Exogenous excitatory amino acid (EAA) agonists (glutamate or aspartate) have convulsant action when administered focally into cortical or subcortical structures [1]. Likewise, more potent agonists acting selectively at the N-methyl-D-aspartate (NMDA) or at the a-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)/kainate (KA) receptors have both excitotoxic and proconvulsant/convulsant activity when administered systemically to rodents or primates (see [2-3]). Recently, a selective agonist acting at the metabotropic receptor, 1-amino-cyclopentane-trans-1,3-dicarboxylic acid (t-ACPD) has also been shown to induce convulsions in rats when administered focally in the hippocampus (see Schoepf, this colloquium). Conversely, antagonists acting at both NMDA receptors (competitive antagonists, non-competitive channel-site antagonists, non-competitive glycine site antagonists) and at non-NMDA (AMPA/KA) receptors have consistently exhibited anticonvulsant activity in a wide range of experimental seizure models (see [4]). Potent, selective antagonists for the metabotropic glutamate receptor are still lacking. Convolusions induced by t-ACPD can, however, be blocked by 1-2-amino-3-phosphonopropionic acid (AP3), known to act as an antagonist at the metabotropic receptor (see Schoepf, this colloquium).

The proconvulsant activity of EAA agonists and anticonvulsant activity of EAA antagonists is consistent with an up-regulated EAA transmitter system being one of the causative agents for enhanced seizure susceptibility in animal and human epilepsy. Numerous studies have been undertaken to establish a link between seizure susceptibility in animals or man and abnormalities in excitatory (or inhibitory) amino acid transmitter systems. On the whole, it has been difficult to correlate seizure susceptibility with any definitive alterations in endogenous, regional transmitter levels, turnover or release, or with abnormalities in regional excitatory and inhibitory receptor densities or affinities (see [3, 5, 6]). However, recent studies (conducted during and following surgery for refractory epilepsy), summarized in Table 1, point to a functional up-regulation of EAA transmission in brains of patients with partial (focal) seizures (temporal lobe epilepsy or epilepsy with frontal cortical foci) which resembles changes observed in certain chronic seizure models such as amygdala-kindled seizures. Whereas the altered hippocampal EAA binding pattern in chronic seizure models [7-11] or in human temporal lobectomy tissue [12-14] does not argue in favour of an overall up-regulation of the density of EAA receptors in epileptic tissue, there is accumulating evidence [15-18] of enhanced activity of NMDA or metabotropic receptors in limbic structures of chronically epileptic animals. The mechanism for such a functional upregulation (e.g. altered subunit composition, receptor phos-
Excitatory Amino Acids

Table I
Altered excitatory amino acid properties in human partial epilepsy and in amygdala-kindled rats

<table>
<thead>
<tr>
<th>Partial epilepsy (humans)</th>
<th>Amygdala-kindled rats</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vivo release</strong></td>
<td></td>
</tr>
<tr>
<td>Enhanced Asp and Glu release in focus during ictal bursts [19–22]</td>
<td>Enhanced spontaneous Glu release in hippocampus [23, 24]</td>
</tr>
<tr>
<td><strong>In vitro release</strong></td>
<td></td>
</tr>
<tr>
<td>Functional up-regulation of NMDA receptors in cortical focus (agonist-induced Ca²⁺ influx enhanced in deeper cortical layers) [15]</td>
<td>Functional up-regulation of NMDA receptors in hippocampus (agonist-induced Ca²⁺ influx enhanced in Stratum radiatum) [16]</td>
</tr>
<tr>
<td>Altered NMDA-, KA- and AMP-binding in anterior temporal lobectomy specimens [12–14]</td>
<td>Unchanged or altered hippocampal binding of NMDA, KA and AMPA [7–11]</td>
</tr>
</tbody>
</table>

Phosphorylation, modulatory interaction) remains speculative. When extracellular EAA levels are determined by in vivo microdialysis (dialysis probes implanted in combination with routine electroencephalography (EEG) depth-electrodes) in patients with partial epilepsy, during either surgery or chronic EEG-monitoring for localization of epileptic focus, there is a sharp and transient increase in the focal extracellular levels of aspartate and glutamate concomitant with the epileptic discharge [19–22]. It has been more difficult to establish a link between increased extracellular levels of EAA and the onset of seizure activity in experimental animals. Many studies have reported no change in extracellular aspartate and glutamate levels during different types of experimental seizures, even in the presence of glutamate-uptake inhibitors (see [3]). There is, however, evidence both in vivo and in vitro for enhanced hippocampal and cortical EAA release in kindled rats [23–26].

Anticonvulsant properties of competitive NMDA-antagonists

Potent, selective antagonists that act competitively at the NMDA-recognition site have been available for more than 10 years, and their anticonvulsant activity has been established convincingly in a wide range of experimental seizure models (see [4]). The anticonvulsant properties of the competitive NMDA antagonists are summarized in Table 2.

NMDA-antagonists are effective anticonvulsants against limbic seizures (e.g. pilocarpine-induced) and against generalized clonic/tonic seizures. The antagonists are less potent against spontaneous 6–8 Hz spike-and-wave seizures in rodents, a syndrome with similar pharmacological response (inhibited by ethosuximide; not protected by phenytoin; worsened by GABAmimetic drugs), similar corticothalamic EEG-abnormalities and similar behavioural correlates to human absence seizures [27]. Amygdala-kindled seizures in rats are considered a model of partial seizures in man. Complex partial seizures represent a large portion of epilepsy cases that do not respond to clinically available antiepileptic drugs, and are therefore the initial clinical target in ‘add-on’ trials of novel anticonvulsant drugs. Although the epileptogenic kindling process in rats is effectively inhibited by competitive NMDA antagonists, the fully amygdala-kindled seizures are relatively resistant to protection by competitive NMDA antagonists [27–32], with anticonvulsant efficacies of the antagonists being
Anticonvulsant activity of non-competitive NMDA antagonists

MK-801 is the most potent of the antagonists acting at the channel site of the NMDA receptor. MK-801 (0.01–0.03 mg kg\(^{-1}\) day\(^{-1}\)) and another non-competitive NMDA-antagonist, dextromethorphan (2 mg kg\(^{-1}\) day\(^{-1}\)), have been tested against partial epilepsy in man [34, 35], but found to be ineffective at the doses tested. At 5–10-fold higher doses MK-801 is fully protective in a wide range of experimental seizure models. However these doses produce severe behavioural side-effects and also a marked two–threefold activation of cerebral metabolism (cerebral blood flow and glucose utilization) in limbic structures (see [4]), making the clinical potential for this group of drugs doubtful. Recently, a structural analogue of MK-801, (±)-5-aminocarbonyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (ADCI), has been described [36] that has anticonvulsant activity in many seizure models and a considerably improved therapeutic index (compared with MK-801).

Antagonists acting at the glycine site of the NMDA receptor also have anticonvulsant activity (see [4]). Antagonists acting selectively at this site include chlorine- and thio-derivatives of kynurenic acid. Most currently available drugs within this group have a very short time course of action and have to be administered intracerebroventricularly (i.c.v.) to exhibit anticonvulsant action. A pyrrolidone, 3-amino-1-hydroxy-2-pyrrolidone (HA-966) has weak antagonist action at the glycine site of the NMDA receptor, whereas a methyl derivative of HA-966, L687414, is a much more potent glycine antagonist. L687414 protects against sound-induced seizures in DBA/2 mice [37] and against photically-induced seizures in baboons following systemic administration [38]. A partial agonist at the glycine site, 1-amino-cyclopropanecarboxylic acid (ACPC) is also anticonvulsant against NMDA-induced seizures [39] and against sound-induced seizures in DBA/2 mice. The anticonvulsant efficacy of ACPC against clonic seizures in DBA/2 mice is potentiated eightfold by a subprotective dose of the competitive NMDA-antagonist, \(\alpha\)CPPene (A. Chapman, unpublished work).

Anticonvulsant properties of non-NMDA antagonists

Anticonvulsant activity has previously been associated with AMPA/KA preferring antagonists with relatively low receptor selectivity (see [4]). The recent availability of the potent, selective antagonists for the AMPA/KA receptor, 2,3-dihydroxy-6-nitro-
Reversal by aniracetam of the anticonvulsant effect of GYKI 52466 against sound-induced clonic seizures in audiogenic DBA/2 mice

GYKI 52466 (6–60 μmol/kg) administered intraperitoneally (i.p.) to groups of mice (n=8–10 per dose) 15 min before testing for seizure-response provided a dose-dependent protection against sound-induced seizures. The complete protection provided by 60 μmol/kg GYKI 52466 was reversed in a dose-dependent fashion when the mice were pretreated with 12.5–100 nmol (i.c.v. administration) aniracetam 15 min before the GYKI 52466 (60 μmol/kg, i.p.) administration.

7-sulphamoyl-benzo(F)-quinoxaline (NBQX) and 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 52466) has permitted a definite identification of non-NMDA antagonists as anticonvulsant drugs. GYKI 52466 and NBQX protect against AMPA-induced seizures, against sound-induced seizures in audiogenic mice and rats, and against photically-induced seizures in baboons [40, 41], and against amygdala-kindled seizures (N. Durmuller, unpublished work) with approximately similar ED₅₀ values (15–30 μmol/kg, i.p., 15–30 min) observed in all of the seizure models. The anticonvulsant activity of the non-NMDA antagonists against fully kindled seizures contrasts with the relatively weak anticonvulsant activity of the NMDA antagonists in the same seizure model and may permit cautious optimism regarding the therapeutic potential of this class of EAA antagonists against partial seizures.

Recently, the nootropic drug, aniracetam (1-p-anisoyl-2-pyrrolidinone) has been shown to potentiate the AMPA response induced in *Xenopus* oocytes [42]. The enhanced response has been suggested to be due to an aniracetam-induced reduced rate of desensitization of the AMPA/KA receptor [43]. We have recently shown that aniracetam pre-treatment (12.5–100 nmol administered i.c.v. 15 min before the administration of 60 μmol/kg i.p. GYKI 52466) completely reverses the anticonvulsant protection provided by GYKI 52466 in a dose-dependent fashion (Figure 1). Aniracetam by itself caused no behavioural or proconvulsant action at these doses. The aniracetam-induced reversal of the anticonvulsant effect was specific for the AMPA/KA antagonists GYM 52466 and, much less potently, NBQX. The anticonvulsant activity of the competitive NMDA antagonist, δ(−)CPPene, was not modified by pretreatment with 12.5–100 nmol aniracetam (A. Chapman, unpublished work).


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