Selective Agonists and Antagonists for Kainate Receptors

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Abstract: Kainate receptors have only recently been characterized both from the pharmacological and biological point of view. Due to the limited number of truly kainate selective ligands, most of the known agonists and antagonists are generally classified as AMPA/kainate receptors ligands. The increasing interest in the search for selective kainate ligands aims at understanding the physiological role played by these receptors and finding out potential therapeutic approaches for the treatment of a number of neurological pathologies, i.e. schizophrenia, as well as acute and chronic neurodegenerative diseases, i.e. epilepsy, cerebral ischaemia, Parkinson's and Alzheimer's diseases. This review will focus on the recently discovered ligands for kainate receptors, with a particular attention given to those molecules displaying a selectivity for the different subunits of the kainate receptors and, on the other hand, to the role played by these receptor subtypes in the pathophysiology of the central nervous system.

INTRODUCTION

Glutamic Acid (*S*-Glu) is the main excitatory neurotransmitter in the central nervous system (CNS), where it plays an important physiological role in mediating synaptic plasticity and processes such as learning and memory. On the other hand, glutamate is involved in neuronal degeneration related to many acute and chronic diseases including, among others, cerebral ischaemia, spinal cord injury, epilepsy, Parkinson's and Alzheimer's diseases [1,2]. *S*-Glu acts through different classes of receptors, divided into ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs) [3]. The iGluRs are multimeric channels, which regulate the flux of cations (Na^+, K^+, and Ca^{++}) across the synaptic membrane. The ionotropic receptors have been pharmacologically classified into three classes: NMDA, AMPA and KA receptors, on the basis of their selective interaction with the agonists *N*-methyl-D-aspartic acid, 2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid and kainic acid, respectively. The mGluRs belong to the superfamily of G-protein coupled receptors and they have been further classified into three different groups on the basis of their degree of shared sequence homologies, mechanism of signal transduction, and pharmacological properties.

Among the different classes of glutamate receptors, the present review will focus on the kainate receptors, whose pharmacological characterization is relatively recent, owing to the lack of highly selective ligands. The pharmacology and physiology of the kainate receptors have been the subject of recently published detailed reviews [4, 5]. The recent progresses in the field of molecular biology allowed the cloning of five different subunits, which form the kainate receptors through both a heteromeric and a homomeric assembly. The five different kainate subunits that, up to date, have been cloned in rat and human are the GluR5-GluR7 and the KA1 and KA2 subunits [6-8]. The KA1 and KA2 subunits show a high affinity for kainic acid and have a 68% sequence homology. Conversely, the GluR5-7 subunits, which share 75% homology, display a lower affinity for kainic acid. Another major difference between the above mentioned subunits is that GluR5-7 are able to form homomeric channels, at variance with KA1 and KA2 which only assemble heteromerically. Even though recombinant homomeric receptors have been extensively used as a pharmacological tool in the characterization of kainate receptors ligands, it has to be taken into account that their functional properties may significantly differ from those of the native ones, particularly in terms of activation and desensitization [4,9]. In this respect, the expression of the heteromeric co-assembly of different kainate subunits could provide functional channels, which appear to better mimic the properties of native kainate receptors [9].

Native kainate receptors are widely distributed in the mammalian CNS, particularly in the cerebellum, hippocampus and spinal cord. In analogy with the other ionotropic glutamate receptors, kainate receptors are mainly located postsynaptically, even though a number of these receptors have also been identified presynaptically at both excitatory [10, 11] and inhibitory terminals [12, 13] and their activation would produce an inhibition of the release of the endogenous neurotransmitters. It has been proposed that the potent convulsant properties of KA are due to the activation of presynaptic kainate receptors at GABA terminals, which causes an inhibition in the release of GABA [12-13]. Clarke *et al.* [13] showed that this kind of receptors is composed of, or contains, GluR5 subunits. Their activation with GluR5 selective agonists causes a depression of monosynaptically activated inhibitory post-synaptic currents (IPSCs). These results were questioned by Frerking *et al.* [14], who demonstrated that application of KA caused a decrease in the size of monosynaptic IPSCs in pyramidal cells, but without any evidence of an inhibition of GABA release. The same Authors described the presence of

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KA receptors in the hippocampal interneurons. They proposed that a decrease in the size of IPSCs could be indirectly produced through a depolarization of such interneurons. The activation of hippocampal interneurons causes, in fact, a profound increase in the frequency of the spontaneous IPSCs, leading to a repetitive firing that finally may cause the discharge of interneurons, with a reduction in the size of the IPSCs. However, subsequent studies demonstrated that an increase in the interneurons firing rate does not produce a reduction of the inhibitory drive. The two effects are not related to each other and they are mediated by two different populations of kainate receptors, both located in hippocampal interneurons [15]. One population is responsible for the membrane depolarization and the increase in the interneurons firing rate, whereas the other one behaves as a metabotropic receptor and triggers a second messenger cascade which ends up in a reduction of presynaptic GABA release [15]. Also Frerking *et al.* [16], based on new experiments, supported the conclusion that the depression of IPSCs size is not directly related to the increase of the firing rate. However, these Authors proposed an alternative mechanism to explain the reduction of the IPSCs size caused by kainate. KA would act at the interneuron receptors with a dual mechanism, which include both a decrease in postsynaptic responsiveness to GABA and an increase of spontaneous GABA release, which in turn would activate presynaptic $GABA_B$ receptors producing a downregulation of GABA release [16]. Even if with different proposed mechanisms, there is at present a general agreement on the fact that kainate reduces the inhibitory drive through the inhibition of GABA release. At variance with initial hypotheses, this effect is mediated by a specific population of KA receptors, which contain the GluR5 subunit and are located in the interneurons.

The presence of KA receptors in hippocampal interneurons and their role in the modulation of GABAergic inhibition was also described by Cossart *et al.* [17]. According to these Authors the epileptogenic action of kainate involves GluR6-containing receptors located postynaptically in the CA3 region of the hippocampus, while the activation of the interneurons GluR5-containing receptors produces an enhancement of tonic GABAergic inhibition and therefore may represent an endogenous protective mechanism to prevent epileptogenesis.

From all these observations it can be concluded that kainate plays a complex role in epilepsy: its epileptogenic role derives from a combination of excitation of postsynaptic receptors in the CA3 region and inhibition of GABA release, actions that are in part counterbalanced by an increase of the spiking frequency of inhibitory neurons. In analogy, it has been demonstrated that synaptic released endogenous glutamate produces, as a net effect, a reduction of GABAergic inhibition, which might contribute to seizure induction [18].

The physiological relevance of KA receptors seems to be also associated to the synaptic plasticity. The phenomenon of long-term potentiation (LTP), which is a type of synaptic plasticity involved in some forms of hippocampus-mediated learning and memory processes, is certainly associated to the activation of NMDA receptors. Nevertheless, Bortolotto *et al.* [19] recently demonstrated that kainate receptors are involved in the induction of LTP at synapses where NMDA receptors do not have a role, in particular at mossy fiber synapses in the hippocampus. In their experiments, they showed that LY382884, a selective GluR5 antagonist [Fig. (**6**)], could inhibit the induction of LTP at hippocampal mossy fiber synapses, while it does not block NMDA-dependent LTP.

The KA receptors mediating LTP are thought to contain both the GluR5 and GluR6 subunits, but their pre- or postsynaptic localization is still uncertain.

While NMDA-induced LTP has been widely studied, little is known about the mossy fiber LTP, and the availability of ligands such as LY382884, able to discriminate the two effects, represents a valuable tool to deepen the investigation of the physiological role of mossy fiber plasticity in learning and memory.

SELECTIVE AGONISTS OF THE KAINATE RECEPTORS

The pharmacological characterization of KA receptors has been hampered for many years by the lack of selective

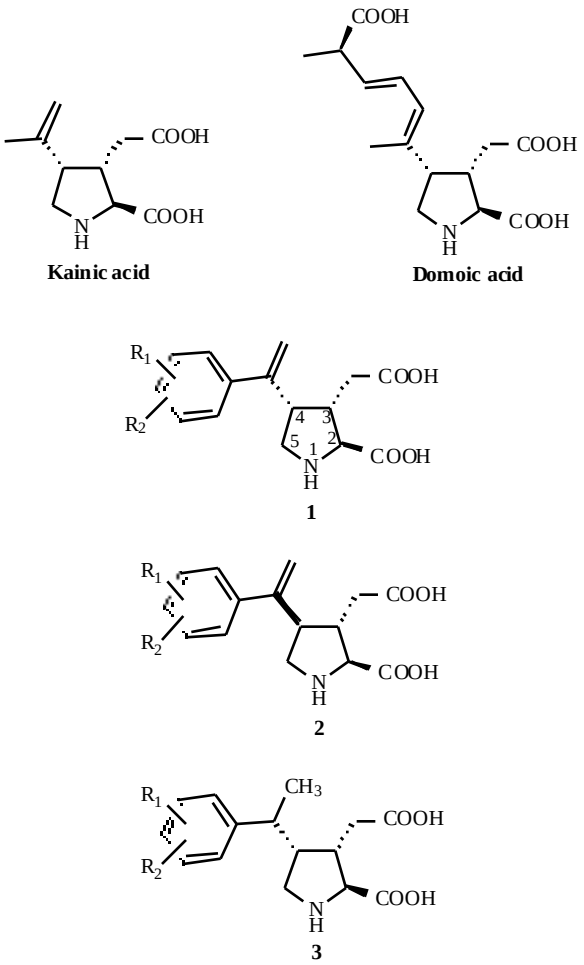
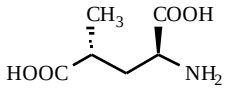


Fig. (1). Natural kainate receptor agonists and structurally related compounds.

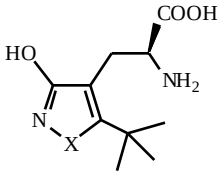
ligands. Typically, natural products such as kainic acid and domoic acid [Fig. (**1**)] were used as reference standard agonists, although the two ligands interact also with AMPA receptors.

Taking advantage of an efficient preparation of kainic acid [20], some novel KA analogs have been synthesized following the same strategy. The subsequent pharmacological and electrophysiological evaluation of this set of KA analogs allowed a better understanding of their structure-activity relationships. A series of 4-aryl substituted kainic acid analogs [compounds **1**, **2**, **3**, Fig. (**1**)], bearing at the 3' or 4' position a wide variety of substituents such as halogens and alkyl, aryl, alkoxy and aryloxy groups, was prepared and tested for agonist and antagonist activity in cells stably expressing human GluR6 kainate receptors. This study demonstrated that a large lipophilic group in a region of the molecule that does not affect the shape of the pharmacophoric moiety is well tolerated by the ligand binding site of GluR6. In fact, several compounds of this series displayed high affinity for the homomeric expressed GluR6 and a marginal affinity for the AMPA receptors. Moreover, it has been clarified that both the inversion of the absolute configuration at C-4 [compd. **2** versus **1**; Fig. (**1**)] or the introduction of a saturated chain [compd. **3**; Fig. (**1**)] caused a marked reduction in receptor affinity [21].

Interesting results were obtained with the four stereoisomers of 4-methylglutamic acid. The (2*S*,4*R*) enantiomer of 4-methylglutamic acid [SYM2081, Fig. (**2**)] emerged as a remarkably selective ligand for the KA receptors. Its IC_{50} is 35 nM, a value comparable to that found for kainic acid itself (IC_{50} 11nM) and quite different from that observed for AMPA receptors (IC_{50} >100 μM). SYM2081 behaved as an agonist both at GluR5 (EC_{50} = 0.17 μM) and GluR6 (EC_{50} = 0.7 μM) [22-25]. Surprisingly, as result of in vivo studies performed on animal models, SYM2081 behaved as an antagonist of the KA receptors and reduced allodynia and hyperalgesia associated to neuropathic pain. It has been suggested that this unexpected behavior could be the result of a block of the kainate-induced currents through a process of agonist-induced desensitization, involving receptors containing the GluR6 subunit [24, 26, 27].

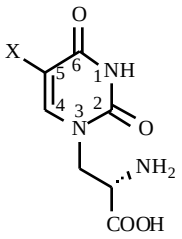


SYM2081



(*S*)-ATPA: X = O

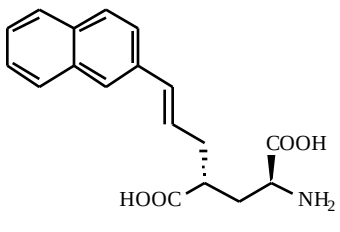
(*S*)-thio-ATPA: X = S



(*S*)-5-fluorowillardiine: X = F

(*S*)-5-iodowillardiine: X = I

(*S*)-5-trifluoromethylwillardiine: X = CF_3

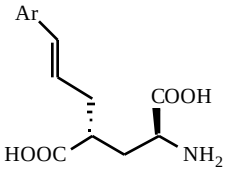


LY339434

Fig. (2). AMPA/kainate receptor agonists.

Two further selective agonists, (*S*)-ATPA and (*S*)-5-iodowillardiine [Fig. (**2**)], have also been recently discovered. ATPA was initially designed as an analog of AMPA able to penetrate more efficiently the blood brain barrier due to its higher lipophilicity. However, when tested both in vitro and in vivo, ATPA showed a relatively weak agonist activity at AMPA receptors [28]. Subsequently, ATPA has been recognized as a quite potent agonist of the GluR5 subtype of kainic acid receptors [13]. This result demonstrates that, unlike AMPA receptors, the ligand binding site of GluR5, a kainate subtype, is able to accommodate large lipophilic groups i.e. the *tert*-butyl group of ATPA. The two enantiomers of ATPA were obtained in a very high enantiomeric purity from the racemic mixture by means of a preparative chiral HPLC. Both enantiomers were tested in vitro towards native receptors and cloned AMPA-preferring or kainate-preferring receptors, and it was found that the observed agonist activity of ATPA at kainate receptors has to be ascribed exclusively to its (*S*)-enantiomer [29]. A similar behavior was observed for the corresponding isothiazol-3-ol analog of ATPA, whose enantiomers have recently been prepared and pharmacologically characterized [30]. The (*S*)-enantiomer of thio-ATPA [Fig. (**2**)], which behaves as a weak agonist at all AMPA receptor subtypes with EC_{50} values spanning the range 5-20 μM, has a remarkable agonist activity at the homomerically expressed GluR5 receptors. At such a receptor (*S*)-thio-ATPA displayed a potency (EC_{50} = 0.1 μM), which is five-fold higher than that showed by its parent compound (*S*)-ATPA (EC_{50} = 0.48 μM).

The pharmacological characterization of a series of willardiine analogs put in evidence that, whereas the introduction of a small electron-withdrawing group (i.e. fluorine) in the 5 position of the uracil nucleus increases the selectivity for the AMPA receptors, the presence of a bulky and lipophilic electron-withdrawing group (i.e. iodine) is required to achieve a selectivity for the kainate receptors [Fig. (**2**)]. Thus, among a series of willardiine analogs bearing an electron-withdrawing group on the 5 position, (*S*)-5-iodowillardiine turned out to be the most selective compound for KA receptors [31-33]. (*S*)-5-Trifluoromethyl-willardiine is even more potent, though less selective than its iodo analog [31-33]. Unfortunately, none of the compounds so far described is totally selective for kainate receptors, since they possess a detectable activity at NMDA and/or metabotropic glutamate receptors. Nevertheless, the quite recent availability of cloned homomeric receptors has allowed the testing of the ability of the new ligands to discriminate the different KA receptor subtypes. As a matter of fact, when tested at the homomeric GluR5 and GluR6 subtypes, (*S*)-5-iodowillardiine displayed an outstanding subtype selectivity for GluR5 over GluR6 (Ki = 0.24 nM for GluR5 versus Ki >100 μM for GluR6) [34,35].



Ar	GluR5 Ki (μM)	GluR6/GluR5 ratio
4: 2-Cl-Ph	0.254	6
5: 3-Cl-Ph	0.060	19
6: 4-Cl-Ph	0.008	504
7: 2-naphtyl (**LY339434**)	0.015	980

Fig. (3). Binding affinity and GluR6/GluR5 selectivity of glutamic acid analogs **4**-**7**.

The (2*S*,4*R*,6*E*)-2-Amino-4-carboxy-7-(2-naphthyl)hept-6-enoic acid [LY339434, Fig. (**2**)] is also a glutamic acid analog characterized by a selective action at GluR5. This compound is in fact a potent kainate agonist, with a negligible activity at AMPA receptors. Unfortunately, LY339434 possesses an activity at NMDA receptors, which is comparable to that of NMDA itself. Nevertheless, despite this lack of selectivity between KA and NMDA receptors, LY339434 showed a remarkable selectivity among KA receptor subtypes. In fact, LY339434 exhibited a 10^3-fold selectivity for GluR5 over GluR6 when tested on recombinant receptors (Ki = 0.015 μM for GluR5 versus Ki = 15.4 μM for GluR6). Such a behavior makes LY339434 a useful tool to elucidate the physiological role of the GluR5 receptors, highly expressed in the rat dorsal root ganglion (DRG) neurons [36]. LY339434 was identified as a lead compound among a series of 4-cinnamyl glutamic acid analogs, whose structure-activity relationships were examined [37]. This study revealed that the coplanarity between the aromatic moiety and the double bond increases the GluR5 selectivity: indeed, the highest selectivity (GluR6/GluR5 ratio = 980) was achieved with the 2-naphtyl group [**7**; Fig. (**3**)]. The presence of an electron-withdrawing group, i.e. chloro in the *para* position of the phenyl ring [**6**; Fig. (**3**)] also increases the GluR5 selectivity (GluR6/GluR5 ratio = 504), whereas a substituent in the *ortho* or *meta* position of the phenyl ring, i.e. 2-chloro, 3-chloro drastically reduces the GluR6/GluR5 selectivity [**4**, **5**; Fig. (**3**)]. The Authors have also examined the effect of an aliphatic side chain at the 4 position of glutamic acid on both the activity and selectivity profiles at KA receptors. As shown in Fig. (**4**), the presence of an unsaturation in the side chain increases the affinity but leaves the selectivity unaffected. The lowest affinity is associated to the 4-*n*-propyl substituted amino acid **8**, with a gradual increase on passing to the related 2-propenyl (**9**) and 2-propinyl (**10**) derivatives. The same Authors extended their study to a series of 4-alkylidenyl glutamic acids [38]. As depicted in Fig. (**5**), the selectivity for GluR5 over GluR6 is strictly dependent upon the bulkiness of the substituent appended at the double bond. As a matter of fact, whereas compound **11**, the unsubstituted derivative, is almost non selective (**11**: GluR6/GluR5 = 1.67), the insertion of an ethyl group gives rise to a remarkable selectivity (**12**: GluR6/GluR5 = 298), which is further increased with a *n*-propyl group (**13**: GluR6/GluR5 = 711) and a *n*-butyl moiety (**14**: GluR6/GluR5 = 833). Among the monosubstituted alkyl derivatives (**11-17**), the GluR6/GluR5 selectivity reaches its highest value with branched substituents, i.e. *tert*-butyl group (**15**) or *iso*-propyl group, (**16**, **17**) [Fig.(**5**)]. In this series of compounds, the potency is increased by the presence on the double bond of an alkyl group of limited size. Quite interestingly, the most potent and selective amino acid within this series is the disubstituted derivative **18** [LY339624, Fig. (**5**)]. A further increase in the size of the substituent on the double bond produces a decrease in activity at GluR5 receptors. On the whole, this study demonstrates that the introduction of a lipophilic alkylidene group of appropriate size in the 4 position of glutamic acid represents an efficient structural modification leading to GluR5 selective ligands, with a concomitant reduction of the affinity for the GluR6 receptors. All these unsaturated derivatives of glutamic acid behave as agonists at GluR5 receptors expressed on HEK 293 cells. LY339624 was also tested in a native preparation of rat DRG neurons and exhibited an EC_{50} of 1.05 μM. It is worthwhile to notice

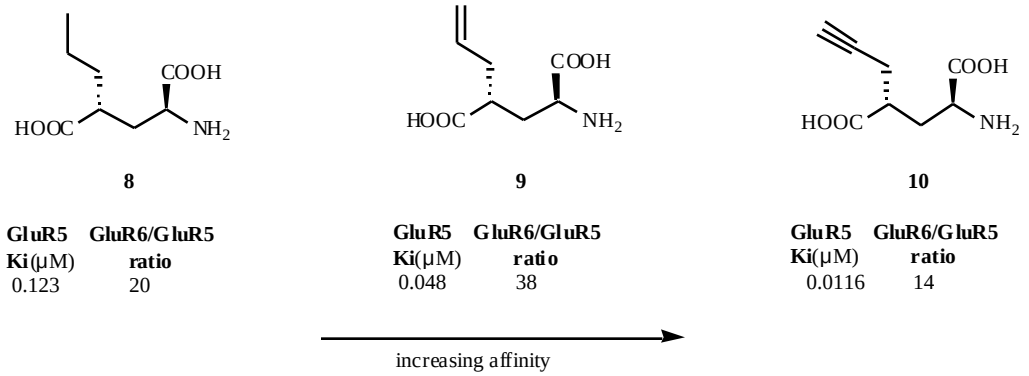
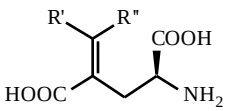
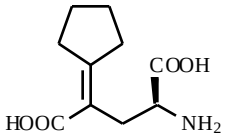


Fig. (4). Binding affinity and GluR6/GluR5 selectivity of derivatives **8**-**10**.



	GluR5 Ki (μM)	GluR6/GluR5 ratio
11: R' = H; R" = H	0.27	1.67
12: R' = H; R" = Et	0.0605	298
13: R' = H; R" = nPr	0.0804	711
14: R' = H; R" = nBu	0.150	833
15: R' = H; R" = tBu	0.0857	>1167
16: R' = H; R" = iPr	0.0544	1517
17: R' = iPr; R" = H	0.0936	>5342



18	0.0326	>3060

LY339624

Fig. (5). Effect of the substituent on the affinity/selectivity towards GluR5 and GluR6 receptors of a series of 4-alkylidenyl glutamic acid analogs.

that compound **15** was recently prepared and tested also by Bunch et al., together with its (*R*)- enantiomer and other related compounds [39]. According to their data, **15** shows an affinity for GluR5 3.5 times higher than that previously reported (K_i = 0.024 μM vs. 0.0857 μM), thus appearing as the most active compound of the series **11-18**.

As mentioned above, the availability of new selective agonists for kainate receptors is an essential tool for the elucidation of the pharmacological properties of this relatively new class of receptors. Moreover, the involvement of kainate receptors in LTP discloses new therapeutic perspectives for kainate agonists, which might be clinically useful as memory enhancers in pathologies accompanied by memory and learning impairments.

Quite recently, the complex of the GluR2 ligand binding core and kainic acid has been crystallized and its structure completely defined by X-ray analysis [40]. Therefore, it was possible to visualize how KA binds to such an AMPA-preferring subunit. Hopefully, in the near future, a similar information on the complex of KA with GluR5 and/or GluR6 subunits will be available and will help the design of new highly selective agonists for the different kainic acid receptors.

SELECTIVE ANTAGONISTS OF THE KAINATE RECEPTORS

The search for selective kainate antagonists represents an attractive goal for medicinal chemists. At present, only a limited number of compounds have been described as selective antagonists of the KA receptors. Most of the known antagonists, notably those belonging to the quinoxaline 2,3-dione family, act at both kainate and AMPA receptors. The isatinoxime NS-102 [Fig. (**6**)] is one of the first KA antagonists discovered [41]. NS-102 was proposed to be a selective KA receptor antagonist based on the observation that the antagonist activity of NS-102 was specifically directed to the low affinity [^{3}H]kainate binding site [41]. Moreover, when tested on cloned receptors, NS-102 behaved as an antagonist at the homomeric GluR6 receptors, with a potency almost identical to that displayed at the brain low affinity [^{3}H]kainate binding sites [42] and about 20 times lower than that required for AMPA receptors. However, recent results show that, in hippocampal neurons, NS-102 is able to inhibit at similar concentration both KA (IC_{50} = 2.2 μM) and AMPA receptors (IC_{50} = 4.1 μM) [43]. The same Authors pointed out that, at 10 μM, NS-102 was unable to abolish the responses at both receptors, leaving about 30% of the current. These results, combined to the low solubility of NS-102, which does not allow its use at higher concentrations, seriously limit the utility of this compound.

A relevant group of AMPA-kainate receptor antagonists is represented by a series of 6-substituted decahydroisoquinolines developed by Eli Lilly & Co. [44]. In Fig. (**6**) the structures of LY293558, LY280263, LY377770, LY307190, LY382884, LY289178, LY292025, LY302679, and LY289525 are reported. Many of these compounds displayed a neuroprotective action against global cerebral ischaemia when tested in *in vivo* models [44].

LY377770 and LY382884 are the most selective kainate antagonists so far reported and were found to be remarkably selective for GluR5 over GluR6, AMPA and NMDA receptors.

In a recent work, the study of LY377770 as neuroprotective agent was extended through its evaluation on models of global and focal cerebral ischaemia [45]. LY377770 turned out to be a systemically active GluR5 antagonist able to produce a significant neuroprotection, even when administered within 2 hours after occurrence of the ischaemic damage. Unlike the majority of AMPA-kainate receptor antagonists, especially those belonging to the quinoxaline 2,3-dione family, the decahydroisoquinolines are characterized by a good solubility, a property that could overcome the nephrotoxicity deriving from the precipitation of the drug in kidneys. Furthermore, LY377770 does not show relevant side effects, such as psychotomimetic effects typical of NMDA antagonists, and therefore it might be a promising neuroprotectant capable of reducing cerebral damages after focal and global ischaemia in humans.

Based on these results, it was argued that the kainate receptors, notably the subtypes containing the GluR5

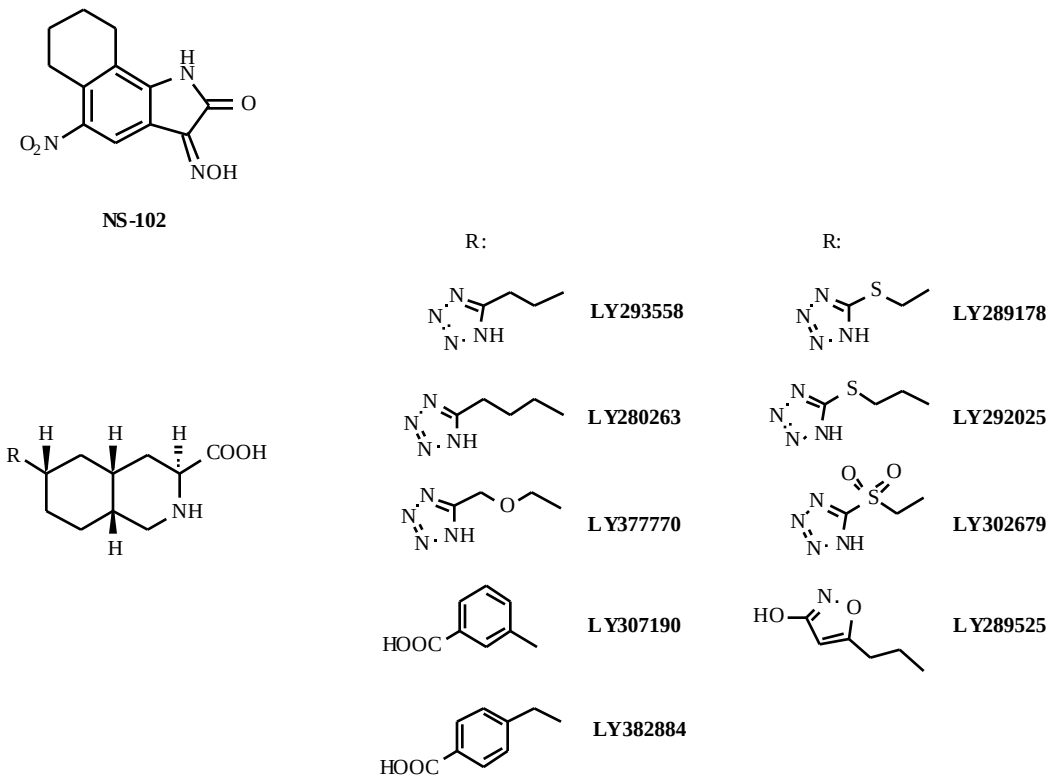


Fig. (6). AMPA/kainate receptor antagonists.

subunit, might be deeply involved in the ischaemic damage. However, the role of GluR5 still remain uncertain since LY382884, the most selective GluR5 antagonist, failed to produce neuroprotection at doses of 200 mg/Kg. Therefore, the potent neuroprotective activity of LY377770, might be explained by taking into account both its weak activity at AMPA receptors and a more favorable pharmacodynamic profile, when compared to other decahydroisoquinoline derivatives.

The importance of compounds such as LY377770 and LY382884 as pharmacological tools has been previously underlined. Their high selectivity for the GluR5 subunit has allowed the identification of KA receptors characterized by the presence of such a subunit in specific areas of the brain, i.e. hippocampal interneurons or mossy fibre synapses, thus contributing to clarify their physiological role.

THERAPEUTIC PERSPECTIVES

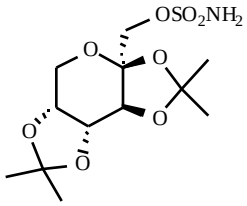
The potential of AMPA/KA antagonists as therapeutic agents is related to their neuroprotective action and, accordingly, they could be utilized to reduce the damages provoked by ischaemia, spinal cord injury or prolonged status epilepticus [46].

Studies on animal models demonstrated that the use of several 6-substituted decahydroisoquinolines acting as AMPA-kainate antagonists prevent neuronal loss consequent to focal or global ischaemia [44, 45]. In particular, LY377770 appears more promising than NMDA antagonists, due to 1) a larger therapeutic window for delayed administration, 2) a more consistent level of neuroprotection, and 3) the absence of psychotic side effects. In view of a potential clinical usefulness of these compounds, a multiple therapy approach seems to be more appropriate to reduce the ischaemic damage, since neuronal degeneration during ischaemia is the result of many different factors.

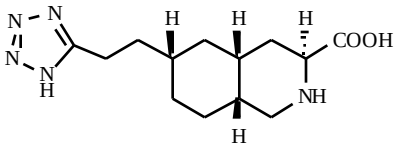
The administration of kainate antagonists following spinal cord injury could provide an excellent level of neuroprotection. In vitro studies demonstrate that the neuroprotection obtained after administration of NMDA and non-NMDA antagonists at the injury site is due to a blockade of the glutamate receptors and is not related to an increase of blood flow in the spinal cord, as it was previously suggested [47].

Furthermore, the use of kainate receptors antagonists as anticonvulsant agents may represent a new strategy for the treatment of epilepsy [46]. As previously discussed, GluR5 receptors located in the CA1 and CA3 areas of the hippocampus are involved in the epileptogenic activity. Moreover, an involvement of GluR6 receptors in epilepsy has been hypothesized since mice deprived of the GluR6 gene are less sensitive to seizures induced by kainic acid [48]. Topiramate [Fig. (**7**)], a new recently approved anticonvulsant drug, reduces seizures induced by kainic acid but not by AMPA [49]. The antiepileptic activity of Topiramate has to be ascribed to a number of concomitant mechanisms of action, such as an inhibition of the sodium currents, a potentiation of the GABA-ergic transmission and the blockade of the kainate-evoked ion currents. It has to be

remarked that the usefulness of kainate antagonists in epilepsy is not only limited to the inhibition of the seizures, but also to their action as neuroprotectants and, therefore, to their ability to reduce the death of neurons, which might be a consequence of the seizures.



TOPIRAMATE



LY293558

Fig. (7). Kainate antagonists with clinical application

A further potential therapeutic application of kainate antagonists refers to their analgesic activity. In fact, a stimulation of the AMPA-kainate receptors seems to be involved in both acute and chronic pain. In particular, compound LY293558 [Fig. (**7**)] has been clinically evaluated for its analgesic efficacy in an oral surgery model of acute pain, but it displayed a modest activity in acute post-operative pain [50]. The receptors involved in pain, which are the targets of kainate antagonists, are located in the spinal cord, specifically in the superficial laminae of the spinal dorsal horn, but it has also been suggested that analgesia produced by AMPA-kainate antagonists could be due to a blockade of the receptors located in the brain. In addition, a peripheral action of kainate causing hyperalgesia and allodynia has been hypothesized [51].

Although the above-mentioned potential clinical applications are related to the use of selective kainate antagonists, a growing interest is also related to the use of selective kainate agonists as therapeutic agents. The discovery that KA receptors are responsible for the induction of LTP at mossy fiber synapses in the hippocampus suggests that KA agonists could act as memory enhancers. As a consequence, kainate agonists should be regarded as a new class of potential candidates in the treatment of Alzheimer's disease or other age-related memory disorders.

Finally, it has recently been demonstrated that an altered KA receptors expression in the prefrontal cortex is associated to schizophrenia [52]. In fact, the post-mortem brain from patients affected by schizophrenia evidenced, when compared to controls, a reduced number of KA receptors along with a modification in the subunit composition, which reduces their sensitivity to kainate. Accordingly, a potential therapeutic role of KA agonists in the treatment of schizophrenia has been proposed.

ABBREVIATIONS

S-Glu	=	(*S*)-Glutamic acid
CNS	=	Central nervous system
iGluRs	=	Ionotropic glutamate receptors
mGluRs	=	Metabotropic glutamate receptors
NMDA	=	N-Methyl-D-aspartate
AMPA	=	α-Amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid
KA	=	Kainic acid
GABA	=	γ-Aminobutyric acid
IPSCs	=	Inhibitory post-synaptic currents
LTP	=	Long term potentiation
ATPA	=	2-Amino-3-(5-*tert*-butyl-3-hydroxy-4-isoxazolyl) propionic acid
Thio-ATPA	=	2-Amino-3-(5-*tert*-butyl-3-hydroxy-4-isothiazolyl)propionic acid
DRG	=	Dorsal root ganglion

REFERENCES

[1] Danysz, W.; Parsons, C.G.; Bresink, I.; Quack, G. *Drug news & Perspectives*, **1995**, *5*, 261-277.

[2] Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E.Ø.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.*, **2000**, *43*, 2609-2645.

[3] Nakanishi, S. *Science*, **1992**, *258*, 597-603.

[4] Bleakman, D. *Cell. & Molec. Life Sciences*, **1999**, *56*, 558-566.

[5] Lerma, J.; Paternain, A.V.; Rodriguez-Moreno, A.; Lopez-Garcia, J.C. *Physiological Reviews*, **2001**, *81*, 971-998.

[6] Egebjerg, J.; Bettler, B.; Hermans-Borgmeyer, I.; Heinemann, S. *Nature*, **1991**, *351*, 745-748.

[7] Chittajallu, R.; Braithwaite, S.P.; Clarke, V.R.J.; Henley, J.M. *Trends in Pharmac. Sci.*, **1999**, *20*, 26-35

[8] Bleakman, D.; Lodge, D. *Neuropharmacology*, **1998**, *37*, 1187-1204.

[9] Cui, C.; Mayer, M.L. *J. Neurosci.*, **1999**, *19*, 8281-8291.

[10] Chittajallu, R.; Vignes, M.; Dev, K.K.; Barnes, J.M.; Collingridge, G.L.; Henley, J.M. *Nature*, **1996**, *379*, 78-81.

[11] Vignes, M.; Clarke, V.R.J.; Parry, M.J.; Bleakman, D.; Lodge, D.; Ornstein, P.L.; Collingridge, G.L. *Neuropharmacology*, **1998**, *37*, 1269-1277.

[12] Rodriguez-Moreno, A.; Herreras, O.; Lerma, J. *Neuron*, **1997**, *19*, 893-901.

[13] Clarke, V.R.J.; Ballyk, B.A.; Hoo, K.H.; Mandelzys, A.; Pellizzaro, A.; Bath, C.P.; Thomas, J.; Sharpe, E.F.; Davies, C.H.; Ornstein, P.L.; Schoepp, D.D.; Kamboj, R.K.; Collingridge, G.L.; Lodge, D.; Bleakman, D. *Nature*, **1997**, *389*, 599-603.

[14] Frerking, M.; Malenka, R.C.; Nicoll, R.A. *Nature Neurosci.*, **1998**, *1*, 479-486.

[15] Rodriguez-Moreno, A.; Lopez-Garcia, J.C.; Lerma, J. *Proc. Natl. Acad. Sci.*, **2000**, *97*, 1293-1298.

[16] Frerking, M.; Petersen, C.C.H.; Nicoll, R.A. *Proc. Natl. Acad. Sci*., **1999**, *96*, 12917-12922.

[17] Cossart, R.; Esclapez, M.; Hirsch, J.C.; Bernard, C.; Ben-Ari, Y. *Nature Neurosci.*, **1998**, *1*, 470-478.

[18] Min, M.Y.; Melyan, Z.; Kullmann, D.M. *Proc. Natl. Acad. Sci*., **1999**, *96*, 179932-179937.

[19] Bortolotto, Z.A.; Vernon, R.J.; Delany, C.; Parry, M.C.; Smolders, I.; Vignes, M.; Ho, K.H.; Miu, P.; Brinton, B.T.; Fantaske, R.; Ogden, A.; Gates, M.; Ornstein, P.L.; Lodge, D.; Bleakman, D.; Collingridge, G.L. *Nature*, **1999**, *402*, 297-301.

[20] Monn, J.A.; Valli, M.J. *J. Org. Chem*., **1994**, *59*, 2773-2778.

[21] Cantrell, B.E.; Zimmerman, D.M.; Monn, J.A.; Kamboj, R.K.; Hoo, K.H.; Tizzano, J.P.; Pullar, I.A.; Farrel, L.N.; Bleakman, D. *J. Med. Chem.*, **1996**, *39*, 3617-3624.

[22] Gu, Z.Q.; Hesson, D.P.; Pelletier, J.C.; Maccecchini. M.L. *J. Med. Chem.*, **1995**, *38*, 2518-2520.

[23] Gu, Z.Q.; Lin, X.F.; Hesson, D.P. *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 1973-1976.

[24] Zhou, L.M.; Gu, Z.Q.; Costa, A.M.; Yamada, K.A.; Mansson, P.E.; Giordano, T.; Skolnick, P.; Jones, K.A. *J. Pharmacol. Exp. Ther*., **1997**, *280*, 1422-1427.

[25] Jones, K.A.; Wilding, T.J.; Huettner, J.E.; Costa, A.M. *Neuropharmacology*, **1997**, *36*, 853-863.

[26] Ta, L.E.; Dionne, R.A.; Fricton, J.R.; Hodges, J.S.; Kajander, K.C. *Brain Res.*, **2000**, *858*, 106-120.

[27] Sutton, J.L.; Maccecchini, M.L.; Kajander, K.C. *Neuroscience*, **1999**, *91*, 283-292.

[28] Lauridsen, J.; Honoré, T.; Krogsgaard-Larsen, P. *J. Med. Chem*., **1985**, *28*, 668-672.

[29] Stensbøl, T.B.; Borre, L.; Johansen, T.N.; Egebjerg, J.; Madsen, U.; Ebert, B.; Krogsgaard-Larsen, P. *Eur. J. Pharmacol*., **1999**, *380*, 153-162.

[30] Stensbøl, T.B.; Jensen, H.S.; Nielsen, B.; Johansen, T.N.; Egebjerg, J.; Frydenvang K.; Krogsgaard-Larsen, P. *Eur. J. Pharmacol*., **2001**, *411*, 245-253.

[31] Jane, D.E.; Pook, P.C.K.; Sunter, D.C.; Udvarhelyi, P.M.; Watkins, J.C. *Br. J. Pharmacol.*, **1991**, *104*, 333P.

[32] Blake, J.F.; Jane, D.E.; Watkins, J.C. *Br. J. Pharmacol.*, **1991**, *104*, 334P.

[33] Wong, L.A.; Mayer, M.L.; Jane, D.E.; Watkins, J.C. *J. Neurosci*., **1994**, *14*, 3881-3897.

[34] Jane, D.E.; Hoo, K.; Kamboj, R.; Deverill, M.; Bleakman, D.; Mandelzys, A. *J. Med. Chem.*, **1997**, *40*, 3645-3650.

[35] Swanson, G.T.; Green, T.; Heinemann, S.F. *Mol. Pharmacol*. **1998**, *53*, 942-949.

[36] Small, B.; Thomas, J.; Hoo, K.; Ballyk, B.; Deverill, M.; Ogden, A.M.; Rubio, A.; Pedregal, C.; Bleakman, D. *Neuropharmacology*, **1998**, *37*, 1261-1267.

[37] Pedregal, C.; Collado, I.; Escribano, A.; Ezquerra, J.; Dominguez, C.; Mateo, A.I.; Rubio, A.; Baker, S.R.; Goldsworthy, J.; Kamboj, R.K.; Ballyk, B.A.; Hoo, K.; Bleakman, D. *J. Med. Chem.*, **2000**, *43*, 1958-1968.

[38] Baker, S.R.; Bleakman, D.; Ezquerra, J.; Ballyk, B.A.; Deverill, M.; Hoo, K.; Kamboj, R.K.; Collado, I.; Dominguez, C.; Escribano, A.; Mateo, A.I.; Pedregal, C.; Rubio, A. *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 1807-1810.

[39] Bunch, L.; Johansen, T.H.; Bräuner-Osborne, H.; Stensbøl, T.B.; Johansen, T.N.; Krogsgaard-Larsen, P.; Madsen, U. *Bioorg. Med. Chem*., **2001**, *9*, 875-879.

[40] Armstrong, N.; Gouaux, E. *Neuron*, **2000**, *28*, 165-181.

[41] Johansen, T.H.; Drejer, J.; Wätjen. F.; Nielsen, E.Ø. *Eur. J. Pharmacol*., **1993**, *246*, 195-204.

[42] Verdoorn, T.A.; Johansen, T.H.; Drejer, J.; Nielsen, E.Ø. *Eur. J. Pharmacol*., **1994**, *269*, 43-49.

[43] Paternain, A.V.; Vicente, A.; Nielsen, E.Ø.; Lerma, J. *European J. Neurosci*., **1996**, *8*, 2129-2136.

[44] O'Neill, M.J.; Bond, A.; Ornstein, P.L.; Ward, M.A.; Hicks, C.A.; Hoo, K.; Bleakman, D.; Lodge, D. *Neuropharmacology*, **1998**, *37*, 1211-1222.

[45] O'Neill, M.J.; Bogaert, L.; Hicks, C.A.; Bond, A.; Ward, M.A.; Ebinger G.; Ornstein, P.L.; Michotte, Y.; Lodge, D. *Neuropharmacology*, **2000**, *39*, 1575-1588.

[46] Lees, G.J. *Drugs*, **2000**, *59*, 33-78.

[47] Li, S.; Tator, C.H. *Neurological Res*., **2000**, *22*, 171-180.

[48] Mulle, C.; Sailer, A.; Perez-Otano, I.; Dickinson-Anson, H; Castillo, P.E.; Bureau, I.; Maron, C.; Gage, F.H.; Mann, J.R.; Bettler, B.; Heinemann, S.F. *Nature*, **1998**, *392*, 601-605.

[49] Perucca, E. *Pharmacol. Res.*, **1997**, *35*, 241-256.

[50] Gilron, I.; Max, M.B.; Lee, G.; Booher, S.L.; Dionne, R.A. *Clinical Pharmac. Therap.*, **2000**, *67*, 93.

[51] Gilron, I.; Max, M.B.; Lee, G.; Booher, S.L.; Sang, C.; Chappel, A.S.; Dionne, R.A. *Clinical Pharmac. Therap.*, **2000**, *68*, 320-327.

[52] Meador-Woodruff, J.H.; Davis, K.L.; Haroutunian, V. *Neuropsychopharmacology*, **2001**, *24*, 545-552.

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