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Effects of Aerobic and Resistance Exercise on Brain-Derived Neurotrophic Factor and Cognitive Benefits in Alzheimer's Disease

Stephanie Cullen
Western University, scullen8@uwo.ca

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Abstract

Cognitive function below age-matched controls is the hallmark of Alzheimer's disease. Brain derived neurotrophic factor is a biochemical molecule that mediates neuronal survival, but its expression is reduced in Alzheimer's disease, causing neurodegeneration. Exercise has been shown to increase Brain-Derived Neurotrophic Factor, which mediates improvements in cognition in Alzheimer's patients and slows cognitive decline. Evidence is presented to show that aerobic exercise is well known to increase serum Brain-Derived Neurotrophic Factor, while resistance training studies have not yet shown a conclusive effect. Increased Brain-Derived Neurotrophic Factor from aerobic exercise has been shown to mediate improvements in hippocampal volume and executive function. No clinical guidelines have been developed for exercise to improve cognition in Alzheimer's patients, so clinicians are encouraged to follow the Canadian Physical Activity guidelines and include both aerobic and resistance training in exercise programs to achieve maximum cognitive benefits. Exercise prescription is especially important for those at high risk of developing Alzheimer's disease, as they will greatly benefit from the protective effects of Brain-Derived Neurotrophic Factor before converting and exercise adherence is increased in Alzheimer's patients if they have found exercise they enjoy.

Keywords: Brain-Derived Neurotrophic Factor, Alzheimer's disease, aerobic exercise, resistance training, cognition

Introduction

As life expectancy increases, the proportion of older adults in the world's population also increases, as well as the prevalence of age-related diseases, such as heart disease, diabetes and dementia. This puts more pressure on research facilities to develop healthy aging strategies and preventative interventions to prolong the healthy lifespan (Rizvi and Jha 2010). Cognitive decline is a normal part of the aging process; however, cognitive decline can become more severe in some older adults than their aged-matched controls, which is the manifestation of clinical conditions such as mild cognitive impairment (MCI), dementia, and Alzheimer's disease (AD). There is an increasing body of evidence that environmental factors can play a role in healthy cognitive aging (Bherer et al. 2013). Three environmental factors have been described as being the most important in later life for slowing cognitive decline and preventing against dementia: an active social network, cognitively stimulating leisure activities, and physical activity participation (Fratiglioni et al. 2004). Many reviews argue that physical activity is the most important of these factors for maintaining cognitive function (Bherer et al. 2013; King and Kitchener 2014).

Cognitive function is mediated by many biochemical factors in the brain, and as the aging population grows, these molecules become more and more important for understanding the decline in cognitive health. Brain-Derived Neurotrophic Factor (BDNF) is one of these molecules, a protein that belongs to the neurotrophins family, which mediates the survival and maintenance of neurons through binding with the receptor Tyrosine receptor kinase B (TrkB). Both BDNF and TrkB are decreased in the brains of those with AD (Fumagalli et al. 2006). Resistance training and aerobic exercise have been shown to affect serum levels of BDNF (Coehlo et al., 2013), but in different magnitudes and methods, which may be the key to

understanding how exercise programs mediate improvements in cognitive function. This article will focus on the role of BDNF in AD and current evidence to show that exercise may be a valuable treatment for improving cognitive status in older adults through improving the biochemical environment of the brain.

BDNF Function in AD

BDNF and TrkB are produced in the brain and throughout the central and peripheral nervous systems. In early development, BDNF is produced to differentiate neurons from stem cells and promote synapse formation. BDNF is continually produced throughout the life span in low amounts, but even at low concentrations, it is highly effective at preventing neuronal cell death. When BDNF binds to the TrkB receptor, a complex downstream signalling pathway is turned on that leads to improved DNA damage repair in neurons and the production of proteins involved in neuronal survival and plasticity (Marosi and Mattson 2014). BDNF expression is controlled by many factors, such as sensory stimulation, bioelectric activity, pharmaceuticals, and a wide array of neurotransmitters (Murer et al. 2001).

There is a large body of evidence that shows that BDNF expression is decreased in the brains of AD patients (Murer et al. 2001; Fumagalli et al. 2006). Most of this research is done in the post-mortem brains of AD patients, as performing a brain biopsy on living patients is not possible without severe damage to surrounding brain tissue; however, decreased serum BDNF has also been measured in living patients with both early and late stage AD (Gezen-Ak et al. 2013). A detailed study of the various mRNA transcripts of BDNF showed that three of the seven identified mRNA transcripts for BDNF were decreased in the parietal cortex of the post-mortem AD brain compared to age-matched controls: transcripts 1 and 3 were decreased two-

fold, while transcript 2 was decreased five-fold compared to controls (Garzon et al. 2004). Furthermore, in a study by Murer and colleagues (1999), chemical staining done of the brains of deceased AD patients showed that those neurons that had large neurofibrillary tangles, a major symptom of AD, did not contain BDNF. Most of the neurons that stained positive for BDNF did not have the large degrading tangles in them.

In living patients, there has been evidence that high serum BDNF levels decreases risk for developing dementia and AD. In a large longitudinal cohort of American adults, it was found that for each standard-deviation increment increase in BDNF level, the ten-year risk for developing dementia or AD was decreased by 23% in educated older women (Weinstein et al. 2014). Higher BDNF levels have also been associated with slower cognitive decline in AD patients after one year follow-up, although further longitudinal studies are needed to corroborate these findings (Laske et al. 2011).

BDNF Response to Aerobic Exercise

There is a large evidence base supporting the positive effect of aerobic exercise on BDNF concentrations and its mechanism in maintaining cognitive health. A meta-analysis of 18 aerobic exercise studies showed that BDNF concentrations in peripheral blood supply increased after aerobic exercise interventions (Dinoff et al. 2016). Similar findings were also reported by Coelho et al. (2013), Schmolesky et al. (2013), and Huang et al. (2013). These human studies are also corroborated by many studies using rodent models (Hertzeg et al. 2008). Acute aerobic exercise was shown to increase BDNF concentrations in both cognitively normal older adults and those with AD (Coelho et al. 2014).

A randomized control trial of cognitively normal community-dwelling older adults by Leckie et al. (2014) showed that increases in BDNF concentration after aerobic exercise also mediated improvements in executive function. Those who completed the aerobic exercise intervention showed improvements in their ability to switch between two tasks as a result of their increased levels of BDNF. Executive function is the cognitive process used to plan, initiate and regulate behaviour, and is impaired even in the early stages of AD (Farina et al. 2016). The effect of exercise derived increases in BDNF on executive function may be important in understanding the decline in executive function in AD patients and how it can be slowed using aerobic exercise interventions.

Another study by Erickson et al. (2011) compared the effects of aerobic exercise and a control stretching exercise program on serum BDNF concentrations and hippocampal volume in older adults without previous cognitive impairment. Increases in BDNF concentrations correlated with increased hippocampal volume only in the aerobic exercise group. The one year aerobic exercise intervention was able to increase hippocampal volume by 2%, which is equivalent to reversing the 1-2% deterioration per year normally seen in older adults without dementia.

Aerobic exercise has been shown many times to improve multiple aspects of cognition in both cognitively normal participants and those with AD. Many of these improvements are mediated by BDNF level increases, which is important for understanding how aerobic exercise improves cognition as a whole. While many of these studies give promising results, there are still no defined guidelines for aerobic exercise programs specifically to slow cognitive decline, whether through maximizing BDNF response or through other exercise mediated improvements.

BDNF Response to Resistance Training

Evidence of the relationship between resistance training and BDNF concentrations is less abundant and conclusive than that for aerobic exercise. A meta-analysis of twelve randomized control trials using a resistance training intervention showed that BDNF levels in the blood did not change significantly following the exercise protocols, which ranged in frequency, duration, time and type (Dinoff et al. 2016). Walsh and colleagues (2016) also found that resistance training had no effect on basal BDNF concentrations. Blood samples were taken in 20-minute increments for two hours total, with time zero at the beginning of exercise, as well as under rest conditions. The blood concentrations of BDNF did transiently increase during exercise, but dropped back to baseline within two hours, and the rising and falling response of BDNF concentrations to exercise was the same both before and after the eight-week exercise program. This program consisted of four sets of eight to ten reps of three different lower body exercises, increasing from 60% to 80% of 1-repetition maximum (1RM) over an eight-week period.

Alternatively, some resistance training programs have been shown to be effective in increasing BDNF levels in older adults. In a study by Coelho et al. (2012), older female participants completed three one-hour training sessions a week for ten weeks, consisting of three sets of eight reps of various lower body exercises. The weight was set at 50% of participant's 1RM for the first two weeks and 75% of their 1RM for weeks two through ten, with a re-evaluation of 1RM at weeks five and eight. Participants' BDNF levels were increased significantly after the intervention. In another study by Church et al. (2016), participants were randomized to either a high intensity/low volume (HI) or low intensity/high volume (HV) resistance exercise protocol. The HI protocol included three to five reps at 90% 1RM, while the HV protocol included ten to twelve reps at 70% 1RM, each four times a week for eight weeks.

Blood samples were collected at baseline and on the last day of exercises immediately following the exercises, as well as thirty and sixty minutes after completion of the exercise session. Plasma BDNF levels were significantly elevated after both protocols at all three post-exercise time-points.

The effect of resistance training on BDNF levels varies across different experimental designs and participant samples. Further research on this topic needs to be done before a conclusive effect can be determined, and if there is a positive effect, which program design is best for inciting this effect.

Discussion and Clinical Implications

The evidence discussed above shows that physical activity participation has many positive effects on cognition through increasing BDNF concentrations. However, because no guidelines have been set for exercise specifically to improve cognition, clinicians should focus on having patients meet the Canadian Physical Activity guidelines for adults 65 and older, which includes 150 minutes of aerobic activity per week, plus two days of strength training per week and balance exercises as needed (Canadian Society for Exercise Physiology 2011). As less than 15% of adults aged 60-79 in Canada are meeting these guidelines (Statistics Canada 2015), this is an important first step for clinicians until special programs to increase cognition are developed.

Even though resistance training has not shown conclusive results in increasing BDNF concentrations, this type of exercise is still important to include in exercise programs for older adults for many reasons. Resistance training has been shown to improve cognition through increasing other biochemical factors important for brain health, such as insulin-like growth

factor-1 (IGF-1) and homocysteine (Liu-Ambrose and Donaldson 2008). Also, exercise programs that include both aerobic and resistance training exercise combined produce a greater improvement in cognition than aerobic exercise alone (Colcombe and Kramer 2003). Finally, strength training exercise programs have been shown to offset the decrease in physical capacity to do activities of daily living (ADLs) in those with AD and to decrease falls risk, which improves quality of life for AD patients (Santana-Sosa et al. 2008). Even though resistance training has not been shown to increase BDNF conclusively, it is still important for increasing cognition and overall physical health in both cognitively normal older adults and AD patients.

Exercise prescription is especially important for those at high risk of converting to AD, such as those with family history of AD or patients with MCI. Once converted to AD, retention rates of exercise programs vary much more than in programs for cognitively normal older adults (Yu 2013). Participants with lower scores on cognitive tests, meaning those further along in cognitive decline, are also more likely to drop out of aerobic exercise programs (McCurry et al. 2010). However, one of the major barriers to exercise cited by AD patients and their caregivers is the patient's dislike of structured exercise (Suttanon et al. 2012). If patients can find a type of exercise they like before converting to AD, participation in exercise may slow their cognitive decline through increased BDNF, with the additional effect of increasing adherence to the liked program if they do eventually convert.

Increasing BDNF concentrations through exercise is an emerging therapy for neurodegeneration caused by AD. While this relationship has been proven for aerobic exercise, more research is needed into the effects of strength training and combined programs before guidelines can be set for exercise prescription. The current Canadian Physical Activity Guidelines for adults 65 and older should be used for all older patients, but especially those at

risk for cognitive decline, as the positive relationship between exercise, cognition, and overall health has been proven in many different mechanisms, not just increased BDNF concentrations.

Take Home Points

- BDNF is a small protein in the neurotrophins family that improves the growth and survival of neurons and is decreased in the brains of AD patients.
- BDNF concentrations have been shown to be increased by aerobic exercise, which mediates improvements in hippocampal volume and executive function.
- Resistance training programs may increase BDNF concentrations, but further research is needed before a conclusion can be made.
- No specific exercise guidelines have been established yet to improve cognitive function. The current Canadian Physical Activity Guidelines for older adults should be used for exercise prescription, as they suggest combined aerobic and resistance training exercise, which has the greatest positive effect on cognition.
- Exercise prescription is especially important for those at high risk for AD, as increasing BDNF concentrations may slow their cognitive decline and prior exercise may increase adherence if they do convert to AD.

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