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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.
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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

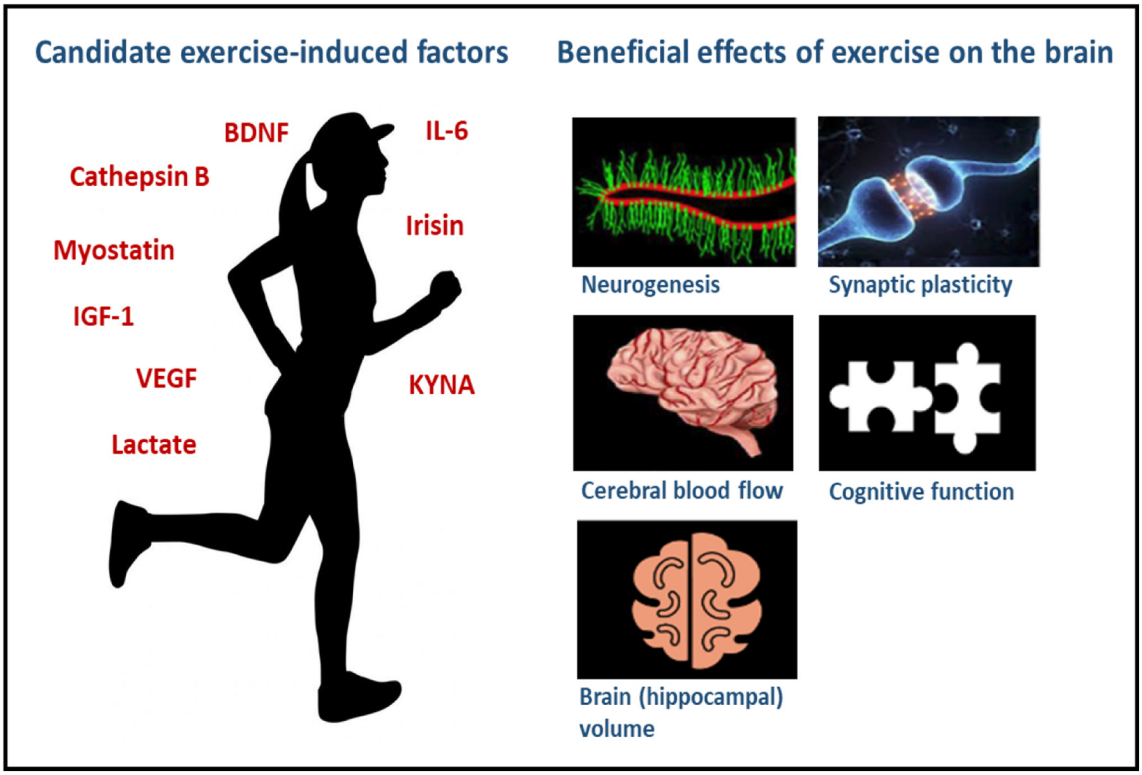

Fig. 1. Candidate factors for PA-induced neuroprotection.

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.

References

1. World Health Organization. *Aging and Life Course*. 2015; Available from: , http://www.who.int/ageing/en/.
2. Winblad B, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol 2016;15(5):455-532.
3. Livingston G, et al. Dementia prevention, intervention, and care. Lancet 2017;390(10113):2673-2734.
4. The L. Dementia burden coming into focus. Lancet 2017;390(10113):2606.
5. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimers Res Ther 2014;6(4):37.
6. Qiu C. Preventing Alzheimer's disease by targeting vascular risk factors: hope and gap. J Alzheimers Dis 2012;32(3):721-731.
7. Exalto LG, et al. Midlife risk score for the prediction of dementia four decades later. Alzheimers Dement 2014;10(5):562-570.
8. Tolppanen AM, et al. Midlife vascular risk factors and Alzheimer's disease: evidence from epidemiological studies. J Alzheimers Dis 2012;32(3):531-540.
9. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011;10(9):819-828.
10. Colcombe SJ, et al. Aerobic fitness reduces brain tissue loss in aging humans. J Gerontol A Biol Sci Med Sci 2003;58(2):176-180.
11. de Bruijn RF, Ikram MA. Cardiovascular risk factors and future risk of Alzheimer's disease. BMC Med 2014;12:130.
12. Levine DA, Langa KM. Vascular cognitive impairment: disease mechanisms and therapeutic implications. Neurotherapeutics 2011;8(3):361-373.
13. Rovio S, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol 2005;4(11):705-711.
14. Qiu C, Xu W, Fratiglioni L. Vascular and psychosocial factors in Alzheimer's disease: epidemiological evidence toward intervention. J Alzheimers Dis 2010;20(3):689-697.
15. Mahley RW. Apolipoprotein E: from cardiovascular disease to neurodegenerative disorders. J Mol Med (Berl) 2016;94(7):739-746.
16. Norton S, et al. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol 2014;13(8):788-794.
17. Ahlskog JE, et al. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Mayo Clin Proc 2011;86(9):876-884.
18. Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia?: a systematic review and meta-analysis of longitudinal studies. BMC Public Health 2014;14:510.
19. Aarsland D, et al. Is physical activity a potential preventive factor for vascular dementia? A systematic review. Aging Ment Health 2010;14(4):386-395.
20. Williams, J.W., et al., *Preventing Alzheimer's disease and cognitive decline*. Evid Rep Technol Assess (Full Rep), 2010(193): p. 1-727.

21. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychol Med 2009;39(1):3-11.
22. Brown BM, et al. Physical activity and amyloid-beta plasma and brain levels: results from the Australian imaging, biomarkers and lifestyle study of ageing. Mol Psychiatry 2013;18(8):875-881.
23. Brasure M, et al. Physical activity interventions in preventing cognitive decline and Alzheimer-type dementia: a systematic review. Ann Intern Med 2018;168(1):30-38.
24. Andrieu S, et al. Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions. Lancet Neurol 2015;14(9):926-944.
25. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nat Rev Neurol 2018;14(11):653-666.
26. Ngandu T, et al. A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 2015;385(9984):2255-2263.
27. Kivipelto M, et al. The Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER): study design and progress. Alzheimers Dement 2013;9(6):657-665.
28. Ngandu T, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 2015;385(9984):2255-2263.
29. Ross R, et al. Importance of assessing Cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. Circulation 2016;134(24):e653-e699.
30. Horder H, et al. Midlife cardiovascular fitness and dementia: a 44-year longitudinal population study in women. Neurology 2018;90(15):e1298-e1305.
31. Defina LF, et al. The association between midlife cardiorespiratory fitness levels and later-life dementia: a cohort study. Ann Intern Med 2013;158(3):162-168.
32. Kurl S, et al. Cardiorespiratory fitness and risk of dementia: a prospective population-based cohort study. Age Ageing 2018;47(4):611-614.
33. Kulmala J, et al. Association between mid- to late life physical fitness and dementia: evidence from the CAIDE study. J Intern Med 2014;276(3):296-307.
34. Schultz SA, et al. Cardiorespiratory fitness alters the influence of a polygenic risk score on biomarkers of AD. Neurology 2017;88(17):1650-1658.
35. Liu R, et al. Cardiorespiratory fitness as a predictor of dementia mortality in men and women. Med Sci Sports Exerc 2012;44(2):253-259.
36. Lautenschlager NT, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 2008;300(9):1027-1037.
37. Young, J., et al., *Aerobic exercise to improve cognitive function in older people without known cognitive impairment.* Cochrane Database Syst Rev, 2015(4): p. Cd005381.
38. Lamb SE, et al. Dementia and physical activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. Bmj 2018;361:k1675.
39. Scarmeas N, et al. Physical activity and Alzheimer disease course. Am J Geriatr Psychiatry 2011;19(5):471-481.
40. Sobol NA, et al. Change in fitness and the relation to change in cognition and neuropsychiatric symptoms after aerobic exercise in patients with mild Alzheimer's disease. J Alzheimers Dis 2018;65(1):137-145.
41. Sofi F, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. J Intern Med 2011;269(1):107-117.
42. Northey JM, et al. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. Br J Sports Med 2018;52(3):154-160.
43. Lee HJ, Don Kim K. Effect of physical activity on cognition and daily living activities of the elderly with mild dementia. J Phys Ther Sci 2018;30(3):428-433.
44. Swain RA, et al. Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. Neuroscience 2003;117(4):1037-1046.
45. van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci 1999;2(3):266-270.
46. van Praag H, et al. Functional neurogenesis in the adult hippocampus. Nature 2002;415(6875):1030-1034.
47. Zhao C, et al. Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J Neurosci 2006;26(1):3-11.
48. van Praag H, et al. Plant-derived flavanol (−)epicatechin enhances angiogenesis and retention of spatial memory in mice. J Neurosci 2007;27(22):5869-5878.
49. Ge S, et al. Synaptic integration and plasticity of new neurons in the adult hippocampus. J Physiol 2008;586(16):3759-3765.
50. van Praag H, et al. Exercise enhances learning and hippocampal neurogenesis in aged mice. J Neurosci 2005;25(38):8680-8685.
51. Kronenberg G, et al. Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. Neurobiol Aging 2006;27(10):1505-1513.
52. Wu P, et al. Calorie restriction ameliorates neurodegenerative phenotypes in forebrain-specific presenilin-1 and presenilin-2 double knockout mice. Neurobiol Aging 2008;29(10):1502-1511.
53. Marlatt MW, et al. Running throughout middle-age improves memory function, hippocampal neurogenesis, and BDNF levels in female C57BL/6J mice. Dev Neurobiol 2012;72(6):943-952.
54. van Praag H, et al. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci U S A 1999;96(23):13427-13431.
55. Zhao G, et al. Treadmill exercise enhances synaptic plasticity, but does not alter beta-amyloid deposition in hippocampi of aged APP/PS1 transgenic mice. Neuroscience 2015;298:357-366.
56. Farmer J, et al. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. Neuroscience 2004;124(1):71-79.
57. O'Callaghan RM, Ohle R, Kelly AM. The effects of forced exercise on hippocampal plasticity in the rat: a comparison of LTP, spatial- and non-spatial learning. Behav Brain Res 2007;176(2):362-366.
58. van Praag H. Neurogenesis and exercise: past and future directions. Neuromolecular Med 2008;10(2):128-140.
59. Maass A, et al. Vascular hippocampal plasticity after aerobic exercise in older adults. Mol Psychiatry 2015;20(5):585-593.
60. Erickson KI, et al. Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus 2009;19(10):1030-1039.
61. Erickson KI, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A 2011;108(7):3017-3022.
62. Firth J, et al. Effect of aerobic exercise on hippocampal volume in humans: a systematic review and meta-analysis. Neuroimage 2018;166:230-238.
63. Rovio S, et al. The effect of midlife physical activity on structural brain changes in the elderly. Neurobiol Aging 2010;31(11):1927-1936.
64. Johnson NA, et al. Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: initial experience. Radiology 2005;234(3):851-859.
65. Ruitenberg A, et al. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam study. Ann Neurol 2005;57(6):789-794.
66. Kobilo T, et al. Running is the neurogenic and neurotrophic stimulus in environmental enrichment. Learn Mem 2011;18(9):605-609.
67. Wrann CD, et al. Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway. Cell Metab 2013;18(5):649-659.
68. Agudelo LZ, et al. Skeletal muscle PGC-1alpha1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. Cell 2014;159(1):33-45.
69. Moon HY, van Praag H. Muscle over mind. Cell Metab 2014;20(4):560-562.
70. Sleiman SF, Chao MV. Downstream consequences of exercise through the action of BDNF. Brain Plast 2015;1(1):143-148.
71. Villeda SA, et al. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nat Med 2014;20(6):659-663.
72. Katsimpardi L, et al. Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. Science 2014;344(6184):630-634.
73. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci 2007;30(9):464-472.
74. Fabel K, et al. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. Eur J Neurosci 2003;18(10):2803-2812.
75. Bouchard J, Villeda SA. Aging and brain rejuvenation as systemic events. J Neurochem 2015;132(1):5-19.
76. Trejo JL, Carro E, Torres-Aleman I. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J Neurosci 2001;21(5):1628-1634.
77. Pereira AC, et al. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A 2007;104(13):5638-5643.
78. Palmer TD, Willhoite AR, Gage FH. Vascular niche for adult hippocampal neurogenesis. J Comp Neurol 2000;425(4):479-494.
79. Shen Q, et al. Endothelial cells stimulate self-renewal and expand neurogenesis of neural stem cells. Science 2004;304(5675):1338-1340.
80. Thored P, et al. Long-term neuroblast migration along blood vessels in an area with transient angiogenesis and increased vascularization after stroke. Stroke 2007;38(11):3032-3039.
81. Villeda SA, et al. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature 2011;477(7362):90-94.
82. Steffenach HA, et al. Spatial memory in the rat requires the dorsolateral band of the entorhinal cortex. Neuron 2005;45(2):301-313.
83. Kordower JH, et al. Loss and atrophy of layer II entorhinal cortex neurons in elderly people with mild cognitive impairment. Ann Neurol 2001;49(2):202-213.
84. Gomez-Isla T, et al. Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. J Neurosci 1996;16(14):4491-4500.
85. Scheff SW, et al. Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. Neurobiol Aging 2006;27(10):1372-1384.
86. Vivar C, Peterson BD, van Praag H. Running rewires the neuronal network of adult-born dentate granule cells. Neuroimage 2016;131:29-41.
87. Smith LK, et al. beta2-microglobulin is a systemic pro-aging factor that impairs cognitive function and neurogenesis. Nat Med 2015;21(8):932-937.
88. Castellano JM, et al. Human umbilical cord plasma proteins revitalize hippocampal function in aged mice. Nature 2017;544(7651):488-492.
89. Sha SJ, et al. Safety, Tolerability, and Feasibility of Young Plasma Infusion in the Plasma for Alzheimer Symptom Amelioration Study: A Randomized Clinical Trial JAMA Neurol. 2018.
90. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci 2002;25(6):295-301.
91. Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. Nat Rev Neurosci 2013;14(1):7-23.
92. Markham A, et al. Changes in mitochondrial function are pivotal in neurodegenerative and psychiatric disorders: how important is BDNF? Br J Pharmacol 2014;171(8):2206-2229.
93. Kuipers SD, Bramham CR. Brain-derived neurotrophic factor mechanisms and function in adult synaptic plasticity: new insights and implications for therapy. Curr Opin Drug Discov Devel 2006;9(5):580-586.
94. Poo MM. Neurotrophins as synaptic modulators. Nat Rev Neurosci 2001;2(1):24-32.

95. Sleiman SF, et al. Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body beta-hydroxybutyrate. Elife 2016;5.
96. Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur J Neurosci 2004;20(10):2580-2590.
97. Gomez-Pinilla F, Vaynman S, Ying Z. Brain-derived neurotrophic factor functions as a metabotrophin to mediate the effects of exercise on cognition. Eur J Neurosci 2008;28(11):2278-2287.
98. Vaynman SS, et al. Exercise differentially regulates synaptic proteins associated to the function of BDNF. Brain Res 2006;1070(1):124-130.
99. Griffin EW, et al. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. Physiol Behav 2011;104(5):934-941.
100. Araya AV, et al. Effect of exercise on circulating levels of brain-derived neurotrophic factor (BDNF) in overweight and obese subjects. Horm Metab Res 2013;45(7):541-544.
101. Seifert T, et al. Endurance training enhances BDNF release from the human brain. Am J Physiol Regul Integr Comp Physiol 2010;298(2):R372-R377.
102. Walsh JJ, Tschakovsky ME. Exercise and circulating BDNF: mechanisms of release and implications for the design of exercise interventions. Appl Physiol Nutr Metab 2018;43(11):1095-1104.
103. Maass A, et al. Relationships of peripheral IGF-1, VEGF and BDNF levels to exercise-related changes in memory, hippocampal perfusion and volumes in older adults. Neuroimage 2016;131:142-154.
104. Choi, S.H., et al., *Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model.* Science, 2018. **361**(6406).
105. Bostrom P, et al. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 2012;481(7382):463-468.
106. Safdar A, et al. Exercise increases mitochondrial PGC-1alpha content and promotes nuclear-mitochondrial cross-talk to coordinate mitochondrial biogenesis. J Biol Chem 2011;286(12):10605-10617.
107. Wu Z, et al. Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. Cell 1999;98(1):115-124.
108. Van Giau V, An SSA, Hulme JP. Mitochondrial therapeutic interventions in Alzheimer's disease. J Neurol Sci 2018;395:62-70.
109. Li X, et al. Characterization of fibronectin type III domain-containing protein 5 (FNDC5) gene in chickens: cloning, tissue expression, and regulation of its expression in the muscle by fasting and cold exposure. Gene 2015;570(2):221-229.
110. Jedrychowski MP, et al. Detection and Quantitation of circulating human Irisin by tandem mass spectrometry. Cell Metab 2015;22(4):734-740.
111. Wrann CD. FNDC5/irisin - their role in the nervous system and as a mediator for beneficial effects of exercise on the brain. Brain Plast 2015;1(1):55-61.
112. Lourenco MV, et al. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat Med 2019;25(1):165-175.
113. Gulaj E, et al. Kynurenine and its metabolites in Alzheimer's disease patients. Adv Med Sci 2010;55(2):204-211.
114. Guillemin GJ, et al. Indoleamine 2,3 dioxygenase and quinolinic acid immunoreactivity in Alzheimer's disease hippocampus. Neuropathol Appl Neurobiol 2005;31(4):395-404.
115. Varga N, et al. Targeting of the kynurenic acid across the blood-brain barrier by core-shell nanoparticles. Eur J Pharm Sci 2016;86:67-74.
116. Schlittler M, et al. Endurance exercise increases skeletal muscle kynurenine aminotransferases and plasma kynurenic acid in humans. Am J Physiol Cell Physiol 2016;310(10):C836-C840.
117. Ding Q, et al. Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. Neuroscience 2006;140(3):823-833.
118. Schwarz AJ, et al. Acute effect of brief low- and high-intensity exercise on circulating insulin-like growth factor (IGF) I, II, and IGF-binding protein-3 and its proteolysis in young healthy men. J Clin Endocrinol Metab 1996;81(10):3492-3497.
119. Carro E, et al. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. J Neurosci 2001;21(15):5678-5684.
120. Puglielli L. Aging of the brain, neurotrophin signaling, and Alzheimer's disease: is IGF1-R the common culprit? Neurobiol Aging 2008;29(6):795-811.
121. Westwood AJ, et al. Insulin-like growth factor-1 and risk of Alzheimer dementia and brain atrophy. Neurology 2014;82(18):1613-1619.
122. Berg U, Bang P. Exercise and circulating insulin-like growth factor I. Horm Res 2004;62(suppl 1):50-58.
123. Licht T, et al. Reversible modulations of neuronal plasticity by VEGF. Proc Natl Acad Sci U S A 2011;108(12):5081-5086.
124. Licht T, et al. VEGF preconditioning leads to stem cell remodeling and attenuates age-related decay of adult hippocampal neurogenesis. Proc Natl Acad Sci U S A 2016;113(48):E7828-e7836.
125. De Rossi P, et al. A critical role for VEGF and VEGFR2 in NMDA receptor synaptic function and fear-related behavior. Mol Psychiatry 2016;21(12):1768-1780.
126. Religa P, et al. VEGF significantly restores impaired memory behavior in Alzheimer's mice by improvement of vascular survival. Sci Rep 2013;3:2053.
127. Morland C, et al. Exercise induces cerebral VEGF and angiogenesis via the lactate receptor HCAR1. Nat Commun 2017;8:15557.
128. Breen, E.C., et al., *Angiogenic growth factor mRNA responses in muscle to a single bout of exercise.* J Appl Physiol (1985), 1996. **81**(1): p. 355–61.
129. Annex BH, et al. Induction and maintenance of increased VEGF protein by chronic motor nerve stimulation in skeletal muscle. Am J Physiol 1998;274(3 Pt 2):H860-H867.
130. Karnib N, et al. Lactate is an antidepressant that mediates resilience to stress by modulating the hippocampal levels and activity of histone deacetylases. Neuropsychopharmacology 2019 https://doi.org/10.1038/s41386-019-0313-z.
131. El Hayek L, et al. Lactate mediates the effects of exercise on learning and memory through SIRT1-dependent activation of hippocampal brain-derived neurotrophic factor (BDNF). J Neurosci 2019 https://doi.org/10.1523/JNEUROSCI.1661-18.2019.
132. Moon HY, et al. Running-induced systemic cathepsin B secretion is associated with memory function. Cell Metab 2016;24(2):332-340.
133. Embury CM, et al. Cathepsin B improves ss-Amyloidosis and learning and memory in models of Alzheimer's disease. J Neuroimmune Pharmacol 2017;12(2):340-352.
134. Hook G, Hook VY, Kindy M. Cysteine protease inhibitors reduce brain beta-amyloid and beta-secretase activity in vivo and are potential Alzheimer's disease therapeutics. Biol Chem 2007;388(9):979-983.
135. Hook G, et al. Brain pyroglutamate amyloid-beta is produced by cathepsin B and is reduced by the cysteine protease inhibitor E64d, representing a potential Alzheimer's disease therapeutic. J Alzheimers Dis 2014;41(1):129-149.
136. Kindy MS, et al. Deletion of the cathepsin B gene improves memory deficits in a transgenic Alzheimer's disease mouse model expressing AbetaPP containing the wild-type beta-secretase site sequence. J Alzheimers Dis 2012;29(4):827-840.
137. Sundelof J, et al. Higher cathepsin B levels in plasma in Alzheimer's disease compared to healthy controls. J Alzheimers Dis 2010;22(4):1223-1230.
138. Tiribuzi R, et al. Lysosomal beta-galactosidase and beta-hexosaminidase activities correlate with clinical stages of dementia associated with Alzheimer's disease and type 2 diabetes mellitus. J Alzheimers Dis 2011;24(4):785-797.
139. Morena, F., et al., *A Comparison of Lysosomal Enzymes Expression Levels in Peripheral Blood of Mild- and Severe-Alzheimer's Disease and MCI Patients: Implications for Regenerative Medicine Approaches.* Int J Mol Sci, 2017. **18**(8).
140. Scheller J, et al. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta 2011;1813(5):878-888.
141. Pal M, Febbraio MA, Whitham M. From cytokine to myokine: the emerging role of interleukin-6 in metabolic regulation. Immunol Cell Biol 2014;92(4):331-339.
142. Funk JA, et al. Voluntary exercise protects hippocampal neurons from trimethyltin injury: possible role of interleukin-6 to modulate tumor necrosis factor receptor-mediated neurotoxicity. Brain Behav Immun 2011;25(6):1063-1077.
143. McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. Nature 1997;387(6628):83-90.
144. Feng XH, Derynck R. Specificity and versatility in tgf-beta signaling through Smads. Annu Rev Cell Dev Biol 2005;21:659-693.
145. Heineke J, et al. Genetic deletion of myostatin from the heart prevents skeletal muscle atrophy in heart failure. Circulation 2010;121(3):419-425.
146. LeBrasseur NK, et al. Myostatin inhibition enhances the effects of exercise on performance and metabolic outcomes in aged mice. J Gerontol A Biol Sci Med Sci 2009;64(9):940-948.
147. Lin YS, Lin FY, Hsiao YH. Myostatin is associated with cognitive decline in an animal model of Alzheimer's disease. Mol Neurobiol 2018;56(3):1984-1991.