

Mini review

Antagonists and agonists at the glycine site of the NMDA receptor
for therapeutic interventions

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Dedicated to Prof. Dr. Ulf Pindur, University of Mainz, Germany, on the occasion of his 60th birthday.

Abstract

For decades neuroreceptor research has focused on the development of NMDA glycine-site antagonists, after Johnson and Ascher found out in 1987 about the co-agonistic character of this achiral amino acid at the NMDA receptor. Contrary to the inhibitory glycine receptor (glycine_A) the glycine binding site on the NMDA receptor (glycine_B) is strychnine-insensitive. A great diversity of diseases showing a disturbed glutamate neurotransmission have been linked to the NMDA receptor. Glycine site antagonists have been investigated for acute diseases like stroke and head trauma as well as chronic ones like dementia and chronic pain.

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Keywords: Glycine site; NMDA receptor; Excitatory amino acid receptor; Stroke; Epilepsy; Dementia; Pain; Schizophrenia

1. Introduction

The central nervous system (CNS) is governed by inhibitory amino acids on the one hand (e.g. γ -amino butyric acid, GABA) and excitatory amino acids on the other (e.g. glutamate). The receptors for excitatory amino acids can be divided into metabotropic and ionotropic receptors. The latter ligand-gated ion channels (LGICs) comprise kainate, (*S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA), and *N*-methyl-D-aspartic acid (NMDA) receptors. NMDA receptors are permeable to sodium, calcium and potassium ions, following the direction of their natural gradient. The most characteristic feature of the NMDA receptor is its voltage-dependent regulation by magnesium [1,2], which means that the channel pore can only be opened if a partial depolarization (e.g. by neighboring AMPA receptors) has preceded. A multitude of different binding sites besides the glutamate site allows a vast number of allosteric interactions [3–6]:

glycine site, polyamine site(s), phencyclidine (PCP) site, zinc site, magnesium site, phosphorylation site(s), as well as sites which are prone to modulation by different pH or redox states. The glycine-cotransmitter site on the NMDA receptor enables a sole amino acid to be at the same time inhibitory (via the glycine_A receptor which is strychnine-sensitive) and excitatory [7,8] (via the glycine_B receptor which is strychnine-insensitive).

The NMDA receptor is a complex consisting of different subunits: NR1, NR2A–D, NR3A,B [5,9–13]. The NR1 subunit is expressed ubiquitously in the CNS and is crucial for essential functions of the NMDA receptor, whereas the other subunits show limited expression and time-dependent importance during different developmental stages. NMDA receptors are not only expressed in the central nervous system, but also in extraneuronal tissues, e.g. heart [14], lung [15], β -cells of the pancreatic islets [16].

The therapeutic benefit of antagonists at the strychnine-insensitive glycine_B site is under investigation for acute and chronic disorders of the central nervous system (CNS), e.g. stroke, trauma, Alzheimer's disease [17–19], amyotrophic lateral sclerosis (ALS) [20,21],

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Parkinson's disease [22,23], Huntington's chorea [24], anxiety disorders [25], depressions [26,27], epilepsy [28,29], chronic pain [30]. This great interest is underlined by the better therapeutic index, e.g. lack of vacuolization, learning impairment or psychotomimetic effects, for glycine antagonists compared to competitive antagonists at the NMDA receptor or channel blockers [31–34].

The systematic names of the compounds referred to in the text by acronyms or code numbers are given in Table I.

2. Potential therapeutic uses of glycine site ligands

2.1. Pain

The complex phenomenon of pain can be divided into neuropathic pain—which is associated with the characteristic symptoms of hyperalgesia and allodynia—and nociceptive pain—which arises for example after tissue or nerve injury or inflammation. Allodynia is defined as the perception of pain in response to stimuli which are non-noxious under normal conditions, whereas hyperalgesia means an exaggerated response to painful stimuli [35]. Both pain states are combined with central sensitization, a process in which prostaglandins, nitric oxide (NO), excitatory amino acids and substance P are involved [36–38].

Up to now neuropathic or chronic pain states represent difficult therapeutic challenges. Today's treatments are far from being satisfactory owing to the development of tolerance, to severe side effects as well as to the lack of adequate drugs for special pain states. Fibromyalgia syndrome (FMS) is characterized by chronic widespread pain of unknown etiology and pathogenesis. FMS patients show symptoms including hyperalgesia and allodynia. In a study with patients suffering from FMS changes in the CSF were investigated, indicating that besides an increase in substance P and arginine as a precursor to NO, metabolic changes such as glutamine and asparagine increase were also observed and therefore reflect increased excitatory amino acid (EAA) release [39].

The involvement of the glycine site of the NMDA receptor in pain states is very clearly proved by the fact that the concentration of its endogenous antagonist kynurenate is increased by nonsteroidal anti-inflammatory drugs (NSAIDs) thus mediating a prostaglandin-independent antinociceptive effect [40]. Acute nociception is thought to be mediated principally in the spinal cord [41] where NMDA receptors do not seem deeply involved. However, they do play a key role in chronic pain states and hyperalgesia [42], both conditions in which thalamic neurons are involved [43–45] (Table II). NMDA agonists can evoke hyperalgesic states, whereas

Table I
Systematic names (INNs) of the acronyms and code numbers used in the text

Acronym/code number	Systematic name (INN)
7-CK	7-Chlorokynurenate
ACEA-1011	5-Chloro-7-trifluoromethyl-1,4-dihydro-2,3-quinoxalinedione
ACEA-1021	5-Nitro-6,7-dichloro-2,3-quinoxalinedione (Licostinel)
ACEA-1328	5-Nitro-6,7-dimethyl-1,4-dihydro-2,3-quinoxalinedione
ACEA-1416	5-Nitro-6-methyl-7-chloro-1,4-dihydro-2,3-quinoxalinedione
AP-5	5-Aminophosphono pentanoic acid
AP-7	5-Aminophosphono heptanoic acid
CNQX	6-Cyano-7-nitroquinoxaline-2,3-dione
Eliprodil	1-(4-Chloro-phenyl)-2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-ethanol
Felbamate	2-Phenyl-1,3-propanediol-dicarbamate
GV150526	3-[2-(Phenylamino-carbonyl)ethenyl]-4,6-dichloro-indole-2-carboxylic acid sodium salt (Gavestinel)
GV196771A	(<i>E</i>)-4,6-Dichloro-3-(2-oxo-1-phenylpyrrolidin-3-ylidenemethyl)-1 <i>H</i> -indole-2-carboxylic acid sodium salt
(+)-HA-966	(+)-(1-Hydroxy-3-aminopyrrolidine-2-one)
Ifenprodil	2-(4-Benzyl-piperidino)-1-(4-hydroxyphenyl)-1-propanol
L-689,560	4- <i>trans</i> -2-Carboxy-5,7-dichloro-4-phenylaminocarbonylamino-1,2,3,4-tetrahydroquinoline
MDL 100,458	3-(Benzoylmethylamino)-6-chloro-1 <i>H</i> -indole-2-carboxylic acid
MDL 100,748	4-Carboxymethylamino-5,7-dichloroquinoline-2-carboxylic acid
MDL 102,288	5,7-Dichloro-1,4-dihydro-4-[[[4-[(methoxycarbonyl)amino]phenyl]sulfonyl]imino]-2-quinolinecarboxylic acid monohydrate
MDL 104,653	3-Phenyl-4-hydroxy-7-chloro-quinolin-2(1 <i>H</i>)-one
MDL 29,951	3-(4,6-Dichloro-2-carboxyindol-3-yl)propionic acid
MK-801	(+)-5-Methyl-10,11-dihydro-5 <i>H</i> -dibenzo[<i>a,d</i>]-cyclohepten-5,10-imine maleate (Dizocilpine)
MNQX	5,7-Dinitroquinoxaline-2,3-dione
Mrz2/576	(8-Chloro-4-hydroxy-L-oxo-1,2-dihydropyridazino[4,5- <i>b</i>]quinolin-5-oxide choline salt
Mrz2/579	1-Amino-1,3,3,5,5-pentamethyl-cyclohexane HCl
Remacemide	(+/-)-2-Amino- <i>N</i> -(1-methyl-1,2-diphenylethyl)-acetamide
Riluzole	2-Amino-6-trifluoromethoxybenzothiazole
Ro 63-1908	(1-[2-(4-Hydroxy-phenoxy)-ethyl]-4-(4-methyl-benzyl)-piperidin-4-ol)
SM-31900	(3 <i>S</i>)-7-Chloro-3-[2-((1 <i>R</i>)-1-carboxyethoxy)-4-amino-methylphenyl] amino carbonylmethyl-1,3,4,5-tetrahydrobenz[<i>c,d</i>]indole-2-carboxylic acid hydrochloride
ZD9379	7-Chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5- <i>b</i>]quinoline-1,10-dione sodium salt

NMDA antagonists can block these states. There is much evidence for the involvement of the NMDA receptor in the induction and maintenance of hyperalgesia [46,47]. Furthermore, NMDA receptor activation results—via calcium influx—in the production of prostaglandins, which themselves are pro-inflammatory,

Table II

Overview of the different models used for investigating the influence of glycine site NMDA antagonists on pain

Test	Model	Receptors involved
Formalin test	Tonic/inflammatory pain	Non-NMDA, NMDA
Tail-flick test	Phasic pain	Non-NMDA
Chronic constrictive injury (CCI) of the sciatic nerve	Chronic/neuropathic pain, allodynia	NMDA
Thermal escape latency	Acute nociception	Non-NMDA

and NO, which acts as a retrograde transmitter that evokes further glutamate release at the presynaptic site when released from the postsynaptic neuron [48].

Therefore, antagonists at the glycine site of the NMDA receptor have been investigated for the treatment of pain (Fig. 1): ACEA-1011, which is an antagonist at the NMDA receptor glycine site and, to a lesser extent also at the AMPA receptor, showed analgesic properties in animal models of tonic pain [49]. ACEA-1416 was also antinociceptive in an animal model of tonic pain (formalin test). The formalin test is a widely accepted model of tonic pain. This test shows a biphasic nociceptive response to formalin: an acute or early transient phase of 0 to 5 min and a prolonged, inflammatory tonic phase of up to 60 min. The long-lasting late phase of the nociceptive response was treated chronically with no observation of development of tolerance, whereas interestingly the side-effects (disturbances of motor coordination, rotarod test) as well as the response in the early phase decreased following chronic administration [50]. Another compound of the quinoxalinedione series, ACEA-1328 is also a systemically bioavailable antagonist at the glycine site of the NMDA receptor. In the tail-flick test in mice this compound significantly increased the antinociceptive effect of morphine when administered concurrently. In addition development of tolerance to morphine was prevented by this co-administration and also reversed when it had been pre-established [51,52]. However, when

NMDA antagonists were examined for their interaction in acute nociception (thermal escape latency) they had no effect alone and no synergistic effects together with morphine. This holds true for both the competitive antagonists AP-5, and the glycine site antagonist ACEA-1021. AMPA antagonists displayed synergy with morphine in the same model which makes them a promising target in the development of acute pain strategies [53]. ACEA-1021 produced antinociception in the tail-flick and formalin test [54] which might contribute to its additional inhibition of non-NMDA receptors [55]. Another study showed synergistic antinociceptive effects against tonic pain (formalin test) together with morphine [56]. In contrast to selective NMDA receptor antagonists, non-selective NMDA/AMPA antagonists are antinociceptive in the tail-flick test, in which it was shown that antinociceptive activity generally correlates with the inhibition of non-NMDA receptors [57].

It was also shown that prostaglandin E2 (PGE2) induced hyperalgesia can be blocked with the glycine site antagonist 7-CK [58]. In a different study the effect of 7-CK on formalin-induced inflammatory pain was investigated. Both pre- and post-administered 7-CK inhibited the second phase of the formalin response significantly [59].

The glycine site partial agonist/antagonist (+)-HA-966 is able to potentiate the antinociceptive effect of morphine in a dose-dependent manner, when it is administered in combination with doses of morphine that are not or hardly antinociceptive [60,61]. The management of chronic pain states is hampered by the development of tolerance to analgesics such as morphine and other opioids. Also in the context of morphine tolerance (+)-HA-966 showed ameliorative effects, both in preventing morphine tolerance and in some models also in reversing an already established morphine tolerance [62].

GV196771A is under investigation for the treatment of neuropathic pain [30]. The substance exerts its effects not only in the spinal cord, but also in the thalamus.

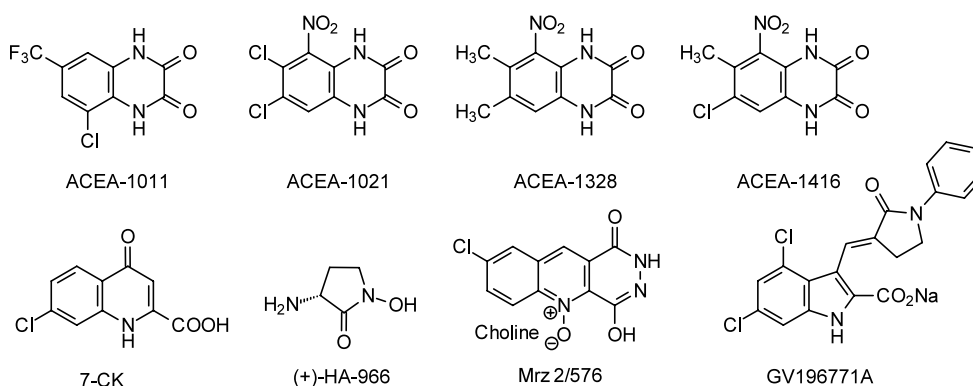


Fig. 1. Glycine site antagonists evaluated for pain treatment.

GV196771A has no effects on the activity of ventroposterolateral nucleus of the thalamus in normal rats, whereas in a model of chronic/neuropathic pain (chronic constrictive injury (CCI) of the sciatic nerve) the substance blocked responses to noxious stimulation in a dose-dependent and reversible manner [63]. In the formalin test in mice GV196771A showed analgesic activity comparable to morphine and to the channel blocker MK-801 in the late phase, whereas in the early phase this indole derivative was inactive. In behavioral studies GV196771A reduced the hyperalgesic response in CCI-treated rats but did not induce a change in normal rats. In comparison, the open-channel blocker MK-801 is very unselective because it also interferes with the activity (firing rates) of non-nociceptive neurons in normal animals. The antihyperalgesic activity of GV196771A is not accompanied by development of tolerance, which is in line with the view that the NMDA receptor plays a pivotal role in events underlying plastic phenomena. Not only was the development of hyperalgesia blocked, but also already-developed hyperalgesia reversed [64]. The effects of this compound on mechanical allodynia (CCI of the sciatic nerve) were also investigated, showing a strong dose-dependent inhibition of established allodynia [65]. GV196771A is active even after p.o. administration and is devoid of behavioral side effects (hyperactivity, motor dysfunction). Along with the lack of tolerance, this makes GV196771A a promising compound for the future treatment of neuropathic pain.

Tricyclic pyrido-phthalazine-dione derivatives, e.g. Mrz2/576 are systemically active antagonists of the glycine site of the NMDA receptor. They show an outstanding systemic availability and/or penetration of the blood-brain barrier and are under investigation for the treatment of chronic pain as well as other disorders that have been associated with disturbances of the glutamatergic system such as e.g. acute excitotoxicity, chronic neurodegenerative diseases, chronic pain, drug tolerance, dependence and addiction, and epilepsy [66].

However, most animal models of pain investigate somatic nociceptive pathways, which differ from visceral ones. In the case of visceral nociceptive input NMDA-receptor antagonists (ketamine, memantine) and NMDA-glycine site antagonists (Mrz2/576) are effective in analgesia also after acute stimulation [67].

In conclusion NMDA glycine site antagonists are interesting compounds for treating different pain states which are hard to control with currently available drugs. In addition these substances can be used to prevent the establishment of tolerance to drugs like morphine, which is a major disadvantage of such opioids.

Highly selective antagonists for the NR2B subunit of the NMDA receptor, e.g. ifenprodil, eliprodil, Ro 63-1908 (Fig. 2), are also very promising for chronic and acute pain treatment [68–71].

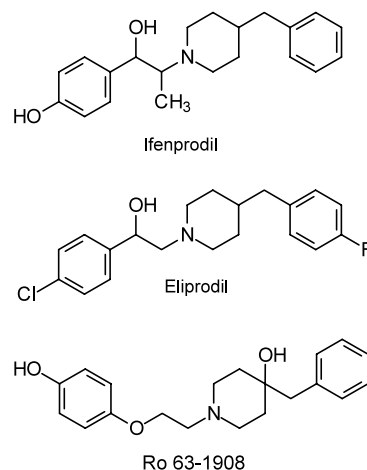


Fig. 2. NR2B antagonists.

2.2. Epilepsy

Epilepsy is a very common disorder of the CNS, which affects up to 1% of the world population. The disease is chronic and often progressive. Although many antiepileptic drugs (AEDs), which exert their action via a variety of mechanisms such as sodium- or calcium channel inhibition, enhancement of GABA inhibitory transmission by allosteric mechanisms or influence on enzymatic systems, are clinically available, the therapeutic outcome shows a great need for improvements. Besides a high percentage of therapy-resistant epileptic patients the main disadvantage of the medication available is the high incidence of severe adverse effects, e.g. cognitive impairment, decrease in overall energy level. Already two decades ago a study with DBA/2 mice (audiogenic seizure model) and AP-5 and AP-7 (NMDA glutamate site antagonists) showed [72] that the NMDA-receptor is deeply involved in the initiation or spread of epileptic neuronal hyperactivity [73]. Studies of neuroactive amino acids in surgically excised focally epileptic human brain tissue depict the involvement of these amino acids in epilepsy, in that concentrations of glutamate, aspartate and glycine are significantly increased in epileptogenic cerebral cortex [74].

Felbamate, remacemide and riluzole (Fig. 3) are anticonvulsant medications which—at least in part—convey their effect via antagonism at the glycine_B site [75]. To test the anticonvulsant activity of new chemical entities (NCEs) different models exist (see Table III).

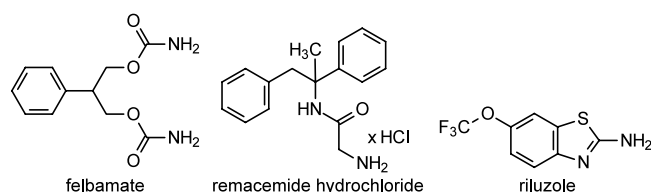


Fig. 3. Antagonists of the Glycine_B site with anticonvulsant potency.

Table III
Different models for the evaluation of anticonvulsants

Model	Seizure type
DBA/2 mouse model	Audiogenic seizures
30-min stimulation of the perforant path (PPS) through implanted electrodes	Self-sustaining status epilepticus (SSSE)
Maximal electroshock-induced seizures	Generalized tonic-clonic seizures
Subcutaneous pentylenetetrazole (Met, PTZ)	Generalized absence and/or myoclonic seizures, 'kindled' seizures
Genetic Absence Epilepsy Rats from Strasbourg (GAERS), spike and wave discharges (SWD)	Absence Seizures
(Amygdala) Kindling	Complex-partial seizures, limbic epilepsy

Known treatments of convulsions do not always exert an action in all experimental protocols used to test anticonvulsant activity. But the pattern of activities of a substance might be characteristic for the mechanism of action or its special therapeutic use. Remacemide also inhibits NMDA receptors by channel blocking [76]. The known treatments felbamate and riluzole—besides a variety of other mechanisms—interfere both with glycine/NMDA and AMPA/kainate receptors [77,78]. In the DBA/2 mouse model the different anticonvulsant mechanisms of riluzole have been elucidated after intraperitoneal (i.p.) administration. In biochemical models riluzole displays 'antiglutamate' activity [79,80], and additionally inhibits sodium channels [81].

In a model of self-sustaining status epilepticus (SSSE) felbamate was more effective than phenytoin or diazepam in shortening seizure duration. Neuronal injury was also milder than in the control animals [82]. 5,7-DiCK (Fig. 4) was also examined in this model, where it showed remarkable advantages over the AMPA/kainate antagonists CNQX and also over standard anticonvulsants such as diazepam and phenytoin, because NMDA-antagonists were effective in terminating SSSE at a time when diazepam and phenytoin were no longer able to do so [83]. Thus NMDA antagonists represent promising agents for treating status epilepticus.

MNXX (Fig. 4) which is an antagonist at the glycine B site is active in the DBA/2 mice model, when administered i.p. [84]. In the same model MDL 29,951 (Fig. 4), MDL 100,748 (Fig. 4), 7-CK, and 5,7-DiCK were shown to be anticonvulsant after i.c.v. administration [85], as well as MDL 104,653 was active after i.c.v., i.p. and p.o. administration [86]. The latter substance also reduced amygdala-kindled seizures. In a study with MDL 100,458 and MDL 102,288 (Fig. 4) only the first substance was active in the DBA/2 mouse model, although both substances showed comparable results in binding assays for the glycine binding site of the

NMDA receptor [25]. SM-31900 (Fig. 4), a glycine site antagonist with high selectivity and affinity [87], was shown to be anticonvulsant after systemic administration (i.v.) in NMDA-induced convulsions, whereas L-689,560 (Fig. 4), 5,7-DiCK and 7-CK were inactive in the same protocol [88]. Other indole carboxylic acid ligands are under investigation as well [89]. In contrast to 7-CK its sugar-prodrugs show availability to the brain, e.g. the glucos-3'-yl ester and the glucos-6'-yl ester act protectively against seizures induced by NMDA after i.p. administration [90] (Fig. 4).

One point to be mentioned when the anticonvulsant effect of NMDA-glycine site antagonists is discussed, is the functional difference brought about by substances acting at the NMDA receptor (HA-966 as a partial agonist/antagonist at the glycine site; memantine, ketamine as channel blockers) in kindled and in non-kindled rats [91]. There is evidence from studies with kindled rats, that functional NMDA glycine antagonists with weak intrinsic activity, bear the risk of proconvulsant activity.

2.3. Stroke

In the Western world stroke is the third leading cause of death and an important cause of serious, long-term disability. The incidence of stroke in the USA is ca. 600 000 per year, 500 000 of which are first attacks. Stroke is the result of a rupture or clogging of a blood vessel, which supplies the brain with nutrients and oxygen. Hypoglycemia and hypoxia produce an energy failure, which leads to excessive stimulation of the excitatory glutamatergic system. As a consequence NMDA-receptors become highly activated, so that the result is a massive calcium influx into the cells. The high intracellular calcium concentration then contributes to the vicious circle by starting a complex biochemical cascade. Hence it is justifiable to antagonize the glycine site of the NMDA receptor in order to treat stroke. Although many efforts have been made in the past years to develop drugs for acute intervention, there are urgent and still high needs for efficient medications.

Felbamate, which is in use as an anticonvulsant, was tested in a gerbil model of global ischemia, where—given at higher doses than are necessary for anticonvulsant therapy—it was effective in preventing delayed apoptosis secondary to global ischemia when administered ad hoc to occlusion [92]. GV150526 (Fig. 5) administered up to 6 h after stroke onset, was able to reduce infarct size by 50% in a rat middle cerebral artery occlusion model of ischemic stroke [93]. In two clinical trials (glycine antagonist in neuroprotection trials, GAIN 1 and 2) no beneficial outcome (functional capability after 3 months) was observed in ischemic stroke patients treated with GV150526 [94,95]. Also ACEA-1021 was shown to be an effective neuroprotec-

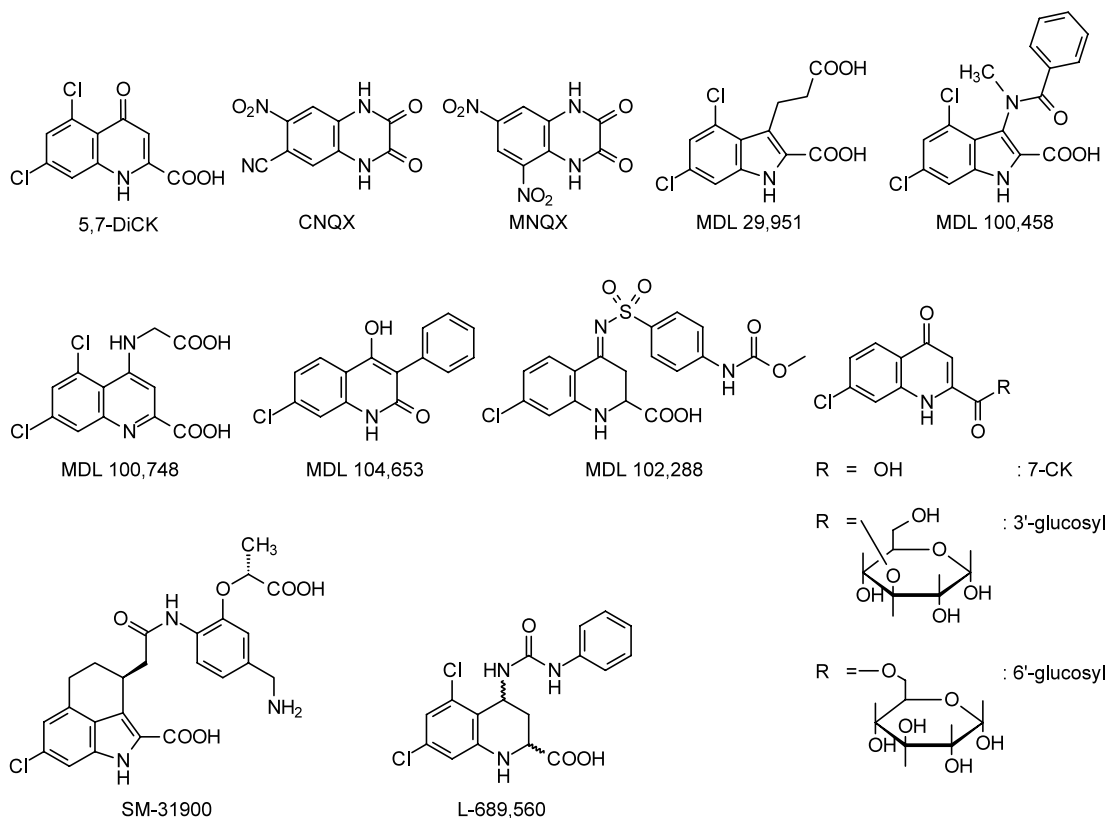


Fig. 4. EAA antagonists investigated as anticonvulsants.

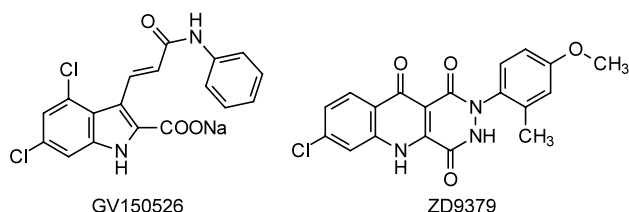


Fig. 5. Glycine antagonists tested as stroke treatments.

tive agent in animal models of cerebral ischemia. In a dose escalation study the substance was verified to be safe and tolerable in acute stroke patients [96], but was dropped from development soon after. Other compounds, e.g. SM-31900, ZD9379 (Fig. 5) and Mrz 2/576, have also been investigated in animal models of stroke, indicating that they are effective in treating acute brain ischemia [97–99].

Although a lot of compounds have been reported to be beneficial in animal models of stroke, none of these substances was able to proof its efficacy in clinical trials. Explanations are, e.g. that animal models are an imperfect representation of human stroke; that the time window between onset of stroke and drug administration in clinical trials was very large (average 12 h) compared to the animal models, where the medication was given before the ischemic insult or very soon after its onset; that the optimal duration of administering the neuroprotectant is not known; that the outcome which

is measured in animal studies is very different from that in clinical studies or that even the choice of outcome measures can be crucial for success or failure of a study (for review see [100]). For a proof-of-concept for certain medications in stroke a prophylactic administration (e.g. before certain surgical procedures, or for certain patients with an elevated risk of getting stroke) could be a way to collect the necessary data.

2.4. NMDA-receptor hypofunction

Some neurologic disorders are—at least in part—the result of NMDA receptor hypofunction. The most prominent examples are schizophrenia and dementia, and another example is bipolar disease.

2.4.1. Schizophrenia

Schizophrenia affects 1–1.5% of the US American population. Though the disease is not curable, current treatments with antipsychotic drugs (neuroleptics) enable a high percentage of patients to lead a normal life. Schizophrenic patients can show positive symptoms such as hallucinations, delusions, language disorders as well as negative symptoms, which mean the absence of normal behavior, e.g. loss of affect, apathy, social withdrawal. Medications can be divided into conventional neuroleptics (e.g. haloperidol, chlorpromazine)

and atypical neuroleptics (e.g. clozapine, risperidone, ziprasidone, olanzapine).

The NMDA channel blocker phencyclidine (PCP)—also known as the illegal drug ‘angel dust’, which was formerly used as a dissociative anesthetic in humans—induces symptoms in healthy volunteers which are almost indistinguishable from schizophrenia. Together with the finding that the concentrations of glutamate are reduced in the CSF of schizophrenia patients [101] the involvement of NMDA receptor hypoactivity in this neurologic disease is palpable [102,103]. The disadvantages of direct agonists at the NMDA receptor—e.g. excitotoxic risks—indicate that these substances are not ideal for chronic therapeutic intervention in schizophrenia [104]. Chronic disability in schizophrenia is due to persistent negative symptoms to a great extent. The major approach to treating the negative symptoms is the use of atypical antipsychotics such as clozapine, risperidone, and olanzapine [105]. The NMDA receptor-stimulating agents glycine, D-serine, and D-cycloserine (Fig. 6) were evaluated as add-ons to neuroleptic therapy. Glycine after high-dose oral administration [106] as well as D-serine [107] improved the negative symptoms. The partial agonist D-cycloserine was able to reduce the negative symptoms when given together with risperidone [108] or conventional antipsychotics [109], but worsened symptoms in patients treated with clozapine. In general neither of the substances seems to be able to augment the clozapine effect [106–108]. This can be attributed to the fact that clozapine itself acts by enhancing glutamatergic activity [110–114] and affects the strongest reduction of negative symptoms compared to other atypical neuroleptics [115]. On the whole the glycinergic agonists are able to improve the negative symptoms, a fact which makes these compounds interesting for therapy [116]. However, schizophrenia is also accompanied by other perturbations of the central nervous system, so that other therapeutic strategies e.g. interference with AMPA-receptors (positive modulators)[117–120] and GABA-receptors are under investigation as well. The fact that a recent study with chronic PCP treatment resulted in an increase in NMDA-receptor function and a decrease in GABA_A-receptor function points out that the underlying mechanisms and the consecutive therapeutic points of attack need further elucidation [121].

2.4.2. Dementia

Several disorders that cause a progressive loss of memory are subsumed under the term dementia. Dementia includes Alzheimer’s, Parkinson’s, Creutzfeld–Jacob, and Huntington’s disease, as well as AIDS dementia. Due to a loss of brain function these neurologic impairments are fatal. The duration of the diseases and their time of onset are variable. The prevalence of Alzheimer’s is 10% of people over the age of 65 and nearly 50% over 85. The incidence for Parkinson’s is 1% of people over 60 and 2% over 70. The implication of NMDA receptors in processes such as learning and memory represents its direct link to dementia [122–124].

Alzheimer’s disease is associated with a progressive loss of primarily cholinergic and glutamatergic neurons [125–127]. The β -amyloid protein accumulates in the brains of Alzheimer patients and forms characteristic plaques. This β -amyloid protein is able to aggravate the excitotoxic effects of glutamate [128,129]. In addition the learning and memory deficits of Alzheimer patients indicate hypoactivity of the glutamatergic system. Since the hyperactivity of EAA receptors is important in early Alzheimer stages [130] and the hypoactivity is a result of a decreased number of glutamatergic neurons when the disease is already in a progressed stadium, the decision for agonists or antagonists as treatments seems to depend on the stage of the disease. In the early stages, glycine_B antagonists and low affinity channel blockers of the NMDA receptor are interesting and so far successful approaches to treat the disease [131,132]. Concerning the treatment of impaired cognition and memory, D-cycloserine was shown to facilitate memory in Alzheimer patients [133]. In animal models milace-mide, a glycine prodrug which failed in Alzheimer patients [134], also showed cognitive benefits [135,136]. In other animal paradigms D-cycloserine did not produce beneficial effects [137], so the true possibilities of partial agonists at the glycine site of the NMDA receptor remain unresolved.

In Parkinson’s disease oxidative stress produces a loss of dopaminergic neurons [138–140]. The medication consists in drugs that increase dopaminergic neurotransmission e.g. by dopamine-prodrugs or -agonists and substances that inhibit the enzymatic degradation of dopamine in the brain. Since the neurotransmitter glutamate acts opposite to dopamine, glutamate receptor antagonists are potential candidates for the treatment of Parkinson’s disease [141]. Amantadine—a NMDA receptor channel blocker—is used for treating dyskinesia induced by levodopa and may also be beneficial as an agent against ‘wearing off’ fluctuations [142]. Glycine antagonists (L689,560, 5,7-DiCK, 7-CK) were also successful in treating Parkinson’s disease in animal models [143], but non-competitive antagonists of the NMDA receptor, e.g. Mrz 2/579, were shown to be

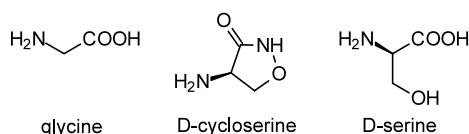


Fig. 6. Glycine agonists evaluated for treating schizophrenia.

advantageous over glycine antagonists [144]. This is due to different projection mechanisms of the involved neurons in the striatum. Glycine antagonists are only able to abolish catalepsy induced by D2 dopamine receptor antagonists, whereas competitive and non-competitive NMDA antagonists block in addition the catalepsy caused by D1 dopamine receptor antagonists [145–147].

3. Conclusion

With respect to the side effect profile, influencing the NMDA receptor via the glycine site offers advantages over other possibilities such as direct modulation or interference with the cation channel with high affinity ligands. Glycine site antagonists and partial agonists are devoid of the serious side effects such as vacuolization, neurodegenerative or psychotomimetic effects that competitive antagonists and high affinity channel blockers have. Antagonists and agonists at the glycine site have therefore been considered for the treatment of a great variety of neurologic disorders. Pain, epilepsy, schizophrenia, stroke, dementia represent the diseases for which glycine antagonists/agonists at the NMDA receptor have been researched to the greatest extent. Among these disorders of the CNS are incurable and fatal diseases, where intervention at glycine sites at least offers some hope for improving therapy and prolonging life.

Preliminary problems with NMDA receptor glycine site antagonists included poor systemic availability, a drawback which has now been overcome with agents that are not only of very high affinity, but also have improved pharmacokinetic and physicochemical properties, such as good brain permeation and solubility.

Since the beneficial use of memantine in dementia has been shown and owing to the deep involvement of the NMDA receptor in processes such as learning and memory, another field of interest for the future might be the development of more effective cognition enhancers by making use of modulation of the NMDA receptor function.

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