Effect of Physical Exercise on the Appearance and Development of Alzheimer’s Disease in Animal Body

Chaoran Li

A-Level program, Beijing National Day School, Beijing, 100039, China.

Abstract

While physical activity was believed to have numerous benefits on animal memory, it is still unknown whether physical exercise may also function to decrease the risk of infecting Alzheimer's disease or retard the development of Alzheimer's disease in the human brain. In this study, two approaches involving genetic knockout mice with a herpes-virus-1 infection under the genetic background of APOE4 allele and with rare Familial -Alzheimer's -Disease genes were used to provided relevant biological background, and further testing on the intensity of beta-amyloid protein was used to illustrate the effect of the intensity of physical exercise on both prevention and control of Alzheimer's disease. In this research, both experiments are hypothesized that mice groups with high intensity of physical exercise in a certain experimental period may reflect lower percentage growth on concentration of beta-amyloid, therefore supporting the hypothesis that physical exercise have positive effect on both prevention and control of Alzheimer's disease in animal brains. This study suggests a new possibility for Alzheimer's patients to take initiation in self-controlling the disease through physical exercise aside from intaking ineffective medical drugs with severe side effects. Besides, the study also alludes that under continuous physical exercise, patients may provide a potentially new body condition for further biological studies to be based upon, therefore promoting future investigation on efficient drugs.

Keywords

Physical activity, Alzheimer’s disease, Herpes virus 1, APOE4 allele, Beta-amyloid, Brain, Familial Alzheimer’s disease, Memory, Genetic modification.

1. Introduction

Alzheimer’s disease is a chronic neurodegenerative disease that usually occurs in aged human brains that are over 65 years old. It is said to account for 70% of all cases of dementia and is responsible for numerous difficulties in memorization, language disorder, and serious disorientation; as Alzheimer’s disease is currently revealed to have no effective treatments for a cure, the few medications that involved in clinical use, Namenda® and Aricept®, hardly revealed any benefits for disease control but to merely decrease daily symptoms and allow a longer-functioning period of the brain. Neither are there effective vaccines or drugs for the prevention of disease before the appearance of Alzheimer’s. However, despite biological treatments and clinical medications that have not yet show effectiveness on both prevention and control, it is implied that there may be natural regulations in the human body that lower the risk of infection with Alzheimer’s disease and enhance cognitive learning ability.

In discovering the factors that improve natural ‘treatment’ toward brain function, the relationship between physical activity and animal memory was studied to promote further studies on Alzheimer’s.
Physical activity was supported to have multiple beneficial effects on the human body, both physically and mentally. For example, a study [1] comparing high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) shows that both ways of physical activity induce acute improvements in peripheral insulin sensitivity, which lowers peripheral insulin resistance and enhances the sensitivity on target tissues to increase glucose disposal in response to the secretion of insulin, therefore resulting in positive effects on diabetes control. Other strong scientific evidence [2] also supported the beneficial influences on the prevention and management of cardiovascular disease through the non-tradition mechanisms.

Nevertheless, concerning mental health, physical activity is also being studied intensely on its potential benefits toward brain function and memory in recent decades. A study [3] showed its positive influence toward cognition with a preventive role in depression, and other studies [4] suggested the improvement toward spatial learning and memory under the neuroplasticity-related animal model mechanism. Similarly, physical exercise that benefits brain function is also hypothesized to contribute to Alzheimer’s disease. According to The Revolutionary New Science of Exercise and the Brain by John Ratey and Eric Hagerman, while 40% of Alzheimer’s patients carry Apolipoprotein E4, the most prevalent genetic risk factor of AD, 30% of normal people also carry this genetic factor without developing AD. Although genetic factors have been long considered as a crucial factor in the formation of Alzheimer’s disease, it is not accurate. Physical exercise is proposed to decrease the risk of developing Alzheimer’s despite one may carry the genetic factor. Supportively, in the first randomized controlled trial with supervision on moderate-to-high intensity exercise in mild-AD patients [5], the Symbol Digit Modalities Test (SDMT) revealed the effect of aerobic exercise in reducing neuropsychiatric symptoms, improving dual-task performance, and preserving cognition.

Here, cognitive improvements inside the brain after intense physical exercise seemed to be approved. However, the sixteen-week experiment on a small number of mild Alzheimer’s patients was not sufficient enough to generate a consistent increase on the whole brain or regional cerebral blood flow, despite some improvements in cognitive abilities; there are also similar experiments [6] that failed to show the supportive effect of exercise on the change in hippocampal volume by contradictory experimental results. Whether physical exercise has a direct impact on the progression of Alzheimer’s remained to be investigated.

In the work, we aim to deal with not only the effect of different levels of physical exercise on both the prevention and control of Alzheimer’s disease, but also the differentiation between the direct and indirect impact of physical activity on Alzheimer’s development. This experimental design allows for the short term, fast-developing, and obvious trend of progression in Alzheimer’s Disease. It also ensures the initial phase of the clinical trial to involve safe and efficient animal experiments on laboratory mice before entering the direct experiment on human patients.

2. Methods and Materials

2.1 Experiment I

This experiment aims to investigate the effect of pre-exercise on the prevention of Alzheimer’s Disease and identify whether its positive effect will directly influence the appearance of Alzheimer’s. Our hypothesis proposed that long term exercise prior to the infection of herpes virus may play a direct role in preventing the occurrence of Alzheimer’s disease. If support, we expect a lower percentage of Alzheimer’s appearance in groups with high-intensity exercise and a relatively higher percentage in groups with few or no physical exercise.

2.1.1 Assumptions

1 Herpes virus 1 play a major role in causing Alzheimer’s disease in the body carrying genetics of APOE4 allele.
2 Beta-amyloid has negative effect to the brain function.
3 Alzheimer’s severity and development are directly proportionate toward the amount of beta-amyloid protein plaques found in brain.

2.1.2 Experimental subject

This study includes 120 genetically identical C57BL/6 laboratory mice, each with same age (one month after birth), same sex (male mice), same size and weight, same body condition, and same genetic background. Before the beginning of study, each of the 120 mice were being genetically knocked out to create genetic knockout mice. A targeting vector was injected into the mouse to replace murine Apoe gene with the human APOE4 allele in E14TG2a ES cells while the targeting cells were injected into blastocysts. They are subsequently divided into six different experimental groups, each group with 20 mice. Investigators were to separate six groups independently, and each group will be arranged in the same housing condition (same size of cage) with constant temperature, moisture, and outer environmental factors (e.g. noise and vibration). They are fed with same diet twice a day, and with controlled light cycle that begins at 7 AM and ends at 9 PM. Basic health status of 120 experimental mice has been checked before the start of experiment.

2.1.3 Material and Procedure

Six experimental groups were numbered from 1 to 6 according to the intensity of daily physical activity, with group 1 as control group that did not include physical activity in experiment. Group 2 was required to experience 20 minutes of physical activity every day, while group 3, group 4, group 5, and group 6 were supervised to receive 40, 60, 80, and 100 minutes of physical activity respectively. The physical activity was designed to be running wheels, and same investigators will be creating activity opportunity intentionally for each of the mice in a group to ensure the different requirements for the variable, the amount of physical activity per day, are achieved.

Continue the experiment for 24 weeks. At the beginning of the 25th week, all physical activities were ceased. Investigators injected 3 × 10^3 PFU of herpes virus-1 diluted in sterile, endotoxin-free saline into 120 mice. For the following week, monitor each group daily for any clinical symptoms or deaths. Use Magnetic resonance imaging (MRI) to visualize the concentration of beta-amyloid plaques in Alzheimer’s-infected mice every three days in the following twelve days to determine the level of infection and the possibility of occurrence of Alzheimer’s disease.

Calculate the average percentage of infection with Alzheimer’s disease after the injection of herpes virus and compare the rate of deaths and Alzheimer’s infection for each group using t-test. Collect and summarize the concentration of beta-amyloid in the brain of mice for each group using standard curve with statistical data, with measures of variability recorded in percentage.

2.1.4 Explanation

Herpes-virus-1 is proposed to play a crucial role in infecting Alzheimer’s disease under the presence of APOE-epsilon 4 allele [7,8], so by creating genetic knockout mice carrying mutated genes of APOE4 allele and injecting moderate amount of herpes virus inside the mice, this experiment allows the possible infection of AD to occur despite its innate gene do not carry relevant factors. Magnetic resonance imaging is also used to detect the level of concentration of beta-amyloid plaques, small dense deposits that scatter in brain and prevent signals from being transferred between neurons, by using powerful magnets and radio waves to produce a detailed picture inside subject body. Exercise are given before the injection of herpes-virus-1 to test on whether continuous physical activity prior to the induction of risk factors of Alzheimer’s disease may function to decrease the possibility of infection.

2.1.5 Predictions

It is predicted that for no-physical-activity group, the death rate would be approximately 35%-40% in the following 12 days [9], and there should be a decreasing trend of death rate and infection following the sequence of 20-min-activity group, 40-min-activity group, 60-min-activity group, and 80-min-activity group. The concentration of beta-amyloid plaques is also predicted to have a decreasing trend from the least-intensified-activity group to the most-intensified-activity group.
2.2 Experiment II

This experiment aims to test on whether physical activity can directly slow down or control the progression of Alzheimer’s disease after one has already developed AD. Our review hypothesized that physical activity will positively influence, or effectively control, the progression of Alzheimer’s disease even after its appearance. Prediction with a final decreasing growth rate of development on higher-intensity-physical-activity and a relatively higher growth rate of AD progression on lower-intensity-physical-activity has been proposed to be confirmed.

2.2.1 Assumptions
1. FAD disease is mainly caused by three mutated genes: PS1, PS2, and APP.
2. The endurance of FAD before death may last longer than 16 weeks.
3. Beta-amyloid has negative effect to the brain function.
4. Alzheimer’s severity and development are directly proportionate toward the amount of beta-amyloid protein plaques found in brain.

2.2.2 Experimental subject

This study includes 120 genetically identical C57BL/6 laboratory mice, each with same age (one month after birth), same sex (male mice), same size and weight, same body condition, and same genetic background. Before the beginning of study, each of the 120 mice were being genetically knocked out to create genetic knockout mice. Investigators injected a targeting vector into 120 subject mice’s embryonic stem cells, which are then injected into a blastocyst. This targeting vector include a reporter gene, which replaces the targeted gene with PS1, PS2, and APP, three of the mutated genes in Familial Alzheimer’s Disease (FAD).

They are subsequently divided into six different experimental groups, each group with 20 mice. Investigators were to separate six groups independently, and each group will be arranged in the same housing condition (same size of cage) with constant temperature, moisture, and outer environmental factors (e.g. noise and vibration). They are fed with same diet twice a day, and with controlled light cycle that begins at 7 AM and ends at 9 PM. Basic health status of 120 experimental mice has been checked before the start of experiment.

2.2.3 Material and Procedure

Begin the experiment 14 days after the injection of mutated FAD gene. At the 15th experiment day, six experimental groups numbered from 1 to 6 according to the intensity of daily physical activity were to start with their corresponding amount of exercise. While group 1 as the control group did not include any physical activity, group 2 was required to experience 20 minutes of physical activity every day, and group 3, group 4, group 5, and group 6 were supervised to receive 40, 60, 80, and 100 minutes of physical activity respectively. The physical activity was designed to be running wheels, and same investigators will be creating activity opportunity intentionally for each of the mice in a group to ensure the different requirements for the variable, the amount of physical activity per day, are achieved.

Continue the experiment for 16 weeks. Monitor each group for any clinical symptoms or deaths. Use Magnetic resonance imaging (MRI) and Elecsys blood test, a blood-based biomarker test, to visualize the concentration of beta-amyloid plaques in Alzheimer’s-infected mice every week in the 16 weeks to determine the degree of disease severity and level of AD development in certain condition.

Calculate the average degree of development (disease severity) on Alzheimer’s disease for all six groups for 16 weeks and compare the rate of deaths for each group using t-test. Collect and summarize the concentration of beta-amyloid in the brain of mice using standard curve with statistical data, with measures of variability recorded in percentage.

2.2.4 Explanation

This review is based on the injection of mutated genes of Familial Alzheimer’s disease. Familial Alzheimer’s disease is a rare form of Alzheimer’s that is entirely inherited through genetics,
accounting for 2%-3% of all cases of Alzheimer’s. It is chosen for its early onset, with symptoms developing in people in their 30s or 40s, so as a result can carry out faster disease development in a limited time (few weeks) and exhibit more effective experimental trend. Elecsys blood test is also used in the study design as a supplemental support for MRI. It is a blood-based biomarker test that could accurately predict whether beta-amyloid has started to accumulate in people’s brains before symptoms, developed initially by Roche Diagnostics and researchers at Lund University.

2.2.5 Prediction

Our hypothesis proposed that the rate of growth in beta-amyloid protein concentration should be highest for no-physical-activity group and should be lowest for 100-min-physical-activity group. Death rate for each group is also predicted to have decreasing trend across group 1 to group 6, with most severely developed disease occurring in group 1 and least severe disease carried out in group 6.

3. Discussion

In Experiment 1, which is testing the efficacy of physical exercise on prevention of AD, the hypothesis, as stated before, predicts the direct and positive influence of physical exercise on its prevention. Hypothetically, if there is a decreasing trend of death rate and infection following the sequence of 20-min-activity group, 40-min-activity group, 60-min-activity group, and 80-min-activity group, and if the concentration of beta-amyloid plaques has shown a decreasing trend from the least-intensified-activity group to the most-intensified-activity group, then it is plausible to conclude that physical exercise prior to the aged period or infection phase is effective in preventing Alzheimer’s final occurrence, given that genetic factors are present from the beginning. Following the recognition of several prevention programs and strategies [10], there appeared to be more science attention toward the effect of lifestyle and mental status on Alzheimer’s; and one investigation [11] highlighted the 12-minute meditation technique which functions to successfully enhance the memory in studied people who are in increased risk of subsequent development of Alzheimer’s disease in addition to the improved spiritual fitness that is important for the prevention of AD. It is now well-believed for the possibility of prevention of Alzheimer’s disease by intentionally changing lifestyle and diet. However, though studies have shown the positive effects of exercise on the prevention of Alzheimer’s ranging from an improvement in multiple-task physical performances [12] to an increased stimulation and preservation of neurotransmission [13], few studies have the opportunity to show the direct influence of physical exercise toward prevention of Alzheimer’s on a quantitative scale. This review, based on the knowledge from previous studies, aims to discover whether physical exercise have direct and effective influence on preventing Alzheimer’s or does it only benefit part of the brain structure in front of the inevitable appearance of AD. Beta-amyloid, in this experiment, is used as the biomarker that gives specific data for quantification to determine the occurrence of Alzheimer’s disease; death rate is also employed as a supportive data that further integrates the experiment in the opposing aspect.

In Experiment 2, we aim to study the effect of physical exercise on the control of Familial Alzheimer’s disease, a rare form of AD. Our hypothesis proposed that the rate of growth in beta-amyloid protein concentration should be highest for no-physical-activity group (group 1) and should be lowest for 100-min-physical-activity group (group 6), which is suggesting the positive effect of physical exercise on the control of disease after its symptoms have been established or disease being appeared. Death rate for each group is also predicted to have decreasing trend across group 1 to group 6, with most severely developed disease occurring in group 1 and least severe disease carried out in group 6. Since no effective medical treatment is currently available to cure the disease, this second experiment proposed a possibility of prolonging life span and increasing cognition despite the disease has been developed.

However, there are still many details from this study that is waiting to be approved. Whether the artificial induction of Alzheimer’s gene have the same effect on mice compared with human is still an uncertainty, and the complex relationship between physical exercise and Alzheimer’s disease
cannot be confirmed just by reflecting the simple reaction on mice. Further investigations are also needed to verify the more specific function of physical exercise on human memory.

4. Conclusion

In this study, by investigating the effect of different intensities of physical exercise on both the prevention and control of Alzheimer’s disease, we successfully modelled a new method that could be utilized to slow down the progression of disease development. If this hypothesis is tested to be true, more self-controllable “treatments” can be introduced into the lives of Alzheimer’s patients, and more initiation can be found for one to deal with the disease, instead of merely waiting for the invention of new medical treatments. Additionally, from the potential improvements brought by continuous physical activity, more biological and medical studies can be made based on the ‘new’ body condition, alluding to the possibility of complementary drugs or vaccines that act as supplemental support aside from physical exercise.

For future investigations, more connective factors should be considered to involve. Referring to the nature of herpes virus 1, the crucial injection made in Experiment 1, the reactivation of herpes virus under depression and stress should be combined in the next phase of experiment to deepen the study on the relationship between physical exercise and long-term development of Alzheimer’s. Different groups of experimental subjects should be separated according to level of severity, whether it is mild, moderate, or severe, to test for specific development of the Alzheimer’s and its potential different requirements for improvements. Accordingly, instead of testing the positive and negative relationship between the two, more attention should be focused on the optimal amount of physical exercise and the best-fit type of exercise for different aged groups and different level of disease development. In this way, specific investigations for phase-II clinical trials on human subjects can be carried out subsequently, and more reliable methods for human patients can be introduced, therefore realizing the clinical-trial-based application on human body.

References


