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BRAIN RESEARCH

Research Report

Selective improvement of cognitive function in adult and aged APP/PS1 transgenic mice by continuous non-shock treadmill exercise

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ABSTRACT

Exercise may contribute to prevention of the cognitive decline and delay the onset of the Alzheimer's disease (AD). We evaluated the effects of continuous non-shock treadmill exercise in adult and aged male APP/PS1 double mutant transgenic mice. Adult (7–8 month-old) and aged (24 month-old) male APP/PS1 transgenic and wild-type mice were randomly assigned to either sedentary or exercise groups. The exercise program included a one-week treadmill acclimatization to adapt to the novel environment. After acclimation, mice ran on a treadmill 5 days/week until sacrificed for pathological analyses. During exercise training, no tail shock was used in the exercise paradigm; only gentle tail touching was used to induce the mice to run, to minimize the stress otherwise associated with treadmill exercise. We found that the exercise program selectively improved the spatial learning and memory associated with an increase in both cholinergic neurons in the medial septum (MS)/vertical diagonal band (VDB) and serotonergic neurons in the raphe nucleus of aged APP/PS1 transgenic mice. In adult APP/PS1 transgenic mice, the exercise paradigm increased exploratory activity and reduced anxiety with an associated increase in numbers of serotonergic neurons in the raphe nucleus. In addition, the exercise paradigm also reduced amyloid-β peptide (Aβ) levels and microglia activation, but not enough to reduce the plaque loading in the hippocampus of the APP/PS1 transgenic mice. Therefore, these findings suggest that there may exist an age-related difference in the effect of continuous non-shock treadmill exercise training on AD.

1. Introduction

Successful treatment for Alzheimer's disease (AD) remains to be developed. Lifestyle treatments for AD, such as exercise, have been studied in both animal and human models (Adlard et al., 2005; Larson et al., 2006). Several epidemiological studies have shown that the transition from a sedentary to an active lifestyle may be sufficient to enhance cognitive abilities and delay the onset of dementia in human and mice (Churchill et al., 2002; Larson et al., 2006; Nichol et al., 2008; Perez and

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Cancela Carral, 2008). At present, the most common exercise modalities in animal studies are the treadmill and the running wheel. Of these, a treadmill exercise regime is closer to human physical training and allows better correlation between the amount of exercise and any potential benefits (Garland et al., 2011). Furthermore, many studies have found that treadmill exercise training with tail shock in animals induced stress (Sennott et al., 2008; Yanagita et al., 2007; Yuede et al., 2009). One recent study also suggests that the repeated short-term stress derived from shock-stimulated treadmill training may overwhelm any benefit to learning and memory (Ang et al., 2006). Therefore, a continuous non-shock treadmill exercise paradigm was used in this study to evaluate the effects of exercise on cognitive function in the AD mouse model.

Pathologic characterization identified senile plaques, neurofibrillary tangles, reactive astrocytes, and activated microglia in the brain of AD patients, which lead to progressive cognitive decline and dementia (Marcello et al., 2008). The core of the senile plaque is the Aβ, of which Aβ1–40 and Aβ1–42 peptides are the most common types. Transgenic mice expressing mutant human genes associated with the familial form of AD offer a good model to study the role of Aβ in AD pathology (Janus, 2004). Transgenic mice with a double genetic mutation in the amyloid precursor protein (APP) and the presenilin 1 (PS1) human mutation result in the deposition of mutant Aβ protein and the formation of amyloid plaques at 9 months of age, with pronounced accumulation after 12 months (McGowan et al., 1999). There is much evidence that exercise in AD rescues spatial learning and memory; the extent of such benefit was dependent on the exercise duration and modality and the subject's age (Berchtold et al., 2010; Garcia-Capdevila et al., 2009; Hoveida et al., 2011; Liu et al., 2009; Lopez et al., 2011; Ren et al., 2010). One study in particular found that 1 month of forced treadmill exercise in aged mice had detrimental effects on motor behavior, and no effects on exploratory activity and cognition parameters (Fabene et al., 2008). Therefore, adult and aged male APP/PS1 double mutant transgenic mice were used to evaluate the effects of a non-shock exercise paradigm in this study.

2. Results

2.1. *Animal body weight was not affected by exercise*

In order to evaluate the exercise effect on physiological status of mice, mouse body weight was measured before and after exercise/sedentary treatment (Fig. 2). Before treatment, the body weight of mice in adult group was lower than aged mice ($F(1,55)=19.0265$, $p<0.001$). APP/PS1 transgenic mice were also lighter than wild-type mice ($F(1,55)=38.4317$, $p<0.001$ for adult group; $F(1,55)=31.7152$, $p<0.001$ for aged group). However, there was no significant interaction of age × genotype ($F(1,55)=2.9511$, $p>0.05$).

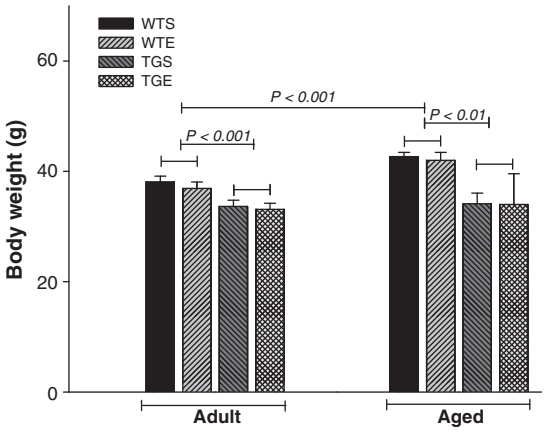

Fig. 2 – Body weight changes in mice treated or not with continuous non-shock treadmill exercise. Data are expressed as means ± S.E.M. ($n=15$ per group for adult mice, $n=6$–9 per group for aged mice).

After the treatment, the body weight of APP/PS1 transgenic mice was still lower than wild-type mice regardless of the age of the mice (adult: $F(1,36)=13.6974$, $p<0.001$; aged: $F(1,15)=13.3692$, $p<0.01$). In addition, there was no significant difference between treatments ($p=0.44$ for adult group; $p=0.75$ for aged group) or genotype × treatment interaction ($p=0.76$ for adult group; $p=0.99$ for aged group). In general, APP/PS1 transgenic mice were lighter, and exercise had no effect on body weight in any of the experimental groups.

In addition, we also conducted metabolic analyses of blood glucose, total cholesterol, and high density lipoproteins on these mice. The exercise paradigm had no effects on the blood metabolic parameters in either wild-type or transgenic mice in both adult and aged groups (data not shown).

2.2. *Exercise did not affect aversive learning and memory in adult or aged APP/PS1 transgenic mice*

After four weeks of treadmill exercise, the aversive learning and memory of mice was assessed by a two-day passive avoidance (PA) test. In both adult and aged mice, the retention of aversive learning and memory was not significantly

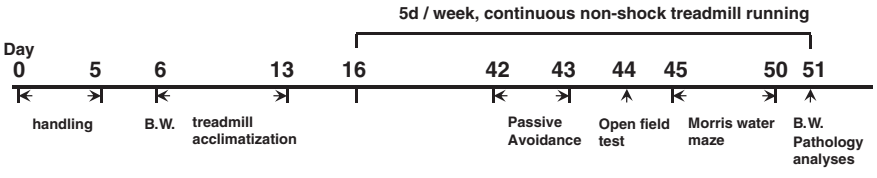

Fig. 1 – Experimental timeline of this study. Body weight (B.W.) was measured before treatment (day 6) and after treatment (day 51). After acclimatization to the treadmill (day 6 to day 13), mice were trained with a continuous non-shock exercise program. During the training period, mice were subjected to a testing session composed of three different behavioral tests: passive avoidance, open field test, and Morris water maze.