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Are the neuroprotective effects of exercise training systemically mediated?

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ABSTRACT

To date there is no cure available for dementia, and the field calls for novel therapeutic targets. A rapidly growing body of literature suggests that regular endurance training and high cardiorespiratory fitness attenuate cognitive impairment and reduce dementia risk. Such benefits have recently been linked to systemic neurotrophic factors induced by exercise. These circulating biomolecules may cross the blood-brain barrier and potentially protect against neurodegenerative disorders such as Alzheimer's disease. Identifying exercise-induced systemic neurotrophic factors with beneficial effects on the brain may lead to novel molecular targets for maintaining cognitive function and preventing neurodegeneration. Here we review the recent literature on potential systemic mediators of neuroprotection induced by exercise. We focus on the body of translational research in the field, integrating knowledge from the molecular level, animal models, clinical and epidemiological studies. Taken together, the current literature provides initial evidence that exercise-induced, blood-borne biomolecules, such as BDNF and FNDC5/irisin, may be powerful agents mediating the benefits of exercise on cognitive function and may form the basis for new therapeutic strategies to better prevent and treat dementia.

Contents

Abbreviations and acronyms: AD, Alzheimer's disease; BDNF, Brain-derived neurotrophic factor; CRF, Cardiorespiratory fitness; CV, Cardiovascular; CVD, Cardiovascular disease; FINGER study, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; FNDC5, Fibronectin type III domain-containing 5; HCAR1, Hydroxycarboxylic acid receptor 1; IGF-1, Insulin-like growth factor 1; IL-6, Interleukin 6; KYNA, Kynurenic acid; MET, Metabolic equivalent of task; PA, Physical activity; PGC-1 α, Peroxisome proliferator-activated receptor γ co-activator α; TIMP 2, Tissue Inhibitor of Metalloproteinase 2; TrkB, Tyrosine-kinase receptor kinase B; VEGF, Vascular endothelial growth factor.

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Introduction

The global number of people above the age of 60 has doubled since 1980, and this segment of the population is forecast to reach 2 billion by the year 2050.[1] With increased longevity comes the challenge of preventing and managing age-related impairment of cognitive function, which culminates in chronic conditions such as dementia. Dementia is a term encompassing the end stage in a wide range of brain diseases that cause memory impairment and decline in other cognitive functions. Alzheimer's disease (AD) is the most common of dementing diseases, making up about 50–70% of dementia cases.[2] Vascular dementia, dementia with Lewy bodies, frontotemporal dementia and dementia with mixed pathologies make up the majority of the remaining cases.[3] The worldwide prevalence of dementia was 47.5 million in 2015 and is forecast to reach over 152 million by 2050.[4] This increase translates into a tripling of costs, 85% of which are related to family and social care expenses.[3] These costs will amount to 3% of the world's gross domestic product.[4] To date there is no cure or effective treatment available for dementia; AD-drug candidates have a failure rate of 99.6%, while all treatment options are, at best, marginally effective. Thus, the need for optimized prevention, diagnostics and treatment of AD and other forms of dementia is obvious.[5]

A growing body of evidence suggests that brain health is closely linked to the overall health of the cardiovascular (CV) system, and that there are inter-related risk factors between CV disease (CVD) and dementia.[6–8] A healthy heart and healthy blood vessels deliver the sufficient supply of oxygen needed for normal brain function. Indeed, CVD and its risk factors, such as obesity, hypercholesterolemia, hypertension, impaired glucose and lipid metabolism, smoking and diabetes, are also associated with higher risk of developing AD.[6–15] About 30% of AD cases are due to these risk factors and may therefore be preventable.[9,16]

Physical activity (PA) and risk of developing dementia

Current conventional therapies are far from optimal, however, a large body of literature documents significant benefits of PA on cognition, dementia risk and dementia progression, as reviewed elsewhere.[17,18] These studies provide the basis for the hypothesis that regular PA may act as a prophylactic as well as a disease-slowing treatment for dementia. For instance, two meta-analyses demonstrated that regular PA was associated with 30–40% reduction in the risk of developing AD, when compared to physical inactive individuals.[19,20] Another meta-analysis including 16 prospective studies following more than 160,000 subjects without dementia (aged 30–93 years) found that PA reduces the risk of dementia and AD by 28% and 45%, respectively.[21] Consistent with the hypothesis that PA is involved in modulating AD-related pathogenic changes, a study by Brown et al. in 546 cognitively healthy participants (aged 60–95 years) found that those engaging in high levels of aerobic PA (self-reported) had lower plasma and brain amyloid load, both strong AD biomarkers, when compared to participants carrying out a stretching regime.[22]

Although cumulative findings support the notion that regular PA is protective against dementia, there are some challenges in studying the effect of exercise on dementia risk. Limitations include large heterogeneity in study designs, intervention content and duration, choice of target groups and outcome measures. In line with this, some systematic reviews conclude that the evidence of a protective effect of PA on dementia is still insufficient.[23,24] To date, intervention studies aiming to prevent dementia have mainly been single-domain, and it might be that there is a need to undertake multi-domain interventions targeting several risk factors and mechanisms simultaneously in order to obtain an optimal preventive effect.[25] The first large multi-domain randomized controlled trial, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER study) included, among other lifestyle-related domains such as cognitive training and vascular risk monitoring, a 2-year exercise intervention. The results showed a beneficial effect on cognition in elderly persons at risk of cognitive decline,[26,27] and demonstrate the promising effect of a multi domain intervention approach.[28]

Cardiorespiratory fitness (CRF) and risk of developing dementia

Several studies indicate that CRF is a better health marker compared to PA per se.[29] Unfortunately, the literature lacks reports from randomized controlled trials that have tested the link between *CRF* and risk of dementia. However, a few observational studies have been conducted. One recent longitudinal study including 191 Swedish women examined the association between CRF and dementia risk. CRF was tested in 1968, at the time at which the participants had a mean age of 50 years. During a mean follow-up of 29 years, 44 women (23%) developed dementia. Strikingly, stratifying the subjects into low, medium, and high fitness groups, revealed that among those in the latter group, the incidence of dementia was reduced by about 90% compared to those in the medium and low fitness groups.[30]

Prospective studies in both men and women support the association between high CRF and lower incidence of dementia. In a study by Defina et al.[31] CRF was assessed for 19,458 generally healthy individuals (mean age of 50 years) over a mean follow-up of 24 years. Of these, 1659 individuals subsequently developed dementia. An important observation from this study was that those in the higher quintiles of CRF had 36% lower risk of dementia compared to those in the first quintile (lowest CRF).[31] In line with this, another prospective study assessed CRF of 3021 men with a mean age of 52.8 years. With a mean follow up of 23 years, where 208 individuals developed dementia, this study revealed an inverse relationship between CRF and risk of dementia,

where one standard deviation increase in CRF was found to be associated with a 20% decrease in dementia risk.[32]

Only one study has assessed the effect of changing CRF on dementia risk. The authors found that a decreased self-perceived CRF over time was associated with higher risk of dementia, whereas an increase in self-perceived CRF was not associated with subsequent lower risk of dementia.[33] In a study from the Wisconsin Registry for Alzheimer's Prevention, with 95 individuals at increased genetic risk of AD (genotyped for APOE4, CLU and ABCA7; common AD risk variants), Schultz et al. observed that high CRF attenuated the influence of genetic vulnerability on AD biomarkers in cerebrospinal fluid, and concluded that high CRF may be beneficial to those at increased genetic risk of AD.[34]

CRF has also been found to be a predictor of dementia-related mortality. A study following men and women aged 20–88 at baseline for an average of 17 years showed that individuals with higher levels of CRF had significantly lower dementia mortality.[35] The authors reported that each 1-MET (oxygen uptake of 3.5 mL/kg/min, equivalent to resting metabolic rate) higher CRF was associated with a 14% lower risk of mortality due to dementia (adjusted for age). To date, no studies have assessed the association of changes in CRF over time with risk of dementia-related mortality.

Effects of PA and high CRF on cognition

Lautenschlager et al.[36] conducted the first randomized trial to test the hypothesis that PA reduces the risk of cognitive decline and dementia among older adults at risk. A total of 170 individuals with memory problems but who did not meet the criteria for dementia diagnosis, were randomized to 24 weeks of PA or to an education and usual care group. In the individuals with subjective cognitive impairment, the PA intervention improved cognitive function, an effect which persisted for 12 months after discontinuation of the intervention.[36] Since this study, the literature regarding the effect of PA and CRF on cognition has been somewhat conflicting. A 2015 Cochrane report found no evidence that PA, including PA which successfully improved CRF, had any cognitive benefit in cognitively healthy older adults, and concluded by emphasizing the need for larger trials.[37] A recent randomized controlled trial in individuals with mild to moderate dementia found that PA increased CRF[38] but had no beneficial effect on cognition.[38] This observation is similar to findings by Scarmeas et al., who observed no effect of PA on the rate of cognitive decline in subjects with AD.[39] However, the same study also showed that PA levels were correlated with longevity after AD diagnosis.[39] Contrary to these two studies, Sobol et al. observed that an exercise-induced increase in CRF in patients with AD was associated with beneficial changes in cognitive function.[40] A meta-analysis including 15 prospective studies with a total of 33,816 subjects without dementia followed for 1–12 years investigated the association between PA and risk of cognitive decline. This study reported a significant and consistent protection against cognitive decline, for all levels of PA, but with highest levels of PA being the most protective.[41] A more recent 2018 systematic review, including 39 studies and 333 individuals, of which 197 had mild cognitive impairment (41 no impairment, 96 unclear), concluded that PA interventions significantly improved cognitive function in individuals 50 years and older, regardless of their cognitive status at baseline. When exercise prescriptions were further studied, it was found that a duration of 45–60 min per session with at least moderate intensity, was associated with benefits to cognition.[42] Another recent study showed that a PA program (30 min, 3 times per week for 8 weeks, moderate intensity) in 60 individuals with mild dementia resulted in an improvement in cognitive function.[43] The higher physical capacity also resulted in better maintenance of their daily living activities.[43]

Mechanisms underlying beneficial effects of PA and high CRF on the brain

The mechanisms underlying the preventive and mitigating effects of PA and high CRF against dementia are not fully understood, but are obviously of high interest. From what is known to date, the potential role of PA and high CRF in brain health may in broad terms be twofold. On one hand, it is established that PA and high CRF are effective in preventing and treating CVD risk factors, such as obesity, hypertension and diabetes, each of which is also a risk factor for dementia (indirect effect). On the other hand, PA and high CRF may directly protect against dementia through a number of different biological mechanisms, including promotion of cerebral angiogenesis[44] and increased hippocampal neurogenesis and plasticity.[45–58] These processes may serve to attenuate age-dependent reduction in cognition.[16,50,59]

Animal studies have extensively documented that regular PA enhances neural progenitor cell proliferation, neurogenesis and synaptic plasticity,[45–47,49–51,53–58] which brings a translational perspective to the context of this review. Importantly, it has also been demonstrated that PA preserves brain volume (hippocampal volume) in both animals and human subjects.[60–62] Preservation of brain volume is associated with better cognitive function[16,50,59,63] and may be an explanation for how PA can partly reverse age-dependent reductions in cognition. Furthermore, a great portion of AD patients suffer from regional cerebral hypoperfusion[64] along with cognitive decline.[65] It is therefore notable that PA has been shown to enhance cerebral vasculature (capillary growth), increase cerebral blood flow and enhance oxygen-rich blood delivery to the brain in adult rats.[44]

It nevertheless remains unclear whether PA or high CRF attenuates cognitive impairment and reduces dementia risk by modifying CVD and metabolic risk factors, or by inducing neurochemical and structural changes in the hippocampus and related areas of the medial temporal lobes important for memory and learning. Several neurotrophic factors are released in response to PA[66–70] and recent research indicates that blood-borne systemic factors abundant during adolescence and young adulthood may have the ability to directly affect the brain to counteract age-related neurodegeneration.[71,72] In the next sections, we review this body of knowledge, focusing on the translational research recently developed in the field.

Are the beneficial effects of PA and high CRF on the brain mediated by systemic factors?

Despite the clear association between PA and high CRF and brain health, our knowledge on cellular and molecular mechanisms triggering such benefits is limited. Interest in this topic is rapidly increasing, as recent advances in genomics and proteomics now allows for the exploration of the production and systemic distribution of biomolecules with much greater precision than in the recent past. Thus, pioneering studies have laid the groundwork for understanding how exercise-induced signals are transmitted to benefit the brain.

Studies have shown that different circulating factors with potential neuroprotective functions are released into the bloodstream upon PA.[73–76] Due to an efficient filtering system, known as the blood-brain barrier, it has traditionally been thought that the beneficial effects of PA on the brain could not be orchestrated through systemic changes.[75] However, studies in both rodents and humans indicate that the effects of PA on the brain are at least partly mediated by changes in the systemic environment.[74,76,77] Since new-born neurons in the dentate gyrus of the adult hippocampus are localized around blood vessels[78] and have been shown to proliferate in response to vascular growth factors,[77–80] it has been suggested that increased cerebral blood flow, such as that occurring during PA, may improve the communication between the systemic environment and the neurogenic niche.[81] In line with this notion, studies in mice have shown that the decline in neurogenesis and cognitive impairment observed during aging can, at least in part, be attributed to changes in blood-borne factors.[81]

Blood-borne factors deliver beneficial effects to the hippocampus

Studies in rodents have demonstrated that systemic administration of blood from young mice into old mice counteracts age-related

degeneration in various tissues, including the brain.[71,72] Villeda et al.[71] showed that old mice receiving young blood displayed greater hippocampal spine density and plasticity than a control group receiving old blood transfusions. Furthermore, they showed that long-term potentiation in the hippocampus was restored in old mice receiving young blood. They also observed that plasma from young mice injected into old mice restored age-related impairment in contextual fear conditioning and spatial navigation tasks. Both of these tasks depend on hippocampal function, while the latter also depends strongly on a functional entorhinal cortex.[82] This is notable as the entorhinal-hippocampal system begins to atrophy already during early, pre-clinical stages of AD.[83–85] Also, input from entorhinal cortex onto new neurons has been shown to increase with exercise.[86] Katsimpardi et al.[72] showed that blood-borne factors in young animals increased brain blood flow and neurogenesis in several areas of aged brains, among them the hippocampus.[72] Conversely, old blood infused into young mice impaired neurogenesis and cognitive function, indicating that an aged circulatory systemic environment contains "age-promoting" factors.[71] Following this, Smith et al.[87] were able to identify the protein β2-microglobulin as a key circulating factor negatively regulating cognitive and regenerative function in the adult hippocampus ("pro-aging" factor). Moreover, a recent translational study found that human plasma of an early developmental stage, namely umbilical cord plasma, enhances plasticity and improves neuronal function in the aged mouse brain - especially in the hippocampus. This study found that the protein Tissue Inhibitor of Metalloproteinase 2 (TIMP2) is enriched in umbilical cord plasma and is also a systemic factor whose abundance declines with aging. In line with the notion of a brain health-promoting effect of TIMP2, systemically injecting this protein into aged mice promoted synaptic plasticity and improved learning and memory.[88]

These findings indicate that soluble factors in blood may have therapeutic effects. These studies also indicate that there is circulatory communication between the systemic environment and the hippocampus, and that systemic factors are capable of inducing changes in the brain despite the blood-brain barrier. Therefore, molecules abundant in a healthy circulatory environment may be identified and provide guidance for development of novel therapeutics. In fact, a first, small randomized controlled clinical trial to explore the safety, tolerability and feasibility of plasma infusions from *young* donors to patients with AD recently reported that such infusions are safe, well tolerable and feasible, and warrant further exploration.[89] An exploratory endpoint assessing the effect of young plasma infusions in AD patients showed improvements on functional abilities, although no changes were found on global cognition, mood or functional connectivity. Another study exploring the same objectives, involving young plasma infusions in patients with Parkinson's disease, has also been initiated and is ongoing (NCT02968433).

Candidate factors for PA-induced neuroprotection (Fig. 1)

Brain-derived neurotrophic factor (BDNF)

The neurotrophin/growth factor BDNF is induced in the brain and most robustly in the hippocampus in response to exercise in animal models.[90] BDNF is believed to be essential for mammalian brain development and hippocampal function, including neuronal cell survival, synaptic plasticity, neurogenesis, neuronal survival and differentiation and mitochondrial biogenesis.[73,91,92] In addition, BDNF promotes learning by modulating synaptic changes, which in turn induces long-term potentiation.[93,94] These effects are triggered when secreted BDNF binds to tyrosine-kinase receptor (TrkB) and activates three important signaling pathways; (i) the Ras-mitogen activated protein kinase (MAPK), (ii) phospholipase Cγ (PLCγ)-inositol trisphosphate (IP3) and (iii) phosphoinositide 3-kinase (PI3K) signaling pathways.[91] In a study on mice housed with a running wheel for 30 days prior to sacrifice, the enhancement of BDNF gene expression as a result of PA was shown to be dependent on TrkB stimulation by the exercise induced metabolite D-β-hydroxybutyrate. Class 1 histone deacetylases occupying BDNF promoter regions were inhibited by D-β-hydroxybutyrate, leading to an increase in BDNF expression.[95] Blocking the BDNF receptor

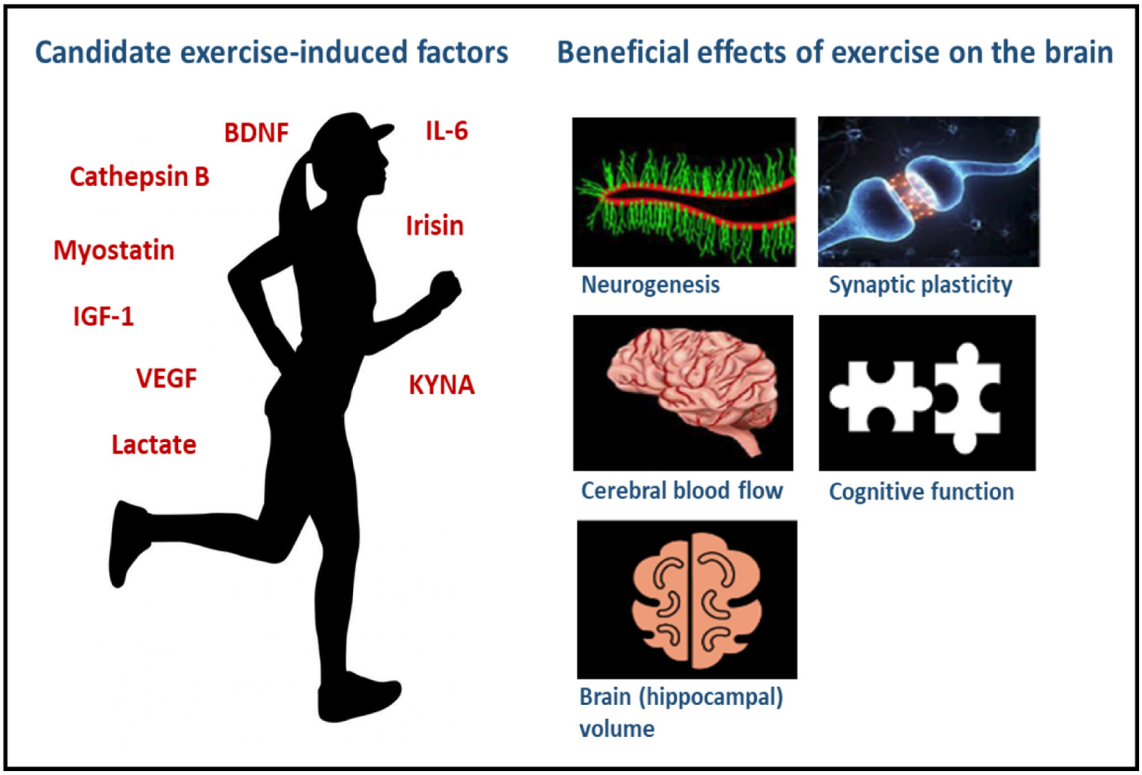

Fig. 1. Candidate factors for PA-induced neuroprotection.

TrkB in exercised rats inhibited exercise-induced benefits on cognitive function in a spatial learning task down to sedentary control levels.[96] Notably, inhibition of BDNF during PA in rats also abolished PA-mediated enhancement in spatial learning as well as the expression of several molecular markers induced by PA.[97,98] In humans, the secreted levels of BDNF have proven to be influenced by PA as shown in some,[99–102] but not all studies.[103] Several studies have sought to explore how this response is involved in improving brain health. A recent study in a mouse model of AD[104] provided novel insights into the link between PA, BDNF and neurogenesis in AD. Using a common AD mouse model (5xFAD transgenic mice), the authors showed that increasing adult neurogenesis by itself is not sufficient to recapitulate the effects of PA on cognition. However, genetic or pharmacological stimulation of BDNF release along with a simultaneous induction of neurogenesis mimicked the memory improvements observed after PA. Overall, these findings provide firm evidence that BDNF production and secretion are increased upon PA, and more importantly, that BDNF has a causative role in the cognitive improvements induced by exercise. Furthermore, low serum levels of BDNF in humans have been linked to neurodegenerative diseases such as AD and high levels of BDNF associated with increased hippocampal volume.[61]

FNDC5/Irisin

Another factor shown to be released by skeletal muscle upon PA is irisin.[105] Irisin is a polypeptide of 112 amino acids and is the secreted form of the transmembrane protein Fibronectin type III domain-containing 5 (FNDC5). Initial reports showed that *Fndc5* expression is regulated by Peroxisome proliferator-activated receptor γ co-activator α (PGC-1α), a transcriptional co-activator widely recognized for its role in muscle adaptations after PA.[67,105,106] PGC-1α is produced in response to prolonged endurance PA, and works as a master regulator of mitochondrial biogenesis, with a protective effect on mitochondrial metabolism.[107] It is interesting to note that mitochondrial dysfunction has in recent years emerged as a key alternative to the amyloid cascade hypothesis in AD research.[108] In response to PGC-1α, the FNDC5 protein is cleaved and secreted as irisin from muscle and various brain regions.[67,105,109] In the central nervous system, PA induces hippocampal BDNF through a PGC-1α/FNDC5 pathway.[67] Importantly, increasing systemic irisin levels in mice via adenoviral expression of FNDC5, primarily in the liver, induced hippocampal expression of *Bdnf,* as well as other important components of hippocampal function (i.e., *Npas4, Fos*, and *Arc* genes).[67] Interestingly, FNDC5 expression is decreased in primary cortical neurons treated with BDNF, suggesting a FNDC5/BDNF feedback loop. Since Irisin is secreted upon PA in mice[105] and humans,[110] where it apparently promotes BDNF release, it deserves attention as a potential circulating mediator of PA benefits in the brain.[111] A recent study explored this further and showed that FNDC5/irisin levels are reduced in the hippocampus and cerebrospinal fluid in late-stage AD patients when compared to age-matched controls, as well as in transgenic AD mice.[112] Knocking out FNDC5/irisin in the brain of transgenic AD mice led to impairment of synaptic plasticity and long-term potentiation, while boosting FNDC5/irisin rescued synaptic plasticity and memory impairment. Also, in transgenic AD mice infused with amyloid-β oligomers, daily PA protected against amyloid-β oligomer-induced memory impairment, and prevented amyloid-β oligomer-induced reduction of FNDC5/irisin mRNA and protein in the hippocampus. Data from this study suggests FNDC5/irisin as a novel factor capable of resisting synaptic failure and memory impairment in AD.[112]

Kynurenic acid (KYNA)

The kynurenine pathway is the main route of tryptophan metabolism in the brain. Kynurenine is a metabolite of L-tryptophan and is involved in regulating immune responses. Low plasma kynurenine concentration is considered to be neuroprotective against stress-induced changes.[68] The kynurenine pathway is known to be upregulated in AD, in both plasma[113] and the brain,[114] indicating an increase in the amount of several metabolites with neurotoxic effects related to cognitive impairment, because several metabolites of the kynurenine pathways are proposed to be involved in AD pathogenesis.[113] During PA, more kynurenine aminotransferase is produced in skeletal muscle, via a PGC-1α-dependent mechanism, shifting the L-tryptophan metabolism pathway from producing kynurenine to KYNA. Notably, while kynurenine can cross the blood-brain barrier, KYNA cannot (or only poorly[115]). PA thus shifts peripheral metabolism of exogenous kynurenine into KYNA, competitively increasing circulating KYNA levels.[116] This shift might help protect neurons against degeneration induced by excessive levels of kynurenine.[68]

Insulin-Like Growth Factor 1 (IGF-1)

Gene expression of *Igf-1* is increased in hippocampal neurons[117] as well as in the periphery[118] in response to exercise. IGF-1 is a neurotrophic hormone with neuroprotective and angiogenic properties capable of crossing the blood-brain barrier.[119] Through its effect on multiple complex signaling pathways, IGF-1 can impact upon the production of amyloid β, while it is also involved in regulation of neurotrophin signaling.[120] Low serum levels of IGF-1 have been linked to an increased AD risk, while high serum levels of IGF-1 are associated with increased hippocampal volume.[121] PA upregulates IGF-1 in skeletal muscles, with a primarily acute effect, which peaks after five to ten minutes of PA.[122] In a study by Carro et al. mice were exercised on a treadmill for 1 h per day, either before or after a neurotoxic insult to the hippocampus, and the results indicated an exercise-induced uptake of IGF-1 by the brain, which prevented brain damage (induced lesions).[119] The same study also showed that brain uptake of IGF-1 after intracarotid injection increased neuronal accumulation of IGF-1 and stimulation of hippocampal BDNF, similar to that observed after PA. Importantly, Ding et al.[117] demonstrated that systemic administration of a specific antibody against the IGF-1 receptor blocked the effect of voluntary PA on BDNF production, as well as on other signaling cascades activated by PA in rats. These results show that several effects induced by PA involve systemic IGF-1 signaling through its receptor.

Vascular endothelial growth factor (VEGF) and lactate

VEGF is crucial in vascular growth and survival, but is also required for neuronal functions, such as synaptic *N*-methyl-D-aspartate (NMDA) receptor action and long-term potentiation, as well as for behavioural plasticity.[123–125] Overexpression of *Vegf* in the central nerve system has also been shown to restore impaired memory in AD mice.[126] Cerebral hypoperfusion is a component of AD neuropathology, and interestingly, recent studies show that PA induces an increase in brain VEGF and angiogenesis, via a lactate receptor identified in the brain, hydroxycarboxylic acid receptor 1 (HCAR1).[127] In rats, a single bout (1 h) of PA resulted in raised *Vegf* mRNA levels in skeletal muscle.[128] Similar findings were obtained after chronic muscle stimulation.[129] Interestingly, a single daily injection of L-lactate (the most abundant form of lactate) over 7 weeks, mimicking blood lactate levels similar to that observed during intense PA, increased VEGF levels and microvascular density in the dentate gyrus, i.e., in the region where adult hippocampal neurogenesis occurs.[127] This indicates that activation of HCAR1 by muscle-generated lactate is one of the mechanisms by which PA benefits the brain. The observations suggest HCAR1 receptor stimulation as a potential target of neuroprotective intervention in AD and other brain pathologies. This could potentially be useful, not as a replacement of PA, but as an adjuvant, for individuals who are unable to perform sufficient PA. In another study in mice exposed to stress, lactate injections counteracted the effect of stress (antidepressant effect), i.e. reproducing specific brain exercise-related changes.[130] In a more

recent study, the authors conclude with lactate being a component of the "exercise pill".[131] Lactate produced in exercised mice was found to cross the blood brain barrier to induce expression of *Bdnf* and signaling of the BDNF receptor TrkB in the hippocampus, resulting in promotion of learning and memory formation.[131]

Cathepsin B

Cathepsin B is a cysteine protease (lysosomal enzyme) secreted by the rough endoplasmic reticulum that can cross the blood-brain barrier.[132] A recent study identified cathepsin B as a PA-induced myokine (i.e., protein/peptides secreted by muscle) that beneficially regulates neurogenesis.[132] Treadmill running resulted in elevated levels of cathepsin B in skeletal muscle and in the circulation. Cathepsin B knock-out mice showed reduced adult hippocampal neurogenesis and impaired spatial learning and memory. Stimulation of adult neuroprogenitor cells with recombinant cathepsin B increased neurogenesis.[132] In another study, transgenic AD mice were injected with a recombinant adenovirus expressing cathepsin B. The data showed an association between cathepsin B and lowered levels of amyloid β production in addition to improved learning and memory.[133] Interestingly, in experiments with transgenic AD mice receiving cysteine protease inhibitors such as E64d, amyloid β is reduced and memory improved.[134,135] Similarly, deletion of the cathepsin B gene resulted in reduced amyloid β levels and improved memory,[136] and these cysteine protease inhibitors have been suggested as potential AD therapeutics. In humans, secreted cathepsin B is found to be present at high levels in the plasma of AD patients,[137] and dysfunction in lysosomal enzymes such as cathepsin B have been associated with neurodegeneration in diseases such as AD.[138] More recently, a study investigating the association of lysosomal enzymes with AD at different stages suggests lysosomal enzymes as potential peripheral biomarkers of AD, as they were found to vary with the progression of AD.[139] Therefore, the role of cathepsin B in relation to AD remains controversial.

Interleukin 6 (IL-6)

IL-6 is a cytokine involved both in pro- and anti-inflammatory processes, as well as in the regulation of metabolic, regenerative and neural processes.[140] It is also known as a myokine, as it is one of the first molecules shown to be produced and secreted from skeletal muscle as a result of PA.[141] After two weeks of voluntary wheel running, mice displayed increased production of neuronal IL-6 in the hippocampus, resulting in downregulation of pro-inflammatory cytokines and inflammation.[142] This study suggests that IL-6 may be protective against neurodegeneration by reducing harmful inflammatory responses. However, more studies with blocking strategies are needed to expand this understanding and test a potentially causative link between IL-6 and exercise-induced neuroprotection.

Other candidate factors

Apart from the candidate factors discussed above, exercise-induced factors are continuously being discovered. For instance, myostatin is identified as a myokine which in contrast to other myokines is reduced in response to exercise.[143] Myostatin is related to the control of muscle growth and body metabolism, and functions to limit muscle growth (induces muscle atrophy when activated).[144] The atrophic component of myostatin is particularly obvious in patients with disorders resulting in cachexia, which can only be reversed by depletion of the myostatin gene.[145] Inhibition of myostatin has also been shown to upregulate PGC-1α, a transcriptional co-activator that in turn enhances mitochondria biogenesis.[146] Recently, a study in transgenic AD mice explored the association between muscle atrophy and cognitive deficits.[147] The authors found that the transgenic AD mice at older ages exhibited muscle atrophy with elevated myostatin levels when compared to sex- and age-matched wild type controls. Knocking out the myostatin gene leads to increased muscle mass and strength in addition to memory improvements.[147]

Conclusions

Currently, reduction in lifestyle-related risk factors seems to be one of the most promising options to reduce the prevalence of dementia. In particular, due to the convincing epidemiological evidence associating PA with reduced AD risk, recent research has adopted a multidomain interventional focus that includes PA alongside mechanistic investigations. Promising data in both animals and humans indicates that targeting the systemic circulatory environment may be a potential strategy to prevent neurodegeneration and dementia. Given that PA and high CRF associates with reduced risk of dementia development, and has widespread systemic benefits, we hypothesize that blood from exercised individuals has rejuvenating properties, similar to, or stronger than, those found in young blood. If this hypothesis is confirmed, and the underlying mechanisms are understood, this could be an important step towards enabling development of novel therapeutics against neurodegeneration, dementia and AD.

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Conflict of interest

None.

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