AMPA Glutamate Receptors and Neuropathic Pain

Susana Morales-Alcelay†, Laura Rubio† and Ana Martinez*

Neuropharma S. A. Avda. de la Industria 52, 28760 Tres Cantos, Spain

Abstract: Glutamate receptors are implicated in many actions in the central nervous system, as an excitatory amino acid, and one of the more relevant is its role in excitotoxicity. Apart from this, it also has a role as pro-nociceptive agent, so that antagonizing its actions could be of interest for developing new analgesic agents. Furthermore, between the analgesics agents, it is of outstanding interest the fact that there is no specific therapy against the neuropathic pain, and glutamate receptor subunits have elicited as new potential targets for this disturbance.

Keywords: Neuropathic pain, allodynia, hyperalgesia, AMPA, ionotropic receptor.

INTRODUCTION

Glutamic acid is the principal excitatory neurotransmitter in the mammalian central nervous system. Glutamic acid binds to a variety of excitatory amino acid receptors, which are ligand-gated ion channels. It is activation of these receptors that leads to depolarisation and neuronal excitation. In normal synaptic functioning, activation of excitatory amino acid receptors is transitory. However, if for any reason, receptor activation becomes excessive or prolonged, the target neurones become damaged and eventually die. This process of neuronal death is called *excitotoxicity* and appears to involve sustained elevations of intracellular calcium levels. Impairment of neuronal energy metabolism may sensitise neurones to excitotoxic cell death.

A role for excitotoxicity in the aetiology or progression of several human neurodegenerative diseases has been proposed, which has stimulated much research recently. This has led to the hope that compounds that interfere with glutamatergic neurotransmission may be of clinical benefit in treating such diseases (Alzheimer, Parkinson, global ischemia, amyotrophic lateral sclerosis and analgesia among others).

Two main classes of glutamate receptors (GluR) have been characterized: the metabotropic (mGluRs) and ionotropic (iGluRs) receptors. The mGluRs regulate the activity of ion channels or enzymes by producing second messengers via GTP-coupled proteins [1]. The iGluRs are ligand-gated ion channels directly responsible for the fast depolarisation of postsynaptic cells. The iGluRs are classified into three heterogeneous types based on their pharmacology and functional prop.acid (NMDA) receptor and two non-NMDA receptors named (*R*,*S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propionic acid (AMPA) and kainic acid (KA) receptors [2,3] Fig.(**1**).

AMPA and Kainate receptors are built from closely related subunits (AMPA-GluR1-4; Kainate-GluR5-7, KA-1,2). Whereas the NMDA receptor complex is composed by two groups of subunits: NR1 and NR2A-NR2D. Each of the AMPA subunits can exist in a flip or flop variant, created by alternative splicing of a 115 base pair region of the mRNA [4]. Furthermore, RNA editing occurs for the GluR2 resulting in a glutamine residue in the proposed ion pore-forming region being changed to an arginine residue. This RNA editing difference between GluR2 and the other AMPA receptor subunits influences the divalent cation permeability and the rectification properties of the channel [5].

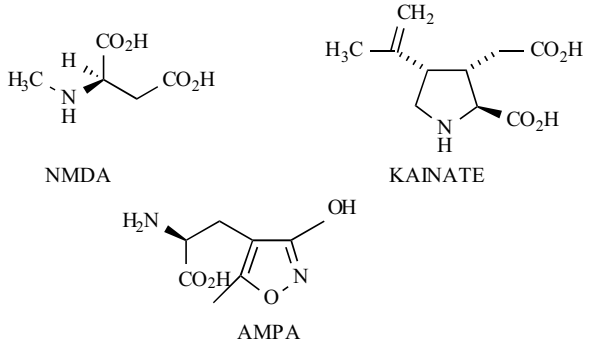


Fig. (1). Classification of glutamate receptors.

The AMPA receptor subunits co-assemble to form functional homomeric and heteromeric receptor channel complexes [6] but the exact number of subunits and the stoichometric composition of native AMPA receptors are still unclear.

The subunits contain a large extra-cellular and four membrane-associated domains showing considerable homology among different subunits. In contrast, the cytoplasmic carboxyl termini of these subunits are either long (GluR1 and GluR4), or short (GluR2 and GluR3) [7].

In hippocampus, GluR4 is mainly expressed early in development while GluR1 to GluR3 expression increases with development [8]. In adult hippocampus, these three AMPA receptor subunits combine to form two distinct populations, GluR1/GluR2 and GluR2/GluR3 [9].

The diagnostic agonist for these two receptors (AMPA and Kainate, respectively) also activates the other receptor. The synthesis of compounds that can discriminate between these closely related receptors has thus proved a great challenge to medicinal chemist.

*Address correspondence to this author at NeuroPharma, Avda. De la Industria, 52, 28760 Tres Cantos, Madrid (Spain); Tel: 34-91-8061130; E-mail: amartinez@neuropharma.es

† Both authors have contributed equally to this work

1389-5575/03 $41.00+.00

These glutamate receptors have been characterized in neurons [10] as well as in non-excitable cells such as astrocytes and oligodendrocites [11].

GLUTAMATE AND ANALGESIA

Regarding analgesia, glutamate and aspartate are the main transmitters of nociceptive pathways in the spinal cord. Glutamate induces depolarisation only of C fibers (fibers known to carry nociceptive information). So that, excitatory amino acids are principal mediators of the pain sensation in the spinal cord. Several experiments and laboratories can confirm these actions.

Inducing experimental pain, glutamate is enhanced [12] and this release is inhibited by well-known AMPA/Kainate antagonists[13].

Glutamate is released simultaneously with substance P and calcitonin gene related peptide, because they are stored in the same terminals [14].

Upon subcutaneous injection of formalin into the hind paw of rodents, glutamate and aspartate are released locally [15].

Injections of AMPA and NMDA in the skin of the paw also induce mechanical allodynia and hyperalgesia [16].

Also following peripheral nerve injury, AMPA receptors are upregulated in the superficial layers of the dorsal horn [17], and also during chronic pain induced by ligation of the sciatic nerve. This process may implicate AMPA receptors in neuropathic pain, together with the observation that vocalization response evoked by the administration of AMPA was significantly increased in the neuropathic model [18]. In this context, in neuropathic pain models there have been developed quinoxaline-2,3-diones, which have demonstrated to diminish mechanical allodynia by spinal cord hemisection [19] or by incision in the paw [20]. Also after spinal transection, intrathecal administration of the AMPA antagonist 6 cyano-7-nitroquinoxaline-2,3-dione, produced dose dependent antinocioception on the tail flick reflex [21].

Although the main glutamate receptor implicated in neuropathic pain has been traditionally the NMDA one, these data confirm that the AMPA receptor can play a role in this type of nociception. On the other hand and due to the toxic effects for the NMDA blockers used in antinociception, to have another target may be of enormous interest.

Probably with the AMPA receptor may happen the same as it has been proposed for the NMDA receptor, regarding the use of subunit selective agents rather than the non-specific ones [22].

AMPA ANTAGONISTS AS ANALGESIC COMPOUNDS

Decahydroisoquinoline AMPA Antagonist

One class of the amino acids, which have shown significant AMPA receptor activity, are the decahydroisoquinoline analogs.

Lilly is developing the racemic compound LY-215490 (**1**) Fig. (**2**), a selective and competitive AMPA antagonist, as a potential treatment for cerebral infarction cerebrovascular ischemia, epilepsy and analgesic agents. These AMPA receptor activities were due to the (-)isomer of the compound (3S,4aR,6R,8aR)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydro-isoquinoline-3-carboxilic acid (LY293558) (**2**) Fig. (**2**) [23-25].By January 2000, LY-293558 was undergoing phase II trials for pain treatment [26] .

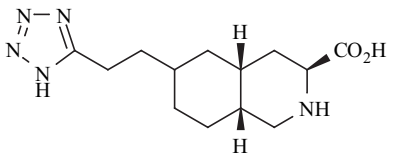
These compounds are representative of the pioneering work done by scientists at Eli-Lilly and demonstrate that the AMPA receptor activity seen in these series depends on the stereochemistry as well as the overall distance of the polar group (tetrazole moiety) at C-6 from the amino acid functionality of the decahydroisoquinoline nucleus.

The structure-activity relationship studies (SAR) is further complicated by the fact that this template has four stereocenters and hence eight possible diastereomers. The trans ring junction analogs gave inactive compounds indicating a more angular conformation for the decahydroisoquinoline nucleus rather than the linear motif.

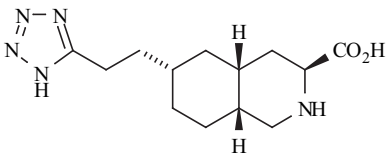
The C-6 epimer was 12-fold less active at the AMPA receptors whereas the C-3 epimer was inactive. The spacer length also had an effect on the receptor selectivity in that one-carbon spacer (n=1) was NMDA selective, a two-carbon space (n=2,(-)-LY293558) was AMPA selective and the analog with no spacer (n=0) has mixed activity and is weaker than the other analogs [27].

It has been observed that intrathecal administration of the competitive AMPA/KA receptor antagonist (with higher efficacy for AMPA one), LY293558, produced reversible, sustained sensory and motor blockade of the hind limbs in rats [28]. The data indicated that LY293558 could be useful for producing spinal anaesthesia in humans.

The rank order of potency for displacing AMPA binding by LY293558 is GluR2>GluR1>GluR3>GluR4, and the highest affinity is for GluR1 and GluR2. It also displaces KA binding form GluR5 with similar affinity but weakly antagonizes agonist binding to GluRs 6 and 7 and KA2 receptors. It was surprising not to find hypotension as a side effect after LY293558 injection, which could permit spinal anaesthesia in patients with sub-optimal hemodynamic



1



2

Fig. (2). Structure of compounds LY215490(**1**) and LY293558(**2**).

status, although there are limitations in translating it to human spinal anaesthesia using a small rodent model, because the length of the spinal axons exposed to drugs is much shorter.

There has also been made a trial in humans with the LY293558 inhibitor in clinical pain [29]. Single doses of LY293558 appear safe in human beings, although administration is associated with dose-dependent and reversible side effects such as hazy vision and sedation.

The novel glutamate receptor ((-)LY293558) and +/- racemate (LY215490) was examined for neuroprotectant effects against excitotoxic injury *in vitro* and *in vivo* [30]. Furthermore this compound is highly water-soluble and readily enters the central nervous system after systemic administration [31] and elicits anticonvulsant, and antinociceptive effects. Systemic administration of LY215490 reduced or completely abolished the rhythmic bladder contractions in the spinal cord intact rat. The combined intrathecal administration of MK-801, NMDA antagonist, and LY215490 showed that NMDA and AMPA receptor antagonists interact synergistically at synapses in the spinal cord to control bladder activity.

2.3-Benzodiazepines as AMPA Receptor Antagonists

An important group of non-competitive AMPA receptor antagonists are represented by 2,3-benzodiazepines. The 2,3-benzodiazepines derivates in contrast to their 1,4-analogues, have no affinity for the γ-aminobutyric acid ($GABA_A$) receptor but block both native and recombinant AMPA receptors, and in addition they show a high degree of selectivity for AMPA receptor over Kainate one [32].

The prototype of these non-competitive AMPA receptor antagonists is GYKI 52466 (**3**), Fig. (**3**).

GYKI 52466 is a highly selective non-competitive antagonist of AMPA/Kainate receptors acting on a novel modulator site coupled allosterically to them [33].

GYKI 52466 selectively block the convulsions induced by AMPA and kainate but not by NMDA. Székely and co-workers have demonstrated the antinociceptive action of GYKI 52466 on several antinociceptive and anti-inflammatory assays [34].

GYKI 52466 and two 3-N substituted analogues GYKI 53773 (**4**) and GYKI 53784 (**5**) had a potent antinociceptive action in rat tail flick and mouse phenylquinone writhing assays but were nearly inactive in the mouse hot plate test. It was observed that this action does not seem to be related to opioid mechanism. These compounds are chiral and comparing the two isomers, it has been shown that only the (-)isomers are active biologically. Institute for Drug Research (Budapest) licensed the analogues to Eli Lilly names LY300164 (Talampanel) and LY303070 respectively. These authors also reported that GYKI 52466 significantly reduced the adjuvant arthritis (and carrageenan)-induced hyperalgesia.

SAR studies revealed that several structural features are important to maintain and/or to potentiate the pharmacological properties of GYKI 52466. Indeed, by analysing the pharmacological profile of a series of analogues of GYKI 52466, it is possible to deduce the following observations.

The presence of 4-aminophenyl groups in position 1 of the benzodiazepine ring is of utmost importance for the antiepileptic effect of this class of compounds. The replacement of the amino group with a halogen atom eliminates all the antiepileptic effects [35]. The presence of an acyl group on the aromatic amine moiety is always detrimental to the *in vitro* activity but it is sometimes advantageous for the *in vivo* potency [36]. In addition, the replacement of the aryl ring with other heterocycles as well as it is replacement with aryl vinyl group [37] affords derivates marginally active.

Saturation of the 3,4-double bond of GYKI 52466 afforded GYKI 52895 (**6**), a derivate characterized by a different mechanism of action. GYKI 52895 is in fact a selective dopamine uptake inhibitor endowed with antidepressive and antiparkisonian properties [38].

Interestingly, the presence of substituents at position 3 transform GYKI 52895 from a dopamine uptake inhibitor into non-competitive AMPA antagonist, in some cases considerably more potent and selective than GYKI 52466.

From the same series of compounds there exist the so-called GYKI 53655 (**7**) with also antinociceptive effect [39]. Actually it effectively reduced both reflex and dorsal horn nociceptive responses following systemic administration and it also reduced responses to noxious heat.

Furthermore, racemic GYKI 53405 (**8**), was resolved into its enantiomers and the 4-R isomer GYKI 53773 (**4**) (LY 300164, Talampanel) proved to be the eutomer. Among this set of non-competitive AMPA antagonist, LY 300164 is the sole agent submitted to clinical trials due to its selectivity and oral bioavailability [40,41]

The reduction in size of the seven-membered ring of 2,3-benzodiazepines was also studied. Dihydrophthazines, such as the 3-N-butylcarbamoyl derivate SYM 2207 (**8**) [42], showed selective and non-competitive inhibitory properties at the AMPA receptor complex. The same structural modification, applied to derivates in which the lactam functionality was present, led to the identification of a compound namely 4-(4-aminophenyl)-2-N-butylcarbamoyl-6,7-methylenedioxyphthalazin-1(2H)-one, which displayed an anticonvulsant potency 11-fold higher than that of GYKI 52466.

QUINOXALINE-2,3-DIONES

The quinoxaline-2,3-diones form the single most important class of compounds in this area. Compounds such as NBQX (**10**),CNQX (**11**),YM872 (**12**), and YM90K (**13**) Fig (**4**), have been reported in the past few years as potent, competitive AMPA receptor antagonist bearing the quinoxaline-2,3-dione motif. These compounds have been used as reference standards in this area and form the basis of the AMPA receptor antagonist.

NBQX (**10**) is one of the most potent inhibitor of AMPA receptors, and administered intrathecally produced a dose-dependent antinociceptive effect in the tail flick test, although it induced some degree of hind-limb paralysis for a

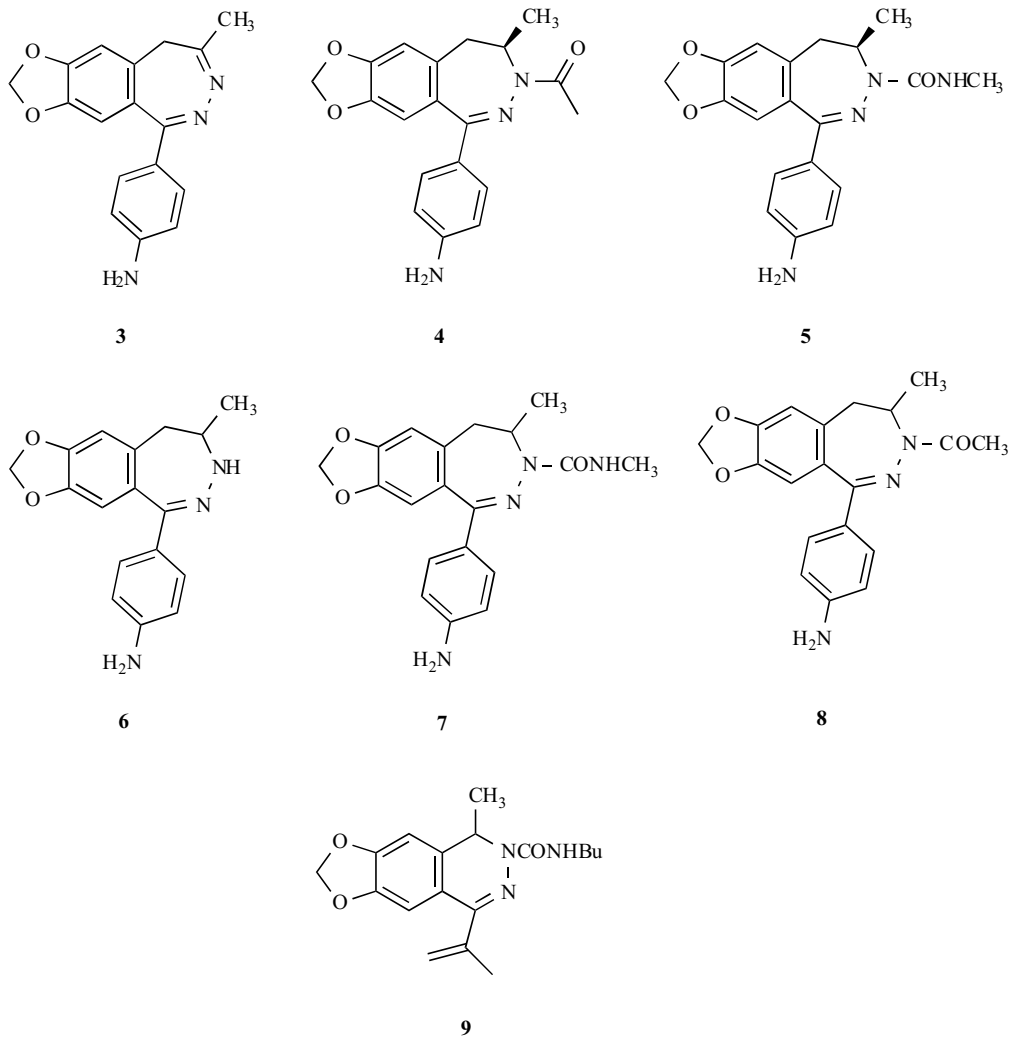


Fig. (3). Main structures of 2,3-benzodiazepines derivates.

short time. Its antinociceptive effect was maximal at 15 minutes and lasted for 60 minutes and it has also shown analgesic effect in post-surgical pain [43].

On the other hand there had been founded some compounds which mode of action is the inhibition of the NMDA receptor, but they are also active inhibiting the AMPA one. That is the case of ACEA-1031(**14**), ACEA-0593 (**15**) and ACEA-1328 (**16**) Fig.(**4**) which all increased the tail flick latencies in a dose-dependent manner.

ACEA-1031 is an antagonist of the glycine-binding site in the NMDA receptor that produced long lasting antinociceptive effect in the tail flick test, and its effect lasted for one hour. ACEA-0593 has a broader spectrum of the ionotropic glutamate receptor antagonism, also has a great antinociceptive effect in the same test whereas the duration of the action was less than one hour. ACEA-1328 appeared to be slightly less potent than the former ones in prolonging the tail flick latencies, and its effect lasted for 30 minutes. The compound ACEA-1021 (**17**) did also show antinociceptive effect in the tail flick test.

Alternatively it has been observed that the co-administration of morphine and ACEA 2085 intrathecally showed a significant analgesia on acute thermal nociception compared with morphine or ACEA 2085 alone, without an increase in the side effect profile [44]. This is another probe that the development of acute pain strategies may focus on the AMPA receptor on the spinal cord.

As in the brain, AMPA receptors are co-localized with NMDA receptors, it has been studied the effect in nociception of the co-administration of AMPA antagonist (ACEA 2085) and the NMDA antagonist AP-5 as compared with the administration by itself. Intrathecal administration of AP-5, ACEA1021 (NMDA glycine site antagonist) and ACEA 2085 resulted in dose-dependent increases in the thermal response latency [45].

While the NMDA receptor antagonist (AP-5) had no interaction with the AMPA antagonist (ACEA 2085), the NMDA glycine site antagonist (ACEA 1021) intensified the antinociceptive effect of the AMPA receptor antagonist.

The AMPA pharmacophore model is shown with a quinoxaline-2,3-dione template Fig. (**5**). The most important interaction sites for the receptor are in the southern portion of the template. Hence, for clarity reasons, the quinoxaline-2,3-dione template has been divided into both northern and southern halves as indicated in figure. In general, the southern half needs to be conserved for good AMPA binding

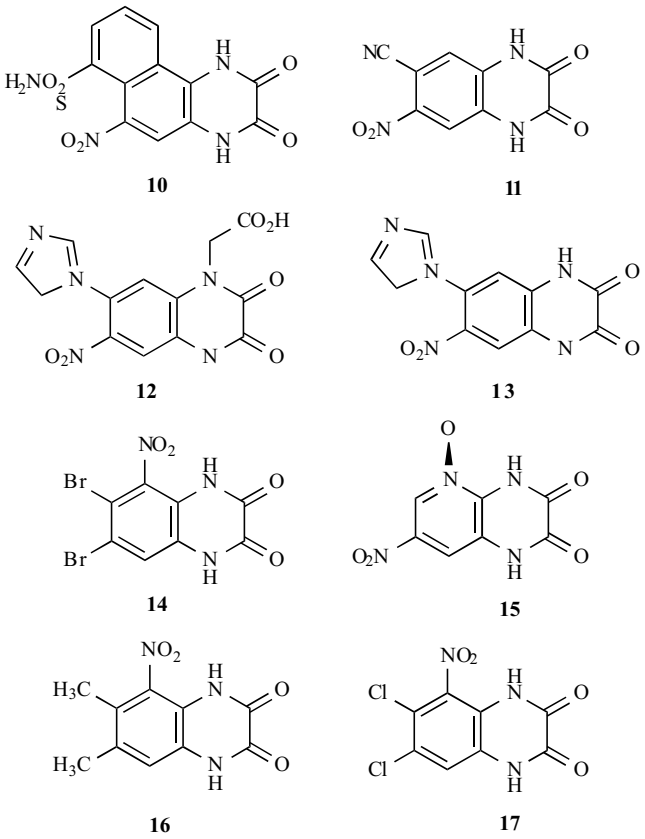


Fig. (4). 2,3-Quinoxalines antagonist AMPA receptor.

activity, whereas the northern half can be modified. These modifications can be used to increase the selectivity at either receptor as well as to improve the physical properties of the new antagonist to de designed. The important features of the pharmacophore model are as follows:

1) The primary interaction attributed to the C-2 and C-3 amide carbonyl groups. The placement of these groups in the quinoxaline template is unique, in that it lends a considerable double bond (or keto) character to the amide functionality resulting in significant negative charge at the carbonyl oxygens in the eastern region. This effect is amplified by the out-of-plane deformation of the carbonyl groups, especially in 6- and 7-substituted quinoxaline-2,3-diones.

2) The N-H bond is important for activity as a H-donor bond. Protection of this nitrogen with any group results in total loss of activity.

3) A strong electron-withdrawing group such as nitro, trifluoromethyl or halogen such as Br or Cl is required at C-7 for good AMPA activity. The utility of this group is twofold:

   a) It enhances the Coulombic interaction at the C-3 carbonyl by making the proton at N-4 more acid.

   b) It provides a weak hydrogen bond interaction with the receptor, especially if the group is nitro or sulphonamide.

Alternatively, the requirement of an acidic functionality at N-4 can also be satisfied by H-bond donating groups such as carboxylic, phosphonic and hydroxamic acids which can be attached to the N-4 nitrogen via a carbon tether.

4) The northwestern region of the quinoxaline-2,3-dione template can be utilized to modulate the physical properties, especially the aqueous solubility and lipophilicity.

Smaller and weakly polar groups are well tolerated at C-5 and C-6 position, suggesting a defined volume in this region and weak electropositive hydrogen bonding interaction with the receptor. The orientation of these groups is extremely important for selectivity between the AMPA and glycine (Gly_N) receptors. The northwest orientation is preferred for AMPA binding affinity; in general, polar groups at C-6 have greater affinity for the AMPA receptor.

One of the problems in using glutamate antagonists in animal models and clinical trials is their low water-solubility. This is one of the advantages of the YM872 (**12**), its high water solubility could reach from 500-1000 times the solubility of NBQX (**10**), CNQX (**11**) or YM90K (**13**) [44].

The N-4 position in various quinoxaline-2,3-diones has been invariably substituted with polar and hydrophilic groups such as carboxyalkyl and phosphonoalkyl groups which have been responsible for better aqueous solubility and improved binding affinity for AMPA receptor [45,46]. The systematic SAR done on the 4-phosphonomethyl quinoxaline-2,3-diones has been of immense value for medicinal chemist in this area.

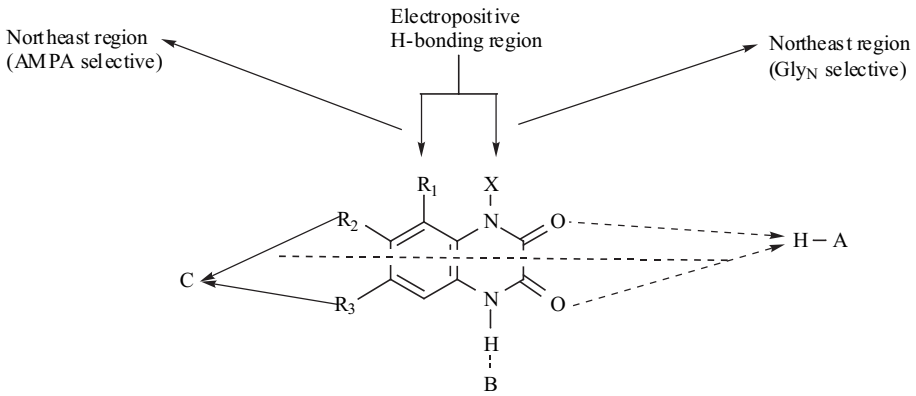


Fig. (5). Pharmacophore model for AMPA antagonist [27].

YM872 has the highest affinity for the AMPA receptor, it bounds only weakly to high-affinity kainate receptors, and fails to affect the glutamate and glycine binding sites of NMDA receptors. This compounds had weak affinity for the benzodiazepine-binding site of the ($GABA_A$) receptor-complex.

This compound apart from its antinociceptive effect has also been tested for its neuroprotective potential in some *in vivo* ischemia models, and it has shown some reduction in the neuronal damage.

As an antinociceptive agent, YM872 intrathecally administered produced a dose-dependent increase in the tail flick test and in the hot plate test in rats, having application on acute pain [47]. It has also analgesic effect in the hyperalgesia thermal paw withdrawal test after peripheral mononeuropathy and in affecting electrophysiological nocioceptive indices. YM872 showed an apparent analgesic effect in both Phase 1 and Phase 2 of the formalin test.

It can be considered as a more useful analgesic than NMDA receptor antagonists because it has analgesic effects on both acute and chronic pain, whereas NMDA receptor antagonists are effective only for facilitated pain, and it also has fewer side effects than the NMDA counterparts.

CLINICAL TRIALS WITH GLUTAMATE ANTAGONISTS IN THE TREATMENT OF PAIN

Most of the clinical trials with glutamate antagonists have been made with Ketamine, which is a NMDA receptor antagonist. Ketamine Fig.(**6**) is an analogue of phencycline, and it is used as short-term analgesic agent when muscle relaxation is not required, i.e. for non-abdominal surgery, mostly in cases of traumatic injuries of the limbs.

Recently LY293558 the non-selective AMPA/Kainate antagonist was used for the management of postoperative pain after oral surgery. Upon i.v. application it did provide some dose-dependent analgesic action. In healthy volunteers the compound suppressed the hyperalgesia induced by intradermal injection of capsaicin. However, in healthy skin the threshold of pain elicited by thermal or electrical stimulation was not modified. It was well tolerated; the only side effects included temporary clouding at the periphery of the visual field and mild sedation.

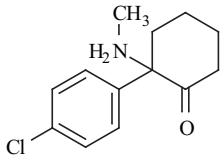


Fig. (6). Ketamine structure.

CONCLUSION

Neuropathic pain is a class of chronic pain that has a tremendous interest among the analgesic market. Current therapies have a lot of side effect, being an unmet medical need. It is one of the most debilitating pathologies that exist nowadays and it affects approximately 1% of the population. The most common ones are the diabetic neuropathy and the post-herpetic neuralgia with a 7.5% and 10% respectively. Its prevalence is enormous and it has been estimated to be around 63 million patients in the seven major markets in 2001. Neuropathic pain is been treated with drugs that have not been developed primarily to combat this type of pain. Such is the case of the anticonvulsants, tryciclic antidepressants and many others. Being an urgent need the existence of neuropathy specific treatments.

Since a wide amount of novel compounds with NMDA and AMPA/Kainate antagonist activities are under early phases of clinical investigation, we need time to see whether the classical ketamine-type non-competitive NMDA antagonists or the AMPA/Kainate antagonists prove to be useful in the clinical practice.

ABBREVIATIONS

NMDA	=	N-Methyl-D-Aspartate
AMPA	=	R, S, -amino-3(3 hidroxy-5-methilisoxazol-4-yl) propionic acid
KA	=	Kainic acid
SAR	=	Structure activity relationship studies
($GABA_A$)	=	γ-Aminobutyric acid
Gly_N	=	Glycine
CNQX	=	6-Cyano-7-nitro-quinozalinedione
DNQX	=	6, 7-Dinitroquinoxaline-2, 3-dione
Glu-R	=	Glutamate receptor
mGluR	=	Metabotropic glutamate receptor
iGluR	=	Ionotropic glutamate receptor

REFERENCES

[1] Conn, P.J.; Pin, J.P. *Annu. Rev. Pharmacol. Toxicol.,* **1997**, *37*, 205.
[2] Krogsgaard-Larsen, P.; Hansen, J.J. *Eds. In Excitatory Amino Acid Receptors: Design of Agonist and Antagonist*, Ellis Horwood:Chichester, **1992.**
[3] Monaghan, D.T.; Wenthold, R.J. *Eds. In The Ionotropic Glutamate Receptors*, Humana press: New Jersey, **1997.**
[4] Sommer, B.; Keinänen, K.; Verdoorn, TA.; Wisden, W.; Burnashev, N.; Herb, A.; Köhler, M.; Tagaki, T.; Sakmann, B.; Seeburg, P.H. *Science*, **1990**, *249*, 1580-1585.
[5] Sommer, B.; Köhler, M.; Sprengel, R.; Seeburg, P.H. *Cell,* **1991,** *67*, 11-19.
[6] Boulter, J.; Hollmann, M.; O´Shea-Greenfield, A.; Hartley, M.; Deneris, E.; Maron, C.; Heinemann, S. *Science,* **1990**, *249*, 1033-1037.
[7] Köhler, M.; Kornau, HC.; Seeburg, PH. *J. Biol. Chem.,* **1994**, *269*, 17367-17370.
[8] Zhu, J.J.; Esteban, J.A.; Hayashi, Y.; Malinow, R. *Nat. Nerurosci*., **2000**, *3*, 1098-1106.
[9] Wenthold, R.J.; Petralia, R.S.; Blahos, J.; Niedzielski, A.S. *J. Neurosci*., **1996**, *16*, 1982-1989.
[10] McLennan, H. *Prog. Neurobiol*., **1983,** *20,* 251-271.
[11] Patneau, D.K.; Wright, P.W.; Winters, C.; Mayer, M.C.; Gallo, V. *Neuron.,* **1994**, *12*, 357-371.
[12] deGroot, J.F.; Carlton, S.M. *Soc. Nerurosci. Abs*., **1998,** *24*, 1869.
[13] Paleckova, V.; Palecek, J.; McAdoo, D.J.; Willis, W.D. *Neurosci. Lett*., **1992,** *148*, 19.
[14] Battaglia, G.; Rustioni, A.; Altschuler, R.A,; Petrusz, P. *Soc. Neurosci. Abst.,* **1986**, *12*, 333.
[15] Omote, K. ; Kawamata, M. ; Namiki, A. *Brain. Res.,* **1988**, *787*, 161.

[16] Zhou, S., Bonasera, L.; Carlton, S.M. *Neuroreport,* **1996**, *7*, 895.
[17] Harris, J.A.; Corsi, M.; Quartaroli, M.; Arban, R.; Bentivoglio, M. *Neuroscience*, **1996**, *74*, 7.
[18] Kontinen, V.K.; Meert, T.F. *Anesth. Analg.*, **2002**, *95*, 997-1001.
[19] Bennet, A.D.; Everhart, A.W.; Hulsebosch, C.E. *Brain Res.,* **2000**, *859*, 72.
[20] Zahn, P.D.; Umali, E.; Brennan, T.J. *Pain,* **1998**, *74*, 213.
[21] Advocat, C.; Rutherford, D. *Pharmacol. Biochem. Behav*., **1995**, *51*, 855-860.
[22] Chizh, B.A.; Headley, P.M.; Tzschentke T.M. *Trends in Pharmacological Sciences,* **2001**, *22*, 636-642.
[23] Schoepp, D.D.; Lodge, D.; Bleakman, D.; Leader, J.D.; Tizziano, J.P.; Wring, R.A.; Palmer, A.J.; Salhoff, C.R.; Ornstein, P.L. *Neuropharmacology,* **1995**, *34*, 1159-68.
[24] Ornstein, P.L.; US 5 356 902 (1994).
[25] Huff, B.E.; ES2 087 812 (1996).
[26] Gilron, I. *Curr. Opin. Investing Drugs,* **2001**, *2*, 1273-8.
[27] Sham, S.; Nikam and Brian Kornberg, E. *Curr. Med. Chem.,* **2001**, *8*, 155-169.
[28] Von Bergen, N.H.; Subieta, A.; Brennan, T.J. *Anesthesiology,* **2002**, *97*, 177182.
[29] Gilron, I.; Max, M.B., Lee, G.; Booher, S.L.; Sang, C.N.; Chappell, A.S.; Dionne, R.A. *Clin. Pharmacol. Ther.,* **2000**, *68*, 320-327.
[30] Schooepp, D.D.; Salhoff, C.R.; Fuson, K.S.; Sacaan, A.I.; Tizzano, J.P., Ornte, P.L.; May, P.C. *J. Neural. Transm.,* **1996**, *103*, 905-16.
[31] Yoshiyama, M.; Roppolo, J.R.; de Groat, W.C. *Journal of Pharmacology and Experimental Therapeutics,* 1997, *280*, 894-904.
[32] Zappalá, M.; Grasso, S.; Micale, N.; Polimeni, S.; De Micheli, C. *Mini Reviews in Medicinal Chemistry*, **2001**, *1*, 243-253.
[33] Donevan, S.D.; Rogawski, M.A. *Neuron,* **1993**, *10,* 51-59.
[34] Székekt, J.I.; Kedves, R.; Máté, I.; Török, K.; Tarnawa, I. *Eur. J. Pharmacol*., **1997**, *336*, 143-154.
[35] Marinelli, S.; Gatta, F.; Sagratella, S. *Eur. J. Pharmacol.,* **2000**, *391*, 75.
[36] Tarnawa, I.; Berzseny, P.; Andrási, F.; Botka, P.; Hámori, T.; Ling, I. ; Körösi. *J. Bioorg. Med. Chem. Lett.,* **1993**, *3*, 99.
[37] Vago, P.; Reiter, J.; Gyertyan, I.; Gigler, G.; Andrasi, F.; Bakonyi, A.; Berzsenyi, P.; Botka, P.; Birkas, Faigl, E. *et al. Eur. Pat. Appl.,* EP 726, 256 (*Chem. Abs.,* **1996**, *125*, 195698 p).
[38] Horváth, K.; Szabo, H.; Patfalusi, M.; Berzsenyi, P.; Andrasi, F. *Eur. J. Pharmac.,* **1990**, *183*, 1416.
[39] Procter, M.J.; Houghton, A.K.; Louise Faber, E.S.; Chizh, B.A.; Ornstein, P.L.; Lodge, D.; Headley, P.M. *Neuropharmacology,* **1998**, *37*, 1287-1297.
[40] Anderson, B.A.; Hansen, M.M.; Harkness, A.R.; Henry, C.L.; Vincenzi, J.T.; Zmijewski, M.J. *J. Am. Chem. Soc.,* **1995**, *117,* 12358.
[41] Anderson, B.A.; Harn, N.K.; Hansen, M.M.; Harkness, A.R.; Lodge, D.; Leander, J.D. *Bioorg. Med. Chem. Lett*., **1999**, *9*, 1953.
[42] Pelletier, J.C.; Hesson, D.P.; Jones, K.A.; Costa, A.M. *J. Med. Chem.,* **1996**, 39, 343.
[43] Lutfy, K.; Cai, S.X.; Woodward, R.M.; Weber, E. *Pain,* **1997,** *70*, 31-40.
[44] Nishiyama, T., Yaksh, T.L.; Weber, E. *Anesthesiology*, **1998**, *89*, 715-722.
[45] Nishiyama, T. *Can. J. Anesthesyology*., **2000**. *47*, 693-698.
[46] Kohara, A.; Okada, M.; Tsutsumi, R.; Ohno, K.; Takahashi, M.; Shimizu-Sasamata, M.; Shishikura, J.; Inami, H.; Sakamoto, S.; Yamaguchi, T. *J. Pharm. Pharamcol.,* **1998**, *50*, 795-801.
[47] Takahashi, M.; Ni, J.W.; Kawasaki-Yatsugi, S. *et al. J. Pharmacol. Exp. Ther.,* **1998,** *287*, 559.
[48] Kawasaki-Yatsugi, S.; Yatsugi, S.; Takahashi, M. *et al. Brain Res.,* **1889**, *793*, 39.
[49] Nishiyama, T.; Gyermek, L.; Lee, C.; Kawasaki-Yatsugi, S.; Yamaguchi, T. *Anesth. Analg.,* **1999**, *89*, 143-147.