Glutamate and Epilepsy

Astrid G. Chapman

Department of Clinical Neuroscience, Institute of Psychiatry, London, England

ABSTRACT  Epileptic syndromes have very diverse primary causes, which may be genetic, developmental or acquired. In rodent models, altering glutamate receptor or glutamate transporter expression by knockout or knockdown procedures can induce or suppress epileptic seizures. Regardless of the primary cause, synthetically released glutamate acting on ionotropic and metabotropic receptors appears to play a major role in the initiation and spread of seizure activity. In rodent models of acquired epilepsy and in human temporal lobe epilepsy, there is evidence for enhanced functional efficacy of ionotropic N-methyl-D-aspartate (NMDA) and metabotropic (Group I) receptors. In animal models of epilepsy, antagonists acting at NMDA receptors or at Group I metabotropic receptors have potent anticonvulsant actions.  J. Nutr. 130: 1043S–1045S, 2000.

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Our understanding of the molecular basis of epilepsy is limited. Recently, a number of mutations underlying naturally occurring epileptic syndromes in animals and humans have been identified (involving mainly ion-channel defects: voltage-sensitive calcium-, potassium- or sodium-channels, but also sodium/hydrogen exchangers and nicotinic cholinergic receptors) (see Bate and Gardiner 1999, Burgess and Noebels 1999). To date, no mutations directly involving glutamatergic transmitter mechanisms have been identified (see Meldrum and Chapman 1999b). Nevertheless, seizures can be provoked in epileptic and nonepileptic animals and humans by a wide number of glutamatergic molecular mechanisms. Despite the varied primary pathology of epileptic seizures, the mechanisms involved in generating and spreading epileptic discharges converge on a common cellular pathology in which the excitatory glutamatergic system plays a key role. Compelling neurophysiologic, pharmacologic, biochemical and anatomical evidence has been accumulated over the last several decades firmly implicating ionotropic N-methyl-D-aspartate (NMDA), 2 and α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA)/kainate and metabotropic glutamate receptor-mediated mechanisms in epileptic seizures. Excitatory glutamatergic mechanisms are involved during both acute, transient, evoked seizures and long-term, adaptive cellular plasticity associated with epileptogenesis in chronic epilepsy models such as amygdala-kindled rats or rats with spontaneous, recurring seizures after an early episode of induced status epilepticus. This brief overview will list some of the key observations supporting such a link.

Ionotropic glutamate receptors

Convulsant and anticonvulsant action of ionotropic glutamatergic ligands. Glutamate (and aspartate or other excitatory endogenous compounds such as quinolinic or some sulfur-containing amino acids, as well as more potent selective agonists including NMDA, AMPA, kainate, ibotenic acid and domoic acid) can cause convulsions when administered focally or systemically to experimental animals. Glutamate exerts its excitatory action via ligand-gated ion channels (NMDA and non-NMDA receptors) to increase sodium and calcium conductance, and a myriad of reciprocal regulatory interactions exist between the activation of glutamatergic receptors and other transmitter systems, ion transport, gene activation and receptor modification. The flexibility and complexity of these interactions place glutamate-mediated transmission in a pivotal position for modulating the excitatory threshold of pathways involved in seizure generation.

Intracellular recordings in an epileptic focus during “spike discharges” or in a normal cortical neuron during generalized seizure activity reveal a so-called “paroxysmal depolarizing shift” associated with a burst of membrane spikes. This depolarization is analogous to a giant excitatory synaptic potential; its earliest component is due to activation of AMPA receptors and its later component to activation of NMDA receptors. The anticonvulsant properties of ionotropic glutamate receptor antagonists have been comprehensively reviewed recently (Chapman 1995, Meldrum 1995, Meldrum and Chapman 1999a, Rogawski 1992). All classes of NMDA receptor antagonists (competitive NMDA antagonists, channel site
antagonists, glycine site antagonists, polyamine site antagonists), as well as competitive and noncompetitive AMPA/kainate antagonists, display wide-spectrum anticonvulsant properties in acute and chronic animal epilepsy models, with varying degrees of behavioral side effects, ranging from minimal for some of the glycine site or competitive NMDA antagonists, to extensive for some of the high affinity open-channel NMDA antagonists. To date, limited “add-on trials” in epileptic patients with some of the NMDA antagonists [CPP, dizocilpine (MK-801) and dextromethorphan] have failed to demonstrate a therapeutic benefit of these antagonists against refractory complex partial epilepsy.

Although it has been shown that complete elimination of the NR1 subunit of the NMDA receptor is incompatible with survival in NR1 “knockout” mice (Forrest et al. 1994), the modest down-regulation of NMDA receptor subunits produced by antisense probes against the NMDA receptor NR1 subunit provides complete protection against sound-induced seizures in audiogenic mice (Chapman et al. 1996) or increases the latency to NMDA-induced seizures in Swiss mice (Zapata et al. 1997). Conversely, the overexpression (by focal injection of the appropriate vectors) of the kainate receptor, GluR6, in the hippocampus, or the AMPA receptor subunit, GluR1, in the deep prepiriform cortex, facilitates seizures (see Chapman 1998).

Changes in ionotropic glutamate receptors and glutamate transporters in epilepsy. The effect of various mutations of glutamatergic receptor subunits on seizure susceptibility can be studied by genetic manipulation in transgenic mice. Conversely, the effect of sustained or chronic seizures on the levels and characteristics of glutamatergic receptors and their corresponding mRNA expression can be studied in resected human epileptic tissue, or in genetic and other chronic animal epilepsy models. Examples of altered glutamate receptors brought about by genetic manipulation include the lethal global elimination of the NMDA receptor subunit NR1 mentioned above. Anatomically restricted (to the hippocampal CA1 region) NR1 knockouts, or combined gene disruption of NMDA-NR2A and NR2C, cause some impairment of plasticity or motor coordination, respectively, but no seizures (see Chapman 1998).

Transgenic mice with an editing-deficient AMPA receptor subunit, GluR2, display early onset of epilepsy. The GluR2 subunit confers an almost complete block of calcium conductance in homomeric or heteromeric AMPA receptors. Both the GluR2 receptor level and the RNA editing process are reduced significantly, and the corresponding AMPA-evoked calcium current in pyramidal neurons increased significantly in accordance with the enhanced seizure susceptibility in these mice (Brusa et al. 1995, see Chapman and Meldrum 1999). Neuronal (EAAC-1) and glial (GLT-1 and GLAST) glutamate transporters facilitate glutamate and aspartate reuptake after synaptic release. A down-regulation of glutamate transporters would be compatible with enhanced excitatory activity. Transgenic mice with GLT-1 knockout display spontaneous epileptic activity (Tanaka et al. 1997), and mice treated chronically with antisense probes to EAAC-1 (and to a much lesser extent with antisense probes to GLT-1 or GLAST) show reduced transporter levels and increased epileptic activity (Rothstein et al. 1996).

The reported changes in glutamate receptors and transporters subsequent to sustained or chronic epilepsy are less consistent and frequently transient in nature; some of these changes reflect patterns of cell loss. A functional enhancement of NMDA receptors is observed in amygdala-kindled rats and in resected tissue from humans with temporal lobe epilepsy (Mody 1998). The molecular alterations in the NMDA receptor responsible for this functional up-regulation are not clearly defined but probably involve altered phosphorylation.

Changes in the editing of the GluR2 AMPA subunit (which confers block of calcium conductance as mentioned above) have been reported in resected hippocampi from some patients with refractory epilepsy (Grigorenko et al. 1997). The mRNA levels of multiple AMPA subunits are also altered in kindled rats and in rats after sustained seizure activity evoked by kainate or pilocarpine (see Chapman and Meldrum 1999).

Metabotropic glutamate receptors

Convulsant and anticonvulsant action of metabotropic glutamatergic ligands. The classification of metabotropic glutamate receptors into three functional groups on the bases of their sequence homology, second messenger effectors and pharmacology is discussed elsewhere in this volume (Dingle and Conn 2000, Meldrum 2000). In brief, Group I comprises mGluR1 and mGluR5, which are linked via G-proteins to activation of phospholipase C. Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7, mGluR8) are both negatively linked to adenyl cyclase activation.

Until recently, the metabotropic ligands available have not had sufficient bioavailability, potency or selectivity to permit a confident assignment of physiologic and pharmacologic properties to the individual metabotropic receptor. A pattern is gradually emerging, however, concerning the proconvulsant and anticonvulsant actions of agonists and antagonists acting at the different groups of metabotropic receptors; this will be summarized below.

Activation of Group I mGluR enhances neuronal excitability by several mechanisms (blockade of accommodation to a steady current, potentiation of the effects of NMDA and AMPA and depolarization); accordingly, agonists acting on Group I receptors (e.g., 3,5-dihydroxyphenylglycine) have convulsant activity (Ghauri et al. 1996, Tizzano et al. 1995). Conversely, Group I antagonists, both those selective for mGluR1 (e.g., AIDA and LY 367385) and for mGlu5 (e.g., MPEP and SIB 1893) have anticonvulsant activity in several experimental seizure models (Chapman et al. 1999 and 2000, Thomsen et al. 1994).

Activation of Group II and Group III receptors by reasonably selective agonists appears to have mixed convulsant/ anticonvulsant action, although a prolonged anticonvulsant action seems to predominate (Tang et al. 1997, Tizzano et al. 1995). The proconvulsant or anticonvulsant action of antagonists acting at Group II and Group III metabotropic receptors fails to conform to any consistent, coherent pattern.

Changes in metabotropic glutamate receptors in epilepsy.

Knockout mutations of metabotropic receptors, in particular mGluR1 and mGluR5, in transgenic mice affect plasticity and long-term potentiation, but produce no overt seizure disorders (Bordi et al. 1997, Ferraguti et al. 1997, Lu et al. 1997).

Long-lasting functional enhancement of Group I mGluR activity (Akaike et al. 1992) and Group II and Group III metabotropic receptors (Neugebauer et al. 1997) has been reported in amygdala-kindled rats. There is a transient inverse alteration of Group I receptor levels (increased mGluR1; decreased mGluR5) in kindled rats (Akbar et al. 1996).

Glutamate release and epilepsy

Glutamate release during seizures in temporal lobe epilepsy patients. It has been possible to measure extracellular
glutamate levels via microdialysis probes implanted into the hippocampus in association with the implantation of electroencephalogram (EEG) electrodes in drug-refractory epileptic patients undergoing depth-electrode EEG recordings and telemetry evaluation of their seizure focus as preparation for an eventual surgical resection (Chapman 1997). During spontaneous seizures in ambulatory patients, there is a marked, bilateral, transient ictal increase in extracellular hippocampal glutamate levels, which is largest in the epileptic hemisphere (During and Spencer 1993, Wilson et al. 1996). Similar increases in glutamate release can be observed associated with evoked seizures during surgery in epileptic patients (Ronne-Engstöm et al. 1992).

**Glutamate release during seizures in rodents with chronic epilepsy.** Enhanced in vivo glutamate release is generally not observed during acute, evoked seizures in experimental animals. However, in chronic epilepsy models in rodents (amygdala-kindled rats, genetically epilepsy prone rats, rats with spontaneous, recurrent seizures after kainate-induced status epilepticus), there appears to be a consistent marked increase in glutamate release during seizures (see Chapman 1998).

**LITERATURE CITED**


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