Psychopharmacology (1993) 111:391–401

Psychopharmacology
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Review

Glutamate: its role in learning, memory, and the aging brain

William J. McEntee[1] **and Thomas H. Crook**[2]

[1] Cognitive Research Services Inc., 1217 East Avenue South, Sarasota, FL 34239, USA
[2] Memory Assessment Clinics Inc., 8311 Wisconsin Avenue, Bethesda, MD 20814, USA

Received September 9, 1992/Final version February 2, 1993

Abstract. L-Glutamate is the most abundant of a group of endogenous amino acids in the mammalian central nervous system which presumably function as excitatory neurotransmitters and under abnormal conditions may behave as neurotoxins. As neurotransmitters, these compounds are thought to play an important role in functions of learning and memory. As neurotoxins, they are believed to be involved in the pathogenesis of a variety of neurodegenerative disorders in which cognition is impaired. Moreover, brain structures which are considered anatomical substrata for learning and memory may be particularly vulnerable to the neurotoxic actions of these excitatory amino acids, especially in the elderly who are also the segment of the population most susceptible to impairments of mnemonic function. This paper is a review of data concerning the role of excitatory amino acids in the processes of learning and memory and in the pathogenesis and treatment of disorders thereof.

Key words: Glutamate – Memory – Excitotoxin – Aging – N-methyl-D-aspartate

L-Glutamate is one of several endogenous amino acids (AA) in the CNS that are thought to act as excitatory neurotransmitters and as such are called excitatory amino acids (EAA). Other identified endogenous EAA agonists are: L-aspartate, L-homocysteine sulphinic acid, L-cysteine sulphinic acid, L-homocysteic acid, L-cysteic acid, quinolinate, S-sulphocysteine and N-acetylaspartylglutamate (Collingridge and Lester 1989). Glutamate is the most studied and the most abundant endogenous EAA and is reputed to be the major excitatory neurotransmitter in the mammalian CNS (Fonnum 1984) and the principal neurotransmitter employed by pyramidal neurons in cerebral cortex and in several hippocampal tracts (Cotman et al. 1987; Collingridge and Lester 1989). Thus, it is not surprising that this putative neurotransmitter is thought to have an important role in learning and memory.

EAA, particularly glutamate and aspartate, are a topic of increasing research interest in regard to their proposed involvement in the pathogenesis of a variety of neurological and psychiatric disorders (Plaitakis et al. 1984; Greenamyre 1986; Choi 1988; Olney 1989), some of which are associated with a loss of learning and memory abilities. In this paper, we will review and discuss data that suggest a role for glutamate and related EAA systems of the brain in learning and memory function and in the etiology and treatment of learning and memory impairments. Because loss of mnemonic function is most common among the elderly, data concerning changes in glutamatergic function as an effect of brain aging will also be reviewed.

Correspondence to: W.J. McEntee

Glutamate neurotoxicity

In addition to their presumed role as excitatory neurotransmitters glutamate and related EAA, under certain conditions, can also be neurotoxic and as such are called excitotoxins. With some exceptions, the excitatory and toxic actions of EAA have a parallel order of potency, i.e., those glutamate analogs that are without neuroexcitatory properties are not neurotoxic and those that are the most powerful neuroexcitants are the strongest excitotoxins (Olney et al. 1971).

As demonstrated in cell culture experiments, EAA produce their neurotoxic effects by two proposed mechanisms. The first is dependent on extracellular Na^+ and Cl^- and is manifest by acute swelling of neuronal cell bodies and dendrites (Rothman 1985; Olney et al. 1986; Choi 1987; David et al. 1988). In this instance, continuous exposure of neurons to toxic concentrations of EAA presumably opens membrane cation channels to an excessive influx of Na^+ and a secondary passive influx of Cl^- and water which results in acute neuronal swelling.

The second is a slower process of neuronal degeneration and is dependent on extracellular Ca^{2+} (Choi 1985, 1987; Garthwaite and Garthwaite 1986). In this situation, brief exposure (5 min) of neurons to glutamate or related agonists induces an influx of Ca^{2+} which accumulates in the cell and eventually causes cell death, possibly by activation of catabolic enzymes (see Choi 1988). Under pathologic states, this mechanism is considered the more important of the two because neuronal damage occurs in response to a lower concentration and a much shorter duration of EAA exposure than that required to produce acute neuronal swelling by the Na^+/Cl^- dependent mechanism (see Choi 1988 and Olney 1989).

Pertinent aspects of glutamate receptors

Glutamate and related EAA act at pharmacologically distinct receptors characterized according to their relative affinities for selective exogenous agonists and antagonists. Presently, five types of EAA receptors are recognized, all of which bind glutamate with high affinity (see Watkins et al. 1990). These are: N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) (also known as quisqualate), kainate, 1-2-amino-4-phosphonobutyrate (AP4), regarded as an inhibitory autoreceptor, and trans-1-amino-cyclopentane-1-3-dicarboxylic acid (ACPD), a metabotropic receptor that stimulates inositol phosphate metabolism and is also activated by quisqualate.

NMDA, kainate and AMPA receptors are coupled to ion channels having diverse conductance capacities that are regulated by various ionic- and voltage-dependent mechanisms. While AMPA and kainate receptors are thought to mediate fast synaptic neurotransmission, synaptic transmission mediated by the NMDA receptor is identified with a slow tise rime (for more details see review of Collingridge and Lester 1989).

The NMDA receptor is the best defined of all glutamate receptors (Monaghan and Cotman 1986) and is coupled to a membrane ion channel that is permeable to Na^+, K^+ and Ca^{2+}. Although the NMDA channel molecule itself is not voltage-gated, it is blocked in a voltage-dependent manner by Mg^{2+}; a block that must be removed by neuronal membrane depolarization to enable activation of the receptor-ionophore (Nowak et al. 1984; Mayer and Westbrook 1985).

The NMDA channel can also be blocked noncompetitively by Zn^{2+} at a site that is probably distinct from that which binds Mg^{2+} (Peters et al. 1987; Westbrook and Mayer 1987; Mayer et al. 1988) and by a large group of chemically different compounds that are classified as, or related to, the dissociative anesthetics such as phencyclidine (PCP), ketamine and dizocilpine (MK-801) (see Lodge et al. 1987). These compounds presumably block the NMDA channel by binding to a specific site in the channel that has a high affinity for PCP, and thus is named the PCP site.

Since the PCP site is located within the NMDA receptor-coupled ion channel, ligands with affinity for this site bind only when the channel is open, i.e., when membrane depolarization is sufficient to remove the Mg^{2+} block (Honey et al. 1986; Kemp et al. 1987; Davies et al. 1988; Huettner and Bean 1988). Some PCP-like drugs may produce a long-lasting block of the NMDA channel which may be reversed by prolonged membrane depolarization, more readily at positive membrane potentials (Huettner and Bean 1988).

Glycine, a widely distributed endogenous AA, behaves as an inhibitory neurotransmitter at strychnine-sensitive sites in areas of the lower brain stem and spinal cord. However, at submicromolar concentrations it facilitates NMDA receptor activity, supposedly by binding to the NMDA receptor complex at a specific strychnine-insensitive site separate from the transmitter recognition site, and is believed to exert its effects by increasing the frequency of NMDA channel opening (Johnson and Ascher 1987). Moreover, agonist action at the glycine site is thought to be essential for opening the NMDA channel (Kleckner and Dingledine 1988).

The polyamines spermidine and spermine have been shown to enhance the binding activity of PCP-like radioligands to the NMDA receptor complex; actions that are thought to originate at an allosteric polyamine-sensitive site on the NMDA receptor complex, distinct from the sites that bind NMDA and glycine (Ransom and Stec 1988; Williams et al. 1989) and reported to be functional in vivo (Singh et al. 1990; Sprosen and Woodruff 1990). Enhanced ligand-binding at the PCP site would require an increase in open-time of the NMDA channel; thus polyamines are assumed to be positive modulators of NMDA receptor activity (Ransom and Stec 1988; Robinson et al. 1990).

In summary, the NMDA receptor-ionophore complex contains: 1) an acceptor site for receptor agonists and competitive antagonists; 2) an allosteric strychnine-insensitive regulatory site that binds glycine; 3) a voltage-dependent site in the channel that binds Mg^{2+}; 4) a site in the channel that binds PCP and related drugs; 5) an inhibitory site in the channel that binds Zn^{2+}; and 6) an allosteric modulatory site that recognizes polyamines.

The non-NMDA glutamate agonists, kainate, AMPA and quisqualate, mainly activate the opening of low conductance ion channels that are permeable to Na^+ and K^+ (Ascher and Nowak 1988; Vylicky et al. 1988) and, in general, have low permeability to Ca^{2+} (Mayer and Westbrook 1987). However, recent reports indicate that some non-NMDA glutamate-gated channels, have substantial permeability to Ca^{2+} as demonstrated, in vitro, in hippocampal (Iino et al. 1990) and retinal bipolar (Gilbertson et al. 1991) neurons. Low permeability of non-NMDA receptor-coupled ion channels to Ca^{2+} or other divalent cations has been linked to the presence of an arginine residue in the GluR-B (or GluR2) subunit of the second transmembrane segment of the channel. Substitution of this arginine residue with glutamine results in substantial divalent cation permeability (Hume et al. 1991; Verdoorn et al. 1991). In a more recent study of the properties of AMPA receptor channels, Burnashev and coworkers (1992) concluded that an arginine residue present in any subunit of the second transmem-

brane channel segment causes low divalent cation permeability.

Glutamate and mnemonic function

The connection between glutamate and learning and memory is related to the capacity of NMDA receptors to induce hippocampal long-term potentiation (LTP); a bioelectric phenomenon linked to synaptic plasticity (Collingridge and Bliss 1987) and viewed as a cellular model for learning and memory (Brown et al. 1988; Nicoll et al. 1988). LTP was first described in detail by Bliss and Lomo (1973) who demonstrated that repetitive high frequency stimulation (10–29 Hz for 10–15 s or 100 Hz for 3–4 s) of the medial perforant pathway of the hippocampus, in the anesthetized rabbit, induced a potentiation of synaptic transmission lasting up to 10 h. Subsequent experiments with chronically implanted animals showed that LTP could persist for days and weeks at a time (Bliss and Gardner-Medwin 1973; Douglas and Goddard 1975) and in vitro studies have demonstrated LTP in other excitatory pathways of the hippocampus (Schwartzkroin and Wester 1975; Alger and Teyler 1976). Following the demonstration of Collingridge and coworkers (1983) of a link between NMDA receptors and the induction of hippocampal LTP via the Schaffer collateral-commissural pathway, many experiments employing NMDA antagonists have firmly coupled NMDA receptors to induction of most, but not all, forms of hippocampal LTP (for more details see reviews of Bliss and Lynch 1988 and Collingridge and Lester 1989).

Although the NMDA receptor plays a major role in its induction, mechanisms for maintenance of LTP are unknown and may involve non-NMDA glutamate receptors, particularly AMPA receptors (Davies et al. 1989). Furthermore, non-NMDA EAA receptors may be involved in the induction of certain kinds of hippocampal LTP. For example, the mossy fiber termination area in the CA3 field of hippocampus contains a high density of kainate receptors (Cotman et al. 1987) and LTP in CA3 is insensitive to NMDA antagonists (Harris and Cotman 1986; Kauer and Nicoll 1988). Thus, kainate receptors may induce LTP of the mossy fiber input to CA3.

Behavioral experiments in animals also demonstrate the important roles played by LTP and NMDA receptors in learning and memory processes. LTP has been linked to the changes in discharge patterns of hippocampal pyramidal neurons seen in association with classical conditioning of the rabbit eyelid response (Mamounas et al. 1984). A significant correlation was demonstrated between the number of NMDA binding sites in hippocampus and neocortex of young rats and their performances on tasks of learning and memory (Wenk et al. 1989). More convincing is the study of Morris and coworkers (1986) showing that intracerebroventricular (ICV) injection of the competetive NMDA antagonist, 2-amino-5-phosphonovalerate (AP5), in rats prevented the development of LTP and impaired performance on a spatial memory task.

Other experiments have produced variable effects of NMDA receptor antagonists on learning and memory. Systemic treatment of adult rats with PCP (Handelmann et al. 1987) and MK-801 (Wozniak et al. 1990) resulted in impaired recall of a reversal task, but acquisition of the task was not affected by either drug. In their study, Wozniak et al. (1990) also noted that this deficit in recall of a reversal task occurred only if treatment with MK-801 was given prior to learning, but not if given after the task was learned. Conversely, McLamb and colleagues (1990) showed that systemic treatment of adult rats with MK-801 interfered with acquisition of a water maze task but did not influence its recall. Parada-Turska and Turski (1990) demonstrated a dose-dependent impairment in acquisition of a passive avoidance task in mice treated with intraperitoneal (IP) injections of the competitive NMDA antagonists, 3-(+)-2-carboxy-piperazin-4-propyl-1-phosphate (CPP) and 4-phosphonomethyl-2-piperidine (CGS 19755) and a dose-dependent impairment in performance of a spatial memory task in mice following IP treatment with CPP, CGS 19755 and MK-801. Flood and coworkers (1990) tested the effects of the NMDA competitive antagonists, D-(−)-2-amino-5-phosphonovalerate (APV) and D-glutamylaminomethyl phosphonic acid (GAMP), on retention of a T-maze footshock avoidance task in mice. Drugs were given ICV immediately after or 24 h after training and retention was tested 1 week following training. Both compounds impaired task retention in a dose-dependent manner when administered immediately after training, but task retention was unaffected by treatment given 24 h after training.

These diverse effects of NMDA antagonists on learning and memory may be explained, at least in part, by the experiments of Mondadori and coworkers (1989) which showed either enhancement or impairment in the ability of rats to learn different behavioral tasks following systemic treatment with MK-801 or AP7, a competitive NMDA antagonist; results that led these authors to conclude that the effects of NMDA antagonists on learning are task-dependent.

Flood and coworkers (1990) also showed that non-NMDA receptors affect mnemonic function. They demonstrated the same kind of impairment in retention of a T-maze footshock avoidance task in mice treated by ICV injection with the non-NMDA receptor antagonists, D-glutamylaminomethyl sulphonate (GAMS) and 6,7-dinitro-quinoxaline-2,3-dione (DNQX), as they found in mice given the same behavioral tasks after ICV treatment with the NMDA antagonists, APV and GAMP.

Limited data are reported on the mnemonic effects of drugs that presumably increase glutamatergic activity. In addition to their experiments with glutamate antagonists, Flood et al. (1990) evaluated: 1) the non-specific glutamate agonists, L-glutamic acid and L-aspartic acid; 2) a specific NMDA agonist, DL-beta-chlorophenyl glutamic acid (CPG); 3) kainic acid, and 4) quisqualic acid in mice, for their effects on T-maze footshock avoidance

retention. Drugs were administered ICV into the third ventricle immediately following training and all produced a dose-dependent enhancement of task retention.

Drugs that behave as agonists at the strychnine-insensitive glycine regulatory site on the NMDA receptor complex have attracted interest as memory enhancers. Milacemide, a compound that readily crosses the blood-brain barrier and is converted, in vivo, to glycine, was shown to facilitate performance on learning tasks in normal and memory-impaired rodents (Handelmann et al. 1989) and to enhance performance on a word-retrieval task in young and old healthy adult humans (Schwartz et al. 1991). Rats receiving systemic treatment with the anti-tubercular compound, D-cycloserine, which is thought to act as a partial agonist at the glycine site (Hood et al. 1989; Watson et al. 1990), exhibited improved performance on tasks that evaluate learning abilities (Monahan et al. 1989).

In general, the foregoing data suggest that drugs which increase glutamatergic activity tend to improve, while those that impede such activity tend to impair learning and memory. Although most of the reviewed experiments were directed at drug effects on NMDA-type glutamate receptors, some data suggest that drugs which act at non-NMDA-type glutamate receptors also influence learning and memory. Such data, taken together with evidence suggesting that the effects of glutamatergic drugs on measures of learning are task-dependent, illustrate the unanswered questions about the specific roles played by the different types of glutamate receptors in learning and memory processes.

Glutamate function in the aged brain

Several studies have demonstrated age-related reductions of glutamate content in brains of rats (Himwich 1973; deKoning-Verst 1980; Price et al. 1981; Banay-Schwartz et al. 1989; Dawson et al. 1989). Dawson and colleagues (1989) made the point that this finding could be related to a loss of glutamate from the metabolic pool, the transmitter pool, or both and emphasize the difficulty in resolving this issue.

Data concerning changes in neuronal uptake and release of EAA as a function of age are less consistent. In rats, age-related deficits were reported in the high-affinity uptake of [^{3}H]L-glutamate by cortical (Wheeler 1980; Wheeler and Ondo 1986) and striatal (Price et al. 1981) synaptosomes while this measure was unchanged with aging in brain slices (Dawson et al. 1989). Najlerahim and coworkers (1990) measured high-affinity uptake of [^{3}H]D-aspartate in synaptosomes from several brain regions of young, middle-aged, and aged female rats. Compared with young animals, the middle-aged rats showed a significant reduction in uptake in preparations from neocortex, striatum, nucleus basalis, amygdala and thalamus, but not in hippocampal or cerebellar samples. However, data from the oldest rats indicated that the reduction in high-affinity uptake of aspartate is not progressive with age. This led the authors to suggest that the integrity of certain synaptosomes is disrupted within the first 12 months of aging in rats and that the failure of the oldest rats to demonstrate a progressive decrease with age in synaptosomal EAA uptake may be explained by an age-related increase in the affinity of the EAA carrier for the ligand. Results from earlier studies (Price et al. 1981; Wheeler and Ondo 1986) were cited in support of this interpretation.

As an effect of aging, Ca^{2+}-dependent, K^+-stimulated release of glutamate was shown to be increased in tissue prisms of human neocortex (Smith et al. 1983) and unchanged in frontal cortex of Fisher 344 rats (Dawson et al. 1989) and in nucleus basalis of female rats (Najlerahim et al. 1990). In contrast, Aprikyan and Gekchyan (1988) reported a decrease with age in both Ca^{2+}-dependent and -independent release of glutamate and aspartate in rat brain synaptosomes.

Wenk and colleagues (1989b) demonstrated an increase in Na^+-independent [^{3}H]L-glutamate binding sites in parietal and occipital cortex of aged monkeys. The method they employed supposedly identifies postsynaptic glutamate receptor sites; hence, their findings could suggest postsynaptic receptor upregulation secondary to diminished glutamate innervation. However, glial cells also contain Na^+-independent [^{3}H]L-glutamate binding sites (Bridges et al. 1987); thus, the data of Wenk et al. (1989b) are inconclusive but raise the possibility that glial cells increase in number with age. In a more recent study, Wenk and coworkers (1991) found significant reductions in NMDA-displaceable [^{3}H]L-glutamate binding sites in the brains of both aged rats and monkeys compared to young adult controls. These reductions, which imply that NMDA-type glutamate receptors are lost with age, were demonstrated in most of the brain regions examined in the old rats and in several brain regions of the oldest monkeys (ages 29–34).

Miyoshi et al. (1990) and Kito et al. (1990) demonstrated an age-related decline in strychnine-insensitive [^{3}H]glycine binding sites in telencephalic regions of rat brain including cerebral cortex and hippocampus. Kito et al. (1990) also showed that binding sites for [^{3}H]-CPP (a competitive NMDA antagonist) were unchanged with age in rat telencephalon and suggested that within the NMDA receptor complex, glycine receptors are primarily affected by the aging process. On the other hand, Tamaru and coworkers (1991) reported a decrease with age in binding activity of NMDA-displaceable [^{3}H]glutamate, strychnine-insensitive [^{3}H]glycine and [^{3}H]MK-801 in membrane preparations of rat cerebral cortex and hippocampus which suggests that the entire NMDA receptor complex is affected by age. These authors also determined that their findings were due to a decrease in binding sites rather than to changes in ligand affinities for receptors. In addition, Tamaru et al. (1991) showed that, in their preparations, aging was not associated with changes in binding activity of non-NMDA ligands and suggested that glutamatergic neurotransmission mediated by NMDA-sensitive receptors may be selectively impaired as a result of aging.

Bonhaus et al. (1990) raise an important issue concerning the interpretation of glutamate receptor binding

data in relation to aging. They measured radioligand binding to the NMDA, glycine and PCP recognition sites in hippocampal membranes from young and aged Fischer 344 rats and showed reduced binding to all three sites in the old animals as compared to the young. They also showed that ligand affinity for the three sites was unchanged with age. However, when expressed as binding sites/mg of membrane protein, these workers concluded that the reduced ligand binding activity to NMDA receptor sites in the old rats were a consequence of an age-related increase in the concentration of protein in hippocampal membranes rather than an age-related decrease in binding sites.

In summary, data from experiments with rats suggest that glutamate content in brain diminishes with age and, though not entirely consistent, results from studies of EAA neuronal uptake favor an age-related reduction in that function. However, studies of other aspects of EAA function in the aging brain are inconclusive and signify the need for more work in this area.

Glutamate in disorders of learning and memory

Some investigators have implicated glutamate in the pathogenesis of Alzheimer's disease (AD) and recent reviews (Maragos et al. 1987; Deutsch and Morihisa 1988; Greenamyre and Young 1989) provide thorough discussions on this subject. The link between AD and EAA abnormalities is based on a substantial amount of indirect data, much of which was acquired from studies of brain specimens from AD patients. Such data are subject to disparate interpretations among investigators. The predominant view submits that excitotoxicity may be a causative factor in the neuronal pathology associated with AD (Maragos et al. 1987; Choi 1989; Cotman et al. 1989; Greenamyre and Young 1989) and that treatment efforts should be aimed at preventing EAA neurotoxicity (Choi 1989; Greenamyre and Young 1989). Others believe the data suggest that the cognitive deficits of AD are related to a loss of glutamate function and recommend that treatment efforts for AD patients be directed at increasing glutamatergic activity (Deutsch and Morihisa 1988; Bowen et al. 1992).

Despite the interest in a possible role for glutamate in the pathogenesis of AD, the data thus far have not defined such a role. Although AD usually begins with disturbance of memory it progresses to a state of diffuse cognitive and intellectual dysfunction and widespread brain pathology far beyond the confines of brain structures associated with mnemonic function. Thus, the AD patient does not appear to be a satisfactory model for investigating the role EAA may play in brain pathology that causes a loss of learning and memory abilities. However, recent human and animal investigations have more directly implicated EAA neurotoxicity in the pathogenesis of other brain disorders in which, unlike AD, learning and memory are selectively impaired.

A recent report from Canada has identified domoic acid, a very potent exogenous EAA structurally related to kainic acid, as the pathogenic contaminant in mussels eaten by persons who soon thereafter developed a toxic encephalopathy (Perl et al. 1990). Out of 107 patients studied from this epidemic, 25% had incurred impairment of short-term memory. Fourteen of the more severely poisoned patients underwent neurological and neuropsychological assessment several months following the acute phase of the illness. Of these, 12 demonstrated marked deficits on measures of anterograde memory (Teitelbaum et al. 1990). Postmortem examination of the brains of four victims, who had not undergone neuropsychological testing, revealed a pattern of neuronal loss and necrosis, mainly in hippocampus and amygdala, similar to that seen in experimental animals following administration of kainic acid (Teitelbaum et al. 1990).

Similarities between domoic and kainic acids have also been reported by Stewart and colleagues (1990). They showed that: the currents induced in cultured hippocampal neurons by the two EAA were identical; both compounds produced the same characteristic neurotoxic lesion pattern in chick embryo retina; and the neural excitatory and excitotoxic actions of domoate were blocked by CNQX, a broad spectrum non-NMDA receptor antagonist, but not by NMDA antagonists. These investigators also showed that systemic treatment of adult rats with domoate caused an acute seizure and brain damage syndrome analogous to that produced in rats by systemic treatment with kainate.

It should be noted that coma and seizures occurred prior to death in three of the four autopsied cases of presumed domoate poisoning. Thus, the link between domoate neurotoxicity and postmortem brain lesions in these cases should be viewed with reservation since excitotoxic brain damage may be a result of coma and seizures from any cause. Nevertheless, from an overall viewpoint, data from the various studies of this epidemic strongly suggest that ingested domoic acid can enter the brain and that neuroanatomical substrata of memory function may be selectively vulnerable to its neurotoxic actions.

EAA neurotoxicity may also underlie the brain and behavioral pathology of the Wernicke-Korsakoff syndrome (WKS) (Langlais and Mair 1990; McEntee and Mair 1990; Robinson and Mair 1992); a disorder of learning and memory related to diencephalic pathology and thiamine deficiency (Victor et al. 1989). The notion that excitotoxicity may be a factor in the pathogenesis of WKS is based on data from experiments with a rat model of pyrithiamine-induced thiamine deficiency (PTD); a model characterized by a pattern of subcortical brain lesions similar to that found postmortem in WKS patients (Troncosco et al. 1981; Butterworth 1986; Mair et al. 1988) and by chronic impairments of memory function (Irle and Markowitsch 1983; Mair et al. 1988).

A reduction in levels of glutamate and aspartate demonstrated in the brains of neurologically impaired PTD rats (Gaitonde et al. 1975; Butterworth et al. 1979; Butterworth 1982; Langlais et al. 1988) prompted investigation of a possible role for EAA in the pathogenesis of thiamine deficiency encephalopathy. In this regard, Langlais and Mair (1990) treated a group of PTD rats with MK-801 during induction of thiamine deficiency

just after the animals developed signs of neurological impairment. Following recovery from thiamine depletion experimental animals were sacrificed for neuropathological examination. The brains of MK-801-treated rats displayed less severe lesions than the brains of PTD control animals.

In a subsequent similar experiment, Robinson and Mair (1992) administered MK-801 to a group of PTD rats just prior to the expected onset of abnormal neurological signs. Following recovery from PTD treatment animals were tested on mnemonic tasks and later sacrificed for neuropathologic examination. Eleven of the 12 animals treated with MK-801 had no demonstrable brain lesions and showed no deficits in mnemonic task performance while control animals displayed the typical brain lesions and mnemonic impairments associated with PTD. The one animal not protected by MK-801 received the drug after the onset of neurological dysfunction which in that case occurred earlier than expected. In both experiments the anesthetic effects of MK-801 precluded the opportunity to evaluate any neurological effects of this compound during induction of thiamine deficiency and it should be noted that the anesthetic and hypothermic effects of MK-801 may have been factors in preventing PTD-induced brain damage.

Since thiamine is an essential element in the oxidative metabolism of glucose, it is generally assumed that its deficiency results in diminished cellular energy production. Therefore, excitotoxicity via excessive stimulation of NMDA receptors as an underlying cause of thiamine deficiency encephalopathy is consistent with the in vitro data of Novelli and coworkers (1988), who showed that reduction of intracellular energy levels in cultured neurons (with NMDA receptors) causes depolarizing stimuli sufficient to remove the voltage-dependent Mg^{2+} block of the NMDA receptor ionophore; an event which these investigators suggest predisposes such neurons to the neurotoxic actions of extracellular glutamate.

Although an NMDA antagonist may have protected rats against the neurological sequelae of thiamine deficiency, the distribution of brain lesions in rats subjected to thiamine deficiency and in patients dying with WKS do not correspond with loci of high NMDA receptor density. In fact, the mammillary bodies, the most common site of brain pathology found postmortem in WKS patients (Victor et al. 1989), have a low density of NMDA receptors but are rich in kainate-type receptors (Cotman et al. 1987). Likewise, the anatomy of brain damage in experimental animals following hypoxic-ischemic insult (Brierly and Graham 1984) does not correspond with sites of high NMDA receptor density, yet NMDA antagonists provide protection against such damage (Gill et al. 1987; McDonald et al. 1987; Kochhar et al. 1988; Olney et al. 1988). Thus, mechanisms that determine selective neuronal vulnerability to the neurotoxic actions of EAA remain unexplained.

Olney (1989) has reviewed evidence that indirectly implicates EAA neurotoxicity in the pathogenesis of other neurodegenerative diseases that are associated with impaired memory (and other cognitive and intellectual abnormalities) such as Huntington's disease, ALS-Parkinsonism-Dementia complex and Jakob-Creutzfeldt disease.

Implications for treatment of impaired memory

Some of the data reviewed above suggest that neurons located in brain structures considered critical for learning and memory may be particularly vulnerable to the neurotoxic effects of EAA. Other reviewed data suggest that reduced glutamatergic function in brain results in mnemonic impairment, perhaps by inhibiting hippocampal LTP. Thus, treatment strategies for disorders of learning and memory that involve pharmacological regulation of glutamatergic neuronal systems must address both the prevention of excitotoxic damage and the maintenance or enhancement of glutamatergic activity.

Protection against EAA neurotoxicity in humans would require the availability of safe NMDA and non-NMDA antagonists. Many of these agents may not be safe. In addition to the well-known psychotomimetic effects of PCP, noncompetitive NMDA antagonists such as PCP, MK-801 and ketamine and competitive NMDA antagonists such as AP5 have been shown to induce pathomorphological changes in brains of rats (Olney et al. 1989; Allen and Iversen 1990). Olney and coworkers (1991) showed that the neuropathological effects of these agents can be prevented in rats when they are coadministered with certain anticholinergic or GABAergic drugs. Although these authors suggest that this strategy may have therapeutic utility for protecting neurons from the toxic effects of EAA, a less complicated approach would be to find EAA antagonists that are safe and effective when given alone.

There are commercially available drugs that 1) block NMDA channels at the PCP site, 2) readily cross the blood-brain barrier (BBB), 3) have proven safety in clinical use and 4) being noncompetitive NMDA antagonists can presumably diminish NMDA receptor activity in the presence of high concentrations of EAA. Such drugs that may merit attention as potential treatments for memory disorders that are linked to EAA neurotoxicity are: dextromethorphan (Choi et al. 1987), amantadine (Pellegrini et al. 1991) and its congener, memantine (Bormann 1989; Kornhuber et al. 1989; Pellegrini et al. 1991). Memantine was tested for its effect on cognition in a heterogeneous group of geriatric patients and was reported to have improved subjects' short-term memory, concentration, and vigilance (Ambrozi and Danielczyk 1988). Recently, Chen and coworkers (1992) reported that low micromolar concentrations of memantine prevented NMDA receptor-mediated neurotoxicity in vitro and suggested that the safety of this drug may be related to its very brief blocking action on the NMDA ionophore.

It is important to determine if regulation of NMDA receptor activity with drugs that block the receptor-coupled ion channel (whether the block is brief or long-lasting) is a feasible strategy for treating disordered memory. As discussed earlier, some of these compounds inhibit learning and memory when given to experimental

animals; however, the critical issue seems to be whether they can be titrated, with reasonable facility, to the point where excitotoxicity is prevented and sufficient receptor activity is left intact to generate adequate LTP at doses which are free of adverse side effects. In this respect, Foster et al. (1991) reported improved scores on measures of mnemonic abilities in a group of AD patients following treatment with subanesthetic intravenous doses of ketamine that did not cause significant side effects. These results are not evidence that low-dose ketamine is safe for long-term use in humans, but do suggest possible therapeutic usefulness for NMDA channel blockers as memory enhancers. This strategy may be pursued by testing drugs such as dextromethorphan, memantine and amantadine. However, it may turn out that NMDA channel blockers have clinical utility as anti-excitoxic agents but not as memory enhancers.

Drugs that act at non-NMDA glutamate receptors may also have a role in the treatment of memory dysfunction, but much more preclinical investigation of such compounds is needed before their therapeutic potential can be appraised.

Their hypothesis that deficient glutamatergic function underlies cognitive loss in AD has led Deutsch and Morihisa (1988) to suggest that treatment with monosodium glutamate be tried to restore cognitive function in AD patients. Greenamyre and Young (1989) argue that such treatment is probably not feasible and is potentially dangerous. In support of this view, they suggest that the millimolar magnitude of the concentration of brain glutamate and the restricted passage of acidic AA into brain would, under normal conditions, necessitate extremely high doses of exogeneous glutamate to significantly change its level in brain. They further contend that if exogenously administered glutamate had freer passage into the brains of AD patients due to possible disruption of the BBB (Wisniewski and Kozlowski 1982), the resultant increase in brain glutamate levels may be neurotoxic, particularly if glutamate uptake is disturbed as suggested by the reported reduction of glutamate uptake sites in postmortem brains from AD patients (Procter et al. 1988).

Similar arguments may be advanced against exogenous glutamate treatment of learning and memory impairments in the nondemented aged, such as those with Benign Senescent Forgetfulness (Kral 1962) or Age-Associated Memory Impairment (Crook et al. 1986; Larrabee et al. 1992). Non-disease aging of the brain may be associated with changes in BBB permeability (Mooradian 1988) and, as suggested by animal experiments reviewed above, diminished cellular uptake of glutamate and aspartate. Normal uptake of glutamate and related EAA by neurons and glia may be critical for preventing in vivo excitotoxicity in brain cells exposed to high concentrations of extracellular EAA (see Choi 1988). Hence, treatment of nondemented memory-impaired elders with exogenous glutamate agonists in the presence of a possible reduction in EAA uptake capability and/or changes in BBB that may increase acidic AA entry into brain, appears to entail too great a risk. This risk is underscored by the preponderance of old persons among those who suffered neurological damage following ingestion of shellfish contaminated with domoic acid (Perl et al. 1990; Teitelbaum et al. 1990).

Pharmacological manipulation of the strychnine-insensitive glycine site on the NMDA receptor complex is another strategy that may be worth trying for treatment of memory impairments. Watson and coworkers (1990) proposed such a strategy using the anti-tubercular drug D-cycloserine which they assert acts as a partial agonist at the glycine site when the site is not agonist-saturated, such as might occur in a disease state, and behaves like a competitive antagonist when the site is agonist-saturated. These investigators thus suggest that D-cycloserine (and similar drugs) may be useful for treating disorders of learning and memory by attenuating NMDA receptor abnormalities as follows. As a partial agonist such agents may enhance NMDA receptor function (and reverse glutamatergic hypoactivity) without inducing excessive receptor stimulation; as a competitive antagonist it may effect a down-regulation of the NMDA receptor (and protect neurons from excitotoxicity) without entirely blocking its activity. A similar strategy for treatment of AD with D-cycloserine is recommended by Bowen et al. (1992). These authors base their proposal for such treatment on data suggesting that glutamatergic function is lost early in the course of AD, perhaps by excitotoxic damage to glutamatergic neurons.

Milacemide, a drug which is converted to glycine in vivo and shown to enhance memory in normal and memory-impaired animals (Handelmann et al. 1989) and in normal young and old adult humans (Schwartz et al. 1991) may possibly merit further investigation as a treatment for memory-impaired humans. However, it is difficult to understand how a milacemide-induced increase in brain glycine would potentiate NMDA receptor activity, since the normal concentration of brain glycine far exceeds the concentration required to saturate the glycine site on the NMDA receptor complex (Johnson and Ascher 1987). Perhaps milacemide has memory-enhancing properties other than its role as a glycine prodrug; a possibility that seems to warrant more study.

Pharmacological regulation of the polyamine site on the NMDA receptor complex as an approach for treating impaired memory may eventually be possible as safe drugs are discovered that have specific actions at this site.

In summary, data from animal experiments suggest that regulation of glutamatergic neuronal systems has promise as a strategy for treatment of disordered learning and memory and much work is required to determine if these animal data are applicable to humans with lost mnemonic function. For those investigators interested in exploring this strategy, the potential hazards of using drugs intended to stimulate brain glutamatergic activity cannot be overemphasized.

Directions for future research

Evidence which relates disorders of learning and memory to abnormalities of EAA function is mainly indirect

and has led to much speculation concerning therapeutic strategies for both the disease process and the associated cognitive impairments. Such speculation is illustrated by the clinical trials now in progress evaluating the efficacy and safety of D-cycloserine for treatment of AD. Some investigators (Bowen et al. 1992) believe this treatment provides a double-barrelled approach by affording protection against excitotoxicity, which is thought to underlie the pathogenesis of AD, while relieving the glutamatergic hypoactivity that is thought to result from excitotoxicity and contribute to the cognitive loss in this illness. There are no data which directly link excitotoxicity or glutamatergic hypoactivity to AD; though indirect data do offer arguments in favor of such links. Nevertheless, clinical testing with drugs that modify glutamatergic function is presently the most viable method for investigating the role of EAA in the pathogenesis and treatment of AD and other impairments of learning and memory in humans, including those impairments that affect nondemented aged persons. Furthermore, at this time, pharmacologic manipulation of the glycine regulatory site on the NMDA receptor complex appears to be the safest strategy for such investigations.

Other than clinical trials, imaging technology seems to offer the best prospect for learning more about the role glutamate and related EAA play in disorders of learning and memory in humans. The development of radiopharmaceuticals that are selective for glutamatergic neuronal systems and safe may provide the means, using imaging techniques such as PET and SPECT, to measure central glutamatergic function in living humans with deficient cognition. The availability of such methods may also make it possible to study the role of glutamate in normal learning and memory processes.

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