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Commentary

Amyloid-beta clearance in Alzheimer's disease: Does exercise play a role?

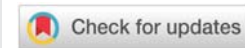## Reza Gharakhanlou* and Davar Khodadadi

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Abstract

Alzheimer's Disease (AD), the most common form of dementia, is characterized by progressive deficits in cognitive function. Amyloid-beta (Aβ) peptides are believed to play a decisive role in the pathology of AD. Improving the clearance of toxic Aβ has, therefore, become a therapeutic strategy for AD. Unfortunately, almost all of the drug candidates tested for AD, including the Aβ centric therapeutic approaches, until now have failed to exhibit any efficacy. Previous evidence suggested that aerobic exercise training contributes to the improvement of cognitive decline and slows down pathogenesis of AD; however, the exact mechanisms for this have not been fully understood. One of the most important beneficial effects of aerobic exercise on AD is modifying Aβ clearance. Accumulating evidence indicates that aerobic exercise not only upregulates the clearance of amyloid plaques and soluble Aβ in the brain but also increases its final removal from the periphery. But there are still many unanswered questions in this regard, including the proper timing of exercise interventions, optimal aerobic exercise mode, intensity, duration, and frequency as well as the possible effect of exercise on potential environmental Aβ-clearing agents, which should be considered in future studies.

Introduction

Alzheimer's Disease (AD), the most common form of dementia, is characterized by progressive deficits in cognitive function. The extracellular amyloid plaques formed by the deposition of Amyloid-Beta (Aβ) peptides are the specific hallmark of AD. The elevated level of Aβ as initiating factor in AD pathogenesis as well as its neurotoxic aggregates in the brain are believed to be associated with the perturbation of synaptic function and neural network activity leading to cognitive deficits and neurodegeneration [1].

It has become evident that an altered balance between production and clearance is responsible for the accumulation of Aβ in the brain [2]. In rare cases, early-onset familial AD, genetic alterations increase the production of Aβ; however, impairment of Aβ clearance is the main reason for Aβ imbalance in the far more common late-onset sporadic AD [3]. Improving the clearance of toxic Aβ has, therefore, become a promising therapeutic strategy for AD [4].

Clearance of Aβ from the brain is a very complex process that is not yet fully understood. It has been demonstrated that

Aβ can be eliminated by degradation, transport from brain into the periphery, and periphery clearance [5]. With functional impairment in the clearance systems during the aging [6] and AD [7], the clearance of toxins including Aβ is subsequently disrupted. Aβ is, therefore, an obvious therapeutic target for AD. Unfortunately, almost all of the drug candidates tested for AD, including the Aβ centric therapeutic approaches, until now have failed to exhibit any efficacy, maybe because the molecular pathogenesis of AD is complex and involves several theories or hypotheses where many diverse factors interrelate. It seems that effective disease management will also require multiple approaches.

Physical activity is an environmental intervention that has widely been investigated as a strategy attempting to delay or slow the progression of AD [8,9]. Among other beneficial mechanisms, however, clearance of Aβ by exercise training has been controversial. Exercise training has been found to either decrease [10-12] or not change [13,14] amyloid plaque load. Likewise, brain soluble Aβ (sAβ) levels have been shown to decrease [10,12,15] or not change [16] with exercise training. Several factors are likely to be involved in the conflicting effects of exercise training on amyloid load. The timing of the exercise

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intervention may be one of the reasons for this contradiction. Cho, et al. [15], for example, found that treadmill running could alleviate Aβ deposition in the hippocampus and cerebral cortex in the advanced, but not the early stage of AD pathology; this finding suggests that the brain can be more amenable to improvement in case of a large amount of Aβ deposition and, thereby, brain impairment. In our own study [12] in a rat model of AD, we also found that hippocampal amyloid plaque load and $sA\beta_{1-42}$ decrease after 4 weeks of treadmill exercise in the developed stage of AD pathology. This amyloid load rescue was accompanied by an elevated level of Aβ clearance factors in the central (neprilysin, insulin-degrading enzyme (IDE), and low-density lipoprotein receptor-related protein-1 (LRP-1) in the hippocampus) and periphery (circulating soluble form of LRP-1 (sLRP-1) and hepatic LRP-1), and. It is likely that exercise training load, expressed by intensity, duration, and frequency, may be another factor that affects the impact of exercise on amyloid load. Moore, et al. [17] reported that sAβ was decreased in the cortex and hippocampus in an exercise training dose-dependent manner in Tg2576 mice following a 3-month treadmill exercise ending at six months of age, well before the onset of plaque deposition in this model. The reduction in sAβ levels were associated with an intensity-dependent upregulation of a number of Aβ clearance proteins (neprilysin, IDE, MMP9, LRP-1 and HSP70) in that study. Another more recent study by Thomas, et al. [18] demonstrated 12 months of treadmill running program decreases brain amyloid plaque load in an intensity-dependent manner and that only high-intensity exercise training robustly improves cognitive function in Tg2576 mice even after the amyloid plaque was formed. On the other hand, high-volume exercise training has been shown exaggerated the amyloid pathology [19]. It seems that there is an optimal training load to induce the positive effects of exercise on the complications of AD, which should be considered in future studies.

On the other hand, in some studies, aerobic exercise training has reduced the amyloid load in the brain, but this has been attributed to reasons other than improved clearance [10,20]. For example, Zhang, et al. [20] reported that 5-month treadmill exercise started at the age of 5 months (the ages after amyloid deposition), triggered the decrease of Aβ deposition mainly by inhibiting amyloidogenic pathway of APP metabolism and Aβ clearance pathways fell down in succession in APP/PS1 mice. Another study on APP/PS1 mice by Lin, et al. [21] revealed that 10 weeks of treadmill training (from 1.5- to 4-month-old, the ages before amyloid deposition) reduced the levels of sAβ and increased the levels of LRP-1 without significant change in Amyloid Precursor Protein (APP) expression. Interestingly, exercise training appears to selectively affect the production and/or clearance of Aβ at different stages of the disease; where amyloid deposition has not yet occurred, primarily by increasing Aβ clearance and after the deposition, predominantly by decreasing its production. Another interpretation is that there are several routes for Aβ clearance from the brain [5], and it is likely that while some clearing proteins remain unchanged [10] and/or even reduced [20] as a result of exercise training in some studies, the clearance occurs through other pathways depending on the type of Aβ peptides and the stages of the disease. Indeed, lack of measurement of the various pathways involved in Aβ clearance may lead to misinterpretation. He, et al. [22], for example, reported that voluntary wheel running attenuated the accumulation of amyloid plaques through accelerated glymphatic clearance of Aβ but not blood-brain barrier permeation.

As we recently reported [12], treadmill exercise not only increase the clearance of Aβ from the brain, but it also improves its final removal from the periphery; this is a notable result as there is a close interaction between Aβ metabolisms in the brain and the periphery [23], dysfunctions of Aβ metabolisms in the periphery might contribute to the development of AD pathology, and targeting peripheral Aβ clearance represents a promising therapeutic strategy for the prevention and treatment of the disease. Therefore, it seems that increased peripheral removal of Aβ independent of its central clearance factors leads to a decrease in amyloid load in the brain.

One of our interesting and unpublished results is that mRNA expression of LRP-1 and IDE increased in skeletal muscles (gastrocnemius and soleus) following aerobic training in both healthy and $A\beta_{1-42}$-treated animals. It was shown overexpression of neprilysin in skeletal muscle decreased brain sAβ peptide levels and amyloid deposits, with no apparent adverse effects in AD mice [24]. However, the possibility of Aβ influx from blood into the skeletal muscle cells through the LRP-1 and its enzymatic degradation as a result of exercise training should be investigated in future studies.

Overall, aerobic exercise appears to improve amyloid clearance in Alzheimer's disease. However, there are still many unanswered questions:

It was reported that Aβ may be clear by some organs other than liver in the periphery, such as kidneys [25], gastrointestinal tract [26], skin [25] as well as some blood component such as monocytes [27], erythrocytes and macrophages [28]. The relative contribution of these mechanisms in Aβ clearance as well as the possible role of exercise in modulating these routes have not yet been determined. Skeletal muscle tends to occupy a large percentage of the body and respond quickly to exercise. The potential role of skeletal muscle in the clearance of Aβ (our unpublished data) and/or its production and release into the bloodstream [29] should be determined, especially in response to exercise. The variables of aerobic training including exercise mode (continuous vs. interval; voluntary vs. forced exercise; treadmill running vs. wheel running; running vs. swimming), exercise intensity, duration, and frequency as well as doing exercise at different times of the day should be defined to optimize amyloid clearance in AD. Finally, the timing of exercise intervention and its optimal intensity in different stages of the disease should be determined. For example, should exercise intensity be the same before and after the development of amyloid plaques? Future studies are needed to address these topics.

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