EDITORIAL REVIEW

Possible therapeutic applications of antagonists of excitatory amino acid neurotransmitters

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The dicarboxylic amino acids, glutamate and aspartate, are excitatory neurotransmitters in many brain regions. Recent animal experiments with analogues of dicarboxylic amino acids that block their excitatory actions, suggest that such selective antagonists could have important therapeutic uses in neurology and psychiatry. The strongest evidence concerns epilepsy and disorders of the motor system. However, there are theoretical and experimental grounds for studying therapeutic applications in cerebral ischaemia and in chronic degenerative disorders. This review summarizes the experimental background, and proposes some key future studies.

Amino acids as excitatory neurotransmitters

Glutamate and aspartate are present in high concentration in the mammalian brain (approximately 10 and 4 mmol/l respectively). That they have a powerful excitatory action on single neurons when applied iontophoretically has been known for more than 20 years [1, 2]. Sulphonic and sulphinic analogues of glutamate and aspartate are also potent excitants and some are found in the brain in low concentration (e.g. cysteate and cysteine sulphinate). A cyclic analogue of aspartate (quinolinate) is also present in low concentration [3]. Evidence that glutamate and aspartate may be endogenous excitatory transmitters at many central sites has been slowly accumulating, and now includes evidence for a calcium-dependent release of glutamate and aspartate after stimulation and a sodium-dependent re-uptake into nerve terminals [4]. Autoradiographic visualization of uptake of [3H]glutamate or [6-3H]aspartate into neurons has been used to identify, tentatively, glutamatergic/aspartergic pathways [5]. Histochemical procedures for the mapping of glutamatergic or aspartergic pathways have not been available. Antibodies have been prepared to purified enzymes concerned with their synthesis (e.g. aspartate transaminase and glutaminase) and the peroxidase-antiperoxidase technique employed to provide selective neuronal staining [6]. Although these enzymes do not provide specific markers for glutamatergic or aspartergic neurons, there is nevertheless preferential staining of neurons believed (on other criteria) to be glutamatergic or aspartergic. Recently an immunocytochemical technique has been developed that allows the demonstration of glutamate in the perfusion-fixed brain [7]. Glutamate is evident within synaptic vesicles in, for example, mossy fibre terminals, in the hippocampus.

Studies of physiological responses to a range of excitants, and their antagonism by different analogues, has led to a classification of postsynaptic receptors in terms of three preferred agonists, i.e. the N-methyl-d-aspartate (NMDA)-, quisqualate- and kainate-'preferring receptors'...
A fourth class of receptor ('glutamate/aspartate') is indicated by studies of induced release of $^{22}\text{Na}_{\text{in vitro}}$ [10, 11]. Binding studies similarly differentiate the three principal receptor types but also identify a L-2-amino-4-phosphonobutyrate (2APB) receptor [12]. Receptors of all main types appear to be present in spinal cord, hippocampus and cerebral cortex [8, 13, 14]. NMDA receptors are not evident in the cerebellum by either the $^{22}\text{Na}_{\text{efflux assay or iontophoresis on to Purkinje cell dendrites}}$ [11, 15]. (However, physiological and biochemical experiments suggest that NMDA receptors activate basket cells [15, 16].)

The use of autoradiography with tritiated ligands (agonists or antagonists) for excitatory amino acid receptors shows a highly selective regional concentration of the three major receptor types [17, 18]. Thus kainate receptors are concentrated around mossy fibre terminals in the hippocampus, and NMDA receptors are prominent in the cortex.

The physiological responses evoked at the three main types of receptor show marked differences that are consistent in various brain regions, i.e. spinal cord, striatum, hippocampus and cortex [19-23]. Glutamate and quisqualate lead to a steady depolarization and sustained increase in firing rate. Kainic acid also increases firing rate progressively but with a slower onset than that due to glutamate. However, aspartate, NMDA and quinolinate produce a pattern of intermittent burst firing associated with paroxysmal depolarizations. Studies of the membrane current-voltage relationship after aspartate application show a voltage-dependent inward current that gives rise to a zone of negative slope conductance and accounts for the sudden transitions in resting potential and the bursting responses [23-25]. This phenomenon can be explained in terms of physiological concentrations of Mg$^{2+}$ acting, in a voltage-dependent manner, to gate the cation channels opened by NMDA [26].

The relationship between the known and unknown endogenous neurotransmitters and the different types of receptor is not understood, and probably varies regionally and even perhaps at different times at one site. Thus it appears probable that glutamate is the endogenous agent commonly acting on the 'quisqualate receptor'. If aspartate is released from cerebellar climbing fibres this must also act on 'quisqualate receptors' on the Purkinje cell dendrites [15]. However, in the spinal cord aspartate is probably released by inter-neurons that provide the polysynaptic excitatory input to motoneurons in the ventral horn and in this site it most probably acts on 'NMDA receptors'. There are also sites where NMDA receptors are important and aspartate appears not to be the endogenous transmitter. Endogenous compounds that are potent agonists at the NMDA receptor include not only aspartate and quinolinic acid but also the sulphonic and sulphinic analogues of aspartate and glutamate, i.e. L-cysteate, L-cysteine sulphinate, L-homocysteate, L-homocysteine sulphinate [27]. However, L-glutamate has a higher affinity than L-aspartate (or the sulphur-containing amino acids) for the D-[H]$^{2}$-amino-5-phosphonovalerate binding site, suggesting that glutamate acts significantly on the NMDA receptors [28].

A wide range of dipeptides and polypeptide derivatives, such as N-acetylaspartyl-glutamate, are also possible endogenous agonists at the dicarboxylic amino acid receptors [29].

There is no endogenous compound that can be confidently proposed as the agonist at the kainate receptor, nor is there a defined physiological role for this receptor. Folic acid (pteroyl-L-glutamic acid) is an endogenous compound with excitotoxic properties. Folate and various of its derivatives have been proposed as agonists at kainate receptors [30, 31] but the specificity of this action is not supported by ligand binding or electrophysiological studies [32, 33].

### Antagonists of excitatory amino acids

Glutamic acid diethylester (GDEE) has been considered as a glutamate antagonist since 1972 [34]. It is active at the quisqualate-preferring receptor but also affects other membrane properties and other types of neurotransmission including cholinergic [35]. Another compound originally shown to possess some glutamate blocking action is a pyridine analogue, HA 966 [36]. However, more potent antagonists have recently been identified through systematic study in vitro of analogues of glutamate [9, 13]. The most potent and selective antagonists of excitatory amino acids are longer chain analogues of aspartate and glutamate with the $\omega$-carboxyl group substituted by a phosphono group (especially 2-amino-5-phosphonovaleric acid, 2APV, and 2-amino-7-phosphonoheptanoic acid, 2APH, and similarly substituted aspartylglycine, ASP-AMP, and glutamyglycine, GLU-AMP). In all cases it is the $\alpha$-isomer that possesses the greater activity. These compounds tested in the spinal cord or cerebral cortex are highly selective as antagonists of excitation at the NMDA-prefering receptor, with little activity at the kainate or quisqualate-preferring receptors. Substituting a sulphonate for the C-terminal in $\gamma$-D-glutamylglycine produces a compound ($\gamma$-D-glutamyl aminomethyl sulpho-
nate, γ-D-GLU-AMS) that is less active at the NMDA receptor and more active at the kainate and quisqualate receptors [37]. A cyclic analogue of aspartate, cis-2,3-piperidine dicarboxylic acid (cis-2,3-PDA), is an antagonist at all three sites.

These compounds are important research tools. By their use it has been possible to differentiate certain pathways and physiological functions as dependent on either NMDA- or on non-NMDA-preferring receptors, i.e. there is preferential blockade by the selective NMDA antagonists, or there is no blockade by the selective NMDA antagonists but there is blockade by non-selective antagonists such as cis-2,3-PDA, γ-D-GLU-AMS, or by GDEE. Thus, in the spinal cord, excitation induced on motoneurons monosynaptically by la afferents is not blocked by specific NMDA antagonists (such as 2APV) but is blocked by non-specific antagonists (cis-2,3-PDA) and by GDEE, and appears to be produced by actions at a quisqualate-preferring receptor. Motoneuronal excitation induced polysynaptically (i.e. dependent on excitatory spinal interneurons) is blocked by the specific NMDA antagonists [38, 39].

In another primary afferent pathway, the auditory nerve input to the cochlear nucleus, NMDA-preferring receptors subserve synaptic responses that are not blocked by GDEE, but are blocked by selective NMDA antagonists [40].

In the striatum there is evidence for glutamate released from corticostriatal fibres acting on a quisqualate-preferring receptor (blocked by GDEE) [41] and for NMDA receptors (blocked by 2APH) that control acetylcholine release [42].

In the hippocampus studies of synaptic potentials indicate the presence of receptors of four types, including NMDA- and kainate-preferring receptors [14]. The Schaffer collateral-commissural input from CA3 (CA, Cornu Ammonidum) pyramidal neurons to the apical dendrites of CA1 neurons is not blocked by 2APV or by GDEE, but is blocked by γ-D-glutamylglycine [21, 22]. The mossy fibre path from dentate granule cells to CA3 neurons apparently acts on non-NMDA receptors; synaptic activation is blocked by cis-2,3-PDA, by γ-D-glutamylglycine and by GDEE, all apparently acting postsynaptically, as glutamate-induced excitation is simultaneously blocked [43]. 2APB blocks synaptic transmission at the lateral perforant path input to dentate granule cells (and the mossy fibre input to CA3 neurons in the guinea pig), but appears to act presynaptically, as responses to excitatory amino acids are little altered [44-47].

In the cortex there is evidence for a functional role for quisqualate and for NMDA receptors [48]. Cortical neurons show a relatively high sensitivity to quinolinic acid compared with glutamate [49].

In the cerebellum there is evidence for the release of glutamate and aspartate by excitatory inputs to the Purkinje cell dendrites (from climbing fibres and from parallel fibres). However, the NMDA receptors appear to be on basket cells rather than on Purkinje cells [11, 15, 16]. Systemic administration of the NMDA antagonist, 2APH, leads to a fall in cerebellar aspartate content in starved rats and mice [50].

Anticonvulsant action of excitatory amino acid antagonists

The 'first generation' antagonists of the excitatory action of glutamate (i.e. HA 966 and GDEE) provide some protection against certain types of chemically induced seizures in animals. However, such effects are weak and variable and their relationship to excitatory amino acid antagonism remains in doubt [51-53]. However, using intra-cerebroventricular injection of a wide range of antagonists in mice genetically susceptible to sound-induced seizures, it was shown a few years ago that compounds blocking excitation at the NMDA-preferring receptor are potent anticonvulsants [54, 55]. The activity of the most potent compounds (2APH and ASP-AMP) is comparable with that of the anticonvulsant benzodiazepines administered by the same route [55-57]. Tested in this way the non-selective antagonists cis-2,3-PDA and γ-D-glutamylglycine are also anticonvulsant, but GDEE is not. These antagonists are highly polar compounds, and cross the blood–brain barrier relatively poorly [58]. Nevertheless they also suppress the sound-induced seizure sequence in susceptible mice when given intraperitoneally, with 2APH showing the highest potency (see Table 1).

NMDA antagonists, administered systemically, are also effective against a variety of chemically induced seizures in rodents [59]. They protect against seizures induced by NMDA, and do not protect against seizures induced by kainate. They also prevent seizures induced by several different convulsants believed to act primarily on GABAergic (GABA, 4-aminobutyric acid) inhibition, including 3-mercaptopropionionic acid, thiosemicarbazide, and the convulsant β-carboline, methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM) [59]. However, these compounds enhance the stimulated release of D-[^3H]aspartate in studies in vitro employing brain ‘mini-slices’ [60, 61]. Thus the anticonvulsant action of 2APH may be related to an important role of excitatory amino acids in the evolution of such seizures.

The threshold current for electroshock seizures in mice is raised by NMDA antagonists, but not by GDEE [62].
TABLE 1. Antiepileptic potency of excitatory amino acid antagonists compared with some standard anticonvulsants

Data from references [54], [56], [57], [63] and [65].

(A) Intracerebroventricular injection in DBA/2 mice

<table>
<thead>
<tr>
<th>Compound</th>
<th>ED₅₀ (μmol)</th>
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<tr>
<td>2-Amino-5-phosphonovaleric acid</td>
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<tr>
<td>2-Amino-7-phosphonoheptanoic acid</td>
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<tr>
<td>γ-D-Glutamylglycine</td>
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<tr>
<td>γ-D-Glutamyl aminomethyl phosphonate</td>
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<tr>
<td>β-D-Aspartyl aminomethyl phosphonate</td>
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<tr>
<td>Sodium valproate</td>
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<tr>
<td>Diazepam</td>
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<tr>
<td>Diphenylhydantoin</td>
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</tr>
<tr>
<td>Phenobarbital</td>
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(B) Intraperitoneal injection in DBA/2 mice

<table>
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<tr>
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<td>Phenobarbital</td>
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(C) Intravenous injection in Papio papio

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<th>Compound</th>
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<tr>
<td>cis-2,3-Piperidine dicarboxylic acid</td>
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<td>Phenobarbital</td>
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Myoclonus and seizure responses induced by intermittent photic stimulation in the Senegalese baboon, *Papio papio*, provide an animal test system corresponding very closely in pharmacological responsiveness to several forms of epilepsy in man [63, 64]. Myoclonic responses to photic stimulation are totally suppressed for several hours by the intravenous administration of 2APH at 1 mmol/kg [65]. Other NMDA antagonists (such as 2APV and cis-2,3-PDA) are somewhat less potent.

Two points relevant to the clinical application of NMDA antagonists emerge from these studies of experimental epilepsy. Firstly, systemic administration of such compounds can produce a therapeutic effect without evident neurological side effects. The principal acute toxic action observed at doses two to three times the anticonvulsant dose in rodents and baboons is loss of muscle tone (most prominent in the hind limbs in rats), with reduced motor activity and ataxia at even higher doses.

Secondly, whereas the most active compounds (2APH, ASP-AMP) are equipotent with diazepam as anticonvulsants when administered intracerebroventricularly, they are 2 orders of magnitude less potent than diazepam when given systemically [57]. This is because of limited entry to the brain [58]. Thus there is a need for the development of antagonists with greater lipid solubility, or for prodrugs enabling the delivery of the active antagonist to cerebral receptors.

Movement disorders

The involvement of NMDA receptors in spinal reflexes and in basal ganglia function (at the level of the striatum and substantia nigra) suggests that NMDA antagonists will modify syndromes with tremor, spasticity and abnormal movements.

Suppression of tremor by NMDA antagonists has been clearly demonstrated in the high pressure neurological syndrome (HPNS). In untreated rats tremor (the first motor manifestation of HPNS) develops at about 40 atmospheres absolute; after 2APH (1 mmol/kg) this onset pressure is increased by more than 100% [66, 67].

There is also a protective action of 2APH against later phases of the HPNS (i.e. myoclonus and convulsions) but this is proportionately less than that afforded against tremor. High doses of GDEE (3 mmol/kg) provide no protection against tremor or myoclonus but slightly raise the onset pressure for convulsions [68].

There is also experimental evidence that NMDA antagonists are potential antispasticity agents. NMDA receptors on motoneurons in the ventral horn are part of the polysynaptic reflex pathways involved in spasticity [38, 39]. The clearest evidence comes from a genetically determined syndrome of spasticity in the Han-Wistar rat [69]. A myorelaxant effect is evident on electromyograph recordings after intraperitoneal administra-
tion of NMDA antagonists, most potently after 2APH, in a dose (2 mmol/kg) significantly higher than the anticonvulsant dose.

Direct evidence concerning other movement disorders is not yet available. However, those dependent on basal ganglia dysfunction are likely to be modified by excitatory amino acid antagonists through actions on the glutamatergic inputs to the striatum and on the NMDA receptors that modulate release of acetylcholine.

Neurotoxic actions of excitatory amino acids

Early observations that glutamate causes neuronal degeneration in the retina and hypothalamus of infant mice [70-72] were extended to provide the basis for the 'excitotoxic' hypothesis. This proposes that dicarboxylic amino acids and related compounds act on receptors mediating excitation to produce a lethal injury [73, 74]. Supporting this is evidence that the relative vulnerability of particular types of neurons is related to the type and number of excitatory amino acid receptors on their dendritic and somatic membranes.

Much research attention has been devoted to α-kainic acid, a cyclic analogue of glutamate, isolated from seaweed and originally utilized as an ascaricide [75, 76]. Kainic acid injected focally into the brain causes local and distant neuronal degeneration, with selectivity for particular cell types, e.g. in the hippocampus, CA3 pyramidal neurons are exceptionally vulnerable, and dentate granule cells relatively resistant [77]. An interaction of kainic acid with excitatory inputs to the vulnerable neurons has been demonstrated in several sites. Thus prior lesioning of the cortico-striatal (glutamatergic) input reduces the vulnerability of striatal neurons to local kainate [78]. A protective effect after destruction of excitatory afferents occurs also in the optic tectum [79] and in the hippocampus [80]. Epileptic activity spreading from the focal site of kainic acid injection contributes to the distant pathology [81].

Autoradiographic and lesion studies provide evidence that some kainate receptors are localized presynaptically, e.g. on mossy fibre terminals in the hippocampus [17] and on parallel fibre inputs to cerebellar Purkinje cells [82].

Focal injections of ibotenic acid, of NMDA or of quinolinic acid also cause local neuronal degeneration [83-86]. However, the selective pattern is different from that seen after kainic acid. In the hippocampus ibotenate or NMDA produce comparable degeneration of dentate granule cells and of CA3 pyramidal neurons, suggesting that NMDA receptors are similarly significant in both regions. Co-injection of 2APH with NMDA or with quinolinic acid protects against neuronal degeneration [87]. The neurotoxic action of ibotenate does not depend on the integrity of excitatory inputs [85]. Systemic administration of NMDA produces neuronal lesions in the arcuate nucleus, and 2APV given systemically blocks this toxic action [88].

Thus there are clearly two distinct types of direct neurotoxic action of excitatory amino acids. The simplest and most direct is that on post-synaptic NMDA receptors, probably associated with induction of calcium spikes in dendrites [89], and with patterns of burst firing.

An action on kainate receptors is less direct in that a complex interaction with the synaptic release of excitatory and also probably inhibitory neurotransmitters is involved. There is also clearly an indirect neurotoxic action associated with the induction and spread of seizure activity that shows patterns of damage identical with those observed in animals undergoing status epilepticus induced by drugs other than neurotoxic amino acids [90, 91].

Ischaemic brain damage

Cerebral ischaemia, if it is not so severe and prolonged as to produce total infarction, leads to a pattern of selective neuronal loss that is broadly similar to that seen after status epilepticus, involving preferentially, for example, pyramidal neurons in hippocampal CA3 and CA1 regions, small pyramidal neurons in cortical lamina III, small inter-neurons in the striatum, and cerebellar Purkinje cells.

In status epilepticus the selectively vulnerable neurons in the hippocampus show a massive intracellular accumulation of calcium as a consequence of sustained excitatory inputs and burst firing [90-94]. In experimental models of forebrain ischaemia the pattern of selective vulnerability in the hippocampus develops during the first 2 h of re-perfusion [95]. At this time selectively vulnerable neurons show accumulation of intracellular calcium, with a distribution in the perikarya and dendrites indicating involvement of excitatory inputs and burst firing [95, 96]. This supports the suggestion that therapy in the post-ischaemic period should be directed towards suppression of excitatory transmission [96] and burst firing. We have demonstrated that focal injection of small quantities of 2APH into the dorsal hippocampus produces a dramatic local protection against the acute neuronal pathological changes induced by forebrain ischaemia in the rat [97-99]. This strongly supports the hypothesis that activation of NMDA receptors and subsequent
burst firing plays an important role in the development of ischaemic brain damage [94, 96].

Previous pharmacological approaches to the therapy of stroke and other manifestations of cerebral ischaemia have emphasized the protection provided by barbiturates in experimental focal ischaemia and the possible improved outcome with calcium entry blockers [96, 100]. Calcium entry controls the responses of all excitable cells, so that calcium entry blockers act on the heart and vasculature and provide a rather non-specific approach. A pharmacological approach involving the membrane receptors on the vulnerable neurons offers great advantages in terms of specificity of action. Antagonists at the NMDA-preferring receptor offer a major novel therapeutic approach in the prevention of cerebral ischaemia and the acute therapy of stroke.

**Chronic degenerative disorders**

The mechanisms responsible for the various patterns of neuronal loss found in chronic degenerative disorders are not understood, but the possibility that excitotoxic mechanisms are involved has aroused great interest. I shall discuss briefly four such disorders: Alzheimer’s disease, Huntington’s chorea, olivopontocerebellar atrophy and Parkinson’s disease.

In senile dementia of the Alzheimer type there is a diffuse loss of neurons in the cortex [101]. Ascending neuronal systems are also affected; in particular there is loss of cholinergic neurons which project from the nucleus basalis to the frontal and temporal cortex [102], and of noradrenergic fibres which ascend from the locus coeruleus [103]. There is no specific evidence for an excitotoxic mechanism as an aetiopathological factor in these pathological changes. However, measurements of the quinolinic acid content in rat brain regions at different ages [104] show an increase with age, such that in aged rats (30 months) there is a notable scatter in cortical quinolinic acid content with some rats having concentrations comparable with those shown to induce pathological change in neuronal cultures [105].

Cholinergic neurons in the nucleus basalis region in the rat are preferentially vulnerable (in comparison with GABA-ergic and cholinergic neurons). Thus activity of glutamate decarboxylase and of choline acetyltransferase is markedly reduced whereas tyrosine hydroxylase is normal in post-mortem striatum. Intrastriatal injection of kainate or glutamate gives rise to a loss of intrinsic neurons and a similar pattern of changes in enzymic activity [111–113]. These observations gave rise to the excitotoxic hypothesis of Huntington’s disease [112, 114, 115]. It is suggested that the pathological changes in the striatum arise from excessive excitatory transmission, and that the cortical glutamatergic input plays some part in this. However, there is also evidence from animal experiments that glutamate injected in the striatum or intracerebroventricularly [116] induces dyskinesias and impairs learning and memory. Thus the acute early features of Huntington’s chorea could be a consequence of relatively enhanced excitatory activity in the striatum. The amino acid content of cerebrospinal fluid in Huntington’s patients is abnormal, suggesting that amino acid transport mechanisms may be primarily altered [117]. Impaired re-uptake of glutamate has been proposed as a possible primary defect [118]. Studies of local glucose utilization (employing computed tomographic scanning and [18F]fluorodeoxyglucose) reveal a reduced metabolic rate in the striatum early in Huntington’s disease [119], which appears to contradict the hypothesis of enhanced excitatory activity.

In olivopontocerebellar atrophy and in some related multiple system atrophies there is progressive degeneration in the brain stem, cerebellum, spinal cord and substantia nigra, producing ataxia and signs of Parkinsonism. A deficiency in glutamate dehydrogenase activity in leucocytes and fibroblasts occurs in a subgroup of such patients with adult-onset and recessive inheritance [120, 121]. In these patients glutamate content is increased and 2-ketoglutarate reduced in fasting plasma, and an oral glutamate load produces a plasma peak concentration three times greater
than in controls [122]. It appears that the recessive disorder is associated with deficiency or absence of a particular isoenzyme of glutamate dehydrogenase, leading to impaired metabolism of glutamate. A consequent increase in glutamate concentration in various central sites could contribute to the development of focal pathology, by an excitotoxic mechanism. This hypothesis, however, does not offer any obvious explanation for the selective involvement of the cerebellum and brain stem.

The mechanism leading to a selective loss of nigrostriatal neurons in Parkinsonism is not known. However, there is evidence for an aspartergic excitatory pathway from striatum to nigra [123]. There are NMDA receptors on nigral neurons, and focal injections of 2APH into the pars compacta nigra have behavioural effects [124], indicating that this system is functionally significant. An involvement of this excitatory system might be part of the explanation for the remarkable selectivity of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) for the dopaminergic neurons of the pars compacta, in preference to other dopaminergic neurons [125-127].

Therapeutic trials of excitatory amino acid antagonists in chronic degenerative disorders would naturally have two objectives. The short term one would be to assess the possible contribution of enhanced excitatory activity to the signs and symptoms of the disorder, and could potentially be evaluated with a single intravenous injection. The long term objective is to assess the contribution of excitotoxic mechanisms to the progressive features of the illness. This requires sustained, possibly life-long, administration of the antagonist. It is, of course, not necessary that an excitotoxic mechanism is part of the primary pathological process for therapeutic success. A protective action of antagonists is to be expected if an excitotoxic mechanism provides a link in the chain between the primary aetiological event and the eventual neuronal loss.

Effects of excitatory amino acid antagonists on psychic function

In the hippocampus brief periods of high frequency stimulation of excitatory inputs to granule or pyramidal neurons give rise to sustained alterations in the firing pattern of the postsynaptic neurons [128, 129].

This phenomenon of long term potentiation can be blocked by local application of 2APB [130] or by NMDA antagonists such as 2APV and phencyclidine [21, 131]. The possibility that long term potentiation provides the physiological basis for engram formation suggests that effects of amino acid antagonists on learning and memory require careful evaluation.

It has been proposed that impaired excitatory transmission may contribute to the symptoms of psychosis, particularly schizophrenia [132]. Cerebrospinal fluid glutamate concentration has been reported as reduced in schizophrenia [133]. Kainic acid binding is apparently enhanced in the prefrontal cortex in schizophrenia [134]. Furthermore the psychotomimetic action of phencyclidine may be related to its antagonist effect at NMDA receptors [135]. Although a link between impaired excitatory amino acid transmission and psychosis is at present largely speculative, close attention to possible effects of antagonists on the sensorium and on behaviour is indicated.

Experimental and clinical prospects

The utility of excitatory amino acid antagonists as tools for investigating the role of different types of excitatory transmission in normal function is clearly established. In this context the immediate need is for more selective and potent antagonists at the quisqualate and the kainate receptor.

The value of the antagonists as tools for investigating neuronal mechanisms involved in epilepsy, tremor and spasticity and in excitotoxic and ischaemic pathology is also clearly established. In such experimental studies focal intracerebral injections are possible and often desirable. Although several of the NMDA antagonists are extremely potent given intracerebroventricularly, their potency after systemic injection is low, owing to relatively poor penetration of the blood-brain barrier. Furthermore the most potent compound, 2APH, is inactive by the oral route (in rodents).

Thus the presently available antagonists are suitable at best for acute therapeutic experiments, to establish for example the possibility of applications in stroke and in Huntington's chorea. They are clearly not suitable for chronic therapeutic trials.

What is needed is either novel compounds with comparable antagonist activity that are lipid soluble (which would be active at doses comparable with those of benzodiazepines) or prodrugs yielding the known antagonists intracerebrally. This is an urgent task for pharmaceutical chemists because the therapeutic potential of antagonists of this type is evident. Present therapies for the neurological disorders under consideration are woefully inadequate. Effective treatments would transform the practice of neurology and the lives of the patients.
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Excitatory amino acid antagonists


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