■ REVIEW

The latest in dementia prevention: A review of the promising role of aerobic exercise

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JAHS 7 (2): 37-45, 2016. Submitted Sep. 15, 2016. Accepted Sep. 25, 2016.

ABSTRACT:

Aerobic exercise (AE) has been widely acknowledged for improving brain health. In particular, AE has a potent impact on promoting the function of the hippocampus. The potential for AE to be applied as a therapeutic or adjunctive intervention for a range of human conditions appears increasingly more promising. Augmenting existing treatment approaches using AE-based interventions may promote hippocampal function. Moreover, incorporating non-pharmacological interventions into clinical treatment may have several other benefits for the patient's wellbeing. This review incorporates both animal and human studies to comprehensively detail the association of AE with cognitive enhancements.

Key words: Aerobic exercise (AE), Alzheimer's disease (AD), Brain health

INTRODUCTION

Alzheimer's disease (AD) is an age-related, progressive, and irreversible neurodegenerative disorder characterized by cognitive and memory impairment. In 2015, a total of 44 million people throughout the world were thought to have AD; it is estimated that this figure will double by 2050[1)]. Therefore, there is currently a particular need to develop effective strategies that alleviate cognitive dysfunction. In late years, Aerobic exercise (AE) and lifestyle has been widely acknowledged for improving brain health. In particular, AE has a potent impact on promoting the function of the hippocampus. There is targeting deficits in the neuroplasticity of crucial areas to cognition like the hippocampus, is a promising approach to remediating cognitive dysfunction. The potential for AE to be applied as a therapeutic or adjunctive intervention for a range of human conditions appears increasingly more promising. This paper will review the cognitive benefits associated with AE and focus on aspects of cognition that are particularly dependent hippocampal functioning such as episodic memory formation (Figure1).

REVIEW

Lifestyle

Lifestyle strategies include physical activity, mental challenges, energy restriction, and socialization as preventive factors for AD[2]. Physical activity, such as aerobic exercise, was associated with a reduction in AD-related deficits in a cohort study[3]. However, a different result was obtained in small cases[4]. Exercise was reported to enhance hippocampal neurogenesis[5,6] and learning in aging rodents[7]. There are three mechanisms proposed to explain the neuroprotective effect of exercise.

(1) The release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1), nerve growth factor (NGF), and vascular endothelial growth factor (VEGF)[8,9] from neurons during synaptic activity, which stimulate neurogenesis and synaptic neural plasticity through the stimulation of the cAMP response element-binding protein (CREB) transcription factor.

(2) The reduction in free radicals in the hippocampus, as well as the increase in superoxide dismutase and endothelial nitric oxide synthase[9].

(3) Peripheral signals that help to support the demands of active neuronal networks, such as BDNF release, in addition to energy restriction in the brain[10-13].

It has been suggested that mental challenges may protect against cognitive decline and potentially against AD[14]. Computer courses and psychoeducation have moderate beneficial effects [15]. Stimulation by cognitive activities has been associated with an increase in neuronal density, which increases the brain reserve and plasticity[2].

The relation between caloric restriction and brain motivation is important; many years ago, humans needed to obtain their food by killing wild animals, which often involved vigorous exercise[16]. The possible mechanism may be associated with SIRT1, a protein with nicotinamide adenine dinucleotide-dependent deacetylase or adenosine diphosphate-ribosyltransferase activity[17], because it was reported to increase in p25 CK mice with characteristics similar to AD. In addition, SIRT1 stimulation by resveratrol protects against neuronal death. SIRT1 levels also increase with NADp *in vitro*, and SIRT induces an increase in α-secretase and decrease in β-amyloid deposition in primary cultures in a mouse model of AD[18]. The relationship between hunger and neuroprotection was demonstrated using ghrelin in a mouse model of AD; the results showed improved cognition in the water maze test and a decrease in amyloid-β levels and inflammation[19].

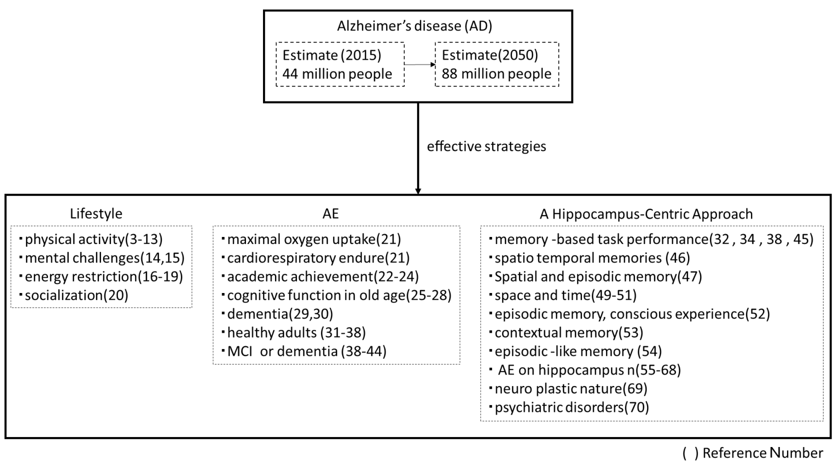

Figure1. Chart of References Number

Socialization is important in mental and physical development. A lack of socialization induces loneliness, which has been associated with various diseases such as depression, alcohol abuse, obesity, diabetes, hypertension, AD, and cancer[20].

Aerobic Exercise

The attention paid to how AE influences cognitive performance has exploded in the past decade. AE generally refers to exercise that improves the efficiency of aerobic energy producing systems by increasing maximal oxygen uptake and cardiorespiratory endurance[21]. Large-scale epidemiological studies have consistently correlated high levels of aerobic fitness with greater academic achievement and IQ scores[22-24]. However, in addition to greater preservation of cognitive function in old age[25-28] and fewer incidences of dementia[29], this capacity to promote cognitive performance implies that AE may have an important clinical relevance in counteracting the cognitive decline associated with aging or dementia[30]; this implication has catalyzed attempts for systematic investigation. Many randomized controlled trials (RCTs) have recently been conducted using moderate intensity AE interventions (such as 30 min of Nordic walking) that generally span 3–12 months and are mostly conducted in older adults. Meta-analyses have found AE interventions to improve cognitive performance across a variety of domains, including attention, executive functioning, processing speed, motor functioning, and memory in healthy young and middle aged adults[31-35]; notably, this effect is observed predominantly in older age groups[31, 32, 36-38] as well as in older individuals with mild cognitive impairments or dementia[38-40].

The available evidence strongly suggests that AE has a positive influence on cognition in individuals of all age groups, particularly in older adults. Some RCTs have stipulated that AE influences divergent cognitive domains, whereas others have suggested AE had no significant impact on cognition at all[38, 40-43]. Such inconsistencies may partially be explained by the methodological variation between RCTs, making it difficult to systematically compare their findings in meta-analyses[43, 44]. The exact nature of how AE affects cognition is not yet clear.

A Hippocampus-Centric Approach

Several meta-analyses have denoted the tendency for RCTs to report improvements in memory-based task performance following an AE-based intervention[32, 34, 38, 45].

The human hippocampus plays a vital role in the formation of declarative memories, most prominently in the formation of episodic and spatiotemporal memories[46]. Episodic memory refers to the recollection of autobiographical events and is related to spatial memory, which refers to one's environment and spatial orientation. Spatial and episodic memory processes are inherently related given their specific reliance on the hippocampus[47] and the fact that episodic memories are encoded in a spatiotemporal context[48], making spatial information important in episodic memory formation. Furthermore, the hippocampus, particularly the dentate gyrus (DG), is crucial in selecting and separating similar events in space and time, and hence pattern separation is a main function attributed to the hippocampus[49-51]. It is important to note that given the requirement of a conscious experience to form an episodic memory, at present episodic memory cannot be directly studied in animals given the lack of behavioral markers for their conscious experience[52]. Contextual memory is a process strongly related to episodic memory that is also highly dependent on the hippocampus and refers to the capacity for an animal to make associations with salient landmark objects and their environmental context[53]. As there is currently no objective proxy for studying episodic-like memory processing in animals[54], hippocampal functioning shall be considered here as a function of contextual and spatial memory task performance when referring to animal literature and as a function of episodic and spatial memory task performance when discussing human literature. Some human studies have focused on assessing the influence of AE on hippocampus-dependent cognition and shown in older adults that AE was associated with improved performance in both episodic[55-59] and spatial[60-62] memory tasks, as well as in pattern separation tasks in young adults[63]. Moreover, some studies have demonstrated in preadolescent children and young adults that AE is selectively associated with improved performance in contextual[64-66] and spatial[67, 68] memory tasks and not with less hippocampus-dependent tasks such as attention, verbal memory, or item recognition.

We will then discuss both animal and human studies, which indicate that these structural changes may be driven by a cascade of micro-scale neuroplastic mechanisms within the hippocampus stimulated by AE. Despite a limited selection of studies, these findings indicate that AE may have a positive influence on hippocampus-dependent forms of cognition in healthy human participants, similar to what has been consistently shown in animal models. Pertaining to its highly neuroplastic nature[69], the hippocampus is particularly vulnerable to structural and functional deterioration in a wide range of neurological and psychiatric disorders[70]. The aforementioned studies demonstrate that AE could have a positive influence on hippocampal functioning, but a significantly greater cohort of systematic investigations using human participants will be necessary to outline this relationship on a broader cognitive level. A growing body of evidence is also accumulating to suggest that AE may have a prominent impact on hippocampal structure in humans, as well as in animal models.

LIMITATIONS

Another issue in the conceptualization of AE-based treatments is the lack of consensus as to what type, intensity, or length of exercise sessions has the strongest impact on the brain. For example, some studies argue that high-intensity exercise is optimal for reducing symptoms in MDD [71], while others have suggested that that a mild [72] or a moderate intensity exercise intervention would be optimal[73]. It is possible that exercise intensities may vary depending on the purpose of the intervention. For example, it has been suggested that improving cognitive performance may require high-intensity, interval training but preserving cognitive function in an aging brain may require a lower intensity, more continuous protocol[74]. Exercise type may also be an important factor. Although most of the current literature has focused on AE, other forms of exercise such as yoga [75] or weight training[76] may also be beneficial in promoting brain health and cognition. Given the growing interest in exercise as a therapeutic intervention, it is surprising that very few studies have attempted a systematic evaluation for the most effective approach in psychiatric populations[77-80]. It is important that future research is concentrated on establishing the merits of different forms of exercise and on detailed elucidation of the dose-response relationship between the intensity and length of AE intervention and therapeutic outcomes in different psychiatric populations.

CONCLUSION

There is, currently, a particular need to develop effective strategies that alleviate cognitive dysfunction. Targeting deficits in the neuroplasticity of areas crucial to cognition, such as the hippocampus, is a promising approach to remediating cognitive dysfunction. AE interventions represent an effective method for promoting hippocampal neuroplasticity and function, which encompasses few risks and several additional benefits for the patient. Future research should be aimed to establish standardized methodologies for investigating AE and to determine the most effective method for maximizing therapeutic outcomes with AE intervention. Improving our understanding of the role of lifestyle factors, such as exercise, in maintaining and promoting brain function could have major impact on the formulation of treatment and preventive strategies for psychiatric and neurological disorders. Research demonstrating the potential of AE in promoting hippocampal structural and functional integrity is growing at an impressive rate as more and more work is translated from animal models to humans.

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