Pathogenesis of epilepsy: the role of excitatory amino acids

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BACKGROUND The clinical and electroencephalographic features of seizures in children differ considerably from those in adults. Recently there has been an increased interest in the biological basis for the unique clinical and electroencephalographic features of childhood epilepsy. It is now clear that studies in adult animals can not be extrapolated to the immature animal.

KEY POINTS Excitatory amino acids bind to several types of receptors in synapses in the brain. Overexcitation of these receptors causes seizures in experimental animals, and experimental agents can block these receptors. However, we will have to be cautious about developing these agents as antiepileptic drugs, since excitatory amino acids and their receptors are involved in brain plasticity and learning in children.

INDEX TERMS: EPILEPSY; RECEPTORS; NEUROTRANSMITTER; AMINO ACIDS
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THE CLINICAL and electroencephalographic features of seizures in children differ considerably from those in adults. Disorders such as infantile spasms, Lennox-Gastaut syndrome, and Landau-Kleffner syndrome occur only in childhood and frequently are treated with drugs rarely used in adults. The biological basis for the unique clinical characteristics and prognosis of childhood epilepsy is poorly understood. Investigators are now using a variety of animal models to study the differences in epileptogenesis between the immature and the mature brain. It is now clear that studies in adult animals cannot be extrapolated to the immature animal.

An in-depth discussion of the developmental aspects of epileptogenesis would be beyond the scope of this paper. The reader is referred to a recent review by Moshé and Cornblath[1] for a detailed discussion of this topic. Rather, because of the immense interest in the relationship between excitatory amino acids (EAAs) and epilepsy (and in experimental drugs that block the action of EAAs), we will review the recent advances of the role of EAAs in epileptogenesis in the developing brain.

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WHAT EAAs DO

EAAs, principally L-glutamate, act as neurotransmitters at numerous synapses in the brain in cortical pathways involved in sensation and motor function.[2,3] EAAs complement the inhibitory neurotransmitter gamma-aminobutyric acid. Axon terminals containing EAAs connect predominantly to spines of the dendritic branches, while axon terminals containing gamma-aminobutyric acid connect to the neuronal cell body and proximal axon. The balance between excitatory and inhibitory neurotransmitters determines whether individual neurons will depolarize.

Glutamate and related EAAs are released from presynaptic neuronal terminals in a calcium-dependent process when the presynaptic neuron depolarizes. Once released into the synaptic cleft, glutamate can depolarize the postsynaptic neuronal membrane by binding to one or more of the EAA receptors (*Figure 1*). Presynaptic reuptake mechanisms remove amino acids from the synaptic cleft.

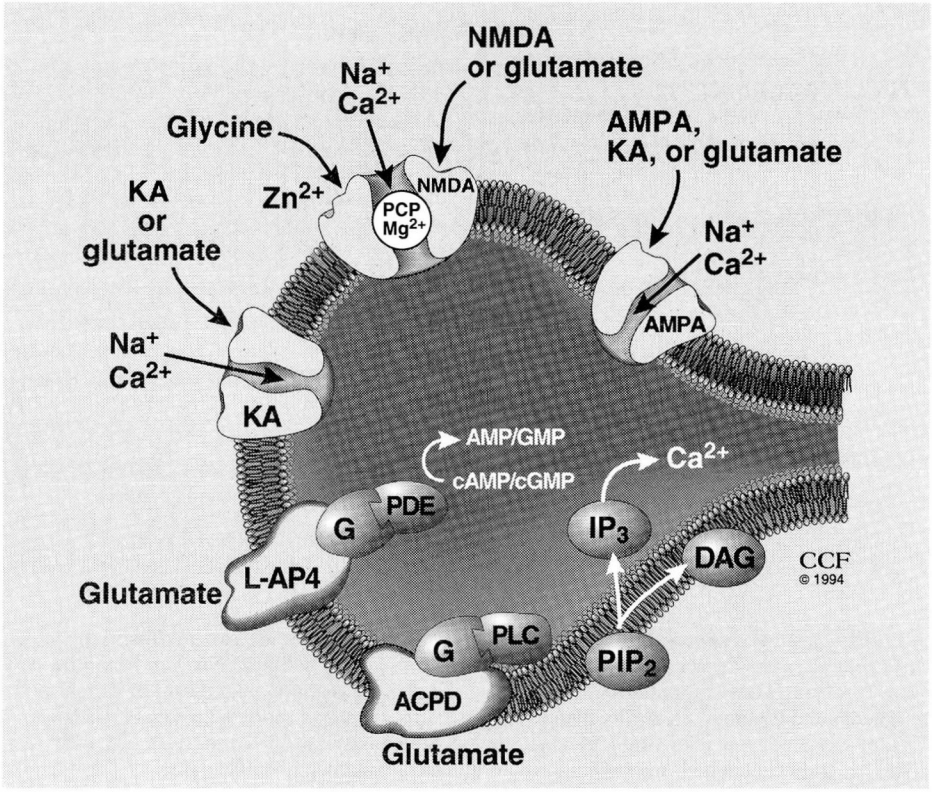

FIGURE 1. Types of glutamate receptors. The three ionotropic receptors (NMDA [N-methyl-D-aspartate], AMPA [amino-3-hydroxy-5-methyl-4-isoxazol propionic acid], and KA [kainic acid] receptors) and two metabotropic receptors (L-AP4 [L-2-amino-4-phosphonopropinonic acid] and ACPD [aminocyclopentyl dicarboxylic acid]) are shown. Glutamate binding occurs at all of the receptor types. The NMDA receptor binds to NMDA or glutamate, the AMPA receptor binds to AMPA, KA, or glutamate, and the KA receptor binds to KA and glutamate. The NMDA receptor also has binding sites for glycine. In addition, the channel is blocked by magnesium (Mg^{2+}) and PCP (phencyclidine). Upon opening of the ionotropic channels, sodium and calcium ions enter the cell. The metabotropic receptors are coupled via G proteins to intracellular enzymes, phospholipase C (PLC) for the ACPD receptor, and phosphodiesterase (PDE) for the L-AP4 receptor. PLC catalyzes the production of inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG) from phosphatidylinositol 4,5-bisphosphate (PIP_2).

EAAs are widely distributed in both developing and mature brains and are distinguishable by their biochemical, electrophysiologic, and pharmacologic criteria.[4–5] The functional diversity of EAAs is reflected by the presence of two distinct groups of glutamate receptors: ionotropic and metabotropic.[6–8] The ionotropic receptors contain integral cation-specific ion channels and are further divided into the following major groups: N-methyl-D-aspartate (NMDA) receptors, amino-3-hydroxy-5-methyl-4-isoxazol propionic acid (AMPA) receptors, and kainic acid receptors. The functionally and pharmacologically distinct metabotropic glutamate receptors are coupled to G protein.[7,9–11] Both the ionotropic[6,12] and metabotropic[13] receptors have been reported to play a role in epilepsy.

The AMPA-receptor channel normally plays an important role in transmitting fast, excitatory postsynaptic potentials and transmits much of the excitatory activity in the brain. However, the NMDA channel has voltage-dependent properties. The amount of current passed by the NMDA channel is reduced when the cell membrane is hyperpolarized beyond −35 mV, and is quite small at the resting potential of the cell, approximately −70 mV.[14,15]

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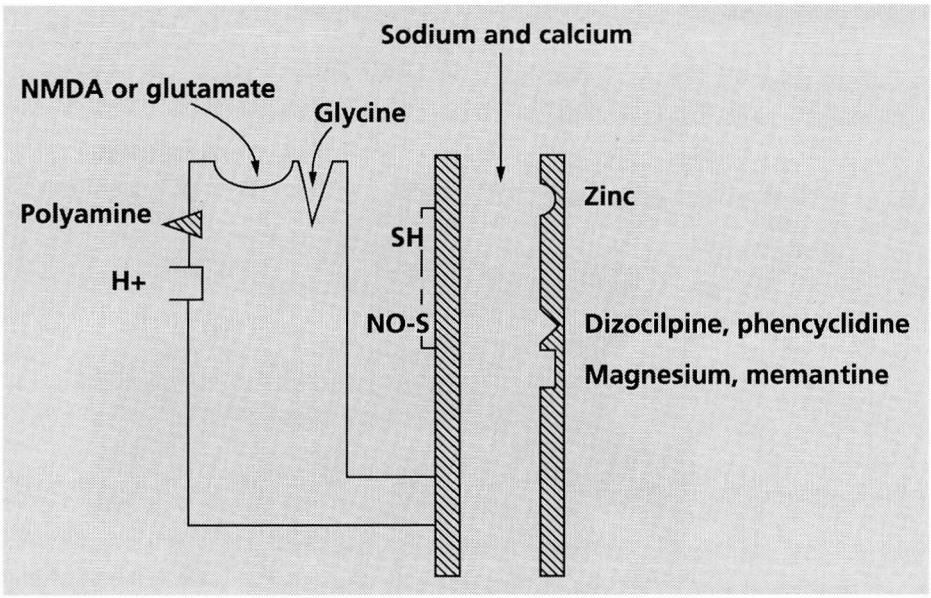

FIGURE 2. NMDA receptor. Glycine acts as a coagonist. There are several modulatory sites that alter the degree of channel opening and subsequent sodium (Na^+) and calcium (Ca^{2+}) influx. These modulatory sites include the channel, where magnesium or drugs such as phencyclidine bind. There are also pH, polyamine, zinc, and redox sites where modification of channel properties can occur. The redox site consists of one or more thiol (sulfhydryl [SH]) groups, which may react with an oxidized congener of nitric oxide.

The NMDA recognition site is coupled to a cation channel permeable to both calcium and sodium ions. A glycine modulatory site is closely associated with the NMDA receptor; glycine is required for channel activation, and enhances NMDA responses. Magnesium ions block the channel in a voltage-dependent manner.[16,17] NMDA-receptor-channel activation requires both NMDA and glycine receptor activation and concomitant membrane depolarization. The excitatory postsynaptic potentials mediated by AMPA receptors need to reach a threshold of activity before the NMDA channel can open. This suggests that the NMDA-receptor-channel complex is ordinarily reserved for "special" activities, including long-term potentiation following repetitive electrical stimulation, activity-dependent neuronal plasticity, encoding of memories, and epileptogenesis following chemical or electrical stimulation.

NMDA and non-NMDA receptors are often found at the same synapse.[2] Where both receptors are found, the synaptic potential has two components: fast (via non-NMDA receptors) and slow (via NMDA receptors).[14,18] The NMDA component of the response has a slow rise time and a prolonged effect that can last 500 msec.[18,19] After the initial activation, the prolonged effect can be shortened by magnesium, which blocks the ion flow through the NMDA channels. However, aminophosphonovalerate (a glutamate blocker) cannot block the prolonged effect.[20] Daw et al[2] conclude that glutamate activation of NMDA channels results in prolonged effects, and that NMDA and its antagonists tend to affect processes that have a low frequency.

Studies suggest that the physiologic activity of the NMDA-receptor-channel complex is enhanced in the developing brain as compared with the adult brain. The NMDA-receptor complex appears to be involved in activity-dependent plasticity.

ROLE OF EAAs IN EPILEPSY

Each of the receptor subtypes moderates normal physiologic excitatory responses, but under conditions of extreme receptor activation, agonists for these receptors are capable of initiating a cascade of events resulting in neuronal death in both adult[21–23] and immature[4,5,24–29] brains. Investigators have suggested that prolonged seizures cause damage by releasing an "endogenous excitotoxin," presumably an EAA, in concentrations that cause irreversible brain damage.[21,23,30–32]

EEA blockers as antiepileptic drugs

For this reason, many investigators have examined the role of EAA-receptor antagonists in epilepsy. The NMDA receptor complex can be blocked pharmacologically in at least three ways: competitive NMDA antagonists such as CPP (3-[2-carboxypiperazin-4-yl] propyl-1-phosphoric acid) compete for binding at the NMDA-recognition site; competitive glycine receptor antagonists such as HA-966 (3-amino-1-hydroxypyrrolid-2-one)

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block the glycine site and reduce NMDA-mediated responses; and noncompetitive NMDA-receptor antagonists such as MK-801 and dissociative anesthetics bind within the ionophore to the phencyclidine (PCP) receptor and prevent ion fluxes (*Figure 2*).[3,4] MK-801 has probably received the most attention.[33–36] Stafstrom and colleagues[37] found that MK-801 pretreatment reduces kainic acid-induced spontaneous seizures in prepubescent rats. MK-801 has also been found to inhibit kindling in developing rats.[38]

DEVELOPMENTAL ASPECTS OF EAA RECEPTORS

Considerable data now demonstrate that kainic acid receptors and NMDA receptors are present at birth but increase dramatically during the first few weeks of life. Miller and colleagues[39] studied the ontogeny of kainic acid-binding sites in rat forebrain using in vitro receptor autoradiography. Specific binding was detectable in the hippocampus by 1 day of age. In the CA3 region, binding increased progressively with age, peaking at 21 days of age. Insel et al[40] also found that specific binding to NMDA and quisqualic acid receptors could be detected at 1 day of age in the hippocampus and striatum, with the adult pattern of binding to NMDA receptors emerging by 14 days of age with high densities of binding in the CA1 region and the dentate gyrus.

There is also increasing evidence that EAAs may have age-related effects.[4,26,27,29,41–44] However, the long-term adverse effects of EAAs are highly dependent on the receptor stimulated. For example, although kainic acid administered to immature animals causes severe seizures and is associated with a high mortality rate, surviving animals have fewer pathologic and behavioral abnormalities than do mature animals receiving the drug.[42–45] Other EAAs appear to have greater neurotoxicity in the immature brain than in the mature brain.[4,26,27,46,47] McDonald and colleagues[46] found that injection of NMDA into the corpus striatum caused more neurotoxicity in 7-day-old rats than in adults. NMDA toxicity in vivo transiently peaks near 7 days of age in rats; the severity of the brain injury resulting from direct intrastriatal infusion of equimolar NMDA was approximately 60 times greater at this age than in adults. The severity of brain injury produced by infusion of NMDA at age 1, 14, 21, and 28 days was comparable to that in adults; intermediate levels of injury were present at 4 and 10 days of age and peak levels are present at age 7 days.

Likewise, AMPA and quisqualic acid, when given by a single injection, have greater toxicity in immature than in mature animals.[26,27] Kainic acid-induced status epilepticus results in long-term deficits in learning, memory, and behavior and susceptibility to seizures in mature rats but has no discernible effect in rats 20 days old or younger.[42–44,48–51]

In summary, each EAA-receptor subtype possess a unique developmental neurotoxic profile. In adult rats, kainic acid is more toxic than NMDA, which is more toxic than quisqualic acid; in 7-day-old rats, NMDA is more toxic than quisqualic acid, which is more toxic than kainic acid.

The behavioral and electroencephalographic effects of EAAs also are age-dependent. Holmes and colleagues[42,48,50,51] found that kainic acid produced different patterns of electroencephalographic and behavioral seizures in 5- to 10-day-old rats compared with older rats. Similarly, Thurber and colleagues[52] found that the behavioral manifestations of seizures produced by quisqualic acid vary as a function of age: young rats demonstrated rigidity and immobility followed by circling activity and intermittent forelimb clonus, while 60-day-old animals had severe, wild running followed by generalized clonic seizures.[52] Neocortical electroencephalographic ictal discharges occurred more prominently in the younger animals; amygdala ictal discharges were more prominent in the older animals.

These age-related differences may relate to differences in the number, distribution, density, or affinity of the EAA receptors.[39,40,53–56] Insel et al[40] found that in 21-day-old rats, the number of quisqualic acid receptors in the neocortex was 50% higher than in adult neocortex, suggesting that the immature neocortex could be especially vulnerable to quisqualic acid-induced seizures. In immature rats, kainic acid receptors in the CA3 region increase sharply during the third week of life, whereas kainic acid receptors in the inner layers of neocortex are transiently overexpressed at this age and thereafter gradually decline to adult levels.[39,57]

When we evaluate the effects of EAAs on the developing brain, it is therefore critical that we closely examine the dosage and method of administration. McDonald et al[46] gave microinjections of a fixed dose of AMPA into the striatum of rats and found that the resulting brain injury was most severe between the ages of 5 and 28 days; the peak sensitiv-

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ity occurred near the age of 10 days. Injection of quisqualic acid produced a developmental pattern of striatal susceptibility similar to that of AMPA, although quisqualic acid was a considerably less potent neurotoxin. However, when Holmes et al[58] administered quisqualic acid through an intraventricular catheter over a period of 1 week, brain damage was no greater in immature than in mature animals.

BRAIN PLASTICITY

"Plasticity" refers to certain adjustments of the nervous system to changes in the internal or external milieu.[59] The term is usually limited to adaptive adjustments, ie, adjustments that tend to return the system to its former state or enable the system to function and the organism to survive under the changed conditions.[60]

There is a general consensus that brain plasticity is greater in children than in adults; ie, the immature brain has a greater opportunity to adjust to environmental changes than does the mature brain.[61,62] Numerous examples of this phenomenon exist in the clinical and experimental literature. Lassonde and colleagues,[60,63] in a series of studies of children and adults who either had congenital absence of the corpus callosum (callosal agenesis) or underwent surgical section of the callosum, found that the age at which the lesion occurred determined whether the disconnection syndrome would develop. Two children who underwent callosotomy in childhood performed as well as their normal peers, while the three others who had the operation in late adolescence or in adulthood showed typical disconnection deficits. The patients with callosal agenesis outperformed all groups. The authors speculated that the remarkable plasticity seen in patients with callosal agenesis or early callosotomy was related to a critical period in development coinciding with a phase of synaptic overproduction and redundancy that would favor the reinforcement of alternative neural pathways. The compensatory mechanisms appeared to become more limited in late adolescence, when synaptic distribution presumably assumed adult patterns.[62]

Children who develop hemiplegia during the first few years of life usually still learn to talk, even if the lesion involves the dominant hemisphere. In addition, children with hemiplegia that develops early can "reorganize" their central motor pathways. Farmer et al[64] found that children with hemiplegic cerebral palsy had a common synaptic input to both hands from abnormally branched presynaptic axons. Furthermore, results of electromagnetic brain stimulation, cutaneomuscular testing, and tendon-reflex testing suggested that these common inputs were provided by abnormally branched corticospinal-tract fibers originating in the undamaged motor cortex.

The brain is most plastic when it is developing.[61] In humans, synaptogenesis in the cerebral cortex takes place before birth and during early infancy. The maximum synaptic density, absolute number of synapses, and number of synapses per neuron are reached by 1 year of age. Subsequently, synapses are progressively eliminated, most rapidly during the preschool years.[62,65] Huttenlocher[62,65] speculates that this overproduction of synapses imparts plasticity to the brain of young children.

Although greatest in the immature brain, plasticity can occur throughout life. For example, experimental models of temporal lobe epilepsy have demonstrated growth of mossy fibers in the hippocampus following prolonged or recurrent seizures.[66–68]

Maximum brain growth ends by age 5 years; thereafter, patients with lesions in the central nervous system are less likely to recover. Children with strabismus provide an important example of this principle.[65] Strabismic amblyopia, if detected early, is invariably treatable. Children younger than 6 years have normal vision; adults with strabismus invariably develop uncorrectable monocular visual loss.[69]

Role of EAAs in brain plasticity and learning

Besides being neurotransmitters, EAAs in the developing brain are involved in plasticity and excitotoxicity.[70] As noted above, EAA receptors, particularly NMDA and quisqualic acid receptors, are transiently more numerous early in life. This transient increase is presumably beneficial to the immature brain because physiological activation of the EAA system plays a critical role in plasticity of early learning and morphogenesis.

Considerable data demonstrate that EAAs participate in synaptic plasticity of the central nervous system.[2,71–73] Much of this evidence is based on the role of NMDA receptors on long-term potentiation at the hippocampal level, and of quisqualic acid receptors and kainic acid receptors in the expression of long-term potentiation. This suggests that EAA systems may have an important role in learning and memory. This was illustrated in a study by Brooks et al,[74] who found that administration of NMDA to

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immature rats (17 and 35 days old) resulted in an increase in synaptic density and number within hours of injection.

Rauschecker et al[75] administered 2-amino-5-phosphono-valerate (APV, a competitive NMDA antagonist), and MK-801 (a noncompetitive NMDA antagonist) intracortically by means of implanted osmotic pumps in kittens, which were monocularly deprived for 1 to 2 weeks. The expected ocular dominance shift was prevented or reduced within a radius of 4 to 5 mm of the pump tip in the visual cortex. The authors concluded that NMDA antagonists interfere with cortical plasticity, although the mode of action remains ambiguous.

Gamma-L-glutamyl-L-aspartate (a pseudopeptide) selectively blocks clonic-tonic seizures induced by NMDA but has no significant action against seizures induced by kainic acid or quisqualic acid. On the basis of these findings and on biochemical studies, we can conclude that this drug is a competitive antagonist at NMDA receptors. When Ungerer et al[71] administered this drug to mice immediately after the mice learned a Y-maze avoidance task, it specifically blocked the spontaneous improvement in performance observed in control animals between the 1st and 24th hour after training, but had no effect on learning or retrieval processes or on short-term memory. Moreover, the drug had no effect on spatial recognition memory in an alternation task in which control animals did not exhibit any improvement in performance after training. Ungerer and colleagues[76] also found that the NMDA-receptor antagonist CPP had a similar effect.

Some evidence exists that drugs that affect the glycine site of the NMDA receptor complex may have less effect on learning than those that act at the ion channel. Chiamulera et al[77] found that intracerebroventricular administration of DL-2-amino-5-phosphonovaleroate (DL-AP7), CPP, and MK-801 resulted in impaired learning performance in a passive avoidance task in mice. However, the glycine antagonists kynurenic acid and 7-chlorokynurenic acid at high doses significantly failed to affect performance in the same model of learning.

This concern about the possible adverse effects of MK-801 and other NMDA-receptor antagonists have raised concern about their development as antiepileptic drugs.

SUMMARY

EAAs appear to have a major role in both the development and the propagation of seizures. However, since EAAs have an important role in learning and brain plasticity, it is important that future investigators study not only the antiepileptic and neuroprotective properties of EAA antagonists, but also their effects on learning, memory, and behavior.

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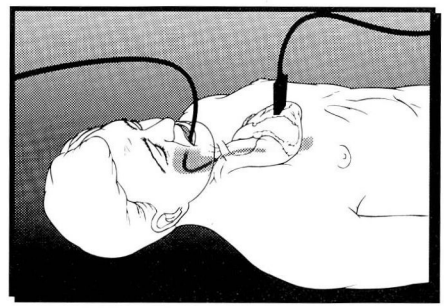

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