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Long-term continuous, but not daily, environmental enrichment reduces spatial memory decline in aged male mice

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Abstract

Although environmental enrichment improves spatial memory and alters synaptic plasticity in aged rodents, it is unclear whether all types of enrichment treatments yield similar benefits. The present study examined the effects in aged male mice of three types of enrichment on spatial memory in Morris water maze and radial arm maze tasks, and on levels of the presynaptic protein synaptophysin in several brain regions. Non-enriched young and aged males were compared with males exposed to one of the following treatments for 10 weeks: 5 min of daily handling, 3 h of daily basic enrichment, or 24 h of continuous complex enrichment. Young controls outperformed aged controls in both tasks. Neither daily handling nor daily enrichment affected spatial memory or synaptophysin levels. In contrast, continuous enrichment significantly reduced age-related spatial memory decline in both tasks, such that this group was statistically indistinguishable from young controls in most measures of performance. Continuously enriched mice were also significantly better than other aged mice in several spatial memory measures. Despite these improvements, synaptophysin levels in the continuous enrichment group were significantly lower than those of young and aged controls in the frontoparietal cortex, hippocampus, and striatum, suggesting a negative relationship between synaptophysin levels and spatial memory in aged males. These data demonstrate that different types of enrichment in aged male mice have disparate effects on spatial memory, and that the relationship between enrichment-induced changes in synaptophysin levels and spatial memory in aged males differs from that we have previously reported in aged female mice.

Keywords: Aging; Reference memory; Working memory; Synaptophysin; Hippocampus; Neocortex

1. Introduction

One of the most common approaches to reducing age-related memory decline in humans and rodents has been to develop drugs that augment the function of specific neurotransmitter systems (Barnes, 1998; Bartus, 2000). However, in recent years, growing attention has been given to the use of behavioral treatments, such as environmental enrichment, as methods of alleviating age-related memory impairments. Environmental enrichment generally refers to any treatment that provides cognitive and/or physical stimulation beyond that which would be received in standard housing conditions (Rosenzweig & Bennett, 1996). Control animals in these standard housing conditions are either housed individually (i.e., isolated controls) or housed in small groups (i.e., social controls). Enriched mice are typically housed socially and are also provided with an array of stimulating objects and running wheels for various periods of time.

Among aging rodents, environmental enrichment alleviates age-related impairments in several types of memory and reduces neural dysfunction in related areas of the brain such as the hippocampus and neocortex. For example, in middle-aged rats and mice, enrichment significantly improves spatial reference memory in the Morris water maze (Frick, Stearns, Pan, & Berger-Sweeney, 2003; Kempermann, Kuhn, & Gage, 1998; Pham et al., 1999) and learning in the Hebb-Williams maze

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(Cummins, Walsh, Budtz-Olsen, Konstantinos, & Horsfall, 1973). It also increases forebrain weight (Cummins et al., 1973), neocortical dendritic branching (Green, Greenough, & Schlumpf, 1983), hippocampal neurogenesis (Kempermann et al., 1998), and neocortical and hippocampal neurotrophin levels (Ickes et al., 2000; Pham et al., 1999). Similarly, in aged rats and mice, enrichment improves spatial reference memory in the Morris water maze (Frick & Fernandez, 2003), reverses short-term memory deficits (Soffié, Hahn, Terao, & Eclancher, 1999), and increases spontaneous alternation (Van Waas & Soffié, 1996), incidental learning, and food-seeking behaviors (Warren, Zerweck, & Anthony, 1982). Furthermore, enrichment in aged rats and mice reduces age-induced hippocampal gliosis (Soffié et al., 1999), and increases cortical thickness (Diamond, Johnson, Protti, Ott, & Kajisa, 1985) and presynaptic vesicle number (Nakamura, Kobayashi, Ohashi, & Ando, 1999).

In aged female mice, enrichment-induced improvements in spatial reference memory in the water maze have been associated with increased hippocampal levels of the presynaptic protein synaptophysin (Frick & Fernandez, 2003), a calcium-binding glycoprotein located in the membranes of presynaptic vesicles containing neurotransmitters (Jahn, Schiebler, Ouimet, & Greengard, 1985; Wiedenmann & Franke, 1985). Reductions in synaptophysin have been associated with age-related cognitive decline in normal and demented humans (Liu, Erikson, & Brun, 1996; Sze et al., 1997) and aged rodents (Smith, Adams, Gallagher, Morrison, & Rapp, 2000). Although changes in synaptophysin levels have been most commonly interpreted as reflecting alterations in synapse number, enrichment in aged rats appears to increase the number of vesicles per synapse rather than the number of synapses (Nakamura et al., 1999). An increase in synaptic vesicles may result in increased neurotransmission, which could lead to the mnemonic improvements seen in aging rodents. Although enrichment-induced increases in synaptophysin levels are associated with improved spatial memory in aged female mice (Frick & Fernandez, 2003), it is unclear whether this relationship extends to aged males. This information is important to understanding the neurobiological mechanisms of enrichment-induced mnemonic improvements in aged rodents because similar relationships between increased synaptophysin levels and improved spatial memory have not been observed in middle-aged male and female mice (Frick et al., 2003) or in young female mice (Lambert, Fernandez, & Frick, 2005). The present study is the first to examine this relationship in aged males.

One difficulty in evaluating the effects of environmental enrichment on memory and neurobiology is the wide disparity among enrichment paradigms used by different laboratories. Enriched housing varies in cage size, composition, duration, social complexity, stimulus object complexity, and frequency of object changing. For example, studies have employed very large home cages containing various objects that were moved or replaced daily (Green et al., 1983), every other day (Green et al., 1983; Soffié et al., 1999; Van Waas & Soffié, 1996), twice a week (Ickes et al., 2000; Pham et al., 1999), or when objects deteriorated (Winocur, 1998). Others used smaller home cages with fewer objects that were changed on a daily basis (Frick et al., 2003). Still others did not house rodents with enriching stimuli, but exposed them to enrichment for 3 h/day (Frick & Fernandez, 2003; Rampon et al., 2000). Other parameters that differ among enrichment studies include the amount of experimenter handling (Diamond et al., 1985), inclusion of supplemental food treats (Kempermann et al., 1998), and exposure to sexually receptive females (Warren et al., 1982). The fact that all of these treatments improved memory or neural function in some way seems to suggest that almost any form of enrichment can improve memory in aging rodents. However, this conclusion is complicated by the fact that all of these studies evaluated different types of memory using different tasks. To date, no study has compared the effects of different types of enrichment on memory in aging rodents using the same methods.

Thus, the present study was designed to simultaneously assess the efficacy of three types of environmental enrichment in reducing age-related spatial memory deficits in aged male mice. Aged mice were divided into four groups (all of which were socially housed): controls, daily handling (5 min of daily handling and exploration of a new cage), daily enriched (enriched in a large cage for 3 h/day), and continuously enriched (housed in a very large home cage with 24 h access to numerous toys and running wheels). Young male non-enriched controls were also included to evaluate the extent to which the three enrichment conditions alleviated age-related spatial memory deficits. Spatial reference memory was first assessed in the Morris water maze, and then spatial reference and working memory were simultaneously measured in a water-escape motivated radial arm maze. To examine the relationship between enrichment-induced changes in spatial memory and synaptophysin levels, synaptophysin levels were measured in the hippocampus, neocortex, striatum, and cerebellum. We expected that aged controls would be impaired relative to young controls in both tasks (Bimonte, Nelson, & Granholm, 2003; Frick, Burlingame, Arters, & Berger-Sweeney, 2000). Although daily handling may reduce the stress associated with handling during behavioral testing, this very mild form of enrichment was not expected to improve memory or affect synaptophysin levels. In contrast, because we have previously shown in aged female mice that the daily enrichment treatment enhances spatial reference memory and synaptophysin levels in the hippocampus and neocortex (Frick & Fernandez, 2003), this treatment was expected to attenuate age-related memory decline in both tasks and augment synaptophysin levels in several brain regions. Finally, because continuous enrichment provides a more intense enrichment experience than daily enrichment, improvements produced by this treatment were expected to