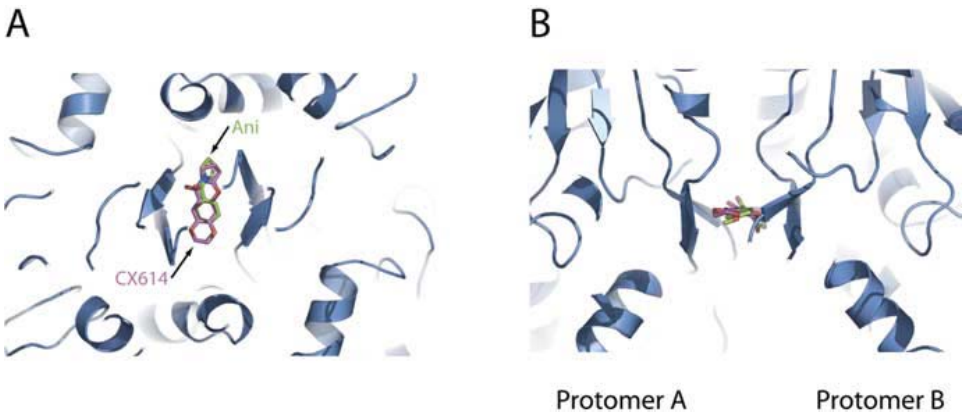


Fig. 3: It shows the binding sites of Aniracetam and CX614 overlap.

A. View parallel to the twofold axis showing that Aniracetam (green) and CX614 (pink) overlap. In fact, rings 1 and 3 are nearly superimposable.

B. View perpendicular to the twofold axis, showing that the modulators bind at the same "depth" in the dimer interface.[22]

Negative allosteric modulators

2,3-benzodiazepines such as 1-(4-aminophenyl)-3-methylcarbamyl-4-methyl-7,8-methylenedioxy-3,4 -dihydro- 5H-2,3-benzodiazepine (GYKI 53655) act as noncompetitive antagonist through allosteric modulation. GYKI 53784 is the most potent of the compounds in the 2, 3-benzodiazepine class, blocking AMPA receptor-mediated responses. In contrast to the compounds of the quinoxalinedione family, that block AMPA as well as kainate receptors, GYKI 53784 does not block the activation of kainate receptors. Furthermore, GYKI 53784 does not act at the same receptor site as positive AMPA modulators (i.e., cyclothiazide, BDP-12, 1-BCP or aniracetam). GYKI 53784 is a powerful neuroprotective agent in both *in vitro* and *in vivo* models of AMPA receptor-mediated excitotoxicity.[23]

Development & structural requirements of negative allosteric modulators

Synthesis of 2, 3-benzodiazepines (later also called homophtalazines) was originally aimed at finding active papaverine-related derivatives with cardiovascular activity. Since the chemical research program generated compounds with the 2, 3-benzodiazepine nucleus they were tested for potential central nervous system activity. Preliminary pharmacological testing in rodents revealed that these substances acted as tranquilizing agents, although they lacked muscle relaxant or anticonvulsant properties. As a result, tofisopam was identified as the lead compound of this series and proposed for the clinical development.[24]

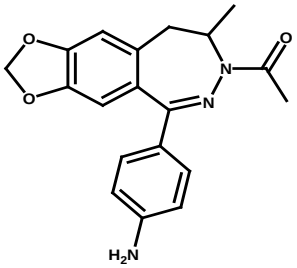
Structural requirement of compounds to be active as negative modulators is the 5*H*-2, 3-benzodiazepine nucleus with 7, 8-dimethoxy, methoxy or hydroxyl substitutions and a phenyl ring substituent at the 1 position. However, relatively small modifications of the 2,3-benzodiazepine nucleus resulted in compounds with quite different behavioral profiles.[25] The first of these, GYKI 52466,carried a 7,8-methylenedioxy bridging function and a 4-aminophenyl substituent in position 1 found GYKI-52466 to be a non-competitive AMPA receptor antagonist and demonstrated its neuroprotective, muscle relaxant and anticonvulsant effects in different pharmacological tests.

Agonists

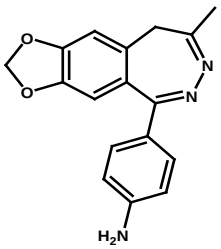
The development of subtype selective AMPA receptor ligands is of high relevance to CNS diseases. As an example, variants of the GRIA1 gene, which codes for the GluR1 AMPA receptor subunit, have been

reported to be associated with certain forms of schizophrenia.6 In the search for such ligands for studies of the physiological role and pharmacological characteristics of the AMPA receptors, much research has been focused on the development of potent and selective agonists.

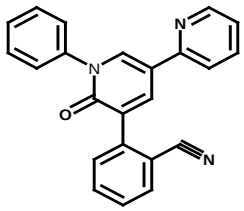
One of the most potent AMPA agonists is (*S*)-2-amino-3-[3-hydroxy-5-(2-methyl-2*H*-5-tetrazolyl)-4-isoxazolyl]propionic acid [(*S*)-2-Me-Tet-AMPA, **2**].However, compound **2** shows little selectivity among GluR1-4 based on receptor affinity studies. Replacements of the methyl group of 2-Me-Tet-AMPA with larger groups such as 2-ethyl (**3**), 2-propyl (**4**), and 2-isopropyl (**5**)do not result in any significant increase in selectivity.[26]



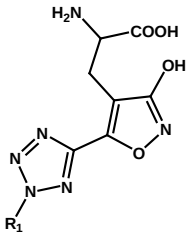
TELAMPANEL



GYKI-52466



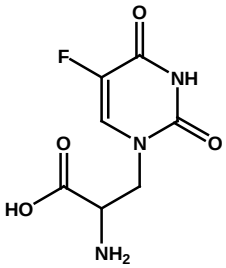
PERAMPANEL



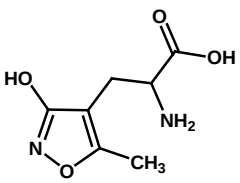
(*S*)-2 Me-Tet-AMPA where R_1=Ethyl, R_2 =Propyl, R_3 =Isopropyl

It was found that tyrosine 702 in GluR2 (Y716 in GluR1) is the most likely structural determinant explaining the observed selectivity.10,11 GluR3 and -4 contain a phenylalanine residue in equivalent positions. Apart from this sequence difference,the ligand-binding pocket is highly conserved.[27]

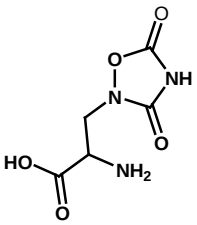
Some other AMPA receptor agonists are as below:



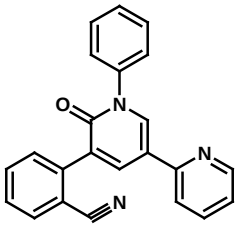
5-FLUROWIILARDIINE



AMPA



QUISQUALIC ACID



PERAMPANEL

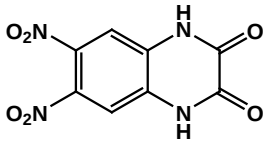
Antagonist

AMPA receptor antagonist are divided in 2 types

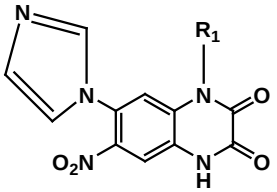
1. **Competitive ampa receptor antagonists**
2. **Noncompetitive ampa receptor antagonists**

Competitive AMPA receptor antagonist

Quinoxaline derivatives are an interesting class of specific and potent competitive non-NMDA glutamate receptor antagonists.[28] some quinaoxaline 2,3- diones such as DNQX, NBQX ,YM-90K, YM-872 have been found to be neuroprotective in various models of ischemia and to have anticonvulsant properties in different models of epilepsy. Using these molecules as templates the synthesis of different quinoxaline derivatives was thus pursued, together with extensive structure activity relationships (SAR) and pharmacophore modelling studies on this class of compounds. Noncovalent interactions between the two molecules and the receptor subunit stabilize an open form of the ligand-binding core, contrarily to agonists which induce substantial domain closure.[29]



DNQX



R=H YM90K

R=CH_2COOH YM872

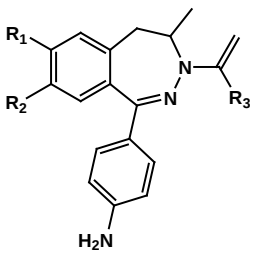
5-aminoalkyl substituted quinoxaline-2, 3-diones

This has efficacy in maximal electroshock seizures but did not show selectivity between AMPA and kainate receptors.[30]

Noncompetitive ampa receptor antagonists

The non-competitive AMPAR antagonists, interacting with an allosteric AMPA binding site, have the advantage of remaining effective independently of the level of glutamate or the polarization state of the synaptic membrane during a neurological diseases.[31] Moreover; they do not influence the normal glutamatergic activity also after prolonged use. Thus, in recent years some important classes of these ligands have been developed.

The first non-competitive AMPA antagonist was 1- (4-aminophenyl)-4-methyl- 7,8 -methylenedioxy-5*H*-2,3-benzodiazepine (GYKI 52466)[32] discovered in 1989 and used as template to develop novel more potent and less toxic AMPAR modulators.



1- (4-aminophenyl)-4-methyl-7, 8 -methylenedioxy-5*H*-2, 3-benzodiazepine

R 1-R2 = -OCH2O-; R 3 = Me GYKI 53733 talampanel

R1 -R2 = -OCH2O-; R3 = NHMe GYKI53784

Pharmacological activity of AMPA receptor antagonists against epilepsy

Excessive glutamatergic neurotransmission is understood to be one of the primary metabolic and pathological mechanisms behind the etiology of numerous types of epilepsy.[33] Since then, a number of functional changes in excitatory amino acid neurotransmission have been reported in seizure-susceptible animals including increased excitatory amino acid-induced Ca2+ influx, altered excitatory amino acid binding, enhanced glutamate and aspartate release, and modulation of glutamate transporter expression and function. Because AMPAR ligands are relatively novel anticonvulsant agents compared for example to benzodiazepines or Na+ channel inhibitors, the potential of AMPA receptor antagonists to attenuate epileptic seizures has not yet been fully investigated. At present, talampanel is the only AMPA receptor antagonist in phase II clinical trial use for the amelioration of epileptic seizures. It is known that AMPA receptors are expressed in the key epileptogenic regions of the brain including the cerebral cortex, the thalamus, the amygdale, the hippocampus, and even the basal ganglia which receives inputs from these regions.[34]

CONCLUSION

The various agonist and antagonist that were use in long term potentisaton as anticonvulsant are giving us fresh insights into the role of the AMPA receptor in disease. The latest data confirm the importance of the AMPA system in the pathogenesis of disease states and help to explain the important role of drugs that bind to AMPA receptor. A clear understanding of the mechanism underlying dependence will also enable us to develop treatment regimes for using current drugs which will optimize benefits and minimizes any unwanted effects. The high resolution crystal structures presented here demonstrate, for the first time, how modulators can differentially affect deactivation and desensitization, they lend insight into the mechanism underlying modulator potency and efficacy, and they provide a structural basis from which to design a new generation of AMPA receptor modulators.

REFERENCES

1. Madden DR The structure and function of glutamate receptor ion channels.Nat.Rev.Neurosci 2002; 3:91-103.
2. Purves, Dale, Augustine GJ, Fitzpatrick D, Hall WC et. Al. Neuroscience. 4th ed.. Sinauer Associates. 2008; 156–7.
3. www.wikipedia.com
4. Paas Y The macro and microarchitectures of ligand binding domain of glutamate receptors. Trends neurosci 1998; 21:117-125
5. Kuusinen A, Abele R, Madden DR, and Keinanen K Oligomerization and ligand-binding properties of the ectodomain of the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor subunit GluRD. J Biol Chem 1999; 274: 28937–28943.
6. Leuschner WD and Hoch W Subtype-specific assembly of alpha-amino-hydroxy-5-methyl-4-isoxazole propionic acid receptor subunits is mediated by their N-terminal domains. J Biol Chem 1999; 274:16907–16916.
7. Pasternack A, Coleman SK, Jouppila A, Mottershead DG, Lindfors M, Pasternack M, and Keinanen K Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor channels lacking the N-terminal domain. J Biol Chem 2002 ; 277:49662–49667.
8. Armstrong N and Gouaux E Mechanisms for activation and antagonism of an AMPA-sensitive glutamate receptor: crystal structures of the GluR2 ligand binding core. Neuron 2000; 8:165–181.
9. Pasternack A, Coleman SK, Fethiere J, Madden DR, LeCaer JP, Rossier J, Pasternack M, and Keinanen K Characterization of the functional role of the N-glycans in the AMPA receptor ligand-binding domain. J Neurochem 2003; 84:1184–1192.
10. Stern-Bach Y, Bettler B, Hartley M, Sheppard PO, O'Hara PJ, and Heinemann SF Agonist selectivity of glutamate receptors is specified by two domains structurally related to bacterial amino acid-binding proteins. Neuron 1994; 13:1345– 1357.
11. Jayaraman V, Keesey R, and Madden DR Ligand–protein interactions in the glutamate receptor. Biochemistry 2000; 39:8693–8697.
12. Armstrong N, Sun Y, Chen GQ, and Gouaux E Structure of a glutamate receptor ligand-binding core in complex with kainate. Nature 1998; 395:913–917.
13. Johansen TN, Greenwood JR, Frydenvang K, Madsen U, and Krogsgaard-Larsen P Stereostructure-activity studies on agonists at the AMPA and kainite subtypes of ionotropic glutamate receptors. Chirality 2003; 15:167–179.
14. Molnar E, McIlhinney RA, Baude A, Nusser Z, and Somogyi P Membrane topology of the GluR1 glutamate receptor subunit epitope mapping by site directed antipeptide antibodies. J Neurochem 1994; 63:683–693.
15. Tikhonov DB, Mellor JR, Usherwood PN, and Magazanik LG Modeling of the pore domain of the GLUR1 channel: homology with K_ channel and binding of channel blockers. Biophys J 2002; 82:1884–1893.

16. Sheng M and Hyoung Lee S AMPA receptor trafficking and synaptic plasticity:major unanswered questions. Neurosci Res 2003; 6:127–134.
17. Matsubara A, Laake JH, Davanger S, Usami S, and Ottersen OP Organization of AMPA receptor subunits at a glutamate synapse: a quantitative immunogold analysis of hair cell synapses in the rat organ of Corti. J Neurosci 1996; 16:4457–4467.
18. Barnes JM, Dev KK, and Henley JM Cyclothiazide unmasks AMPA-evoked stimulation of [3H]-L-glutamate release from rat hippocampal synaptosomes. Br J Pharmacol 1994; 113:339–341.
19. O'Neill MJ, Bleakman D, Zimmerman DM, Nisenbaum ES AMPA receptor potentiators for the treatment of CNS disorders. Curr Drug Targets, 2004; 3:181–194.
20. Vyklicky LJ, Patneau DK, Mayer ML Modulation of excitatory synaptic transmission by drugs that reduce desensitization at AMPA/kainate receptors. Neuron, 1991; 7:971–984.
21. Ingvar M, Ambros-Ingerson J, Davis M, Granger R, Kessler M, Rogers GA, Schehr RS, Lynch G Enhancement by an ampakine of memory encoding in humans. Exp Neurol, 1997; 146:553–559.
22. Partin KM, Fleck MW, Mayer ML AMPA receptor flip/flop mutants affecting deactivation, desensitization, and modulation by cyclothiazide, aniracetam, and thiocyanate J Neurosci.1996; 16:6634–6647.
23. Petocz L, Kosoczky I The main pharmacological characteristics of Grandaxin (Tofisopam, EGYT-341) Ther Hungarica 1975; 23:134-138.
24. Tarnawa I, Farkas S, Berzsenyi P, Pataki A, Andrasi F. Electrophysiological studies with a 2, 3-benzodiazepine muscle relaxant, GYKI-52466. Eur J Pharmacol 1989; 197:193–199.
25. Horvath K, Berzsenyi P, Tarnawa I, et al. Different behavioral profiles among 2,3-benzodiazepines. Psychopharmacology 1988; 96.
26. Bang-Andersen B, Lenz SM, Skjærbæk N, Søby KK, Hansen HO, Ebert B, Bøgesø, KP, Krogsgaard-Larsen P Heteroaryl analogues of AMPA Synthesis and quantitative structure-activity relationships. J. Med. Chem. 1997, 40, 2831-2842.
27. Bjerrum E. J, Kristensen A. S, Pickering D. S, Greenwood J.R.; Nielsen B, Liljefors T, Schousbo A Design, synthesis, and pharmacology of a highly subtypeselective GluR1/2 agonist, (*RS*)-2-amino-3-(4-chloro-3-hydroxy-5-isoxazolyl)propionic acid (Cl-HIBO). J. Med. Chem. 2003, 46, 2246-2249.
28. Stensbol, T. B.; Madsen, U.; Krogsgaard-Larsen, P. The AMPA receptor binding site: focus on agonists and competitive antagonists. Curr. Pharm. Des. 2002, *8*, 857-872.
29. Armstrong, N.; Gouaux, E. Mechanisms for activation and antagonism of an AMPA-sensitive glutamate receptor: crystal structures of the GluR2 ligand binding core. Neuron 2000; 28, 165-181.
30. Kornberg, B. E.; Nikam, S. S. Sulfonamide derivatives of substituted quinoxaline 2, 3-diones as glutamate receptor antagonists. United States Patent 6,096,744 2000.
31. Chimirri, A.; Gitto, R.; Zappala, M AMPA receptor antagonists Exp. Opin. Ther. Patents 1999, 9, 557-570.
32. Szabados, T.; Gigler, G.; Gacsalyi, I.; Gyertyan, I.; Levay, G.Comparison of anticonvulsive and acute neuroprotective activity of three 2, 3-benzodiazepine compounds, GYKI 52466, GYKI 53405, and GYKI 53655. Brain Res. Bull. 2001, 55, 387-391.
33. Ben-Ari Y Limbic seizure and brain damage produced by kainic acid: mechanisms and relevance to human temporal lobe epilepsy. Neuroscience 1985, 14, 375-403.
34. Chapman, A. G Glutamate receptors in epilepsy. Prog. Brain Res.1998, 116, 371-383.