

A Glutamatergic Model of ECT-Induced Memory Dysfunction

Eric Chamberlin, MD, and Guochuan E. Tsai, MD, PhD

Electroconvulsive therapy (ECT) is an efficacious treatment for a variety of neuropsychiatric conditions including major depression, mania, catatonia, Parkinson's disease, and neuroleptic malignant syndrome. However, ECT-induced memory dysfunction complicates the treatment and is a major concern for both patients and providers. We briefly review ECT-induced memory dysfunction and propose a glutamatergic model for it. (Articles examined were retrieved by a Medline search on the terms electroconvulsion and glutamate, with language limited to English.) Specifically, we hypothesize that ECT-induced memory dysfunction results from neuronal insults due to excessive release of excitatory amino acids and activation of their receptors, which produce cation and water flux and reversible oxidative stress. This model offers multiple testable hypotheses; exploring them may help to identify the risk factors for this significant side effect of ECT treatment and may thus yield effective agents for its prevention and treatment. (Harvard Rev Psychiatry 1998;5:307-17.)

Nearly all patients who undergo electroconvulsive therapy (ECT) have some form(s) of measurable memory dysfunction afterward.¹ This dysfunction can be divided into three phases—acute, subacute, and chronic—based on temporal occurrence² (see Table 1). Acute dysfunction is present when the patient awakens from anesthesia and usually resolves within several hours.³ The duration of the acute phase is increased by greater stimulus intensity, sine wave-form stimuli, and perhaps preexisting structural brain

abnormalities.³⁻⁵ The phase is characterized by severe anterograde⁶ and retrograde amnesia (the inability to learn and retain new information and to recall previously learned information, respectively). The retrograde amnesia is often severe enough to produce disorientation to person, place, and time.

The subacute phase typically begins after four to six treatments and persists for several days or weeks.^{1,2,7,8} It is cumulative, becoming more pronounced with increasing number of conventional ECT treatments, and manifests as a "temporal lobe" amnesia with anterograde and retrograde deficits.^{3,9} Clinically, the retrograde deficits appear to conform to Ribot's law, which states that organic amnesia is characterized by a temporal gradient, with better recall of information acquired early in life.¹⁰

Such memory impairment is almost always reversible, returning to normal within a few months after ECT. Memory performance at 6 months is often better than at the pretreatment depressed baseline, corresponding to resolution of the depression and the effect of this disorder on memory and cognition.^{7,8} However, patients commonly have a lacuna in memory immediately around the treatment, perhaps due to the effect of acute and subacute anterograde amnesia on memory consolidation. Some patients also have persistent memory deficit.^{8,10-13} Although rare, these apparently permanent deficits are of concern to both patients and practitioners.

Numerous attempts have been made to reduce these

From the Institute of Living, Hartford, Conn. (Dr. Chamberlin), the Laboratory of Molecular and Developmental Neuroscience, Massachusetts General Hospital, Charlestown, Mass. (Dr. Tsai), and the Department of Psychiatry, Harvard Medical School, Boston, Mass. (Dr. Tsai).

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Reprint requests: Guochuan Tsai, MD, PhD, Laboratory of Molecular and Developmental Neuroscience, Department of Psychiatry, MGH-CNY, Room 2504, 149 13th St., Charlestown, MA 02129.

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TABLE 1. Types of ECT-Induced Memory Dysfunction and Proposed Glutamatergic Mechanisms

Type	Frequency	Duration	Glutamatergic mechanism	Characteristics
Acute	Very common	Hours	Sodium and water influx	Reversible
Subacute	Common	Months	Oxidative stress, calcium-mediated processes	Reversible
Chronic	Very rare	Years	Oxidative stress, calcium-mediated processes, apoptosis	Irreversible

memory deficits by changes in technique. Alteration in stimulus wave-form, with utilization of brief-pulse square waves rather than sine waves, has been shown to decrease both anterograde and retrograde dysfunction in the subacute phase.^{14,15} Similarly, unilateral (D'Elia) placement of electrodes substantially reduces memory impairment.¹⁶⁻¹⁸ Increasing the interval between treatments has also been shown to be useful.^{2,19} In addition, adjustment of stimulus intensity to a minimally suprathreshold level decreases deficits.^{18,20}

With such changes in technique, the ECT-induced memory dysfunction (EIMD) is quantitatively reduced but remains qualitatively similar. And some evidence suggests that such reductions are gained at the expense of efficacy. In particular, unilateral electrode placement and decreased stimulus intensity can be less effective than bilateral placement and moderately suprathreshold treatment.^{18,21} Given the mixed success of these altered techniques, some researchers have examined pharmacological manipulation.

Various medications have been used in an attempt to reduce the memory dysfunction following ECT. This work has been comprehensively reviewed by Krueger and colleagues.²² Based on different hypotheses, vasopressin, adrenocorticotrophic hormone, dexamethasone, thyroid hormone, caffeine, calcium channel blockers, ergoloid mesylates, and various "nootropic" agents have been tried, all without benefit. One study,²³ requiring replication, produced positive results using physostigmine.

To address the prevention or treatment of EIMD, it is necessary to understand the pathophysiology underlying it. Electroconvulsive shock (ECS) also impairs memory in animals. ECS in animals leads to slower learning²⁴ and reduces long-term potentiation (LTP) of synaptic changes in the hippocampus, mediated by excitatory amino acid (EAA) receptors.²⁵⁻²⁷ (LTP is a cellular model of learning and memory.) A similar effect may account for EIMD in humans. Interestingly, the *N*-methyl-D-aspartate (NMDA) antagonist ketamine prevents reduction of synaptic efficacy and of LTP induced by repeated, spaced ECS.²⁸ Although different hypotheses of EIMD have been tested, there have not been any trials exploring manipulation of the EAA system, which is critical in both the function and the dysfunction of memory. The logic of such an approach

becomes apparent in a review of recent discoveries in the neurobiology of EAAs and their implication in seizure disorders.

EXCITATORY AMINO ACIDS AND EXCITOTOXICITY

Glutamate and aspartate are the primary excitatory neurotransmitters in the central nervous system.²⁹ EAA receptors are highly concentrated in the hippocampus and related limbic structures.^{30,31} These receptors comprise a complex family that can be divided into two major classes according to mechanism of transduction: ionotropic receptors, which are coupled to a cation channel, and metabotropic receptors, which are coupled to second messengers such as inositol 1,4,5-triphosphate and mediated by G-proteins (see Table 2). Based on selective response to experimental agonists, the ionotropic receptors have been split into two major classes, NMDA and non-NMDA receptors. Non-NMDA receptors have been further subtyped, again based on their preferential affinity for the experimental agonists α -2-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) and kainate. Activation of glutamate receptor cation channels leads to neuronal changes thought to be the basis of LTP and ultimately memory.³²⁻³⁵

Olney³⁶ was the first to describe the neuronal degeneration resulting from excess glutamate ingestion. Following further study, he³⁷ coined the term "excitotoxicity" to refer to the adverse changes associated with excessive EAA receptor stimulation. Over the past decade a rapidly growing body of literature has supported the role of excitotoxicity in a variety of clinicopathological states including neuronal injury resulting from anoxia, ischemia, hypoglycemia, stroke, trauma, and epilepsy.³⁸ Each of these insults involves an overactivation of EAA receptors and is capable of producing memory dysfunction as a result of hippocampal damage. It appears that glutamate receptor-mediated neuronal insult represents a "final common pathway" for neurological insults of diverse etiologies in that they share the same mechanism of excessive release of EAAs and overstimulation of their receptors.³⁹

As suggested by Choi³⁹ based on work with fetal rodent neuronal cultures, exposure to excess glutamate results in a neuronal insult, which can be separated into two compo-

TABLE 2. Glutamate Receptors

Receptors	Ligands	Subunits (second messengers)	Neurotoxicity
Ionotropic NMDA	NMDA, quinolinate, ibotenate	NMDA R1, 2A–D	Cation flux–mediated (acute), calcium–mediated (subacute, chronic), apoptotic (chronic; oxidative stress–mediated)
AMPA Kainate	AMPA, kainate, quisqualate Kainate, domoate	Glu R1–4 Glu R5–7, KA1–2	Calcium-mediated Calcium-mediated, apoptotic
Metabotropic Quisqualate	Quisqualate, trans-ACPD, L-APB	Group I: mGlu R1a (PI, cAMP, AA) mGlu R1b, 5 (PI) Group II: mGlu R2, 3 (cAMP) Group III: mGlu R4, 6, 7, 8 (cAMP)	(Protective) (Protective) (Protective) Undetermined

AA, arachidonic acid; AMPA, α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; cAMP, cyclic adenosine monophosphate; Glu R, ionotropic non-NMDA glutamate receptor; L-APB, L-2-amino-4-phosphonobutyric acid; mGlu R, metabotropic glutamate receptor; NMDA, N-methyl-D-aspartate; NMDA R, ionotropic NMDA glutamate receptor; PI, phosphoinositol; trans-ACPD, trans-1-amino-1,3-cyclopentanedicarboxylic acid.

nents. The first component is a reversible process mediated by cation channels associated with the NMDA, AMPA, and kainate receptors. When glutamate is added to the neuronal culture, it stimulates NMDA, AMPA, and kainate receptor ion channels, which become permeable to cations. This produces an early, but reversible, swelling of neurons secondary to the influx of cations and water. If the excess glutamate is removed, the cations and water may be pumped out of the cell, reversing the swelling without cell death. If NMDA, AMPA, or kainate receptor antagonists are added to the cell culture, the process of cation influx and swelling may be blocked before it starts.

The second component is mediated by stimulation of NMDA receptors associated with calcium-permeable ion channels. (The remaining ionotropic glutamate receptors—i.e., AMPA and kainate—are associated with ion channels that are relatively impermeable to calcium.) The NMDA receptor ionophore is physiologically blocked by magnesium (see Figure 1). The depolarization of neurons with NMDA receptors by non-NMDA receptors removes the magnesium blockade, and the NMDA receptor channel complex becomes permeable to calcium. Persistent stimulation of EAA neurons thus results in a calcium influx. Calcium is required for a variety of physiological processes, including LTP.³⁸ However, within hours to days after exposure to excess glutamate, the accumulation of too much intracellular calcium irreversibly activates a variety of intracellular cascades, culminating in cell death. These mechanisms remain to be elucidated but probably include calcium-mediated activation of proteases and lipases, with genera-

tion of free radicals and nitric oxide.^{40–43} Like the first component of toxicity described above, the second component can be blocked by NMDA antagonists.

Excessive activation of glutamate ionotropic receptors has long been known to cause selective neuronal degeneration.⁴⁴ In addition to the neurodegenerative processes occurring in hours to weeks, other processes distinct from the two mentioned above take place over months and years. Recent evidence indicates that the delayed form of glutamate-induced neuronal degeneration, a consequence of the excessive activation of NMDA, other ionotropic, and/or metabotropic glutamate receptors, results in oxidative damage.⁴⁰ Oxyradicals, depending on their source, can damage cellular proteins, membranes, and DNA, causing cell death. But oxidative stress can be mitigated by endogenous free-radical scavengers such as vitamin E and glutathione, or the detoxifying enzymes superoxide dismutase, catalase, and glutathione reductase, to prevent neuronal degeneration.

An important aspect of the link between delayed glutamate-induced degeneration and oxidative stress is that it provides a mechanism whereby frequent small-magnitude overstimulation of glutamate receptors, a condition that ECT may simulate, can cause insult to neurons. The process is usually subtle and reversible and rarely causes degeneration. When neurodegeneration does occur due to long-term cumulative oxidative stress, it exhibits many of the characteristics of apoptosis. "Apoptosis" was originally used to describe the drop out of neurons during neurodevelopment. Unlike necrotic neuronal death, apopto-

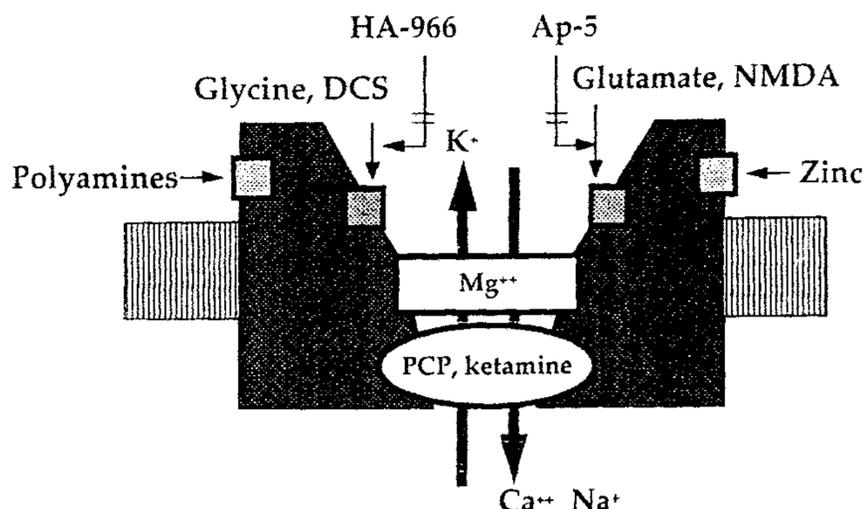


FIGURE 1. A schematic model of the NMDA ionophore receptor channel complex. The receptor is a cation channel consisting of multiple subunits. Six sites of action are shown: the neurotransmitter recognition site, where the agonists (glutamate, NMDA) and the competitive antagonist (AP-5) act; the glycine binding site, where glycine is either an allosteric modulator or a coagonist, HA-966 is an antagonist, and D-cycloserine (*DCS*) is a partial agonist; the PCP or ketamine binding site, where these noncompetitive antagonists act as open channel blockers; a cation binding site, where magnesium can block the channel; and modulation sites for polyamines and zinc. Glycosylation, proton (H^+), and redox sites are omitted. Upon depolarization, there is an influx of calcium (Ca^{2+}) and sodium (Na^+) and an efflux of potassium (K^+).

tic neuronal death does not leave the hallmark of gliosis. Similarly, ECT is not associated with definitive evidence of neuronal loss and gliosis.⁴⁵ This suggests that, as with EIMD, the neuronal insult induced by ECT is mostly reversible. Probably only under extreme conditions do the EIMD and the neuronal insult become irreversible and is the apoptotic process triggered by ECT. Periodically spaced, time-limited, well-controlled ECT does not appear to cause structural neuronal damage and is clinically safe.^{45,46} This hypothesis can also explain the scarcity of histological evidence for neuronal degeneration from ECT.⁴⁵

THE GLUTAMATERGIC MECHANISM IN SEIZURE DISORDERS

Evidence is accumulating to support the hypothesis that glutamate receptor-mediated neuronal insults play a major role in seizure-related brain damage.⁴⁷ Clinically, patients recovering from a seizure often suffer from self-limiting, reversible amnesia and disorientation. Neuropsychological testing has revealed that the memory deficits clear 24 hours

after a single seizure and 2 weeks after a series of complex partial seizures. However, prolonged complex partial status can result in permanent global amnesia.⁴⁸ Histopathologically, patients may develop irreversible neuronal loss with childhood epilepsy,⁴⁹ status epilepticus,⁵⁰ and kindled seizures.^{51,52}

As early as 1880, Sommer⁵³ described the association between epilepsy and structural damage to the hippocampus, which he termed Ammon's horn sclerosis. Clinically, seizure-induced hippocampal damage manifests as memory dysfunction, which has been well documented in a variety of different seizure types.⁵⁴⁻⁵⁷ Within the hippocampus, there appears to be a predictable histological hierarchy of vulnerability, with the CA1 and CA3 regions being more vulnerable than the CA2 region.^{58,59} It is worth noting that the hippocampal pathology of seizure disorders is similar to that of other neurodegenerative conditions mediated by EAAs—e.g., ischemia and hypoglycemia.³⁸

Repetitive depolarization of neurons during seizures results in excessive EAA release. Injection of excess glutamate in the rat hippocampus has been shown to mimic the pattern of neuronal necrosis seen in epilepsy.⁶⁰ This same pattern has also been reproduced by electrical stimulation of the perforant path, which provides the primary input to the hippocampus.^{61,62} Similar to electrical or chemical stimulation of the hippocampus, repeated ECS or prolonged seizures can activate the cortical glutamatergic input in the hippocampus and result in neuronal loss in animals.

Recently, the discovery of the probable mechanism of seizure-related brain insult has allowed development of a glutamatergic model.⁴⁷ This model may also shed light on the pathophysiology of EIMD. ECS in animals leads to slight, transient, reversible edema.⁶³ The edematous change may correspond to the acute phase of excitotoxicity mediated by the influx of cations and water. ECS also increases cerebral blood flow and cerebrovascular permeability.⁶⁴ The disruption of the blood-brain barrier during ECS can augment the extraneuronal concentrations of EAAs, since the serum concentration of EAAs is several magnitudes higher than the synaptic concentration. Coincidentally, the first example of glutamate receptor-mediated neuronal toxicity was discovered in fetal brain that had sustained neuronal injury due to an immature blood-brain barrier.³⁶ Fortunately, the disruption of the blood-brain barrier by clusters of ECS is rapidly reversible and is unlikely to cause sustained glutamatergic insult.⁶⁴ The memory dysfunction induced by ECS is theoretically in proportion to the quantity and duration of the release of EAAs: the greater the amount and duration of the release, the greater the magnitude of deficit expected. This line of investigation can validate the proposed EIMD model. However, there has been no systematic investigation of quantifying glutamate release in the ECS model.

THE GLUTAMATERGIC MODEL IN ECT

Like repeated idiopathic seizures in humans and ECS in experimental animals, ECT is not always completely benign. Both ECT and idiopathic seizures cause memory dysfunction,⁴⁸ while ECS profoundly impairs hippocampal LTP in animals.^{26,27} All three induce generalized neuronal depolarization and, consequently, release of EAAs. EIMD is cumulative—i.e., it increases over a course of ECT.

The glutamatergic effect may explain the memory dysfunction observed after ECT or idiopathic seizures in humans and ECS in animals. If the glutamatergic mechanism is responsible for the insult to the hippocampus during seizures, it probably accounts for the memory dysfunction seen following ECT, via a reversible disruption of the process of hippocampus-mediated memory consolidation. That a process is being disrupted rather than overtly damaged is supported by the paucity of data suggesting ECT-induced structural “brain damage,” even from post-mortem analysis of the hippocampus in ECT-treated patients, and the fact that the memory deficit is almost always reversible.^{45,64}

Whether ECT can cause irreversible neuronal damage is an unsettled issue. Modern magnetic resonance imaging techniques can help to characterize the edematous change after ECT due to the reversible cation and water influx.⁶⁵ No relationship has been found between ECT and anatomical brain damage.^{45,46} The current neuroimaging techniques of computed tomography and magnetic resonance imaging, however, are limited in spatial resolution and cannot discern subtle structural changes in the CA1 and CA3 regions of the hippocampus. Controlled human studies employing modern stereological cell-counting techniques in postmortem brain are required to determine the existence of mild neuronal loss due to irreversible neuronal insult in ECT. In most clinical situations a course of well-spaced brief ECT treatments will probably produce only reversible edematous change due to cation and water flux or reversible oxidative stress corresponding to the acute and subacute phases of EIMD. Nevertheless, frequent ECT could conceivably cause a small amount of long-term neuronal damage, especially in patients who have a preexisting structural deficit or a neuronal disorder such as epilepsy, stroke, or chronic alcohol dependence (which may augment extraneuronal EAA concentration or upregulate NMDA receptors).⁶⁶

NEUROPROTECTION DURING SEIZURES BY EAA RECEPTOR ANTAGONISTS

The discovery of an apparent final common pathway of glutamate receptor-mediated neuronal injury from diverse etiologies has led to the possibility of intervention at a number of steps in this sequence, with the hope of blocking

what has previously been considered irreversible neuronal damage. Experiments utilizing neuronal cell cultures and animal models^{67,68} have demonstrated decreased injury and increased neuronal survival when NMDA antagonists are given following exposure to toxic levels of glutamate. Similarly, following oxygen- and glucose-deprivation experiments in which there is insufficient energy for cellular reuptake, resulting in a net excess of glutamate, NMDA antagonists block both acute swelling and delayed neuronal degeneration.⁶⁹ The calcium channel blocker nifedipine has been successfully used to attenuate the second component of delayed degeneration.⁷⁰ Free-radical scavengers and nitric oxide inhibitors have also been found to be “neuroprotective.”^{71,72} Finally, the addition of non-NMDA antagonists has been shown to augment the neuroprotective effect of NMDA antagonism in models of ischemia.⁷³

Kainic acid is an analog of glutamate capable of inducing seizures that produce a pattern of brain damage very similar to that resulting from idiopathic seizures.^{74,75} This not only supports the role of the glutamatergic mechanism in seizures but also provides a useful model of seizure-induced neuronal damage. Consistent with the idea of neuroprotection discussed above, the NMDA antagonists phencyclidine, ketamine, MK-801, and others have been shown to protect against brain damage from kainic acid-induced seizures.^{76–78} In pilocarpine-induced seizure models, ketamine and MK-801 are also neuroprotective.^{79,80} Of potential relevance to ECT is the apparent dissociation between the neuroprotective effect of some NMDA antagonists and their antiepileptic effect: in the presence of these NMDA antagonists, subclinical seizure activity on the electroencephalogram may persist without significant damage, presumably via the non-NMDA system.⁴⁷ This raises the intriguing possibility that some NMDA antagonists may be used to prevent neuronal insult resulting from ECT, while allowing seizure activity and therapeutic benefit.

Perforant path stimulation provides another seizure model used to explore the possibility of neuroprotection. During seizure, electrical activity spreads to the hippocampus via the perforant pathway, which is the primary route for excitatory input from the entorhinal cortex into the hippocampus. Stimulation of this pathway replicates seizure activity while eliminating the confounding variables of a chemical convulsant and the metabolic changes associated with widespread seizure activity (e.g., hypoxia and hypoglycemia). Through this pathway, the hippocampus can be damaged by glutamate release from its own afferent input. The resulting hippocampal histopathology mimics the damage from seizures of diverse etiologies (idiopathic, kainic acid-induced, glutamate-induced, etc.), with necrosis of the CA1 and CA3 regions.^{60,75,81} Of considerable interest is the finding that pretreatment with NMDA antagonists prevents the typical neuronal loss.^{82,83} These findings sup-

port the notion that treatment with selective NMDA antagonists prior to ECT may ameliorate the early insults of edematous change and oxidative stress and the remote possibility of neuronal loss associated with an ECT-induced seizure.

ECT AND NMDA RECEPTORS

Searching for well-tolerated NMDA antagonists has recently become the prevailing focus of research in the field of EAA-related neuropsychiatric diseases. At this stage, many preclinical trials have demonstrated efficacy in treating stroke and trauma, but no agent has become available clinically. Antagonists have been targeted at different sites of the NMDA receptor channel complex, including the glutamate site (a location of competitive antagonism), the ion channel (a location of noncompetitive antagonism), the polyamine site, and the glycine site⁸⁴ (see Figure 1). Presynaptic release blockers have also been used.⁸⁴ The large scale of the NMDA antagonist search can be informative for neuropsychiatric researchers in selecting an appropriate agent to treat or prevent EIMD.

Several objections may be raised to the possible use of NMDA antagonists prior to ECT in an attempt to reduce EIMD. The first is that NMDA antagonists themselves have temporary amnestic effects when given to subjects with an intact memory. However, NMDA antagonists can attenuate EIMD by protecting the neurons from glutamate receptor-mediated neuronal insult. In fact, MK-801 has decreased memory deficits due to traumatic brain injury, a condition inducing excessive EAA release similar to that in ECT.⁸⁵ Ketamine and MK-801 are noncompetitive NMDA channel antagonists. Although it is not generally used for ECT anesthesia, ketamine is an established alternative to the more commonly employed methohexital.⁸⁶ Nondominant unilateral ECT with ketamine anesthesia has been suggested as a treatment of choice for patients resistant to ECT administered with methohexital anesthesia, since it is associated with a higher percentage of delta energy and a higher magnitude of total energy.⁸⁷ The use of ketamine anesthesia is particularly intriguing, given a recent report that animals subjected to ECS following ketamine had less impairment in LTP than did the control (sham ECT) group, consistent with the glutamatergic model of EIMD.²⁸ Ketamine has also been shown to attenuate memory dysfunction following traumatic brain injury.⁸⁸ Preservation of long-term memory⁸⁹ and immediate recall⁹⁰ in human subjects after challenge with parenteral ketamine suggests that the amnestic effect of NMDA antagonists can be limited. Another option for a noncompetitive NMDA antagonist is magnesium, which is safely used to treat seizures associated with acute nephritis and eclampsia of pregnancy, with few or no amnestic sequelae.

These findings suggest that use of NMDA antagonists in ECT may mitigate subsequent memory dysfunction in humans. Also, the amnestic effects of an antagonist would be expected to last only as long as the drug is present. Memory formation during NMDA antagonist treatment is impaired only when ECT is administered.⁸⁷ With selection of short-half-life agents and titration of dosage, this amnestic period should be considerably briefer than the typical duration of the subacute phase of EIMD.

A second objection to the use of NMDA antagonists is that they tend to be psychotomimetic.⁹¹ However, numerous NMDA antagonists, including the antiparkinsonian agents amantadine and memantine, as well as dextromethorphan and probably others, are fairly well tolerated and do not have clinically significant psychotomimetic effects.^{67,92,93} These agents are potential candidates to attenuate the EAA neurotransmission associated with EIMD, but their clinical efficacy in this respect remains to be determined.

Recently, NMDA antagonists have been reported to cause neuronal loss in the rat posterior cingulate/retrosplenial cortex (for a review, see Olney and Farber⁹⁴). The effect of NMDA antagonists on rodent brains has been variable, depending on the dose and the age and sex of the animals.⁹⁵ The therapeutic window of competitive NMDA antagonists is greater than that of the noncompetitive antagonists.⁹⁶ Also, antagonists acting at the glycine⁹⁷ and polyamine⁹⁸ sites do not produce neurodegenerative changes at and above neuroprotective dose levels. With careful selection and titration of NMDA antagonists, this neurotoxic effect can probably be avoided.

A final objection to the use of NMDA antagonists is that the mechanism underlying the therapeutic effect of ECT is also responsible for the EIMD. The application of NMDA antagonists can be antiepileptic and may therefore prevent what is therapeutic about ECT. Although it is generally true that NMDA antagonists are antiepileptic, the search for NMDA antagonists as potential anticonvulsants has demonstrated that some antagonists are neuroprotective but do not manifest anticonvulsant properties in animals. These include MK-801, ketamine, phencyclidine, CGP 40116, CGP 37849, CGP 39551, and memantine.^{76,77,79,99-102} D-CPP-ene, a competitive antagonist, failed to improve seizures in a clinical trial in patients with epilepsy.¹⁰³ Overall, NMDA antagonists exhibit different potencies and efficacies in attenuating seizure activity due to their different molecular characteristics.¹⁰⁴ Theoretically, they can prevent EIMD by attenuating the NMDA neurotransmission while at the same time allowing the therapeutic effect of seizure to continue through non-NMDA receptors.

The hypoglutamatergic hypothesis of schizophrenia has recently gained attention.⁹¹ The therapeutic effect of ECT on schizophrenia may be due to its activational effect on the

NMDA system. Thus, one reservation to using NMDA antagonists in treating schizophrenic patients receiving ECT is the possibility that NMDA antagonism may worsen the symptoms of schizophrenia. In such patients partial antagonism of NMDA receptors with low doses of a competitive antagonist may provide the best compromise between the goals of improving symptoms and reducing EIMD.

The above dilemma speaks to the difficulty currently faced in the field of EAA research. Clinical trials applying NMDA antagonists in the treatment of stroke have not succeeded due to the neuronal damage and psychotomimetic effects. Fortunately, a new generation of NMDA antagonists is being developed. The novel agents target various sites of the NMDA receptor including the glutamate site, the ion channel, the glycine site, the polyamine site, and the glycine uptake carrier.^{105,106} No evidence is yet available to favor one approach over the others. Any prediction concerning which approach is optimal for the treatment of EIMD is premature. Some new agent(s) may be safer for clinical application. For example, amantadine and memantine are weak channel antagonists shown to improve cognitive function in patients with various neuropsychiatric conditions.¹⁰⁷ For EIMD, rational strategies await further characterization of the molecular mechanism of EAA neurotransmission, clarification of the underlying mechanism of ECT's therapeutic effect, and identification of new agents whose molecular moieties can provide pharmacotherapeutic and neuroanatomical selectivity. On the other hand, pharmacotherapy targeting events downstream of NMDA receptor activation or the augmentative pathway (e.g., voltage-activated calcium channel blockers to reduce calcium load) may be beneficial for EIMD.

RISK FACTORS FOR ECT-INDUCED MEMORY DYSFUNCTION

Although antagonists of NMDA neurotransmission appear to decrease the neuronal damage from a variety of insults, evidence is accumulating that certain factors may enhance neuronal insult through the opposite molecular mechanism. Glucocorticoids act as positive allosteric modulators of NMDA receptors. Some glucocorticoids increase both the frequency of opening and the mean opening time of the NMDA receptor channel.¹⁰⁸ Prolonged glucocorticoid exposure reduces hippocampal neurons in rodents.¹⁰⁹ Reduced hippocampal volume is also associated with elevated cortisol in depressed patients.¹¹⁰ Glucocorticoids have been shown to impair the ability of hippocampal neurons to survive ischemia and seizure by an NMDA-dependent mechanism.¹¹¹ Similarly, chronic ethanol exposure can enhance excitotoxicity through increased release of EAAs, upregulation of NMDA receptor density, and hypomag-

nesemia.¹¹² Decreased serotonin also increases glutamatergic tone.^{113,114}

In the glutamatergic model of EIMD, patients with glutamatergic insults such as seizure, stroke, or hypoglycemia or those with elevated glucocorticoids (exogenous or endogenous), a history of chronic alcohol abuse, or low serotonin states (e.g., due to tryptophan depletion, depression) may be at higher risk for EIMD than patients without these risk factors, due to increased glutamate levels or receptors. In the case of glucocorticoids this is particularly important, given the common occurrence of elevated cortisol in depression.^{110,115-117} As predicted by this model, glucocorticoids have been shown to exacerbate EIMD in humans.¹¹⁸ Similarly, chronic alcohol dependence is common among depressed patients and may predict worse outcome of EIMD.

IMPLICATIONS OF THE GLUTAMATERGIC MODEL OF ECT-INDUCED MEMORY DYSFUNCTION

In summary, we propose that EIMD is analogous to the memory dysfunction seen in various types of seizures. It results from excessive release of EAAs and the consequent activation of glutamate receptors. Unlike in chronic seizure disorders, the predominant forms of EIMD are acute and subacute. They are reversible, suggesting that the underlying mechanism of EIMD is reversible. They may correspond to early-onset (reversible) neuronal swelling due to cation and water influx via both NMDA and non-NMDA receptor channels, as well as to (largely reversible) oxidative stress. The insults result in temporarily impaired hippocampus-mediated memory registration and consolidation. The rare chronic form of EIMD with permanent memory deficits is unlikely to occur with periodically spaced, well-controlled, time-limited ECT. When it does happen, it may result from calcium-mediated neuronal injury and accumulative oxidative stress mediated by NMDA receptors, ultimately leading to apoptosis. Patients with previous glutamatergic insult or enhanced glutamatergic tone (for example, from seizures, stroke, elevated cortisol levels, or alcohol dependence) are particularly vulnerable, especially if they receive a large number of ECT treatments.

Most important, the glutamatergic model offers a specific mechanism for EIMD and allows for additional controlled research and clinical trials. It also suggests potentially critical clinical variables for the reanalysis of extant data (e.g., use of alcohol, glucocorticoids, or calcium channel blockers; history of an EAA-related disorder). Such variables may alter the vulnerability of neurons expressing glutamate receptors and have influenced the interpretation of previous studies examining memory function following ECT. As risk factors for EIMD, these same variables may

prove useful in predicting poor memory outcome in prospective studies.

Finally, our hypothesis offers multiple potential strategies for prevention, including good control of seizure disorders, pre-ECT normalization of cortisol levels in patients with hypercortisolemia and depression, and screening and treatment for alcohol dependence. It also suggests that antagonists acting on NMDA receptors, free-radical scavengers, or calcium channel blockers may prevent EIMD. Exploration of the glutamatergic model of EIMD may lead to the elimination of this troublesome side effect of one of the most efficacious treatments in neuropsychiatry.

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