Commentary

Glutamate, a Neurotoxic Transmitter

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Glutamate, an amino acid found abundantly in the central nervous system, was originally cast primarily in metabolic roles but is currently being seen as a unique and versatile molecule which *inter alia* performs both neurotrophic and neurotransmitter functions at numerous receptor sites throughout the central nervous system and, by aberrant action at these same sites, can literally destroy central nervous system neurons. The neurotoxicity of glutamate, although first described 30 years ago, was relatively ignored until studies in the early 1970s linked the phenomenon to an excitatory mechanism. Over the past decade, additional advances have been made in understanding the neurotoxic (excitotoxic) properties of glutamate. Most notably, several receptor subtypes that mediate glutamate excitotoxicity have been delineated, drugs with antiexcitotoxic actions have been identified, and evidence for the potential complicity of excitotoxins in neurodegenerative disorders, including those occurring during development, has begun to unfold. Here I will review highlights of research developments in excitotoxicology with special emphasis on information relevant to pediatric neurology. For more detailed information see recent, more comprehensive review articles.[1–3]

Glutamate as an Excitatory Neurotransmitter

Although glutamate was not generally recognized as a transmitter until relatively recently, evidence revealing its neuroexcitatory properties began to appear over three decades ago. In the early 1950s, Hayashi[4] reported that sodium glutamate caused convulsions when injected into the cerebral gray matter of dogs and monkeys. In 1959, Robbins[5] and Van Harreveld and Mendelson[6], prompted by their observations on crustacean invertebrates, hypothesized that glutamate might be an excitatory transmitter. In the same year, Curtis and colleagues[7] began applying newly developed microelectrophoretic techniques to the mammalian central nervous system; they examined the membrane-depolarizing properties of numerous amino acid analogs of glutamate and characterized the structural requirements for interaction with an apparent excitatory amino acid (EAA) receptor. However, the myriad metabolic involvements of glutamate, its ability to excite neurons throughout the central nervous system, and the lack of any known mechanism for terminating its excitatory action led neuroscientists of the 1960s to reject glutamate as a transmitter candidate. This view, although not universally held (eg, see Usherwood and Machili,[8] Usherwood,[9] and Takeuchi[10]), prevailed for two decades before yielding very slowly to new evidence pertaining to evoked Ca^{++} dependent release of glutamate from axon terminals,[11] removal of the excitant from the synaptic cleft by a high-affinity uptake system,[12] and antagonists that block the excitatory action of either synaptically released transmitter or EAA agonists in specific central nervous system pathways.[13] Finally, in the 1980s, glutamate has gained widespread acceptance as the front-running transmitter candidate at the majority of excitatory synapses in the mammalian central nervous system.

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Glutamate as an Excitotoxin

Historical Perspective

In 1957, Lucas and Newhouse[14] reported that subcutaneous administration of glutamate to suckling mice caused the inner neural layers of the developing retina to degenerate. This intriguing observation went largely unnoticed until the late 1960s, when Olney reported that systemic administration of glutamate to infant mice destroys neurons not only in the retina,[15] but in several regions of the brain.[16] Since glutamate is naturally present in high concentration in the central nervous system and is a major constituent of food protein and a widely used food additive, these findings were greeted with skepticism However, brain damage following either oral[17,18] or subcutaneous[19] administration of glutamate was readily confirmed in a number of animal species, including primates.[20] In addition, it was shown[21] that specific glutamate analogs known to share the neuroexcitatory properties of glutamate reproduce its neurotoxic effects, that these analogs have a parallel order of potencies for their excitatory and toxic actions, and that analogs lacking excitatory activity also lack neurotoxicity. Moreover, ultrastructural studies[15,19–21] localized the apparent site of toxic action to postsynaptic dendrosomal membranes, where glutamate excitatory synaptic receptors are located. These and related observations gave rise to the excitotoxic concept that glutamate destroys neurons by excessive activation of excitatory receptors located on the dendrosomal surfaces of neurons.

Identification of EAA receptor subtypes differentially sensitive to specific agonists [*N*-methyl-D-aspartate (NMDA), quisqualic acid, kainic acid] and to antagonists that block the excitatory actions of EAA agonists at such receptors[13,22] permitted the excitotoxic hypothesis to be rigorously tested. Shortly after the first EAA antagonists were identified, it was shown that they protect neurons in the in vivo mouse hypothalamus against the neurotoxic actions of glutamate and its more potent analog, NMDA.[23,24] In further confirmation of the excitotoxic hypothesis, many EAA antagonist candidates have now been systematically screened in in vitro preparations and found to have antiexcitotoxic activities corresponding in potency and receptor specificity to their known antiexcitatory activities.[25–27]

Antiexcitotoxic Drugs

In Table 1, the results of several EAA agonist/antagonist studies[25,26–31] are summarized. The first

TABLE 1
Potencies of Antagonists in Blocking NMDA or Kainic Acid Toxicity

Potential Antagonist	NMDA μmol/L	Kainic Acid, mmol/L
Competitive NMDA Antagonists		
D-2-Amino-5-phosphonopentanoate (AP5)	25	—
D-2-Amino-5-phosphonoheptanoate (AP7)	75	—
D-α-Aminoadipate	200	—
NonCompetitive NMDA Antagonists		
MK-801	0.1	—
Phencyclidine	0.5	—
Ketamine	5	—
(±)-Cyclazocine	5	—
(+)-SKF 10,047	10	—
Dextromethorphan	50	—
Antiparkinsonian Agents		
Procyclidine (Kemadrin)	15	—
Ethopropazine (Parsidol)	25	—
Mixed EAA Antagonists		
CNQX	100	15
Kynurenic acid	300	750
(+)-cis-2,3-Piperidine dicarboxylate	1,000	2,000
Barbiturates		
Thiamylal	50	250
Thiopental	200	400

Compounds were rated according to the minimal concentration required to provide total protection against NMDA (120 μmol/L) or kainic acid (25 μmol/L) toxicity. Antagonists were tested over a range of doses from 3,000 μmol/L downward. When no blocking was observed at 3,000 μmol/L, this is indicated by a dash (—).

generation of EAA antagonists identified[13] were competitive NMDA antagonists, which compete with NMDA agonists for binding at NMDA receptors. Agents in this class, although possessing moderately potent antagonist properties, are of uncertain value for clinical applications as they do not readily penetrate blood-brain barriers. The most powerful antiexcitotoxic drugs identified thus far are noncompetitive NMDA antagonists, which act at phencyclidine receptors to block both the excitatory[29,30] and toxic[25,26] actions of NMDA. MK-801, a drug developed by Merck, Sharp and Dohme, is the most potent known compound in this category. Since these compounds do penetrate blood-brain barriers, they are of interest as potential therapeutic drugs. Certain currently marketed drugs, including dextromethorphan[31] and several antiparkinsonian agents,[28] are moderately potent noncompetitive NMDA antagonists. Mixed antagonists, such as kynurenic acid and *cis*-2,3-piperidine dicarboxylate, block the excitotoxic effects of both NMDA and non-NMDA agonists but are of limited interest because of their low potency and inability to penetrate blood-brain barriers. CNQX, a recently described quinoxalinedione,[32] has the important distinction of being the first agent found to block the excitatory[32] and excitotoxic[33] actions of non-NMDA agonists more powerfully than it blocks those of NMDA. Certain thiobarbiturates penetrate blood-brain barriers and are moderately potent against both NMDA and non-NMDA agonists.

Acute Versus Delayed Excitotoxic Cell Death

In vitro ion substitution experiments have provided evidence for more than one mechanism by which excitotoxin-induced neuronal degeneration can occur. In hippocampal cell cultures[34] or in the isolated chick retina,[35] neurons degenerate very rapidly when exposed continuously for 30 minutes to a toxic concentration of glutamate or any of its excitotoxic analogs. In either of these preparations, this acute toxic reaction is abolished by the removal of Na^+ or Cl^- from the incubation medium, but is not affected by the removal of Ca^{++}. However, Choi[36] has described a slow degenerative process triggered by brief (5 minute) exposure of cultured neurons to glutamate, a process which is facilitated by the presence of Ca^{++} in the incubation medium. Thus, there is basis for believing that excitotoxins can destroy neurons by either an acute fulminating process, which is Na^+ and Cl^- (but not Ca^{++}) dependent, or by a slow process, which is Ca^{++} dependent. It is noteworthy that, in the latter case, excitotoxic neuronal degeneration occurs even though the duration of exposure to an abnormal concentration of excitotoxin is only one sixth as long as in the former case.

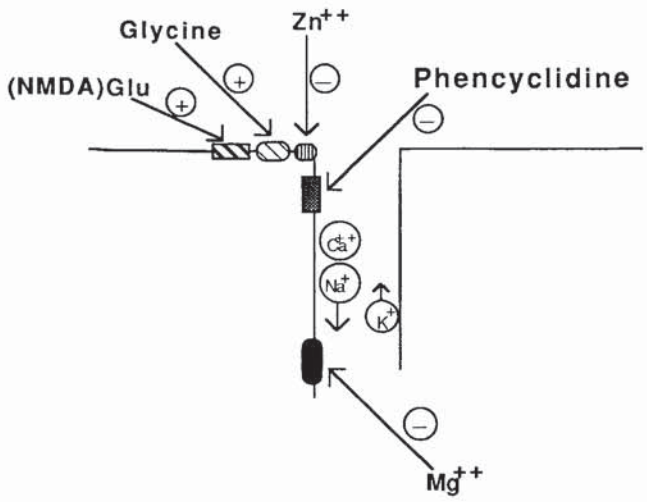

FIGURE 1
A schematic depiction of the various components comprising the NMDA receptor-ionophore complex. The phencyclidine and Mg^{++} recognition sites are believed to be in the cation channel, the Zn^{++} site at the mouth of the channel, and the glycine and glutamate (NMDA) sites on the external membrane.

Special Features of the NMDA Receptor

All three of the above mentioned EAA receptor subtypes are capable of mediating excitotoxic events. The most studied of these, and reportedly the most abundant and widely distributed in the mammalian central nervous system, is the NMDA receptor (Figure 1). Several features of the NMDA receptor (recently reviewed[37]) distinguish it from other subtypes of EAA receptor. This receptor is linked to a Na^+/Ca^{++} ion channel, which has a much higher Ca^{++} conductance than ion channels associated with other EAA receptor subtypes, and the NMDA ion channel is subject to a voltage-dependent Mg^{++} blockade. The NMDA receptor is closely associated with a strychnine-insensitive glycine receptor that facilitates opening of the NMDA ion channel and with phencyclidine receptors that are positioned within this channel, permitting phencyclidine agonists to perform an open channel block. In addition, there is evidence that Zn^{++}, acting at a separate site near the mouth of the NMDA ion channel, is an inhibitory modulator of channel function. Thus, as Figure 1 illustrates, the NMDA receptor system is a remarkably complex entity, the normal function of which depends on a dynamic equilibrium among

multiple facilitative and inhibitory factors. It follows that a pathological process adversely affecting any given factor might create an imbalance, rendering the system hyperfunctional and prone to an expression of excitotoxicity.

Excitotoxins and Neurodegenerative Disorders

Given the abundance of excitotoxins in the environment, the high concentration of these agents in the central nervous system, their intrinsic neurotoxic potential, and the several mechanisms by which such potential might be expressed, excitotoxins are logical candidates for complicity in neurodegenerative conditions. Over the past decade, evidence for such complicity has begun to accumulate. The potential role of excitotoxins in several conditions relevant to child neurology will be discussed.

Food Excitotoxins

Glutamate/Aspartate and Neuroendocrinopathies. Glutamate, in the form of its sodium salt (monosodium glutamate, MSG) is one of the world's most widely and heavily used food additives. Aspartate, an excitotoxic analog of glutamate, comprises half of the molecule of aspartame (Nutrasweet), which is used widely as a sweetener in beverages, cereals, chewing gums, etc. Currently, as in the past, the Food and Drug Administration sanctions the widespread use of excitotoxic food additives and fosters no program for educating against feeding excitotoxins to children. The wisdom of this policy has been questioned.[38] Neurons vulnerable to destruction by oral intake of excitotoxins are those lying in certain brain regions that lack blood-brain barriers, eg, neuroendocrine regulatory neurons in the arcuate nucleus of the hypothalamus. Immature animals are much more sensitive than adults to the neurotoxic effects of MSG and aspartame. Oral intake of excitotoxins in liquids (soups and beverages) poses the greatest risk, since this ensures more rapid and complete gastrointestinal absorption. Humans develop much higher blood glutamate levels from a given oral dose of MSG than any known animal species. Although the issue has not been properly studied, the added MSG in a single bowl of certain commercially available soups is probably enough to cause blood glutamate levels to rise higher in a human child than levels that predictably cause brain damage in immature animals. Since destruction of arcuate hypothalamic neurons in immature animals results in a complex delayed-onset neuroendocrine deficiency syndrome, the question arises whether feeding excitotoxins to human young might have similar neuroendocrinopathic consequences. (For more detailed information and supporting references, see Olney.[38,39])

Other Food Excitotoxins. Excitotoxic analogs of glutamate found naturally in the seeds of certain plants have been tentatively linked to neurodegenerative diseases (neurolathyrism and amyotrophic lateral sclerosis/parkinsonism/dementia complex) occurring endemically in regions of the world where such seeds are heavily ingested. Although it is not understood how these agents enter the central nervous system and initiate chronic neurodegenerative processes, this is an important area of investigation, since an elucidation of the mechanisms involved may help clarify how endogenous excitotoxins might contribute to chronic neurodegenerative diseases (eg, Alzheimer's dementia, Parkinsonism, Huntington's disease, amyotrophic lateral sclerosis) or how exogenous food excitotoxins might combine with endogenous excitotoxins to augment the degenerative process in such conditions. (See recent articles by Spencer and colleagues[40,41]).

Metabolic Disorders

Sulfite Oxidase Deficiency. The first human neurodegenerative condition to receive specific attention as a possible excitotoxin-mediated phenomenon was sulfite oxidase deficiency,[42] a rare, inherited disease in which an abnormal metabolite, cysteine-S-sulfate, accumulates in body tissues, and disseminated degeneration of central nervous system neurons occurs, resulting in blindness, spastic quadriplegia, and death in early infancy. It seems likely that an excitotoxic mechanism underlies neuronal degeneration in sulfite oxidase deficiency, since cysteine-S-sulfate displays powerful excitotoxic activity when administered systemically to infant rats or microinjected into the adult rat brain.[42]

Olivopontocerebellar Degeneration and Amyotrophic Lateral Sclerosis. Plaitakis et al[43] have shown that some patients with olivopontocerebellar degeneration have a deficiency of glutamic dehydrogenase enzyme activity, which impairs their ability to metabolize glutamate. Ingestion of glutamate by such individuals causes abnormally high levels of the amino acid in blood. Although individuals with amyotrophic lateral sclerosis do not have a demonstrable deficiency of glutamic dehydrogenase, it has been shown that they do have abnormally high blood

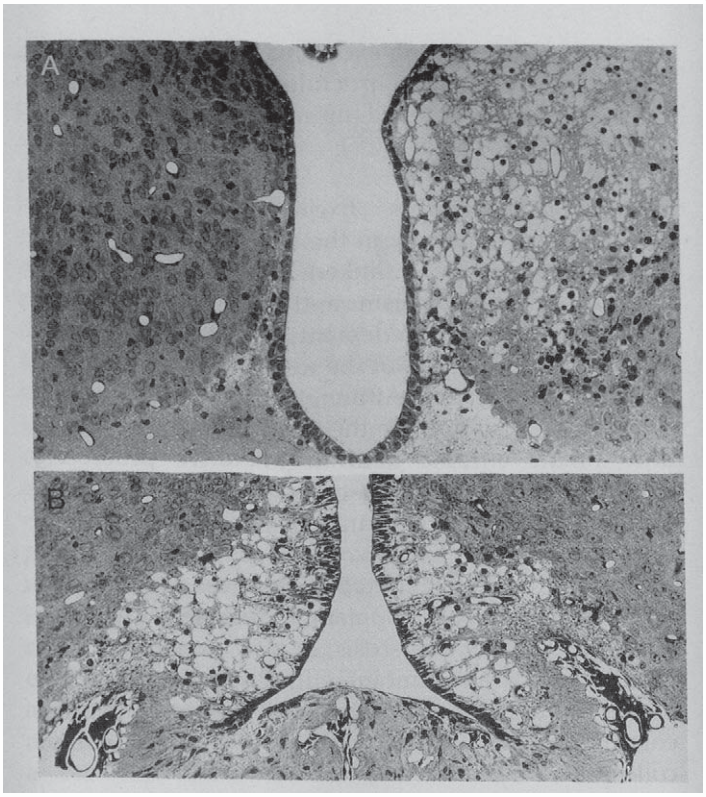

FIGURE 2
A. The medial habenular nucleus of a 10-day-old rat subjected to unilateral carotid ligation and 75 min in a hypobaric chamber followed by 4 hr recovery. The medial habenulum, a bilateral nucleus, exhibits damage unilaterally on the side ipsilateral to the carotid ligation. **B.** The arcuate hypothalamic nucleus of a 21-day-old mouse which, on its own volition, drank a solution containing 10% monosodium glutamate 4 hr previously. Arcuate neurons are destroyed in a bilaterally symmetrical pattern. Note that the hypobaric/ischemic cytopathology (shown in **A**) appears identical to that induced by exogenous glutamate (shown in **B**). Degenerating neurons in each case typically have swollen edematous cytoplasm and dark pyknotic nuclei (original magnification × 200). (Adapted from Ikonomidou et al.[47])

glutamate levels following oral intake of glutamate.[44] Thus, a build up of glutamate at central nervous system synapses on the basis of a metabolic defect has been postulated to account for the degeneration of neurons in these diseases.

Epilepsy, Hypoglycemia, and Hypoxia/Ischemia

It has long been suspected that a common mechanism may underly brain damage associated with prolonged seizures, hypoglycemia, and hypoxia/ischemia because the histopathology in each case has similar characteristics. Energy deficiency has been postulated as a common denominator, although studies have not demonstrated an energy deficit at the site of injury in epilepsy-related brain damage. More recently, evidence implicating endogenous excitotoxins in the pathophysiology of each condition has provided a common denominator that may help clarify the situation. The most compelling evidence has been of three kinds. First, it is evident from both light and electron microscopic studies that similar cytopathological changes are induced in animal brain by each of these three conditions and that such changes are indistinguishable from those demonstrable in certain brain regions following subcutaneous administration of exogenous glutamate[45–47] (Figure 2). Second, there is evidence, especially in the case of hypoxia/ischemia,[56] that these conditions trigger an outpouring of glutamate and aspartate from the intra- to extracellular compartment of brain, which permits these agents to have prolonged contact with excitatory receptors through which they can exert excitotoxic effects. Third, it has been shown for each of these conditions that NMDA antagonists such as MK-801 effectively protect against such damage.[49–51] These three topics are more extensively reviewed elsewhere.[2,3,37,46,48,51] A more detailed discussion of perinatal hypoxic/ischemic brain damage is given below.

Central Nervous System Trauma

It is possible that central nervous system tissue injury may entail an outpouring of endogenous excitotoxins from the intra- to extracellular compartment, much as occurs under anoxic/ischemic conditions. If so, edematous swelling or other brain tissue pathology associated with trauma may be due, in part, to an excitotoxic action of endogenous EAA. Consistent with this interpretation, Katayama et al[52] recently demonstrated that concussive brain injury is associated with a fivefold increase in extracellular glutamate concentrations in the rat hippocampus. Other recent evidence suggests that behavioral morbidity associated with head trauma[53] or spinal cord injury[54] is reduced by timely treatment with NMDA antagonists.

NMDA Receptors and the Developing Central Nervous System

Perinatal Hypoxia/Ischemia and NMDA Receptor Hypersensitivity

Silverstein and colleagues,[55] working with an infant rat model of hypoxia/ischemia (unilateral carotid artery ligation followed by 2½ hours in an 8% oxygen environment), have shown that hypoxic/

ischemic conditions acutely impair the uptake mechanism by which glutamate and aspartate are normally removed from the extracellular compartment (the only known mechanism for terminating their excitatory and/or toxic actions). Consistent with this is the observation of Benveniste et al[56] that these excitotoxic amino acids accumulate in the extracellular compartment of brain under ischemic conditions. McDonald et al,[57] using the same infant rat model of hypoxic/ischemic brain damage, have shown that the NMDA antagonist MK-801 powerfully protects against such damage. These authors have also found that the 7-day-old infant rat brain is much more sensitive than the adult rat brain to the neurotoxic action of NMDA when injected directly into the striatum.[58]

Recently we developed a modified version of the above infant rat hypoxic/ischemic model in which the rat pup is subjected to unilateral carotid ligation followed by 75 minutes in a hypobaric chamber (225 mm Hg). We have shown[47] that this approach results in patches of acute neuronal necrosis disseminated over many brain regions (frontoparietal neocortex, caudate/putamen, thalamus, hippocampus, medial habenulum, septum, and olfactory tubercle) and that the acute neurodegenerative reaction is identical, both in time course and type of cytopathology, to that observed in the hypothalamus of immature rodents or monkeys treated systemically with glutamate[19,20,47] (Figure 2). We have also corroborated[59] the observation of McDonald et al[58] that the infant rat is much more sensitive than the adult rat to the neurotoxic action of NMDA. In fact, injection of nanomolar amounts of NMDA directly into the infant rat brain causes widespread neuronal degeneration that appears identical to hypobaric/ischemic neuronal degeneration, and the neuronal populations most sensitive to NMDA toxicity are the same as those most sensitive to hypobaric/ischemic degeneration.[59] Moreover, administration of the NMDA-specific antagonist MK-801 provides excellent protection against either NMDA neurotoxicity or hypobaric/ischemic neuronal degeneration.[60] These findings strongly implicate the NMDA receptor in perinatal hypoxic/ischemic brain damage and provide hope that NMDA receptor antagonists may eventually prove useful in the clinical management of this important pediatric problem.

We have found that sensitivity to either NMDA neurotoxicity or to hypobaric/ischemic brain damage increases during the first few days of life to reach peak sensitivity in the rat between the sixth and tenth postnatal days and steadily declines thereafter.[59] This suggests that there is a period spanning approximately the first 2 weeks of neonatal life in this species during which NMDA receptors may be hypersensitive to EAA stimulation. We propose that during this period central nervous system neurons housing such receptors may be hypervulnerable to excitotoxic degeneration, ie, even mild anoxia or oxidative stress of any kind may be sufficient to trigger neuronal degeneration. We also have observed that each neuronal group is governed by its own timetable for onset and duration of the period of peak sensitivity.[59] If the developing human is subject to a similar phenomenon, we propose that the period of NMDA receptor hypersensitively in the human may span months rather than weeks and that different combinations of central nervous system neurons may be hypervulnerable at any given time during this period. The implications of this hypothesis will be discussed further below.

Additionally, we have observed that intracranial hemorrhaging occurs in 1 to 4-day-old (but not older) rats when subjected to hypobaric/ischemic conditions or when NMDA is injected directly into the brain.[59] The time dependency of this phenomenon suggests the interesting possibility that there may be a period in early development when an extracellular accumulation of endogenous excitotoxins (eg, secondary to hypoxia) might trigger both an excitotoxic neurodegenerative process and intracranial bleeding. While we know of no specific mechanism, excitotoxic or otherwise, by which EAA might induce bleeding, this issue warrants further investigation, since perinatal brain damage in premature human infants is often accompanied by hemorrhaging[61] originating in a specific brain region (periventricular germinal matrix zone) which, in the infant rat, is exceedingly sensitive to NMDA toxicity.[59]

Hypothesis Linking Excitotoxins to a Spectrum of Neuropsychiatric Disorders

In addition to the toxic potential of EAA systems, one of these—the NMDA system—has recently been shown to have a neurotropic function, which may play a vital role in the normal growth and development of the central nervous system.[62–64] Developing neurons apparently depend on EAA neurotrophism for survival while they are establishing functional connections with other neural central nervous system components. Thus, EAA systems literally have the power to promote the normal development of, or to destroy, many neurons in the mammalian central nervous system. While excitotoxicity is the most obvious mechanism by which they might destroy

neurons, discontinuation of neurotrophic support must be recognized as another potential means of effecting neuronal death. Moreover, a subtle formula for the genesis of neuropsychiatric disorders would be an interference in the neurotrophic functions of EAA systems causing faulty connections to be established during critical stages of central nervous system development. Alternatively, as will now be discussed, an excitotoxic process could also give rise to neuropsychiatric disorders.

In general, one can postulate either hyper- or hypofunction of EAA transmitter systems as basis for neuropsychiatric disorders. As Figure 1 illustrates, normal function of the NMDA receptor depends on a dynamic equilibrium among multiple facilitative and inhibitory factors. Pathological processes that reduce efficacy of glutamate or glycine or increase efficacy of Zn^{++}, Mg^{++}, or the endogenous phencyclidine receptor ligand at their respective recognition sites would render the NMDA receptor system hypofunctional, and a mechanism affecting these factors in the converse direction would render the system hyperfunctional. In excitotoxicology research, the major focus thus far has been on the hyperfunction concept—excessive activation of postsynaptic receptors can cause brain damage. However, when endogenous EAA transmitters, due to a hyperfunctional state, induce brain damage, it is essentially an "auto-excitotoxic" process in which the EAA neural network damages itself, ie, the cells bearing EAA receptors are destroyed, as are the EAA receptors themselves, and the EAA neural system is rendered hypofunctional. In sum, regardless whether the initial aberration is in the hyper- or hypofunctional direction, the eventual result is likely to be a deficiency in EAA neurotransmission.

Recent evidence[28,29] that the psychotomimetic agent phencyclidine powerfully inhibits NMDA receptor function raises the important question whether hypofunction of the glutamate receptor system might be a generic formula for psychotic illness. A possible mechanism by which glutamate hypofunction might occur would be by an auto-excitotoxic process, as mentioned above, in which subtle brain damage induced by an excitotoxic mechanism in early life would destroy postsynaptic cells that house the glutamate receptor system, thereby rendering the glutamate neural network deficient in excitatory receptive units. It has long been proposed that subtle brain damage occurring in early stages of development might be involved in the pathophysiology of schizophrenia. The excitotoxic hypothesis provides a credible mechanism by which such subtle developmental central nervous system damage might occur.

It is difficult to predict what types of behavioral sequelae might be produced by an excitotoxic process early in life. Initially, there would be loss of neurons that are normally excited by glutamate, including, in some instances, cerebrocortical and striatal neurons concerned with motor functions; however, some of these may be inhibitory neurons, and loss of inhibitory neurons from a given pathway might disinhibit that pathway, making it hyperreactive to normal levels of stimulation. Thus, it is reasonable to include both cerebral palsy and attention deficit disorder (hyperkinetic child syndrome) among the conditions that might result from excitotoxic brain injury in fetal life.

Above I have postulated that during human ontogenesis there may be a period of months during which NMDA receptors are hypersensitive and neurons bearing such receptors are hypervulnerable to degeneration. Since different combinations of neuronal groups reach peak sensitivity at different times, a pathological process involving NMDA receptors might produce several different patterns of neuronal loss, depending on the developmental stage in which the pathological event occurred. If so, the neuropsychiatric deficit syndrome resulting in later life might vary, for example, from cerebral palsy to attention deficit disorder, early childhood autism, or schizophrenia.

Conclusions

Here I have discussed current issues in excitotoxicology (neurotoxicity of glutamate and related agents) with special emphasis on the NMDA receptor and its possible role in neuropsychiatric disorders. I have briefly described several classes of antiexcitotoxic agents that are currently under study for their ability to protect neurons against excitotoxin-mediated neuronal degeneration. There is growing interest in the possibility that such agents, especially NMDA antagonists, will prove useful in the clinical management of neurodegenerative disorders; however, neither their efficacy nor their safety has been adequately established at present. With the plethora of new information about the NMDA receptor-ionophore complex, one tends to forget that non-NMDA receptors can also mediate excitotoxic events. Thus, although we know less about the physiology and makeup of non-NMDA receptors, it seems likely that new information, as it becomes available, will reveal new links between endogenous excitotoxins and neuropsychiatric disease processes. It is wise, there-

fore, to keep an open mind regarding the ultimate significance that can be ascribed to excitotoxic processes in human neuropsychiatric disease and regarding the promise of antiexcitotoxic strategies for preventing such diseases.

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