[Frontiers in Bioscience 3, e70-80, May 11, 1998]

THE AGING OF THE NMDA RECEPTOR COMPLEX

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Received 4/15/98 Accepted 4/20/98

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1. ABSTRACT

N-methyl-D-aspartate (NMDA) receptors are present at high density in the cerebral cortex and hippocampus and play an important role in learning and memory. These receptors are negatively affected by the aging process, but this effect does not appear to be uniform throughout the cortex and hippocampus. This review discusses the age-associated changes that occur in the different binding sites of the NMDA receptor complex, in the expression of subunits that comprise the complex, in the electrophysiological properties of the receptor, and in the ability of NMDA to stimulate the release of other transmitters. Spatial memory and some types of passive avoidance memory tasks have been shown to involve NMDA receptors. Aged animals show deficiencies in the performance of these tasks, as compared to young, and some studies have identified an association between lower densities of NMDA receptor binding and poor memory performance. A number of drug and diet interventions have shown potential for reversing or slowing the effects of aging on the NMDA receptor. These studies suggest that the development of treatments that are aimed at preventing or reversing the effects of aging on the NMDA receptor will aid in preventing the memory declines that are associated with aging.

2. INTRODUCTION

Aging causes functional declines in many organs of the body, including the brain. One of the earliest cognitive dysfunctions that humans experience is a decline in learning and memory performance. This deterioration is detectable already in the fifth decade of life (1). These declines in memory can range in severity from "benign senescent forgetfulness" (2), in which individuals have trouble accessing new and old information (3), to the degenerative disorder, Alzheimer's disease, which induces dementia and severe declines in cognitive functions (4). A better understanding of the underlying causes of these memory declines during aging is necessary for the development of appropriate treatments or preventions for memory dysfunction as we grow older. These treatments may also be beneficial in delaying some of the symptoms of Alzheimer’s Disease.

One subtype of the glutamate receptors, the N-methyl-D-aspartate (NMDA) receptor, is expressed in high density in cortical and hippocampal regions and is very important in the initiation steps of learning and memory (5). NMDA receptors are involved in the performance of spatial, working, and passive avoidance memory tasks and in long-term potentiation (LTP), a cellular phenomenon that is believed to be involved in at least some types of memory. The NMDA receptors appear to be more vulnerable to the aging process than other glutamate receptors (6,7) and show declines in their binding densities, electrophysiological functions, and influence on other transmitter systems. The evidence suggests that these changes in NMDA receptor function should have an impact on learning and memory abilities and, in fact, several studies that demonstrate aging changes in the NMDA receptor also show a correlation between these changes and memory performance. This review will present the normal features and

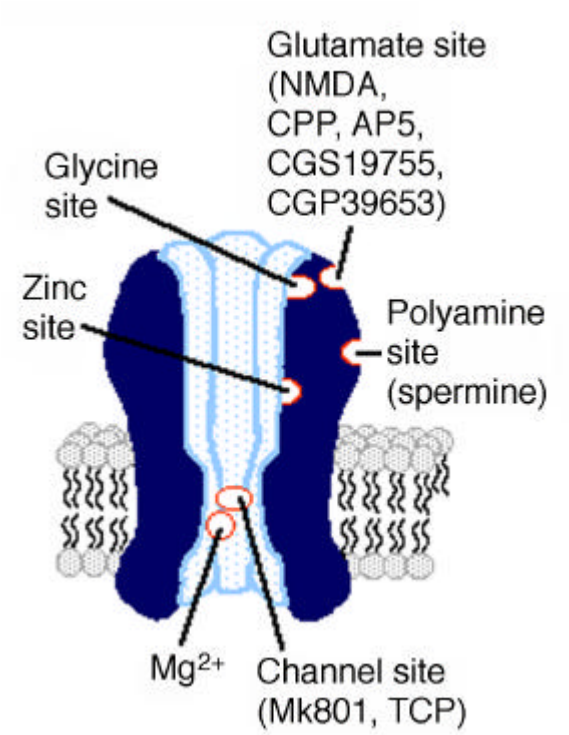

Figure 1. Binding sites associated with the NMDA receptor complex. Other ligands used in the binding or functional studies referenced in this review are indicated in parentheses. Diagram adapted from Corsi, *et al.* (9).

functions of the NMDA receptor complex, discuss the changes that have been reported in the NMDA receptor and its related functions during aging, and suggest future directions for improving or preventing age-related changes in learning and memory processes by targeting the NMDA receptor complex. Some of this information has been reviewed previously (8). This review represents an expansion of certain topics and an update on the progress achieved since 1994.

2.1. NMDA Receptor Complex

The NMDA receptor complex is a large protein assemblage that has multiple binding sites for different ligands, including an NMDA binding site, a strychnine-insensitive glycine binding site, and a binding site within the channel for certain noncompetitive antagonists; each of which can bind several different compounds (figure 1) (5,9). The NMDA site also binds L-glutamate and L-aspartate as endogenous agonists and D-2-amino-5-phosphonopentanoic acid (AP5), [(±)-2-carboxypiperazin-4-yl]propyl-1-phosphonic acid (CPP), CGP39653, and CGS19755 as antagonists. The glycine site binds serine and D-cycloserine, which act as agonists, and 7-chlorokynurenic acid (7-Cl-KYNA) is one antagonist for this site (10). Within the channel, non-competitive antagonists, such as (+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohept-5,10-imine maleate (MK801), ketamine, phencyclidine (PCP) and 1-(1-thienyl-cyclohexyl)piperidine (TCP); can bind. There are also binding sites on the receptor complex for polyamines, protons, redox reagents, zinc and magnesium that can modulate the activity of the receptor (figure 1) (5,9). These different binding sites and their interactions have been exploited to assess the effects of aging on the NMDA receptor complex.

The NMDA receptor has an absolute requirement of co-agonism for channel activity; both glutamate and glycine must occupy their binding sites for channel activation (9,11). However, agonist binding alone is insufficient to activate the channel because at hyperpolarized potentials the channel pore is blocked by magnesium (12). Repetitive synaptic activation, leading to neuronal depolarization, will relieve this block, allowing calcium to enter the neuron (12). This influx of calcium plays an important role in the induction of LTP, which may ultimately be expressed as learning (13,14).

2.2. Subunits

The functional subunits of the NMDA receptor complex have been cloned for rats (15-18), mice (19-22) and humans (23-25). There are two families of subunits identified for the NMDA receptor, in rats and humans they are termed the NMDAR1 (NR1; zeta1 for mice) and NMDAR2 (NR2; epsilon for mice) families. There is a 99% amino acid homology between the rat and human NR1 and the mouse zeta1 subunit (21-24,26). The NR1 subunit has the same distribution as NMDA-displaceable [^{3}H]glutamate binding throughout the cortex and hippocampus (15,21,26). This subunit appears to be necessary and sufficient for the formation of functional channels and, in homomeric receptors, can respond to glutamate, glycine, and MK801 (16,17,20,21), suggesting the presence of these binding sites on the NR1 subunit. Mutational analysis also suggests that the glycine site is associated with the NR1 subunit (27).

There are at least four members of the NR2 family of subunits that show high homology between species (21,22,24) and are designated as NR2A-D for the rat (16,17) and human (24) and as epsilon1-4 for the mouse (19-21). The NR2A-D subunits each enhance the activity of the receptor when coupled with the NR1 subunit (16). The subtypes within this family of subunits confer different agonist/antagonist affinities to NR1/NR2 heteromeric receptors (20,22), as well as producing different gating behaviors, responses to Mg^{++}, and I/V curves (16,17). They also differ from each other and the NR1 subunit in distribution and developmental patterns of mRNA expression (16,17,20,21,28,29). The different spatiotemporal expressions of these subunits suggest that multiple NMDA receptor populations exist in the brain and that they differ both within and between brain regions.

2.3. Learning and Memory

The NMDA receptor appears to play an integral role in memory. Much of the evidence has been derived from studies on rodents performing spatial reference memory tasks; functional NMDA receptors have been shown, with antagonists and subunit-specific knockout mice, to be necessary for successful performance in the

Morris water maze (30-34). In addition, correlations have been seen between NMDA-displaceable [^{3}H]glutamate binding in prefrontal/frontal and hippocampal regions and reference memory performance in the Morris water maze (35,36). NMDA receptors also appear to be involved in some forms of passive avoidance learning (37) and in working memory functions; NMDA antagonists inhibit performance of spatial working memory tasks when a delay is induced between choices (38) and NMDA application to the prefrontal cortex of macaques increases the short term memory retention time (39). Long term potentiation (LTP) is a sustained increase in the efficiency of synaptic transmission that typically is induced by high-frequency stimulation (14,40). Antagonists of the NMDA receptor and knockouts of the NR1 gene block the initiation of LTP in both the hippocampus (14,33,34,41,42) and neocortex (43) and, in some studies, this has been associated with declines in spatial memory performance (33,34). These studies all demonstrate an important role for NMDA receptors in memory processes and suggest that detrimental changes to the NMDA receptor during the aging process may explain, at least in part, the memory declines that people and animals experience during the aging process.

3. CHANGES IN NMDA RECEPTORS AND RELATED FUNCTIONS DURING AGING

3.1. Receptor Binding

The most consistent finding, with respect to binding studies investigating the effect of aging on the NMDA receptor complex, is that binding to the NMDA binding site by agonist (L-glutamate) and/or antagonists (CPP, CGS19755, and CGP39653) decreases with increasing age in the cerebral cortex and hippocampus, regions important to memory processing (44,45). This age-related decline in binding density to the NMDA binding site has been documented in Fischer 344 (35,46-51; but see (52)), Long-Evans (53), Wistar (54) and Sprague-Dawley (55) rats, in C57Bl/6 and BALB/c mice (56,57), and in rhesus monkeys (58). The changes reported for the older animals in these studies range from a 14% to a 63% decrease in binding to the NMDA site relative to the densities present in young adult animals. The concentration response studies that have been performed on homogenates and membrane preparations demonstrate that the decrease in binding is due to a decrease in the maximum binding (Bmax), indicating that the binding changes during aging are due to a decrease in the total number of binding sites (46,50,53-55). Most of these studies found no age-related changes in the affinity of the agonist or antagonist for the NMDA binding site, but a decrease in the affinity (increased K_D) of glutamate for the NMDA binding site with increasing age was seen in our autoradiographic concentration response studies in C57Bl/6 mice (59). A small increase in K_D also was reported in Sprague-Dawley rats, but this difference from young did not reach significance (55). It is possible that the ability to analyze individual brain regions with autoradiography allowed us to see affinity changes within populations of neurons that were not detectable in studies with combined brain regions. Although studies differ in the percent decline in binding detected and the issue of changes in total binding sites versus changes in affinity is not fully resolved, we can conclude that the NMDA binding site is negatively affected by the aging process in multiple mammalian species.

The age-associated changes in the NMDA binding site do not, however, appear to be homogeneous across brain regions. The cerebral cortex of aged rats and mice, in most studies, showed greater decreases in binding to the NMDA binding site than the hippocampus (35,46,50,56,57). However, there are two rat studies in which the change in the hippocampus was equal to or slightly larger than the change in the cortex (54,58). There also appears to be a difference between the cerebrum and hippocampus in the effects of aging on agonist versus antagonist binding. Studies in Long-Evans rats in which there are significant declines with increased age in antagonist binding with [^{3}H]CPP in the hippocampus (60), but no significant change in [^{3}H]glutamate binding to NMDA sites in the same region (61), support our findings in C57Bl/6 mice in which antagonist binding is more affected by aging than agonist binding in the hippocampus (57). The percent declines during aging in [^{3}H]glutamate and [^{3}H]CPP binding in cerebral cortical regions of C57Bl/6 mice, however, are more equivalent to each other (57). These results show that the effects of aging on the NMDA binding site are not uniform throughout the brain.

The effects of aging on the glycine binding site appear to be more variable than the changes in the NMDA binding site. We saw no overall age-related changes in [^{3}H]glycine binding in C57Bl/6 mice and there was a significant difference between the percent decline in [^{3}H]glycine binding and antagonist binding to the NMDA binding site in many cortical and hippocampal brain regions (57). Aged NMRI mice manifest a 130% increase in [^{3}H]glycine Bmax between 3 and 22 months of age in the cortex (62). Significant decreases of 27-49% in [^{3}H]glycine binding occur in Fischer 344 rats with increasing age in both cortex and hippocampus (49,50), but Sprague-Dawley rat cortex exhibits no change in Bmax for [^{3}H]glycine binding during aging (63). This variability in age-associated changes in the glycine binding site may be influenced by both strain/species differences and differences in experimental manipulations. The interpretation of these glycine binding studies also may be complicated by the existence of different populations of receptors in cortical neurons with differing glycine affinities (64), which may be differentially affected by aging.

The binding site within the channel of the NMDA receptor complex is often used to reflect the function of the receptor because an open channel is necessary for entrance of the ligands (65,66). Autoradiographic examination of glutamate-stimulated [^{3}H]MK801 and [^{3}H]TCP binding in different ages of mice showed that there is a decrease in binding of both of these ligands with increasing age (57). This decrease is significant in less brain regions than the age-related changes in [^{3}H]glutamate binding to the NMDA site, but there appears to be more change with age in the channel binding site in the cerebral cortex (up to 24%

declines in binding) than in the hippocampus (up to 14% declines), similar to the results with other binding sites on the complex (57). A decrease in the Bmax (22-35% decreases from Bmax values in young) for [^{3}H]MK801 and [^{3}H]TCP binding sites has been seen with increased age in the cortex and hippocampus of NMRI mice and in Fischer 344 and Wister rats (50,54,67,68). This decrease in Bmax has also been reported in the senescence-accelerated prone mouse (69). These results from the cortex of rodents fit well with changes in human frontal cortex, in which a 36% drop in Bmax for [^{3}H]MK801 was seen between 10-20 year olds and people in the tenth decade of their life (70). No changes in [^{3}H]MK801 binding were detectable across ages in the hippocampus, entorhinal cortex or cerebellum of humans (71), which appears to fit with the higher susceptibility to aging changes in this receptor in the cortex, as compared to the hippocampus, in C57Bl/6 mice (57). Only Sprague-Dawley rats show a non-significant increase in both Bmax and K_D during aging (63). In the majority of mammals studied, therefore, it appears that there is a decrease in the number of channel binding sites, although the percentage change may be less than for the NMDA binding site, suggesting that it may not be a simple case of decreased numbers of receptor complexes.

Age-related changes in the ability of glutamate and glycine binding sites to influence binding within the channel have also been reported. The ability of glutamate and glycine to enhance [^{3}H]MK801 binding in the frontal cortex is reduced from a 44% increase in young adults to a 35% increase in 80-100 year old humans (70). In C57Bl/6 mice, low micromolar concentrations of glycine exacerbate the age difference in [^{3}H]MK801 binding in the cortex and hippocampus, while higher concentrations appear similar to no glycine stimulation, with respect to differences between age groups (72). Glutamate and glycine both show increases in affinity (lower EC_{50}) and stimulate a higher percent increase in [^{3}H]MK801 binding in the forebrain of aged NMRI mice, as compared to young. However, it is interesting that the absolute increase stimulated in young and old is relatively similar to each other and the age-related difference in binding did not change substantially between control and glutamate or glycine stimulation (67). In this respect, these glycine results are similar to ours with a high concentration of glycine (72). Spermine enhancement of [^{3}H]MK801 binding disappears by 80 years of age in humans and zinc inhibition also declines with increased age (70). These changes suggest that, although the direction of change may differ between species and strains, aging appears to alter the affinities of certain binding sites on the receptor complex or changes the ability of the binding sites to influence the channel.

An issue has been raised as to whether the changes in binding, expressed as moles / mg protein, are a true reflection of changes in the number of NMDA receptors or whether there is a change in the total protein during aging. Two reports on Fischer 344 rats indicate that the total protein increases in the hippocampus with increasing age (48,52). Correction for this increase in protein entirely eliminated the significant changes in binding, seen when expressed as pmole/mg protein, to sites on the NMDA receptor in one study (52), but the other still had a significant 51% drop in [^{3}H]glutamate binding to NMDA sites (48). We found no age-related differences in total protein per dry weight of tissue using combined cortex and hippocampus from C57Bl/6 mice (56) and there is no change in protein levels in human frontal cortex between different ages (70). It is possible that this increase in protein content is limited to the hippocampus, but Castorina, *et al.* (46,73) report no change with age in protein content of the hippocampus of Fischer 344 rats. This issue remains unresolved.

The age-associated declines in binding to one or more sites on the NMDA receptor complex and changes in the interactions between sites are present in species ranging from rodents to primates, including humans. Much of the data points to losses in total binding sites, but it is not clear whether this reflects losses of the entire receptor complex, a selective loss of certain subunits, or both. The studies that show alterations in the affinity of certain binding sites argue for an alteration in subunit composition in the remaining complexes. Whatever the cause, it seems likely that these binding site changes alter the functions associated with the NMDA receptor, both at an individual receptor level and with functions that require multiple NMDA receptors to be active together to produce an outcome. In addition, given the importance of this receptor to learning and memory processes, it also seems probable that the binding site changes are, at least in part, responsible for some of the age-related declines in memory.

3.2. Subunit Expression

Although there are many studies that have documented a decline in binding to NMDA receptors during the aging process, almost no follow-up has been done to determine the cause for the change. The effect of aging on subunit expression is only beginning to be elucidated. A decrease in the expression of the NR1 protein occurs in aged macaque monkeys, as compared to young adults, on the distal dendrites of the dentate granule cells (74). The mRNA expression for NR1 also is decreased in the hypothalamus of middle-aged Sprague-Dawley rats, which may play a role in reproductive senescence (75). One set of splice variants of the NR1 subunit, plus or minus the N terminal 21 amino acid insert, however, show no change in ratio or percent of 6 month old expression in either cortex or hippocampus from Wistar rats by 24 months of age. Aged C57Bl/6 mice showed a decrease in the mRNA expression of the epsilon2 (rat NR2B) subunit within most cortical regions and the dentate granule cells, as compared to young adult mice (76). The zeta1 (rat NR1) subunit mRNA density decreased overall in the cortex and hippocampus with increasing age, but few regions showed significant changes, and the epsilon1 (rat NR2A) subunit showed no significant changes (76). Protein expression of the subunits in this strain of mice also exhibited decreases with increasing age in the zeta1 and epsilon2 subunits, but not the epsilon1 subunit (76). The functional significance of these changes is as yet unclear, but subunit specific declines during aging could alter the composition of the NMDA

receptor complex and potentially alter the pharmacology of the binding sites for glycine and ifenprodil, a non-competitive NMDA antagonist, (20,77-79) and/or physiological properties such as desensitization (17,80). Further knowledge about alterations in the subunits of the NMDA receptor during the aging process and the functional consequence may be the key to preventing the changes that aging induces in this receptor.

3.3. Electrophysiology

Changes with aging in the electrophysiological characteristics of the NMDA receptor appear to be highly region-specific. Intracellular responses to applied NMDA in the frontoparietal cortex show a reduced sensitivity in the slices from old Fischer 344 rats, as compared to young, and evidence of long-term potentiation in this same region, using a protocol that produced LTP in the young, is absent in the old rats (81). NMDA responses in both the dentate gyrus and in the CA1 region of the hippocampus, determined by measuring the input / output characteristics following electrical stimulations of axons, show decreased excitatory post-synaptic potentials for a given presynaptic fiber volley in aged Fischer 344 rats (82,83), but NMDA-induced inhibition of the extracellular field potential shows no age-related difference in dose in the CA1 regions of Sprague-Dawley rats (84). Certain aspects of LTP in the hippocampus are altered as rats age; the enhancement reaches maximum slower and the decay rate is faster in older, as compared to younger, rats (85,86). This could be due to NMDA receptor changes or to alterations up- or down-stream from these receptors. NMDA-dependent LTP induction is normal in the CA1 region of old rats when post-synaptic cells are depolarized by intracellular injection of current (87) or when high frequency tetanization is used (84,88-90). Shankar and coworkers (90) suggest that the maintenance of LTP is caused by a decrease in the NMDA-induced LTP and a compensatory increase in calcium channel dependent LTP. Shorter trains of stimulation (88) and primed burst stimulation, a threshold stimulation paradigm (89), for LTP do show a decline in both short-term potentiation (STP) and LTP magnitude in the CA1 region with increasing age. Barnes and colleagues hypothesize that there are fewer synapses per axon in the CA1 region of aged animals and that the deficiencies in NMDA receptor-dependent LTP are only seen with peri-threshold stimulation protocols (82). These results suggest that, although the aged hippocampus is still capable of producing NMDA-dependent LTP under maximal stimulation conditions, it is not as good as the young hippocampus at lower stimulation rates, which are likely to be more physiological. The electrophysiological changes in NMDA receptor function support the binding results showing a greater effect of aging on cortical NMDA receptors than hippocampal (35,46,50,56,57).

3.4. Transmitter release

There is evidence for a decline during aging in NMDA receptor functions that are down-stream from the receptor. NMDA-stimulated release of norepinephrine is diminished in middle-aged and old Fischer 344 and Wistar rats, as compared to young adults (91,92). One group reported a greater percent increase with age in glycine potentiation of NMDA-stimulated release of norepinephrine in middle-aged and old Wistar rats, but again the absolute increase over baseline stimulated by glycine appeared to be the same between the different age groups (92). Dopamine release stimulated by NMDA in the striatum and NMDA-induced inhibition of phosphoinositide hydrolysis in the hippocampus are also reduced with increasing age in Fischer 344 rats. In the senescence-accelerated prone mice (SAM P/8), there is a sharp decline in acetylcholine release stimulated by NMDA in whole brain slices after 2 months of age. In the resistant mice (SAM R/1), the same levels of release are maintained between 2 and 14 months of age. NMDA-stimulated release of leutinizing (LH) and gonadotropin releasing (GnRH) hormones shows decreases by middle age in the hypothalamus of female Sprague-Dawley and Wistar rats (75,93). This decrease in function is associated with a decrease in the mRNA expression of the NR1 subunit, which suggests that the NMDA receptor contributes to the process of reproductive aging (75). These results demonstrate that changes to the NMDA receptor complex during aging probably contribute to age-related dysfunctions that occur in other transmitter systems.

3.5. Learning and Memory

The role of NMDA receptors in learning and memory in the behaving animal has been predominantly studied by Morris and his associates with the use of the Morris water maze in a reference spatial memory task (32,34,94,95). This task (6,96-98) and others, including the Barnes circular platform maze and Olton radial arm maze (99), also have been used extensively in aging research to demonstrate and characterize the age-related declines that occur in spatial memory performance in rodents. Aged humans also show declines in performance (30-80% decreases from young performance) in problems involving spatial memory (100-104), so aging rodents appear to be appropriate models for this age-related human dysfunction. Rodent studies utilizing the water maze have been very effective in relating changes in NMDA receptor binding during aging to memory dysfunctions. Several studies show that lower binding of agonist or antagonist to the NMDA binding site in the prefrontal/frontal cortex and/or hippocampus is associated with poorer performance in spatial memory tasks utilizing the water maze (35,36,53). However, negative correlations, in which lower binding was associated with better performance, have also been reported in the striatum for the water maze task (61) and in the hippocampus for a non-spatial complex maze task (48). The reasons for this "interference" of NMDA receptors in memory processing have not yet been elucidated. Even more curious is the fact that the aged animals in the complex maze were more sensitive to MK801 administration, as manifested by a worsening of performance that was not seen in treated young rats (48). There is also evidence for a role for NMDA receptors in passive avoidance retention memory (37) and there is a significant correlation between [^{3}H]MK801 Bmax and passive avoidance latency during aging; high binding was associated with better retention (68). These results suggest that aging interventions aimed at retaining or improving NMDA receptor function should be

beneficial to relieving some age-related memory dysfunctions.

3.6. Aging Interventions

Many different interventions have been used successfully *in vivo* to attenuate the effect of aging on the NMDA receptor complex. Acetyl-L-carnitine (ALCAR), a compound that demonstrates multiple anti-aging effects in the brain when administered systemically to the animal (see review (105)), improves antagonist binding to the NMDA binding site, slightly in the hippocampus and frontal cortex and significantly in the striatum (46). ALCAR also decreases the age-related difference in NMDA-displaceable [^{3}H]glutamate binding, slightly in the hippocampus (55) and significantly in the anterior cortex (35). In the latter study, there was a slight improvement in spatial memory performance associated with the aged animals that received ALCAR treatment (35). Other cognitive enhancing and free radical scavenging drugs, such as memantine (63), phosphatidylserine (67), piracetam (106), pyrintol (107), and alpha-lipoic acid (108); all produce significant increases in the binding of [^{3}H]MK801 in aged rodents. Mementine, a non-competitive NMDA receptor antagonist, also increases glycine affinity and glycine- and spermine-stimulated [^{3}H]MK801 binding in old rodents, as compared to non-treated old animals, but does not improve spatial memory performance significantly in a radial maze task (63). Bifemalane hydrochloride, a drug used for cerebrovascular diseases, increases CPP binding in most cortical, hippocampal and thalamic regions studied in aged rats (51). D-cycloserine, a partial glycine agonist, improves the NMDA-stimulated norepinephrine release in older treated rats over non-treated, age matched controls (92). Dietary restriction is an aging intervention that has been shown to improve memory performance, particularly in spatial memory tasks (109-111). Diet restriction produces a slight sparing effect on [^{3}H]glutamate binding to the NMDA site in older C57Bl/6 mice (6) and this effect is correlated with spatial memory performance in the water maze (36). These interventions offer some hope for correcting the effects of aging on the NMDA receptor complex. A more in depth examination of how these improvements in the NMDA receptor relate to improvements in receptor function and memory processing is needed before deciding which of these represent the optimal treatment.

4. PERSPECTIVE

There is clear evidence that aging negatively affects some of the binding sites on the NMDA receptor complex. Whether this is a matter of receptor complex loss, overall subunit changes, or alterations within subpopulations of receptors still needs to be determined. More effort is also needed toward determining the underlying cause of the alterations. If different populations of receptors are involved, it behooves us to focus more on subdivisions of the cerebral cortex and hippocampus in order to better understand the regional and cellular changes that are occurring. The declines in electrophysiological output and interactions with other transmitter systems and the correlations with behavioral dysfunctions indicate that the binding changes in the NMDA receptor have a functional consequence to the behaving animal and suggest that further examination of interventions that act on the NMDA receptor will be beneficial in preventing or reversing the memory declines that occur as we grow older.

5. ACKNOWLEDGMENTS

The author would like to thank Dr. Scott Nelson for his helpful comments on the manuscript. The author's work was supported by NIH FIRST award AG10607 and NIH RCDA AG00659.

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Key Words: Aging, NMDA Receptor, Glutamate, Binding, LTP, Memory, Learning

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