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Glutamate, learning and dementia-selection of evidence

Review Article

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Summary. Initial suggestions on the involvement of glutamate in memory came from electrophysiological studies on LTP that is blocked by NMDA-antagonists. Then Morris and colleagues (1986) provided the first evidence that icv infusion of the competitive NMDA antagonist 2-amino-5-phosphonovaleric acid (APV) to rats, inhibits both LTP in vivo and spatial learning in a Morris water maze. This was followed by a great amount of evidence confirming the initial finding in various learning tasks. The present paper is devoted to critical review of the literature focusing on the following problems: which glutamate receptors are involved ?, in which tests NMDA antagonists inhibit learning ?; which types of memory are affected ?; which brain structures are involved ?; do NMDA receptor antagonists invariably impair learning ?; is the effect of NMDA receptors antagonists on learning specific ?; does the stimulation of NMDA receptors result in cognitive enhancement ?.

Keywords: Amino acids Learning – Dementia – Glutamate – NMDA antagonists

Introduction

Glutamate as a major excitatory transmitter in the brain

The glutamatergic system forms widely spread projections covering virtually all brain structures, and is involved in major physiological functions (Fagg and Foster, 1983; Wroblewski and Danysz, 1989). However, the role of glutamate as a major excitatory neurotransmitter in the brain was not recognized until last two decades (Watkins and Evans, 1981). Convincing evidence was obtained due to the availability of specific glutamate antagonists (Watkins and Evans, 1981).

Similarly, most of the evidence for the role of glutamate receptors in memory has been obtained through the pharmacological blockade of specific receptor subtypes (see below; Advocat and Pellegrin, 1992).

Glutamate receptors

Glutamate activates et least 5 subtypes of receptors:-

1. N-methyl-D-aspartate (NMDA) sensitive ionotropic glutamate receptors are coupled to high conductance cationic channels permeable to K^+, Na^+ and Ca^{2+} (Mayer and Miller, 1990). These receptors are modulated positively by polyamines and glycine (Williams et al., 1991; Wroblewski and Danysz, 1989). The presence of glycine acting through its modulatory site (gly_b) is obligatory for the activation of NMDA receptors (Kleckner and Dingledine, 1988). Furthermore, NMDA receptor coupled channels can be blocked by phencyclidine-like compounds and by magnesium in a voltage- and use-dependent manner (Lodge and Johnson, 1990). NMDA receptors seem to be involved not only in learning performance (see below) but also in other forms of neuronal plasticity such as development, lesions-induced changes, and tolerance or sensitization to drug action (Collingridge and Singer, 1990).
2. α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) sensitive subtypes of ionotropic glutamatergic receptors are coupled to channels permeable to K^+, Na^+ and depending on the subunits constitution, also for Ca^{2+} (Burnashev et al., 1992; Mayer and Miller, 1990). 2,3,-Dihydroxy-6-nitro-7-sulfamoyl-benzo(F)-quinoxaline (NBQX) is potent competitive antagonist of AMPA receptors while 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine hydrochloride (GYKI-52466) is an antagonist acting noncompetitively (Donevan and Rogawski, 1993; Sheardown et al., 1990).
3. Kainate receptors are in few cases only clearly distinguished from AMPA receptors (Miller, 1991).
4. 2-amino-4-phosphonobutyric acid (APB) sensitive glutamate receptors which are not fully characterized. They are probably localized presynaptically and are responsible for the regulation of glutamate release (Gannon et al., 1989).
5. Metabotropic receptors – existing in few subtypes coupled through G protein either to phospholipase C or adenylate cyclase (Manzoni et al., 1992; Schoepp et al., 1990).

Glutamate and learning-selection of evidence

The beginning-long term potentiation

Long-term potentiation (LTP) is a long lasting enhancement of synaptic efficacy resulting from short lasting high frequency stimulation. This phenomenon is believed to offer one mechanism of memory formation in the brain. Initial suggestions on the involvement of glutamate in memory came from electrophysiological studies on LTP which is blocked by competitive NMDA-antagonists (Collingidge and Singer, 1990). The NMDA receptors seem to be suitable candidates for involvement in learning and LTP since all undergo a qualitative

modifications in response to quantitative changes in the input. The voltage dependent blockade of NMDA receptors by Mg^{2+} is responsible for this characteristics (Cotman and Monaghan, 1988). According to the model (Collingridge and Singer, 1990; Wigström and Gustafsson, 1985) of the induction of LTP, NMDA receptor channels are a key players in the conjunction between pre- and postsynaptic activity. These NMDA receptor channels are activated due to simultaneous transmitter release and postsynaptic depolarization removing voltage dependent Mg^{2+} block and allowing for a local Ca^{2+} entry, which triggers the induction of LTP (Collingridge et al., 1983; Gustafsson et al., 1987). It is noteworthy, that NMDA receptors seem to be involved in the induction of LTP, while AMPA receptors in the maintenance of this phenomenon (Collingridge and Singer, 1990). Some evidence suggest also the role of metabotropic receptors in LTP (Anwyl, 1991).

Since LTP can be blocked by certain NMDA receptor antagonists (Collingridge et al., 1983), the implication of NMDA receptors in learning was a obvious consequence. One should however realize that a search for strictly pharmacological similarities between LTP and learning is relevant only if an LTP-like phenomenon is accepted as a principle of memory formation. This matter is still controversial (Keith and Rudy, 1990).

Pharmacological studies

Introduction

The major breakthrough in the studies on the role of glutamate in learning was possible after the introduction of selective antagonists, although initially their unfavorable pharmacokinetic properties limited their use to microinjection studies. Soon after the pharmacological characterization of LTP, Morris and colleagues (1986) demonstrated that icv infusion of the competitive NMDA antagonist 2-amino-5-phosphonovaleric acid (APV) to rats, inhibits both LTP and spatial learning in a Morris water maze task (Morris et al., 1986). In this test rats swim in a circular water tank and using apparently spatial cues search for the platform immersed 1–2 cm under the surface of the water. This suggests that some of the pharmacological features of LTP could be extrapolated to the functional learning process in behaving animals. The support for this conclusion has been further advanced after selective NMDA antagonists with better penetration to the brain have been shown to disrupt learning in a variety of tasks.

Which glutamate receptors are involved?

There is a vast collection of publications showing the involvement of NMDA receptors in learning (see below: "In which tests NMDA antagonists inhibit learning?"). However, the role of other receptor subtypes in learning is much more weakly characterized. New generation AMPA receptor antagonists, such as 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) inhibit both the initial phase of LTP-induction which requires partial depolarization to remove magnesium block of NMDA receptors and the expression of this phenomenon as well

(Collingridge and Singer, 1990). However, up to now the involvement of AMPA receptors in LTP *in vivo* has not been reported. Similarly, behavioral studies have not provided such convincing evidence for the involvement of AMPA receptors in learning. Flood and collegues (1990) observed the inhibition of negatively reinforced "T"-maze learning after intraventricullar administration of γ-glutamylaminomethylsulphonic acid (GAMS) and 6,7-dinitroquinoxaline-2,3-dione (DNQX) (both AMPA antagonists). The amnesic action of 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) or l-glutamic acid diethyl ester (GDEE) but not GAMS (AMPA antagonists) have been demonstrated after icv injection in passive avoidance learning (Danysz and Wroblewski, 1989; Lalonde and Cote, 1993). However, AMPA antagonists used are far from being selective and implications for AMPA receptor involvement based on these positive findings would be premature. A new selective AMPA antagonist 2,3,-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)-quinoxaline (NBQX), failed to block learning of sponteneous alternation in "T"-maze and step through passive avoidance learning (Parada et al., 1992). Similarly, negative findings were obtained in the radial maze or "T"-maze after treatment with 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine hydrochloride (GYKI-52466) or NBQX, up to 10–20 mg/kg, i.e. over the dose that blocks AMPA receptor-mediated convulsions (Danysz, not published).

Sahai and collegues (1985) observed the inhibition of active avoidance but not water maze learning after systemic administration of APB (putative antagonist of APB receptors). It is not clear whether the APB hydrophylic molecule passes the blood brain barrier. Intraventricullar injections of APB, failed to affect step through passive avoidance learning in rats (Danysz and Wroblewski, 1989). Hence, there is no clear evidence for the involvement of APB receptors in learning.

In which tests NMDA antagonists inhibit learning?

The antagonism of spatial learning originally demonstrated by Morris and collegues (1986) was replicated soon in other laboratories using the same test (Morris water maze), (Heale and Harley, 1990; Whishaw and Auer, 1989). Then similar findings were obtained in other spatial learning tasks like the positively reinforced 8 arm radial maze where rats are required to collect food pellets placed in the end of each arm (Bischoff and Tiedtke, 1992; Butelman, 1989; Butelman 1990; Danysz et al., 1988; Danysz and Wroblewski, 1989; Pontecorvo and Clissold, 1988; Schacter et al., 1988; Ward et al., 1990). Soon the observation of learning disrupting action of NMDA antagonists was extended to the other tasks not necessarily based on spatial cues. 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) an competitive NMDA antagonist inhibits both place and cue learning in the radial maze (Lyford and Jarrard, 1991). It has been found that various NMDA antagonists given before (but not after) the training of one trial passive avoidance inhibit acquisition (or storage) as evidenced by decreased retention 24 hours latter (Benvenga and Spaulding, 1988; Danysz et al., 1988; Danysz and Wroblewski, 1989; Gandolfi et al., 1990; Jones et al., 1990; Lehmann et al., 1988; Parada-Turska and Turski, 1990Venable and Kelly, 1990). Similarly,

NMDA antagonists impair learning in positively reinforced "T"-maze (Cohn and Cory-Slechta, 1992), in a water maze (Kant et al., 1990), classical conditioning (Kim et al., 1990; Stillwell and Robinson, 1990), fear potentiated startle response (Miserendino et al., 1990) and discrimination learning of both visual (Clissold et al., 1991; Tang and Franklin 1983; Tang and Ho, 1988) and olfactory cues (Staubli et al., 1989). Conditioned emotional response is inhibited by NMDA antagonists as well (Hoehn-Saric et al., 1991). Similarly, different forms of instrumental conditioning, i.e. lever pressing are also impaired by NMDA antagonists (Deacon, 1991).

The above mentioned data indicate that the involvement of NMDA receptor in learning (or plasticity) is much wider than was initially recognized. At the same time however the generalizations from these findings to all types of learning in general should be avoided. Moreover, one should recognize the difference between learning from memory itself (e.g. encoding, storage or retrieval processes), where learning is the acquisition of relationship leading to the fixation of this association referred as memory.

Which types of memory are affected?

Some data suggest that NMDA receptors are mainly involved in short-term memory, as indicated by spontaneous alternation in "Y" maze (Walker and Gold, 1992), working memory in the 8 arm radial maze (Danysz et al., 1988), or delayed discrimination of lever pressing (Tan et al., 1989). Deacon (1991) demonstrated that NMDA antagonists-induced impairment of delayed alternation of level pressing for positive reinforcement is delay-dependent. With longer delays the effect of the NMDA antagonist was stronger indicating what may possibly be a specific action upont the short term working memory. Similar observations were obtained in the DRL procedure when the responses must be delayed for a certain period of time in order to evoke reinforcement. In this paradigm APV given as a infusion increases the number of responses at shorter intervals (errors) i.e. disrupts short term memory, the "sense of time" or even the ability to withhold responding, (Sanger, 1992; Tonkiss et al., 1988). Also a few studies demonstrated inhibition of learning by NMDA blockers when given before, but not after the training trial. This effect was shown for learning in the Morris water maze, passive avoidance and positively reinforced "T"-maze (Danysz and Wroblewski, 1989; Handelman et al., 1987; Jones et al., 1990; Venable and Kelly, 1990). A finding that once again could suggest but does not prove an action on short term memory processes.

However, according to Bolhuis and Reid (1992) APV-infusion does not impair spatial working memory (short term memory) per se but rather inhibits improvement of performance seen with repetitive testing. Similar results were obtained by Shapiro and O'Connor (1992) who found that MK-801 treatment does not affect previously learned responses in the radial arm maze. However, if the experiment was performed in a different room the impairment was produced since a new set of cues and their spatial relationship must be learned. This indicates rather the involvement of long term memory or the involvement of higher-order processes in memory. Similarly Kesner and collegues (Kesner and

Dakis, 1993; Kesner et al., 1993) concluded that PCP (NMDA antagonist) inhibits the consolidation of new learned information but not short term memory maintenance. Similarly the acquisition (short-term memory) of passive avoidance is not affected but the expression of learning response (retention, long-term memory) is attenuated by NMDA antagonists (Handelmann et al., 1987; Sierocinska et al., 1991).

It is difficult to conclude whether NMDA antagonists affect short- or long-term memory or certain aspects of both. It is clear that it is necessary usually to give NMDA antagonists before the training trial in order to impair long term memory but this is no obvious indication that short term memory is affected. Alternatively the initial phase of consolidation may be blocked by this treatment.

Which brain structures are involved?

The precise determination of brain structures involved in the learning of certain task is not always possible, however, certain indications have been obtained with the use of lesioning techniques. Hence, it is accepted that spatial memory is dependent strictly on the integrity of the hippocampus while passive avoidance and fear potentiated startle response involve the amygdala nuclei (Davis, 1992; Olton et al., 1979). The application of NMDA antagonists directly to these structures have a disrupting action on acquisition of each respective task (Halliwell and Morris, 1986; Kim and McGaugh, 1992; Miserendino et al, 1990). However the normal glutamatergic function in other structures may be required for learning as well. Jerusalinsky and collegues (1992) found that microinjection of the NMDA antagonists into amygdala, hippocampus or entorhinal cortex produce retrograde amnesia in a passive avoidance task. On the other hand blockade of NMDA receptors in nucleus accumbens retarded learning in the 8 arm radial maze (Schacter et al., 1988).

In general, from the behavioral point of view the studies based on the microinjections of glutamate antagonists directly into brain structures are rather more convincing evidence for specific involvement of glutamate in learning than those based on systemic injections. In such studies usually "side effects" of NMDA antagonists not related to learning per se my be greatly reduced. These effects involve changes in motor activity, motivation, pain sensation etc. (see "Is the effect of NMDA receptor antagonists on learning specific?").

Do NMDA receptor antagonists invariably impair learning?

Reports providing support for the role of NMDA receptors in learning may favor the impression that this relation is common and universal. Hence, it is important to realize that there are many examples not in line with this assumption. Visual discrimination in a Morris water maze is not inhibited by the NMDA antagonist (APV) in contrast to the spatial discrimination (Morris et al., 1986). Rats can learn the association between unconditioned stimuli (electric shock) and conditioned stimuli (noise) under deep ketamine anesthesia (Edeline and Neuenschwander-El Massioui, 1988). Considering the fact that ketamine is an NMDA antagonist, no activity of NMDA receptors have been expected

under these conditions. Moreover, there are examples that LTP induced in certain brain structures or in particular conditions does not indispensably involve NMDA receptors, e.g. in the CA3 region of the hippocampus (Harris and Cotman, 1986), in the basolateral amygdala (Chapman and Bellavance, 1992) or in avian hippocampus (Wieraszko and Ball, 1993).

There are even some reports that are in opposition to the described role of NMDA receptors in learning procedures. Thus, it has been shown by Mondadori and collegues (1989) that NMDA antagonists administered before the training trials disrupted acquisition of step-through but improved acquisition of step-down passive avoidance in mice as evidenced by retention performance. However administration of NMDA antagonist after the training improved acquisition of both types of tasks. MK-801 can facilitate passive avoidance memory when retention is not present in controls (when the grid is covered during the test) but not when it is present (Weiskrantz and Mondadori, 1991). This apparent contradiction might be due to motivational or emotional differences in the various types of passive avoidance procedures applied. In general, it is possible that NMDA antagonists given after the acquisition of crucial information would inhibit the intereference with subsequent learning of other less relevant associations and this way facilitate consolidation of the primary association.

Additionally it should be stressed that Mg^{2+} which is NMDA antagonist as well, does not inhibit LTP, but may be even necessary for its induction. This may be related the fact that certain signal to baseline ratio is required for LTP and this is realized through a voltage dependent nature of the blockade. In fact, such a strong voltage dependence is characteristic for some NMDA channel blockers with fast blocking kinetics like e.g. memantine (Parsons et al., in press), which does not block LTP up to 100 μM in hippocampal slices which is far over its affinity (Collingridge not published). Moreover memantine may even enhance LTP in vivo as indicated by a preliminary data (Barnes, University of Arizona, preliminary data).

Is the effect of NMDA receptors antagonists on learning specific?

It is not universally clear whether the inhibition of learning seen in many reports is an indication of a malfunctioning memory consolidation and storage processes, learning acquisition per se or just purely the result of nonspecific action. Usually animals treated with NMDA antagonists express ataxia, stereotyped behavior, myorelaxation and enhanced locomotion in doses close to those affecting memory (Danysz and Wroblewski, 1989; Koek et al., 1987; Turski et al., 1985). NMDA antagonists may also modify the sensation of conditioned stimuli such as the analgesic action in tests using shock-induced reinforcement (Aanonsen et al., 1990) or change the hunger drive in positively reinforced tasks (Wirtshafter and Trifunovic, 1988). In both cases the experience of the unconditioned stimuli is altered. Moreover, direct action on motivational processes cannot be excluded (Herberg and Rose, 1990). The role on learning performance through some of these actions can be to a great extent excluded when additional control experiments are performed. It has been shown that PCP, APV, CPP and MK-801 do not affect pain sensation at the doses which attenuate passive

avoidance learning (Danysz et al., 1988; Venable and Kelly, 1990). It is also possible that NMDA antagonists may alter the perception of the conditioned stimuli since NMDA receptors are known to participate in the transmission of sensory, e g. visual or olfactory information (Rigdon and Dyer, 1989; Salt and Eaton, 1989; Sillito et al., 1990). Certainly, also the level of arousal should be of crucial importance for learning and it is known that attentional processes are affected by NMDA antagonists (Benedetti et al., 1988; Leung and Desborough, 1988). Further, it has been suggested that the learning impairment by NMDA antagonist may be state dependent (Jackson et al., 1992). In the case of absence of antagonist during retention test (as opposed to training phase) different response e.g. in a passive avoidance test might occur. In the DRL-17 procedure, where the responses were delayed by at least 17 sec, animals treated with NMDA antagonist respond usually earlier than controls. Responses made in under 17 sec are not reinforced and the rats are required to wait a further 17 sec. Hence antagonists of NMDA receptors may additionally affect timing behavior (Sanger, 1992; Tonkiss et al., 1988).

The problems listed above impose the use of careful designed experiments if any conclusion on the involvement of NMDA receptors in memory is to be made. Optimal in such a situation, would be the use of learning paradigm as a negative control which should be very similar to paradigm inhibited by NMDA antagonists. E.g. after APV infusion in Morris water maze spatial memory (finding of platform immersed under water) is impaired but visual memory (visible platform) is not affected (Morris et al., 1986). Similarly, under certain conditions the acquisition in "T" maze is not affected by PCP in contrast to the retention tested 24 hours later (Handelmann et al., 1987). Immediate memory in passive avoidance is not changed after dextrorphan but retention of the information a day later is impaired (Sierocinska et al., 1991). Hence the control experiment should be based on using different conditioned stimuli (cues) or should discriminate acquisition of the response from consolidation and in such a case conclusion about specific effect on spatial memory or long term memory respectively is justified.

The fact that NMDA receptors are involved in LTP is often used as support for claims for the contention of their involvement in memory formation. The hypothesis of the role of NMDA receptors in memory has been criticized recently (Keith and Rudy, 1990), but some role of NMDA receptors in memory processes is hard to deny. At present, the involvement of NMDA receptors in learning (in its broader meaning) is plausible, while its role in memory formation is tempting to entertain.

Does the stimulation of NMDA receptors result in cognitive enhancement?

If an inhibition of NMDA receptors produces a learning disruption, then it is natural to consider NMDA agonists as potential learning enhancers. This approach is however precluded by the fact that enhanced stimulation of NMDA receptors may lead to convulsions and neurotoxicity. In fact, NMDA receptor overstimulation has been implicated in epilepsy, in ischemia-induced brain damage and in the processes of chronic neurodegenaration occurring in Parkin-

son's, Huntington's and Alzheimer's diseases (Choi, 1988). Hence, the use of full agonists of NMDA receptor is unacceptable in the light of the above-mentioned risks. However, a more plausible approach may involve the use of modulators of NMDA receptors such as agonists (or partial agonists) of the glycine site coupled to NMDA receptors. It has been shown that either milacemide (glycine prodrug) or d-cycloserine (gly_b partial agonist) have beneficial effects on learning of various tasks. They enhance both passive avoidance and positively reinforced alternation in "T"-maze (Handelmann et al., 1988, 1989). Recently d-cycloserine has been shown to antagonize the memory disrupting action of scopolamine in a variety of tasks in animals and in humans as well (Fishkin et al., 1993; Flood et al., 1992; Schuster and Schmidt, 1992; Thompson et al., 1992; Wesnes et al., 1991). In this context it is interesting to note that both in aged rats and in Alzheimer's patients specific deficits in gly_b sites have been observed (see below).

Correlative studies-glutamatergic system function and learning

There are a few reports indicating that some correlates of the glutamatergic system function correspond to measures of learning performance. Crusio and collegues (1987) comparing certain mice strains found that there is a correlation between mossy fiber distribution (glutamatergic input to the hippocampus) and performance in the radial maze task. When genetically different low and high performance rats, are compared, the latter perform better in the active avoidance task and has higher number (or density) of NMDA receptors (Keller et al., 1992). Also, differential inborn learning ability has been related to the function of NMDA receptors, as evidenced by studying effects of APV on LTP (Ramirez et al., 1991). Further, it has been shown that learning may change the function of glutamatergic system. The binding of MK-801 to NMDA receptors but not of AMPA ligands increases after learning in chicken (Steward et al., 1992). Classical conditioning in rabbits (nicitating membrane) leads to enhanced binding to AMPA receptors (Mamounas et al., 1992). Extensive training in the radial maze increases glutamate metabotropic receptor mediated PI hydrolysis in the hippocampus, indicating enhanced sensitivity of metabotropic glutamatergic receptors (Nicoletti et al., 1988).

Additionally, according to some authors, aged animals have a decreased number of NMDA receptor sites which corresponds to the established learning performance (Cimino et al., 1993; Ingram et al., 1992; Pelleymounter et al., 1990; Wenk et al., 1991). Also in "senescence accelerated mice" malfunction of the glutamatergic system has been reported (Kitamura et al., 1992). This includes a decrease in NMDA receptor number in the cortex, but increased potassium stimulated glutamate release. This report may suggest an imbalance of this excitatory system with malfunctioning mechanisms controlling glutamate concentration in the synaptic cleft. Glutamatergic excitotoxicity may reduce NMDA receptor number in aged brains due to loss of neurons bearing these receptors (Advocat and Pellegrin, 1992; Tamaru et al., 1991).

It is however noteworthy that some authors suggest a specific deficit in the gly_b site before any changes in the binding of NMDA recognition site related to overall atrophy are observed (Miyoshi et al., 1990; Miyoshi et al., 1989). Neither

the meaning nor the consequences of this finding are clear, but it could be an early hallmark of age-related progressive glutamatergic system dysfunction.

Glutamate and dementia-selection of evidence

According to the hypothesis proposed by Greenamyre and colleagues (Greenamyre et al., 1988), and subsequently supported by others, glutamate may play an important role in the neuropathomechanism and symptomatology of dementia (Francis et al., 1993; Greenymyre et al., 1988; Greenamyre and Young, 1989; Palmer and Gershon, 1990). The symptomatology (amnesia) may involve a presynaptic glutamatergic deficit that might be related to an excitotoxic action of glutamate on other glutamatergic neurons (e.g. glutamatergic cortical pyramidal cells), (Francis et al., 1993). Additionally, an early deficit of gly_b sites of NMDA receptors has been suggested in Alzheimer patients (Procter et al., 1989a,b; Steele et al., 1989). The presentation of available evidence is beyond the scope of the present paper, however readers could find the extensive compilation in one of the recent reviews (Advocat and Pellegrin, 1992; Albin and Greenamyre, 1992; Beal, 1992; Francis et al., 1993; Greenamyre, 1991; Greenamyre et al., 1988; Greenamyre and Young, 1989; Lees, 1993; Palmer and Gershon, 1990).

Cognitive enhancers and glutamatergic system

This review has been primarily concerned with the concomitants of symptoms that have as their major property some type of cognitive dysfunction. A therapeutic approach for Alzheimer's disease should be aimed both at the inhibition of neurodegeneration and the improvement of symptoms. This could be possibly acomplished by modulation of glutamatergic function. In fact some of the already-existing suggested therapies for dementia affect glutamatergic transmission. These increase glutamate release (bifemelane, oxiracetam) (Kuraishi et al., 1991; Marchi et al., 1990; Raiteri et al., 1992), increase AMPA receptor mediated responses by inhibiting desensitization, (e.g. aniracetam) (Copani et al., 1992; Isaacson and Nicoll, 1991; Ozawa et al., 1991; Tang et al., 1991) or increase NMDA receptors function by stimulation of gly_b site (d-cycloserine, milacemide), (Schwartz et al., 1991; Wesnes et al., 1991). These actions may be responsible for the enhancement of LTP in CA3 seen with many of the cognitive enhancers (Satoh et al., 1988). However, it should be born in mind that in the case of oxiracetam and aniracetam inhibition of AMPA receptors desensitization occurs at mM concentration while in the cerebrospinal fluid low μM levels are expected (Parnetti et al., 1990). Even if this fact is neglected, another major concern is the far-from proven clinical efficacy of most of the existing "nootropic" agents.

Conclusions

There is much overwhelming evidence for an involvement of glutamate in learning, and some hints for its role in dementia. In particular glutamatergic receptors of NMDA type seem to play a major role. Hence, glutamatergic system

has came recently into the focus of the pharmaceutical industry as a potential target for drug development. These include agents which would slow down the progression of the disease and/or enhance cognitive functions by an modulation of glutamatergic function. Conversely, when developing NMDA antagonists for other therapeutic applications, the potential negative effects on learning performance should be considered.

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