Physical Exercise and Dementia

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Approximately 30% of Japanese citizens will be aged 65 or older in 2020, and this ratio will be the highest worldwide. An estimated 4.6 million individuals in Japan and 44 million individuals globally have been diagnosed with dementia. Exercise has been identified as a potential means of preventing or delaying cognitive decline. Several epidemiological studies on older adults demonstrated that gait speed was associated with cognitive function. Randomized control studies on physical exercise interventions also indicated that aerobic exercise is beneficial for cognitive function. In order to determine the effects of short-term treadmill exercise on tau protein modifications, we employed a 3-week treadmill treatment using tau model mice. The results obtained showed increases in oxidative stress, microglial cell proliferation, and C-terminal tau phosphorylation. Previous studies reported that long-term treadmill treatments were beneficial. Therefore, positive compensatory changes may occur with the continuation of treadmill training in mice. The molecular mechanisms underlying the relationship between physical exercise and cognitive function still remain unknown; however, their elucidation may lead to the identification of a novel molecule, which may ultimately result in a cure for dementia.

Key words: exercise, walking, dementia, tau

Introduction

The proportion of elderly citizens in Japan is now the highest worldwide. The aging of Japan has outweighed that in all other nations for a few decades. Approximately 30% of the population will be aged 65 or older in 2020. This proportion will gradually increase and reach 35% in 2040. As a consequence, the percentage of patients with dementia in Japan is also expected to gradually increase. The Hisayama study provided estimates for the percentage of the Japanese population with dementia. Approximately 4.6 million individuals in Japan and 44 million individuals globally were reported to have dementia in 2015. This number will continue to increase in Japan, and will eventually reach 10 million in 2060. Risk factors for dementia need to be identified in an attempt to prevent its development. Several risk factors have

been reported for Alzheimer's disease (AD): aging, female gender, the ApoE ϵ 4 gene, a history of brain contusions, cerebrovascular diseases, and depression. Middle-aged individuals with diabetes mellitus (DM), hyperlipidemia, and hypertension are more likely to develop AD in later life. Low physical activity has also been identified as an important risk factor by extensive epidemiological research.

Physical exercise to prevent dementia

In the care of older adults, the word "frailty" is a term that is often used to describe the general health status. Frailty has recently been associated with an increased risk of poor cognitive outcomes such as AD or mild cognitive impairment (MCI). Frailty is generally characterized by weight loss, fatigue, low physical activity, slowness, and weakness (Table-1). A prospective population-based

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Table-1 Frailty

1. Weight loss
2. Fatigue
3. Low physical activity
4. Slowness (walking speed)
5. Weakness (grip strength)

(Gray SL, *et al*: J Gerontol A Biol Sci Med Sci, 2013; 68: 1083-1090¹⁾)

cohort in Seattle reported a relationship between frailty and the incidence of dementia¹⁾. Participants consisted of approximately 2,600 elderly individuals with normal cognitive function who were followed between 1994 and 2010. Approximately 500 participants developed dementia (448 of which developed AD) over a mean follow-up of 6.5 years. The hazard ratio for frailty is 1.20 for dementia. The hazard ratio for walking speed is the highest among frailty components. The findings of a pooled analysis of 9 cohort studies collected between 1986 and 2000 also revealed that individuals with a high walking speed achieved longer survival²⁾. Several large-scale prospective cohort studies have reported a relationship between cognitive function and walking speed (Table-2)³⁾⁻⁸⁾. In older Mexican-American adults without cognitive impairments at baseline, a slow 8-foot walk time was identified as an independent predictor of a Mini-Mental State Examination (MMSE) score decline over a 7-year period although other sociodemographic factors including education, marital status, body mass index, and medical conditions (stroke, heart attack, DM, depression, and hypertension)³⁾. In North America, the usual gait speed (m/s) over 6 m was measured at baseline in 2,776 participants⁴⁾. After 5 years, 389 (17.1%) participants exhibited declines in the Digit Symbol Substitution Test (DSST). Participants in the lowest quartile of gait speed were more likely to show declines in DSST than those in the highest quartile (>1.35 m/s). The Sydney Older Persons Study examined the 6-year outcomes of 630 community-dwelling participants aged 75 and older⁶⁾. At baseline, participants were defined as having dementia, being cognitively intact, or having a syndrome possibly representing the preclinical phase of AD, vascular dementia, extrapyramidal dementia, or various combinations of the three. Participants with cognitive impairments in combi-

nation with gait and motor slowing were the most likely to develop dementia over the 6-year period (OR 5.6; 95% CI 2.5-12.6).

Walking training has been described as a preventive measure against cognitive decline in the elderly. A previous study reported that walking may increase the size of the hippocampus⁹⁾. In this analysis, 120 older adults were divided into two groups: a walking group and muscle training or stretch group. In the walking group, participants had to walk for 40 minutes 3 times a week. Data were collected after one year. Hippocampal volumes and cognitive test scores were higher in the walking group. Furthermore, blood brain-derived neurotrophic factor (BDNF) levels increased in the walking group. Several studies examined different types of physical training in patients with mild cognitive impairments (Table-3)¹⁰⁾⁻¹⁵⁾. In Western Australia, a randomized controlled trial recruited 311 individuals aged 50 years or older for a 24-week physical activity intervention¹¹⁾. Participants were randomly allocated to a home-based physical activity group or education and usual care group. The Alzheimer Disease Assessment Scale Cognitive Subscale (ADAS-Cog) increased by 0.26 points in the intervention group (95% confidence interval, -0.89 to 0.54), but decreased by 1.04 points in the usual care group (95% confidence interval, 0.32 to 1.82). Thirty-seven adults (17 women) with amnesic MCI were randomized either to a high-intensity aerobic exercise or stretching control group¹²⁾. The aerobic group exercised under the supervision of a fitness trainer at 75% to 85% of the heart rate reserve for 45 to 60 min/d, 4d/wk for 6 months. The control group maintained their heart rate at or less than 50% of their heart rate reserve. In women, aerobic exercise improved performance in multiple tests of executive function, increased glucose disposal, and reduced fasting plasma levels of insulin, cortisol, and BDNF. In men, aerobic exercise increased plasma levels of insulin-like growth factor I and had a favorable effect on Trail making test B only. A recent review published by the Cochrane Collaboration concluded that there is promising evidence to show that exercise programs may improve the ability to perform the activities of daily living by individuals with dementia; however, some caution is advised when interpreting these findings¹⁶⁾.

Table-2 Cohort studies: walking speed and Dementia

Authors	Subjects	Follow-up	Walking assessments	Results
Alfaro-Acha A, <i>et al</i> ⁽³⁾	n=2,070 65 years and above MMSE>21	7 ys	8-foot walk	Risk factor for cognitive decline
Inzitari M, <i>et al</i> ⁽⁴⁾	n=2,276 73.5 years and above	5 ys	6 m walking	OR 1.74 Cognitive decline
Wang L, <i>et al</i> ⁽⁵⁾	n=2,288 65 years and above MMSE>25	6 ys	10-foot walk	Development of dementia
Waite LM, <i>et al</i> ⁽⁶⁾	n=630 75 years and above	6 ys	5 m walking	Slow walking speed MCI→AD
Atkinson HH, <i>et al</i> ⁽⁷⁾	n=558 65 years and above MMSE>24	3 ys	4 m walking	Cognitive decline and physical ability
Marquis S, <i>et al</i> ⁽⁸⁾	n=108 65 years and above MMSE>24	6 ys	30 foots	Prediction of time to onset of persistent cognitive impairment

Table-3 Physical activity intervention for MCI

Source	No.	Patients	Mean age	Exercise	Duration	Outcomes
Lautenschlager NT, <i>et al</i> ⁽¹¹⁾	170	MCI & SCI	69	Home-based physical activity or an education and usual care	24 W	Improvement of the ADAS-cog., verbal memory, and CDR
Baker LD, <i>et al</i> ⁽¹²⁾	33	MCI	70	High-intensity aerobic exercise and stretch	6 M	Difference of executive function
Suzuki T, <i>et al</i> ⁽¹³⁾	50	MCI	75	Multicomponent exercise and education	12 M	Superior improvement of MMSE, logical memory, and verbal fluency
Nagamatsu LS, <i>et al</i> ⁽¹⁴⁾	86	Women with SCI	75	Resistance training Aerobic training Balance training	26 W	Significant difference of executive function
Barnes DE, <i>et al</i> ⁽¹⁵⁾	126	SCI	73	A2 × A2 factorial design 4 group	12 W	Global cognitive score improved

Exercise treatments in mice

We previously generated tau transgenic mice, designated as Tg601, that overexpressed wild-type human tau under the calcium/calmodulin-dependent protein kinase II α (CAMK-II α) promoter⁽¹⁷⁾. Tg601 mice expressed the longest form of human tau predominantly in the forebrain. Numerous phosphorylated tau-positive neurons were mainly detected in the cortex, hippocampus, and limbic system. Anxiety behavior decreased in Tg601 mice by the age of 16 months. In spite of the absence of neurofibrillary tangles, a [¹⁸F] fluoro-2-deoxy-D-glucose PET study revealed that glucose uptake was decreased in young Tg601 mice in the septum only, and this area extended into the hippocampus with old age.

In order to characterize the effects of exercise on the biochemical properties of tau protein, we sub-

jected 17-month-old Tg601 mice to treadmill exercise for 3 weeks (short-term exercise: STE)⁽¹⁸⁾. Treadmill exercise is regarded as a forced exercise because mice receive an electric shock when they do not run. Mice were sacrificed by cervical dislocation after 3 weeks of exercise training. In order to determine the effects of STE on tau solubility, we prepared different detergent-soluble and -insoluble fractions from brain homogenates, and then performed a western blot analysis using various phosphorylation-dependent and site-specific anti-tau antibodies. The findings obtained showed that the amount of C-terminally phosphorylated tau and insolubility increased after STE. We performed an immunohistochemical analysis using an Iba-1 antibody in order to determine whether STE induced any neuroinflammatory responses in Tg601 mice. Iba-1-positive microglia proliferated after exercise (Figure-1A-D). We

Figure-1 Inflammation and exercise

Figure-2 Skeletal muscle: an endocrine organ
(Pratesi A, *et al*: Clin Cases Miner Bone Metab, 2013; 10: 11-14²⁴⁾)

measured the levels of inflammatory cytokines including IL-1 β , IL-6, IL-18, and TNF- α and those of the chemokines CXCL-1 and CXCL-12 (Figure-1E and F). This analysis also revealed that the levels of the cytokines, IL-1 β and IL-18, and chemokines, CXCL-1 and CXCL-12 were higher in exercised groups. Elevations in the levels of the lipid peroxidation markers, 4-hydroxy-*trans*-2-noneal and malondialdehyde indicated the presence of oxidative stress. The beneficial effects of treadmill exercise have always been observed in the case of long-term (> 12 weeks) physical training¹⁹⁾⁻²³⁾; however, our study showed that STE induced completely negative effects. Therefore, we conclude that beneficial compensatory changes may occur with the continuation of treadmill training.

We then subjected 16-month-old normal mice to long-term (5 months) exercise. Mice (n=20) were divided into 3 groups: voluntary running wheel, forced treadmill, and sedentary groups. In contrast to the treadmill treatment, mice in the voluntary running wheel group ran at their own pace. They played for a while and rested. They played again and then stopped. After the exercise intervention had been completed, behavioral batteries were performed. The wheel group achieved the highest score in the Morris water maze test, which assesses learning ability. The treadmill and sedentary groups had the same scores. The elevated plus maze test, which evaluates anxiety behavior, revealed that mice in the wheel group spent less time in the open arms than those in the wheel group ($p < 0.05$). The Y-maze test, which examines working memory, indicated that the wheel group had a higher number of spontaneous alterations than the treadmill group ($p < 0.05$). These findings indicated that mice in the wheel group showed the best cognitive ability among the three groups. After completing the behavioral tests, we sacrificed animals and removed the brains and soleus skeletal muscles. We are now analyzing these samples using biochemical and histochemical techniques. The role of skeletal muscle as a secretory organ was recently shown to be involved in inflammatory processes (Figure-2)²⁴⁾. Contracting skeletal muscle release myokines, including IL-6, IL-8, IL-15, BDNF, and leukemia inhibitory factor, which function in a hormone-like manner, exerting specific endocrine effects on visceral fat or inhibiting glycogen

Figure-3 Patients in my memory clinic

synthase in the liver. BDNF plays a crucial role in regulating the survival, growth, and maintenance of neurons in the brain. Therefore, we hypothesized that another unknown molecule released by muscle may affect brain function during exercise treatments. We are now analyzing muscle and brain extracts using a protein microarray technique.

Patients in our memory clinic

Approximately 500 patients, 60 % of whom have AD and 20 % MCI, regularly visit the memory clinic in our hospital (Figure-3). A 72-year-old man with mild AD visits our memory clinic every 2 months with his wife. He has walked almost every morning for one hour by himself since he retired from his job at the age of 65. His deterioration speed is slower than that of other patients with AD. We speculate that his walking custom may be slowing the deterioration of AD. Therefore, our group has created an original diary, called the "everyday note", for patients to note the number of steps they take every day. We encourage them to walk at least 5,000 steps every day.

Conclusions

Animal research and studies on the elderly or patients with cognitive decline have indicated that physical exercise is a promising intervention for preventing the development of dementia. Since the underlying mechanisms have not yet been elucidated in detail, neuroscientists are now focusing on

this issue. During the process of examining the mechanisms responsible, scientists may discover novel molecules that will ultimately result in a cure for AD.

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