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Environmental enrichment fails to rescue working memory deficits, neuron loss, and neurogenesis in APP/PS1KI mice

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Abstract

Environmental enrichment has been used in a variety of transgenic mouse models of Alzheimer's disease (AD), however, with conflicting results. Here we studied the influence of environmental enrichment in a severely affected AD mouse model, showing a multiplicity of pathological alterations including hippocampal neuron loss. APP/PS1KI and wild type (WT) control mice were housed under standard conditions or in enriched cages equipped with various objects and running wheels. Amyloid plaque load, motor and working memory performance, axonopathy, as well as CA1 neuron number and hippocampal neurogenesis were assessed. Although a partial improvement in motor performance was observed, 4 months of enriched housing showed no beneficial effects in terms of working memory, Aβ plaque pathology, or neuron loss in APP/PS1KI mice. In addition, no changes in hippocampal neurogenesis and even an aggravation of the axonal phenotype were detected with a tendency toward a premature death. The APP/PS1KI model represents a model for mild to severe AD showing early behavioral deficits starting at 2 months of age with fast deterioration. Therefore our data might suggest that physical activity and enriched environment might be more beneficial in patients with mild cognitive impairment than in patients with incipient AD.

Keywords: Alzheimer; Axonopathy; Behavior; Enriched environment; Intraneuronal Aβ; Neurogenesis; Neuron loss; Transgenic mice; Amyloid

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of senile dementias with a continuously increasing incidence in the next years and so far only very limited therapeutic options. A number of observational studies reported that people who are physically active seem less likely to develop an age-related dementia in later life (Abbott, et al., 2004; Weuve, et al., 2004). In addition, evidence from retrospective studies suggested an association of reduced AD risk in people being cognitively active in midlife (Friedland, et al., 2001) and prospective 5-year longitudinal studies in aged humans have suggested that participation in cognitively stimulating activities decreases the AD risk (Wilson, et al., 2002). These findings prompted researchers to subject mouse models of AD to paradigms of environmental enrichment, including either increased physical activity, cognitive stimulation, or a combination of both, to prove or disprove hypotheses based on these clinical observations (for review see Nithianantharajah and Hannan, 2006). The results of these studies are, however, fairly inconsistent and show a range of different outcomes. This becomes evident, e.g., in the case of extracellular plaque pathology, where a reduction following enriched housing (Adlard, et al., 2005; Ambree, et al., 2006; Cracchiolo, et al., 2007; Lazarov, et al., 2005), no effect on plaque load (Arendash, et al., 2004; Wolf, et al., 2006), or even an exacerbation of extracellular plaque pathology (Jankowsky et al., 2003, 2005) has been reported. If extracellular plaque loads have an effect on neuron loss is a matter of scientific debates raising the question whether plaque load per se represents a significant outcome to evaluate a given treatment effect on AD patients. Most of the previously used transgenic mouse models show prominent extracel-

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lular plaque deposition, together with modest behavioral phenotypes, however, the effect of environmental enrichment on neuron loss has so far not been examined. The APP/PS1KI mouse model has been demonstrated to develop a very early and aggressive phenotype (Bayer and Wirths, 2008), showing significant hippocampal neuron loss (Breyhan et al., 2009; Casas et al., 2004), memory and motor deficits (Wirths et al., 2008), as well as axonal degeneration at the age of 6 months (Wirths et al., 2007).

The aim of the present study was to investigate whether a rather mild intervention like environmental enrichment and voluntary exercise is effective in an Alzheimer mouse model that might very well reflect the situation of early AD patients at the starting time point of 2 months of age, with only selective memory impairment but no neuron loss. The mice were housed for 4 months in either standard housing (SH) or enriched environment (EE) conditions and behavioral, as well as stereological analyses of hippocampal neuron numbers and neurogenesis were carried out at 6 months of age. Surprisingly, only a partial improvement of the motor phenotype was detected, however, neither the behavioral phenotype nor the CA1 neuron loss or the impaired neurogenesis could be rescued.

2. Methods

2.1. Transgenic mice

The generation of APP/PS1KI and PS1KI mice has been described previously (Casas et al., 2004). APP/PS1KI mice harbored 1 hemizygous APP751SL transgene in addition to homozygous PS1KI. The mice were kept on a C57BL6/J genetic background. In addition C57Bl6/J wild type (WT) mice were used as control animals. All animals were handled according to German guidelines for animal care. Only female mice were used in the current study.

2.2. Housing conditions

At 2 months (m) of age, wild type and APP/PS1KI mice were randomly assigned to either SH or EE housing conditions until the age of 6 months. Standard laboratory cages (33 cm × 18 cm × 14 cm) were used for SH, whereas larger rat cages (55 cm × 34 cm × 20 cm) were used for the EE living conditions (Fig. 1). In both conditions food and water were provided ad libitum and mice were housed in groups of 4–5. In the EE cages the animals additionally had permanent access to a running wheel, as well as a variety of different objects like tunnels, shelters and nesting material, which were rearranged and exchanged weekly. In the behavioral

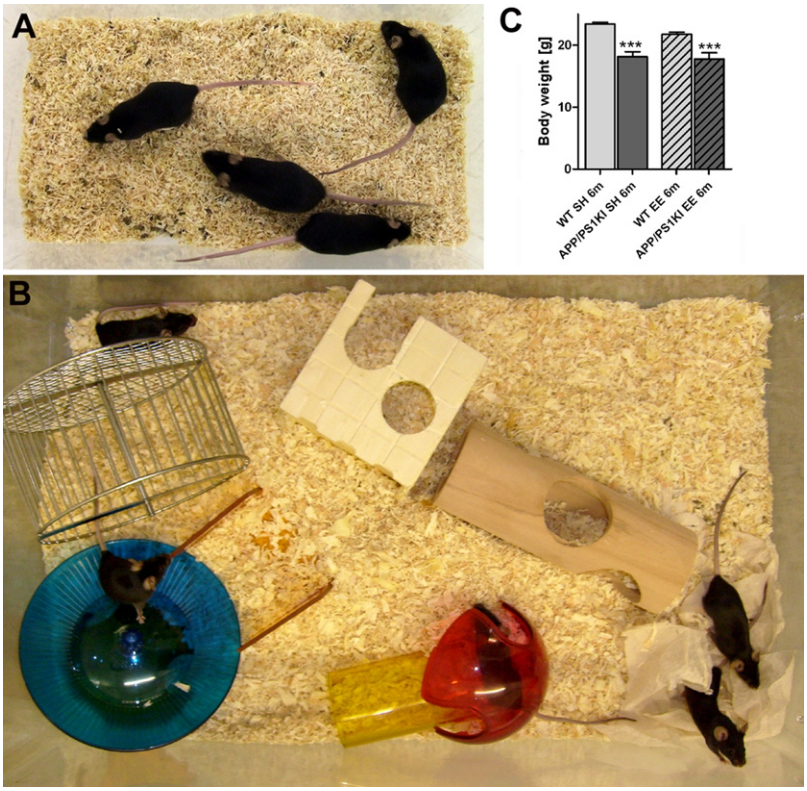

Fig. 1. Female wild type (WT) and APP/PS1KI were randomly assigned to either (A) standard housing (SH) or (B) environmental enrichment (EE) cages where they lived in groups of 4–5 individuals between 2 and 6 months of age. EE cages were equipped with objects of different shapes, colors and textures, a running wheel and nesting material. The environment was modified and rearranged once per week. Housing conditions had no effect on the significantly lower weight of the APP/PS1KI mice (C). All data were given as means ± standard error of the mean (SEM) (***$p < 0.001$).