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MK-801 Improves Retention in Aged Rats: Implications for Altered Neural Plasticity in Age-Related Memory Deficits

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Alterations in *N*-methyl-D-aspartate receptor (NMDAR)-dependent synaptic plasticity, characteristic of aged rodents, may contribute to impaired memory with advanced age. The purpose of the current research was to examine whether NMDARs contribute to rapid forgetting on a spatial memory task. Aged (22–24 months) and adult (3–6 months) male Fischer 344 rats received 18 training trials, over a period of 3 to 4 h, on the spatial version of the Morris water maze. Immediately after training, a standard free-swim probe trial was administered to assess the acquisition of spatial bias, which was determined by the percent of time spent in the goal quadrant and the number of platform crossings. Rats then received injections of the noncompetitive NMDAR antagonist, (+)-10,11-dihydro-5methyl-5H-dibenzo-(a,b)cycloheptene-5,10 imine (MK-801, 0.05 mg/kg, i.p.), or a vehicle injection of equal volume. Approximately 24 h later, rats were administered a second free-swim probe trial to assess retention of spatial bias. All age/drug groups exhibited a spatial bias on the acquisition probe, with adults generally outperforming the aged rats. On the retention probe, this spatial bias continued to be shown by adult rats, regardless of treatment. For the aged group, in contrast, only MK-801-injected rats maintained a spatial bias on the retention probe, suggesting that NMDAR activity may be involved in rapid forgetting during aging. Because blockade of NMDARs also may impair new learning, which may, in turn, protect previously stored information from retroactive interference, rats in a second experiment received post-training injections of scopolamine (0.05 mg/kg), a compound known to inhibit learning. However, scopolamine did not enhance retention in the aged group, consistent with the hypothesis that MK-801 influenced memory in aged rats through its actions on NMDAR-dependent synaptic plasticity.

INTRODUCTION

Aging and age-related neurodegenerative diseases are commonly associated with a decline in cognitive function. Of particular sensitivity to the aging

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process are behaviors that depend on the integrity of the hippocampus, such as spatial navigation (Geinisman, deToledo-Morrell, Morrell, & Heller, 1995). Deficits in spatial cognition are consistently observed in aged rodents performing the Morris swim task (Diana, Domenici, de Carolis, Loizzo, & Sagratella, 1995; Rasmussen, Schliemann, Sorensen, Zimmer, & West, 1996; Foster, Barnes, Rao, & McNaughton, 1991; Gage, Dunnett, & Bjorklund, 1984; Mabry, McCarty, Gold, & Foster, 1996; Rapp, Rosenberg, & Gallagher, 1987). A general finding is that aged individuals exhibit more rapid forgetting over an extended period of time relative to adults. Although the mechanisms underlying this diminished retention remain unknown, increasing emphasis has been placed on alterations in hippocampal physiology, including neural plasticity (Geinisman et al., 1995; Gallagher, Landfield, McEwen, Meaney, Rapp, Sapolsky, & West, 1996).

Glutamate receptors of the *N*-methyl-D-aspartate receptor subtype (NMDAR) are crucial for the induction of several forms of synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD) (for review, see Bear & Malenka, 1994; Foster & Norris, 1997). During aging, NMDAR-dependent synaptic plasticity undergoes specific alterations. In particular, induction of LTP using threshold stimulation parameters is diminished (Deupree, Bradley, & Turner, 1993; Moore, Browning, & Rose, 1993), and the decay of LTP over a period of days is accelerated in memory-impaired aged rats (Barnes & McNaughton, 1985; deToledo-Morrell, Geinisman, & Morrell, 1988). In contrast to LTP, susceptibility to the induction of LTD and the reversal of LTP is augmented during aging (Norris, Korol, & Foster, 1996), providing a rare example of increased synaptic plasticity with advanced age. The importance of this finding may be considerable, since theoretical reports and empirical data indicate that synaptic function is regulated by the interaction of LTP and LTD mechanisms (Hrabetva & Saktor, 1996; Mayford, Wang, Kandel, & O'Dell, 1995; Oliet, Malenka, & Nicoll, 1996; Oliet, Malenka, & Nicoll, 1997). Consequently, it has been suggested that enhanced LTD during aging may underlie the aforementioned age-related deficits in LTP, making synaptic depression a potential candidate mechanism for increased forgetting (Foster & Norris, 1997; Norris et al., 1996).

Because LTD and LTP-reversal in the aged rat are inhibited by antagonism of the NMDAR (Norris et al., 1996), the current research was undertaken to test the paradoxical hypothesis that NMDAR blockers, which disrupt the acquisition of spatial information when given before training, should facilitate retention of a spatial task when given after training. However, in addition to blocking synaptic plasticity it was reasonable to suspect that MK-801 could affect memory through other processes, such as the inhibition of new learning and retroactive interference. Thus, in a second experiment, aged and adult rats received post-training injections of another compound known to inhibit learning (i.e., scopolamine). The findings showed that aged rats which received injections of the NMDAR antagonist MK-801 immediately following training on the spatial version of the Morris water maze continued to exhibit significant retention of the spatial task over a 24-h period. In contrast, aged rats that received post-training injections of scopolamine or vehicle did not exhibit significant retention over 24 h. The results are consistent with the hypothesis that age-related changes in NMDAR-dependent synaptic plasticity are involved in impaired retention during aging.

EXPERIMENT 1

Methods

Subjects. Subjects were 23 adult (3–6 mos) and thirty-three aged (20–24 mos) male Fischer-344 rats, obtained from the National Institute of Aging's colony at Harlan. Animals were individually caged, maintained on a 12:12 h light–dark cycle, and had access to rat chow and water *ad libitum*.

Apparatus. The water maze was a black circular pool (164 cm in diameter, 45 cm in height) located in a well lit room and filled with water heated to 27°C. The subject's movement in the pool was recorded on videotape and analyzed off-line using a Columbus Instruments tracking system. A black platform (12 cm in diameter), located in the center of one of four quadrants of the pool, allowed rats to escape the water.

Drugs. Animals received intraperitoneal (i.p.) injections of either (+)-10,11-dihydro-5methyl-5H-dibenzo(a,b)cycloheptene-5,10 imine (MK-801, Research Biochemicals International) (0.05 mg/kg, dissolved in H_2O) or vehicle alone. Final volume for both MK-801 and vehicle injections was 1 mL/kg. This dose was chosen because previous research indicates that ~0.05 mg/kg MK-801 impairs the acquisition of spatial information without eliciting motor disturbances over a 24-h period (Jerram, Smith, & Darlington, 1996; McLamb et al., 1990; Parada-Turska & Turski, 1990; Whishaw & Auer, 1989; Ylinen, Pitkanen, Sirvio, Hartikainen, Sivenius, Koivisto, & Riekkinen, 1995). Rats were randomly assigned to each drug condition.

Cue discrimination training. Visual contrast between the escape platform and the surrounding room was increased by wrapping the escape platform with white tape, elevating it 1.5 cm above the water's surface, and encircling the pool with black curtains. Prior to cue discrimination training, rats were placed in the water and permitted to mount the escape platform from three different locations. Following the third mount, rats remained on the escape platform for 60 s before being returned to their home cages to await the first training trial (~20 min). Training consisted of six blocks of three trials, with an intertrial interval of 30 s and an interblock interval of 20–30 min. Rats remained on the platform between trials and in home cages (under a heat lamp) between blocks. On each trial, the rat was placed in the water (facing the wall) at one of eight equally spaced locations along the perimeter of the pool. Starting and platform locations were randomized across trials. Rats were permitted 60 s to navigate to the escape platform. If the platform was not located within the allotted time, rats were gently guided to the platform where they remained until the next trial. Path length traveled to escape was used to measure performance on each trial. Animals that could not consistently navigate to the platform were assumed to have sensory-motor, or motivational deficits and were eliminated from the study. Three days following the cue discrimination task, the remaining rats received spatial training.

Spatial training. In the spatial task, the escape platform was all black and located just beneath the water's surface. The platform remained in the same quadrant across trials and the curtains surrounding the pool were removed, revealing a number of extra-maze cues throughout the room (computer, ladder,

cabinets, wall posters, lamps). Starting locations were randomized across trials. Training consisted of six blocks of three trials (60 s/trial) with an intertrial interval of 30 s and an interblock interval of 20–30 min. Path length traveled to escape was used to measure performance on each trial.

Acquisition and retention testing. After the last spatial training block (~20 min), a probe trial (acquisition probe) was delivered. In probe trials, the platform was removed from the pool allowing the rats to swim freely for 60 s. After the acquisition probe, the platform was reintroduced to the pool (in the same location as during training) and rats received a "refresher" block of three trials. Rats were then injected with either MK-801 or vehicle and returned to their home cages where they remained for approximately 24 h until delivery of a second probe trial (retention probe). Percent time spent searching each quadrant and the number of platform crossings (number of times the animal crosses the area where the platform was located) was calculated for each probe trial.

Statistical analyses. For training on cue and spatial discrimination tasks, path length traveled by each animal was averaged across the three trials within each block. These block means were subjected to repeated-measures ANOVA to detect effects of training and age. Percent time spent in the goal quadrant and the number of platform crossings for each of the probe trials were also analyzed using repeated measures ANOVA. For each of the four experimental groups (aged vehicle, aged MK-801, adult vehicle, adult MK-801), Student's *t*-tests were used to determine whether the percent time spent in the goal quadrant differed significantly from chance (i.e., 25%). Significance for all statistical tests was set at $p < .05$.

Results

Cue discrimination. Fifteen aged rats were unable to complete swim training in the cue discrimination task and were not included in the analyses. The results of the cue discrimination task are illustrated in Fig. 1A. Significant effects of age [$F(1, 175) = 17.725$, $p < 0.001$], training [$F(5, 175) = 5{,}195$, $p < 0.0001$], and an age × training interaction [$F(5, 175) = 2.4$, $p < 0.05$] were found. Although both age groups exhibited a decrease in path length from the first to the last training block [aged, $F(5, 70) = 3.4$, $p < 0.01$, $n = 16$]; adult, $F(5, 105) = 11.22$, $p < 0.0001$, $n = 23$], adults showed a greater reduction in path length by the end of training.

Spatial discrimination. For spatial discrimination training, significant effects of age [$F(1, 210) = 9.791$, $p < 0.01$] and training [$F(6, 210) = 35.159$, $p < 0.0001$] were revealed (Fig 1B). Again, even though both age groups exhibited learning [aged, [$F(6, 84) = 14.119$, $p < 0.0001$]; adult $F(6, 126) = 23.574$, $p < 0.0001$], path length for adults was significantly shorter than that for the aged group.

Acquisition and retention testing. Performance on acquisition and retention probes for each age/drug group is shown in Fig. 2. Overall, adults spent more time searching the goal quadrant on both probe trials. Follow-up ANOVAs within each age group indicated a trial × drug interaction only for aged rats [$F(1, 14) = 4.616$, $p < 0.05$], attributable to better performance by MK-

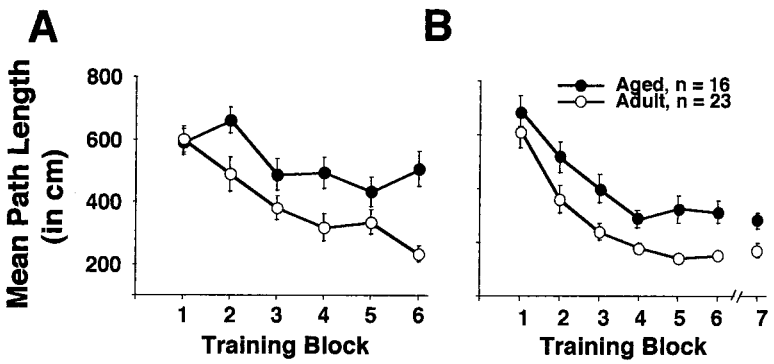

FIG. 1. Effect of age on acquisition of cue (A) and spatial (B) discrimination in Experiment 1. Mean path length for aged (filled circles) and adult rats (open circles) is plotted on the *y* axis as a function of training block. Error bars equal SEM.

801-treated rats on the retention probe relative to age-matched vehicle-treated controls. Further inspection using Student's *t*-tests indicated that, for the acquisition probe, all groups exhibited differential search strategies (i.e., percent of time in goal quadrant was greater than 25%) [aged vehicle, $t(8) = 6.08$, $p < 0.001$; aged MK-801, $t(8) = 5.209$, $p < 0.001$; adult vehicle, $t(13) = 8.153$, $p < 0.0001$; adult MK-801, $t(8) = 8.739$, $p < 0.0001$] (Fig 2A). Conversely, during the retention probe, this differential search strategy was maintained by all groups except the aged vehicle-treated group [aged MK-801, $t(8) = 5.875$, $p < 0.001$, adult vehicle, $t(13) = 2.9$, $p < 0.02$; adult MK-801, $t(8) = 5.563$, $p < 0.001$] (Fig 2B).

The improved retention performance of aged animals, treated with MK-801, was confirmed by analyses of platform crossings (Table 1). Again, adults exhibited greater performance on both probe trials [$F(1, 34) = 11.087$, $p < 0.001$] and an overall reduction in the number of platform crossings was

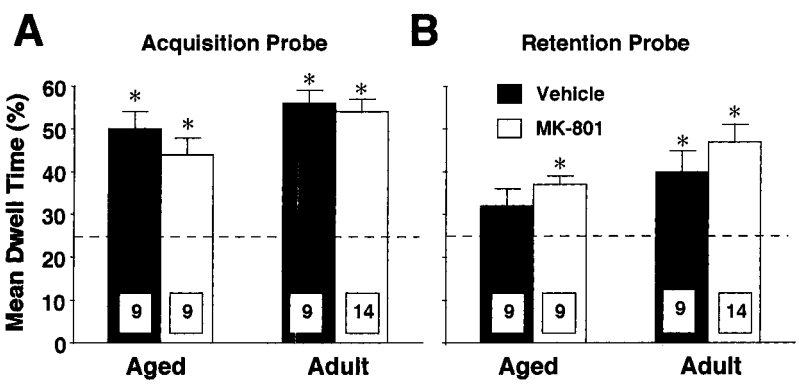

FIG. 2. Post-training administration of MK-801 enhances retention of place learning. Mean dwell time in the goal quadrant (% of total swim time) for acquisition (A) and retention (B) probe trials is plotted on the *y* axis. Animals receiving vehicle or MK-801 are represented by filled and open columns, respectively. Dashed line indicates the percent dwell time expected from chance alone (i.e., 25%). Asterisks denote a significant difference from chance. Note that in the retention probe (B), all groups but the aged-vehicle treated rats performed above chance levels. *n* for each age/drug group is provided in the appropriate column. Bars equal SEM.

TABLE 1
Number of Goal Crossings in Acquisition and Retention Probes for Experiment 1

		Probe	
Age	Drug	Acquisition	Retention
Aged	Vehicle	3.6 ± .6	1.4 ± .5*
	MK-801	3 ± .4	2.78 ± .4
Adult	Vehicle	5.2 ± .4	2.5 ± .6*
	MK-801	6.2 ± .4	3.2 ± .7*

Note. Values are means ±SEM. Asterisks next to retention probe values indicate significant reductions from respective acquisition probe values. $p < .05$.

observed across the 24 h interval. Interestingly, the age × trial interaction reached significance [$F(1, 34) = 10.235$, $p < 0.01$], and the age × trial × drug interaction approached significance [$F(1, 34) = 3.28$, $p = 0.07$]. Follow-up ANOVAs within each age group demonstrated a trial × drug interaction only for aged rats [$F(1, 17) = 6.274$, $p < 0.02$]. These results were due to the fact that, in contrast to all other age/drug groups, MK-801-treated aged rats did not exhibit a substantial reduction in the number of platform crossings from the acquisition to the retention probe trial [aged vehicle, $F(1, 17) = 14.4$, $p < 0.01$; adult vehicle, $F(1, 25) = 42.26$, $p < 0.0001$; adult MK-801, $F(1, 25) = 14.09$, $p < 0.01$]. Together, the evidence suggests that MK-801 improves retention in an age-dependent manner.

EXPERIMENT 2

The findings of the previous experiment indicate that post-training injections of MK-801 enhance the retention of spatial discrimination in aged rats. Although the results are consistent with the idea that MK-801 improves memory via blockade of synaptic plasticity, it should be noted that this drug influences a number of other neural processes that may also contribute to memory function. For instance, NMDAR antagonists impair the acquisition of new information (e.g., Caramanos & Shapiro, 1994; Morris, 1988; Morris, Anderson, Lynch, & Baudry, 1986; Robinson, Crooks, Shinkman, & Gallagher, 1989). As such, MK-801 may protect previously stored information from retroactive interference.

To address this alternative possibility in Experiment 2, rats were injected with the cholinergic antagonist scopolamine following spatial discrimination training. Similar to MK-801, scopolamine impairs the acquisition of spatial information (e.g. Markowska, Olton, & Givens, 1995). Unlike NMDAR antagonists, however, cholinergic antagonists have little or no effect on the induction of LTD (Bear & Abraham, 1996).

Methods

All aspects of this experiment were identical to those in Experiment 1. The only exception being that rats (seven adult and five aged) were injected with

scopolamine hydrobromide (0.05 mg/kg, i.p.) following spatial discrimination training. Seven adult and five aged rats were used in this experiment.

Results

Cue discrimination. Figure 3A illustrates performance on cue discrimination training. A significant effect of training was found [$F(5, 50) = 4.605$, $p < 0.01$], indicating that, overall, path length decreased across blocks.

Spatial discrimination. For spatial discrimination training, significant effects of age [$F(1, 60) = 5.98$, $p < 0.05$] and training [$F(6, 60) = 18.195$, $p < 0.0001$] were revealed (Fig 3B). Similar to Experiment 1, both age groups exhibited learning [aged, [$F(6, 34) = 7.6$, $p < 0.0001$]; adult $F(6, 48) = 11.69$, $p < 0.0001$], however, path length for adults was significantly shorter than that for the aged group.

Acquisition and retention testing. Performance on acquisition and retention probes for each age group is shown in Fig. 4. A repeated measures ANOVA revealed a significant effect of age [$F(1, 10) = 12.29$, $p < 0.01$], in which adults spent significantly more time than aged rats in the goal quadrant on both probe trials. Student's *t*-tests comparing the percent time spent in the goal quadrant to chance indicated that, for the acquisition probe, both groups exhibited differential search strategies [aged, $t(4) = 4.24$, $p < 0.02$; adult, $t(6) = 9.323$, $p < 0.0001$] (Fig. 4A). During the retention probe, however, this differential search strategy was maintained only for the adult group [$t(6) = 3.89$, $p < 0.01$] (Fig. 4B).

Analysis of the number of platform crossings for the acquisition and retention probes (Table 2) revealed significant effects of age [$F(1, 10) = 17.55$, $p < 0.01$] and trial [$F(1, 10) = 13.77$, $p < 0.01$]. Overall, adults crossed the escape platform more than aged rats on both probe trials and the number of crossings decreased on the retention probe trial for both age groups [aged, $F(1, 9) = 7.11$, $p < 0.05$; adult [$F(1, 13) = 8.23$, $p < 0.05$]. Thus, aged rats injected with scopolamine failed to exhibit significant retention of spatial information, similar to vehicle-treated aged rats in Experiment 1.

DISCUSSION

The main conclusion of this study is that the NMDAR antagonist, MK-801, enhances retention in aged rats when administered after training. Similar memory-enhancing effects of MK-801 have been reported for young animals using other hippocampal-dependent behavioral assays (Mondadori, Weiskrantz, Buerki, Petschke, & Fagg, 1989). However, other reports have indicated no effect, or impaired retention of a water maze task following post-training injections of MK-801 (Mondadori et al., 1989; Packard & Teather, 1997). The current study had distinct advantages for examining the acquisition and retention of spatial information. First, in the current report, rats underwent 18 training trials over the course of 2–3 h, whereas daily training sessions in the other studies consisted of only one to eight trials delivered over the course of minutes. Thus, the more extensive training endured by rats in the current research may have permitted a greater level of acquisition prior to drug delivery. Second, spatial discrimination in the current report was determined

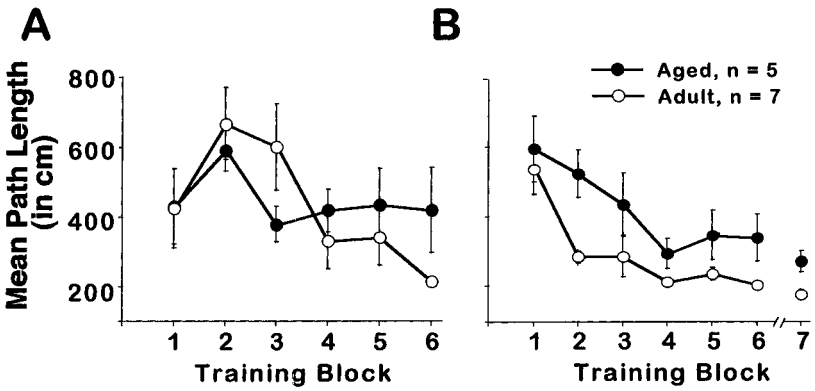

FIG. 3. Effect of age on acquisition of cue (A) and spatial (B) discrimination in Experiment 2. Mean path length for aged (filled circles) and adult rats (open circles) is plotted on the *y* axis as a function of training block. Error bars equal SEM.

using "free-swim" probe trials, which facilitates the distinction between spatial and nonspatial strategies. In contrast, the previous studies used only escape latency measures. While a decrease in latency is indicative of learning, it is unclear from this measure alone whether a spatial or non-spatial strategy is employed to navigate to the platform (Gallagher, Burwell, & Burchinal, 1993). This problem may be substantial if MK-801 influences spatial and nonspatial memory in different ways.

Although both age groups exhibited learning on cue and spatial tasks, age differences in path length were observed in both Experiments 1 and 2. This difference may be related to the age of the animals tested. Our previous work comparing 9- and 24-mos old animals indicated only small differences in path length using a similar training paradigm (Foster et al., 1991). Perhaps more importantly, the pool used in the current report was considerably larger than that used in our previous study (164 cm vs 120 cm), which undoubtedly

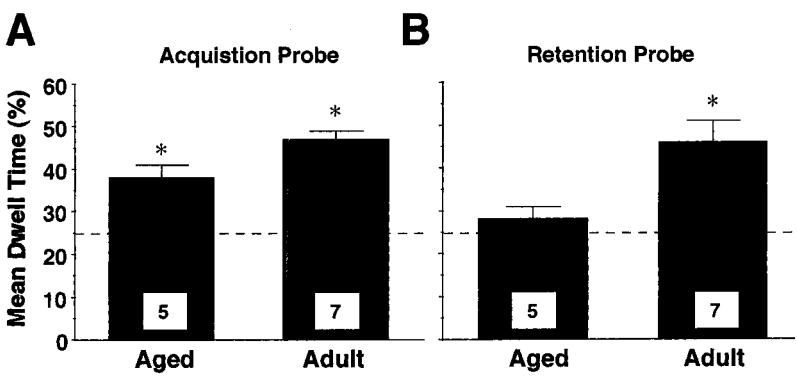

FIG. 4. Effects of scopolamine on the retention of place learning. Mean dwell time in the goal quadrant (% of total swim time) for acquisition (A) and retention (B) probe trials is plotted on the *y* axis. Dashed line indicates the percent dwell time expected from chance alone (i.e., 25%). Asterisks denote a significant difference from chance. Note that in the retention probe (B), only adults performed above chance levels. *n* for each age/drug group is provided in the appropriate column. Bars equal SEM.

TABLE 2
Number of Goal Crossings in Acquisition and Retention Probes for Experiment 2

	Probe	
Age	Acquisition	Retention
Aged	3 ± .3	1.4 ± .5*
Adult	5.4 ± .1	2.8 ± .1*

Note. Values are means ±SEM. Asterisks next to retention probe values indicate significant reductions from respective acquisition probe values. $p < 0.05$.

lengthened the amount of swimming, especially during the early phases of training. In fact, path length for each age group on the first two training blocks was more than double that reported by Foster et al. (1991). Thus, the high elimination level of aged rats following the cue discrimination task, and the inability of the remaining aged rats to achieve adult-like levels of performance may be attributable to a fatigue effect, rather than a learning deficit.

There were at least two indications that MK-801's effects on retention were more pronounced for aged animals. First, while all MK-801-treated rats spent more time in the goal quadrant on the retention probe than control rats, only the aged control group failed to search the goal quadrant above chance levels during retention testing. Thus, in contrast to adults, the retention differences between MK-801-treated and vehicle-treated aged rats may have been underestimated, since search time for the aged control group would be expected to drop no lower than 25%. The finding that vehicle-treated aged rats failed to exhibit a differential search strategy on the retention probe trial is similar to previous reports that have observed rapid forgetting in aged animals (e.g. Barnes & McNaughton, 1985; Diana et al, 1995; Rasmussen et al, 1996; Foster et al., 1991; Gage et al., 1984; Gold, McGaugh, Hankins, Rose, & Vasquez, 1981; Linder, Balch, & VanderMaelen, 1992; Mabry et al., 1996; Rapp et al., 1987; Winocur, 1988). Secondly, when the number of platform crossings was examined for both probe trials (Tables 1 and 2), each group except the aged MK-801 rats exhibited a drop in the number of crossings from the acquisition probe to the retention probe, indicating that aged rats injected with MK-801 continued to focus their search to the location that had contained the platform.

The benefits of MK-801 in facilitating retention may relate to altered synaptic plasticity during aging. Specifically, NMDAR blockade may inhibit LTD-like processes which are enhanced in the aged rat. Functional modifications in hippocampal synaptic transmission properties provide the best correlates for cognitive decline during aging, and as such, may underlie rapid forgetting on tasks that require an intact hippocampus (Barnes, Treves, Rao, & Shen, 1994; Gallagher et al., 1996; Geinisman et al., 1995). It has been suggested that the increased susceptibility to LTD in aged rats may contribute to reduced synaptic strength and accelerated LTP decay (Foster & Norris, 1997). Thus, a shift in plasticity processes, in favor of LTD, may provide a mechanistic basis for rapid forgetting in the aged animal (Foster & Norris, 1997).

This argument predicts that NMDAR antagonists, which inhibit LTD induction, should facilitate retention of spatial information when given after acquisition. The results of the current study were consistent with this prediction. Alternatively, NMDAR blockade may influence other processes that could contribute to forgetting, such as retroactive interference, or the modulation of neural (i.e. theta) activity (Pitkanen et al., 1995; however also see Whishaw and Auer, 1989). However, in the present study, aged rats injected with scopolamine at a dose shown to inhibit learning and theta activity (Markowska et al., 1995), failed to exhibit significant retention of spatial information. The results are, at the least, consistent with the idea that MK-801 differentially influenced memory in aged and adult rats by interacting with age-dependent changes in synaptic plasticity. Some caution in interpreting this latter finding is warranted, however, since spatial bias in the aged group on the acquisition probe, although significant, was not striking. The parametric space available for determining a statistical effect of scopolamine for aged rats therefore may have been relatively limited. It will be important for future research to determine if the effects of MK-801 on retention in aged rats are specific to its actions on hippocampal synapses and also to specify whether MK-801 inhibits LTD in aged animals at a behaviorally relevant dose.

The results raise the intriguing possibility that normal learning and memory reflect the balance and influence of LTP and LTD. As such, the increased rate of forgetting in older animals may result from an activity-dependent mechanism analogous to LTD. Similar to aged rats, adult rats can also exhibit NMDAR-dependent synaptic depression, albeit the susceptibility to LTD-induction is reduced in young adults (Foster and Norris, 1997; Norris, et al., 1996). If processes which are mechanistically similar to LTD underlie forgetting, then one would expect that NMDAR blockade should improve retention in younger animals as well. While adult rats injected with MK-801 generally spent more time in the goal quadrant on the retention probe than age-matched control rats (Figure 2), a significant effect of drug was not observed. Because the 24 hr interval between the two free-swim probes does not appear to challenge the retention ability of adults, (i.e. all adults perform well on the retention probe), it is plausible that our retention task lacked the sensitivity to reveal any effects of MK-801 on memory in the adult group.

Induction of LTD is a Ca^{2+}-dependent process. Dysregulation of Ca^{2+} is a common observation in neurons from aged mammals. A contributing source to altered regulation of neuronal Ca^{2+} is an increase in L-type voltage-dependent Ca^{2+} channels (Campbell, Hao, Thibault, Blalock, & Landfield, 1996; Thibault & Landfield, 1996). The fact that L-channel blockade ameliorates age-related changes in neurophysiology (Moyer & Disterhoft, 1994; Moyer, Thompson, Black, & Disterhoft, 1992), synaptic plasticity (Norris, Halpain, & Foster, 1998) and cognition (Deyo, Straube, & Disterhoft, 1989; Ingram, Joseph, Spangler, Roberts, Hengemihle, & Fanelli; Levere & Walker, 1992; Kowalska & Disterhoft, 1994; Straube, Deyo, Moyer, & Disterhoft, 1990; Soloman, Wood, Groccia-Ellison, Yang, Fanelli, & Mervis, 1995) indicates a potentially important link between Ca^{2+}-dependent processes, such as synaptic plasticity, and memory. Together, the results may provide a useful theoretical framework for exploring the neurobiological basis of cognitive decline during aging.

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