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Contribution of *N*-methyl-D-aspartate receptors to attention and episodic spatial memory during senescence

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ABSTRACT

A decrease in *N*-methyl-D-aspartate receptor (NMDAR) function is associated with age-related cognitive impairments. However, NMDAR antagonists are prescribed for cognitive decline associated with age-related neurodegenerative disease, raising questions as to the role of NMDAR activity in cognitive function during aging. The current studies examined effects of NMDAR blockade on cognitive task that are sensitive to aging. Young and middle-age rats were trained on the five-choice serial reaction time task (5-CSRTT) and challenged with MK-801 (0.025, 0.05, and 0.1 mg/kg or vehicle). Attention deficits were apparent in middle-age and performance of young and middle-age rats was enhanced for low doses of MK-801 (0.025 and 0.05). The beneficial effects on attention were reversed by the highest dose of MK-801. Older animals exhibited a delay-dependent impairment of episodic spatial memory examined on a delayed-matching to place water maze task. Similarly, a low dose of MK-801 (0.05 mg/kg) impaired performance with increasing delay and aged animals were more susceptible to disruption by NMDAR blockade. Despite MK-801 impairment of episodic spatial memory, MK-801 had minimal effects on spatial reference memory. Our results confirm that NMDARs contribute to rapidly acquired and flexible spatial memory and support the idea that a decline in NMDAR function contributes to the age-related impairments in cognition.

1. Introduction

Cognitive aging is associated with weakening of episodic memory and executive function which, in the case of Alzheimer's disease, can progress to more severe cognitive impairments and dementia (Albert, 2011; Alexander et al., 2012). In the case of aging, cognitive decline is associated with altered Ca^{2+} regulation and impaired synaptic function, including a decrease in the function of *N*-methyl-D-aspartate receptors (NMDARs) (Foster, 2007, 2012; Foster & Norris, 1997). The emergence of deficits in episodic memory and executive function are linked to decrease in the NMDAR-mediated synaptic responses in the hippocampus and prefrontal cortex (PFC), respectively (Foster, 2012; Foster & Norris, 1997; Guidi, Kumar, & Foster, 2015; Kumar & Foster, 2013). Similarly, β-amyloid (Aβ) impairs synaptic plasticity (Shankar et al., 2007, 2008; Walsh et al., 2002) and rapidly decreases NMDAR responses (Dewachter et al., 2009; Lacor et al., 2007; Snyder et al., 2005), which may contribute to the onset of memory deficits associated with the early stages of Alzheimer's disease.

While the onset of impaired episodic memory is associated with synaptic dysfunction, clinical dementia is more likely related to loss of connectivity throughout the brain, including cell death (DeKosky & Scheff, 1990; Scheff, Price, Schmitt, DeKosky, & Mufson, 2007; Terry et al., 1991). Similarly, while a decline in NMDAR activation could underlie disruption of synaptic function early in Alzheimer's disease, over activation of NMDARs may contribute to cell death. The idea that NMDAR activity contributes to neurotoxicity provides a basis for use of NMDAR antagonists to treat Alzheimer's disease in order to limit the progression of cell loss (Lipton, 2006; Rogawski & Wenk, 2003). However, there is considerable confusion concerning the utility of NMDAR modulators to treat cognitive aging and Alzheimer's disease. The low affinity activity-dependent NMDAR channel antagonist, memantine, has had mixed success in treating the symptoms of dementia and the progression of the disease (Schneider, Dagerman, Higgins, & McShane, 2011).

There are several reasons to predict that NMDAR blockade will have detrimental effects on cognition in older animals. In young animals, NMDAR antagonists impair the rapid acquisition and

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retention of flexible spatial information (i.e. episodic spatial memory) and an age-related impairment in episodic memory is associated with the decline in NMDAR function (Foster, 2012). Further, a decline in NMDAR function may contribute to the progression of neurodegeneration and cognitive decline. Synaptic NMDAR activity induces the expression of genes involved in the maintenance of neuronal health, which could protect cells from neurodegenerative processes (Gleichmann et al., 2012; Hardingham & Bading, 2010; Papadia et al., 2008). In the same way, a decline in NMDAR activity could underlie the decreased expression of synaptic and neuroprotective genes in aged-memory impaired animals (Aenlle & Foster, 2010; Blalock et al., 2003). Indeed, due to a decline NMDAR function with advancing age, it might be expected that older subjects are more susceptible to impairments following NMDAR blockade (Ingram et al., 1992).

Interestingly, some studies have reported that activity-dependent NMDAR channel antagonists at low doses have little effect or impair memory and yet improve attention and executive function in humans (Ferris, Schneider, Farmer, Kay, & Crook, 2007; Nakamura, Kitamura, Homma, Shiosakai, & Matsui, 2014; Rammsayer, 2001; Riepe et al., 2007; Wroolie et al., 2009) and in animals (Benn & Robinson, 2014; Higgins, Ballard, Enderlin, Haman, & Kemp, 2005; Pehrson, Bondi, Totah, & Moghaddam, 2013; Smith et al., 2011). Given that attention is an important factor in multiple cognitive processes that decline with aging, including executive function and memory, an understanding the dose dependent effect of NMDAR blockade with regard to age-sensitive cognitive processes is a critical question with clinical significance.

In the current study, low doses of the activity-dependent NMDAR channel blocker, MK-801, were used to examine spatial episodic memory and attention, cognitive processes that are sensitive to aging. We confirmed that performance on an attention task, which depends on the PFC, is impaired in middle-age rats (Guidi et al., 2015). NMDAR blockade produced a dose-dependent, biphasic enhancement in measures of attention for conditions that tax attentional demand. This enhancement was reversed by a higher dose of MK-801. An age-dependent impairment in retention of rapidly acquired episodic spatial memory was observed for the delayed-matching to place (DMTP) task, as the retention delay was increased beyond 30 min. MK-801 (0.05 mg/kg) impaired spatial episodic memory for a 30 min delay and aged animals were more susceptible to disruption. Finally, NMDAR blockade had minimal effects on spatial reference memory. The results indicate differential involvement of NMDARs in cognitive processes that depend on the PFC and hippocampus. NMDAR blockade and aging interact to impair hippocampal-dependent episodic memory, a form of memory that declines early in aging and Alzheimer's disease. In contrast, NMDARs are not essential for spatial reference memory.

2. Methods

2.1. Subjects

For study 1, involving the 5-choice serial reaction time task (5-CSRTT), young (3–6 months, $n = 14$) and middle-age (10–14 months, $n = 23$) male Fisher 344 rats were employed. For study 2, involving spatial memory on the water maze, young (4–6 months, $n = 10$) and aged (18–20 months, $n = 32$) male Fisher 344 rats were employed. Five aged animals were unable to complete training on the cue or spatial tasks and were not included in the analysis. Animals were obtained from the National Institute on Aging colony (Taconic) through the University of Florida Animal Care and Service facility. All procedures involving animal subjects were reviewed and approved by the Institutional Animal Care and Use Committee and were in accordance with guidelines established by the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals. The experimental timeline for behavioral characterization and drug testing is depicted in Fig. 1.

2.2. Behavioral tests

2.2.1. 5-Choice serial reaction time task (5-CSRTT)

2.2.1.1. Apparatus. Behavioral training of animals on 5-CSRTT was conducted as previously published (Guidi et al., 2015). Testing was conducted in two identical standard rat testing chambers (30.5 × 25.4 × 30.5 cm; Coulbourn Instruments, Allentown, PA) with metal front and back walls, and transparent Plexiglas sidewalls. Each testing chamber was housed in a sound-attenuating cubicle, illuminated by a 3 W house light. Each cage was equipped with a recessed food pellet delivery trough, located approximately 2 cm above the grid floor, in the center of the back wall. Each trough was fitted with a photobeam sensor to detect head entries

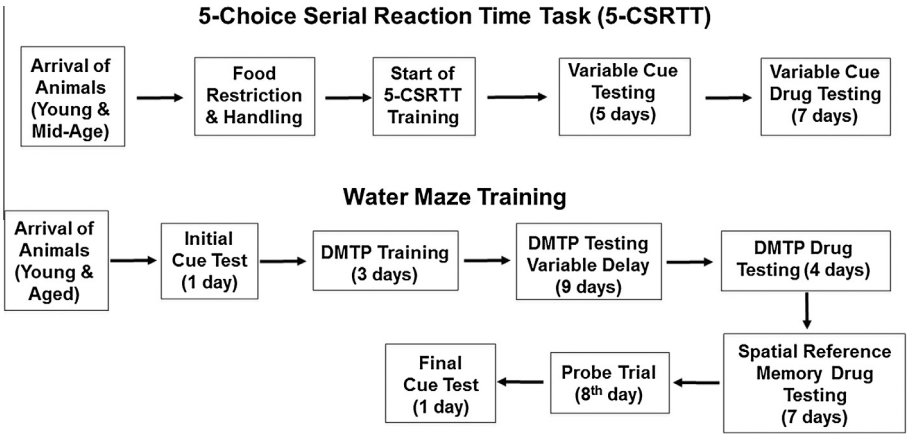

Fig. 1. Schematic of the experimental Timeline. Young and middle-age animals were behaviorally tested on the 5-CSRTT which involved food restriction, training to respond to the light cue, training on a variable cue duration paradigm, and finally testing the effects of drug treatment on the variable cue duration paradigm. For the water maze, young and aged animals were initially tested on the cue discrimination version of the task. This was followed by training on a DMTP task, including training with a variable delay (1, 30, or 120 min) between trial 1 and trial 2. For drug testing on the DMTP task, animals were injected 30 min before trial 1. At the end of DMTP task, a subset of animals was assigned to receive MK-801 (0.05 mg/kg) or vehicle 30 min before training on a reference memory task. Injection and training continued for 7 days. This was followed by a probe trial on day 8, 30 min after injections. A final cue discrimination task was then introduced.