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Exercise builds brain health: key roles of growth factor cascades and inflammation

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Human and other animal studies demonstrate that exercise targets many aspects of brain function and has broad effects on overall brain health. The benefits of exercise have been best defined for learning and memory, protection from neurodegeneration and alleviation of depression, particularly in elderly populations. Exercise increases synaptic plasticity by directly affecting synaptic structure and potentiating synaptic strength, and by strengthening the underlying systems that support plasticity including neurogenesis, metabolism and vascular function. Such exercise-induced structural and functional change has been documented in various brain regions but has been best-studied in the hippocampus – the focus of this review. A key mechanism mediating these broad benefits of exercise on the brain is induction of central and peripheral growth factors and growth factor cascades, which instruct downstream structural and functional change. In addition, exercise reduces peripheral risk factors such as diabetes, hypertension and cardiovascular disease, which converge to cause brain dysfunction and neurodegeneration. A common mechanism underlying the central and peripheral effects of exercise might be related to inflammation, which can impair growth factor signaling both systemically and in the brain. Thus, through regulation of growth factors and reduction of peripheral and central risk factors, exercise ensures successful brain function.

Introduction

Much evidence is converging on the concept that lifestyle factors such as exercise can improve learning and memory, delay age-related cognitive decline, reduce risk of neurodegeneration, and play a part in alleviating depression. As we delineate in the first part of this review, the evidence that exercise can affect these endpoints has become better established in the past few years, and provides a foundation for elucidating more precisely the mechanisms through which exercise modulates brain function. In the subsequent two sections, by focusing primarily on the hippocampus, we discuss how exercise can affect brain structure, from increased neurogenesis and angiogenesis to greater dendritic complexity, and we define the underlying mechanisms. It is increasingly clear that a central mechanism is exercise-dependent peripheral and central regulation of growth factors, which operate in unique cascades to orchestrate structural and functional change. In turn, mechanisms that interfere with growth factor signaling – specifically inflammation – are modulated by exercise in the periphery and in the central nervous system (CNS), as outlined in the last section. We propose that reduction of inflammation by exercise is a common means by which exercise reduces peripheral risk factors for cognitive decline and neurodegeneration. We conclude with a brief analysis of future directions and approaches to optimize the impact of exercise on brain function.

Various functional modalities are improved by exercise

Exercise enhances learning and plasticity

In humans, robust effects of exercise have been most clearly demonstrated in aging populations, where sustained exercise participation enhances learning and memory, improves executive function, counteracts age-related and disease-related mental decline, and protects against age-related atrophy in brain areas crucial for higher cognitive processes [1–3]. Interestingly, a dose–response relationship between exercise duration/intensity and health-related quality of life has been reported, whereby the best outcomes are associated with moderate exercise [4]. Consistent with research in humans, rodent studies demonstrate that exercise can facilitate both acquisition and retention in young and aged animals in various hippocampus-dependent tasks including the Morris water maze [5,6], the radial arm maze [7], passive avoidance [8] and object recognition [9]. Not all studies, however, have consistently demonstrated improvements in both acquisition and retention: some have shown benefits in acquisition or retention only. This variability is probably related to differences in the exercise protocol (voluntary versus forced), in combination with the intensity (in forced exercise models) and duration of exercise exposure. Although both forced exercise and voluntary exercise benefit acquisition and/or learning, voluntary exercise seems to produce benefits more reliably, especially after shorter exercise duration. In addition, although some studies show improvements after 1 week of exercise [6,10], most benefits have been associated with longer-term exercise (3–12 weeks) [5,7–9].

Along with improved behavioral performance, exercise facilitates synaptic plasticity in the hippocampus, a key structure for spatial learning. Facilitated plasticity is most

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evident in the dentate gyrus (DG), where exercise enhances both short-term potentiation and long-term potentiation (LTP) [11] – synaptic analogs of learning. In particular, exercise enhances potentiation in response to theta [11] and high-frequency [9,12] stimulation, and reduces the threshold of theta stimulation required for LTP induction in the perforant path [11]. Exercise-facilitated LTP in the DG is paralleled by altered cytoarchitecture in the DG, including increases in dendritic length, dendritic complexity, spine density and neural progenitor proliferation [13]. Interestingly, no potentiation in response to high-frequency stimulation has been reported in the CA1 after exercise [12]; however, exercise effects in the CA1 have been studied less extensively than those in the DG. In parallel with the effects of exercise on hippocampal cytoarchitecture and electrophysiological properties, exercise increases the levels of synaptic proteins (synapsin and synaptophysin [14]), glutamate receptors (NR2b and GluR5 [11]) and the availability of several classes of growth factor including brain-derived neurotrophic factor (BDNF) [15] and insulin-like growth factor-1 (IGF-1) [16], which can enhance plasticity. The potential central role of growth factors in exercise-dependent benefits in brain maintenance, health and function is explored in more detail below.

Although strong evidence supports the idea that exercise can facilitate learning in humans and other animals, there is a gap in our knowledge regarding the types of learning that are improved with exercise. For example, human studies on exercise-dependent effects on cognition have focused on frontal-brain-dependent tasks (executive function), whereas animal studies have assessed effects primarily on hippocampus-dependent learning and plasticity. A key area of future research will be to refine animal studies investigating the cognitive effects of exercise to increase their relevance and translatability to humans.

Exercise is neuroprotective

In addition to benefitting learning and memory, extensive research demonstrates that exercise has neuroprotective effects. These effects have been best defined with respect to reducing brain injury, and to delaying onset of and decline in several neurodegenerative diseases. For example, engaging individuals affected by stroke in post-stroke therapeutic exercise programs accelerates functional rehabilitation (reviewed in Ref. [17]). Clinical trials assessing the efficacy of post-stroke exercise typically combine cardiovascular training (treadmill or exercise bike) with weight training or targeted movement therapy, and the improvements are probably due to the combination of interventions. Animal models of ischemia (middle cerebral artery occlusions) suggest, however, that cardiovascular training therapies alone can reduce stroke damage and improve recovery. Notably, reduced infarct volume and improved function have been observed when animals engage in either forced [18] or voluntary [19] running, and both pre-stroke [18] and post-stroke [19] exercise shows efficacy. An essential future goal will be to define the type, timing and intensity of exercise interventions to determine how exercise will aid in post-stroke rehabilitation.

In addition to the benefits of exercise in stroke, retrospective and cross-sectional studies suggest that participation in physical activity delays onset of and reduces risk for Alzheimer disease (AD), Huntington's disease and Parkinson's disease, and can even slow functional decline after neurodegeneration has begun [2–4,20]. Intervention studies demonstrate that individuals with AD who exercise show improved function on the daily living scale, slowed rate of decline in cognitive tests, improved physical function and decreased depressive symptoms, as compared with non-exercisers who show continued decline [21,22]. Recent evidence suggests that exercise might have the most cognitive benefits in individuals with the ApoE4 genotype (a risk factor for AD) [23], although this area remains controversial [20]. Similar to studies on AD, clinical intervention studies in individuals with Parkinson's disease demonstrate that aerobic training improves movement initiation and aerobic capacity [24], and improves activities of daily living [25]. In parallel with clinical studies, exercise has been shown to improve function in several animal models of neurodegenerative diseases by, for example, delaying symptom onset and slowing cognitive decline in mice transgenic for Huntington's disease [26], and improving spatial learning and memory in transgenic mouse models of AD [27].

Mechanisms underlying the benefits of exercise in neurodegeneration are in the early stages of investigation in animal models such as transgenic mouse models of AD. In these models, exercise reduces the load of amyloid-β (Aβ) plaques in the hippocampus and cortex, possibly by regulating processing of the amyloid precursor protein and/or increasing degradation and clearance of Aβ [27,28]. Importantly, exercising animals show improved hippocampus-dependent learning [27], indicating that the benefits of exercise are functionally significant in this neurodegenerative condition.

Exercise is therapeutic and protective in depression

Emerging evidence suggests that exercise has therapeutic and preventative effects on depression. The prevention and treatment of depression are important areas to define: depression is linked to cognitive decline [29] and is considered to cause a worldwide health burden greater than that of ischemic heart disease, cerebrovascular disease or tuberculosis [30]. Therapeutic effects of exercise on depression have been most clearly established in human studies. Randomized and crossover clinical trials demonstrate the efficacy of aerobic or resistance training exercise (2–4 months) as a treatment for depression in both young [31] and older [32,33] individuals. The benefits are similar to those achieved with anti-depressants [32]. They are also dose dependent: greater improvements are seen with higher levels of exercise [33].

Furthermore, therapeutic effects of exercise on depressive symptoms have been demonstrated in conditions of neurodegeneration in humans. Specifically, in a randomized clinical trial, 3 months of exercise intervention improved depressive symptoms in individuals with AD, whereas non-exercising subjects showed worsening of depressive symptoms [21]. In addition to a therapeutic effect, evidence from human studies shows that exercise

can provide some protection from the development of depression [34], although further studies are needed to resolve inconsistent findings. A protective effect of sustained exercise (>2 weeks) has been clearly demonstrated in animal models of depression, including stress-induced learned helplessness [35,36]. In addition, a therapeutic effect of exercise on exiting depression has been recently established in an animal model [37]; this therapeutic effect parallels that observed in human studies.

Although exercise seems to have both preventative and therapeutic effects on the course of depression, the underlying mechanisms are poorly understood. Protective effects of exercise from stress have focused on the hippocampus, where exercise-induced neurogenesis [38] and growth factor expression [39] have been proposed as potential mediators, although not without controversy [40]. Other proposed mechanisms include exercise-driven changes in the hypothalamic–pituitary–adrenal axis that regulates the stress response [31], and altered activity of dorsal raphe serotonin neurons implicated in mediating learned helplessness behaviors [36]. It is important to note that the translatability of animal studies is dependent on the animal model of depression and how well it parallels the human condition – an area that remains under active investigation.

Mechanisms of exercise effects on brain health

In parallel with its benefits in learning and depression, exercise modulates a range of supporting systems for brain maintenance and plasticity including neurogenesis, enhanced CNS metabolism and angiogenesis. Neurogenesis and other exercise-induced alterations in neuronal circuitry and function must be met by an adequate nutrient and energy supply, which in turn is supported by changes in metabolic function and blood flow.

Enhanced hippocampal neurogenesis is one of the most reproducible effects of exercise in the rodent brain [12,16,41], and might be a key mechanism mediating exercise-related improvements in learning and memory and resistance to depression (although the role of neurogenesis in these functions is controversial at present). In both young and old animals, exercise stimulates proliferation of the neural progenitor population, increases the number of new neurons, and promotes survival of these new cells [12,16,41]. These new neurons become functionally integrated into the hippocampal architecture [42], but they are unique from mature granule cells in that they have a lower threshold of excitability [43]. This feature makes these new neurons well suited to mediate exercise-stimulated enhanced plasticity, such as facilitated perforant-path LTP [11]. Hippocampal neurogenesis has been linked to learning and memory [44,45] and might be related to the therapeutic effects of antidepressants ([46]; but see Ref. [40]) – two functional endpoints that are improved by exercise. The functional consequences of hippocampal neurogenesis remain under intense debate, and it will be important to determine whether the enhancement of hippocampal neurogenesis with exercise contributes to facilitated plasticity, improved learning and memory, or protection from stress.

To support exercise-induced changes in brain function such as enhanced plasticity, neurogenesis and resilience to insult, the brain must meet increased nutrient and energy needs. Such demands are met with higher expression of enzymes involved in glucose use and metabolism in the hippocampus [47,48] and in other brain regions. In addition, exercise leads to widespread growth of blood vessels in the hippocampus [5], cortex [49] and cerebellum [50]; these blood vessels provide increased nutrient and energy supply. Indeed, a recent *in vivo* imaging study in humans (ages 21–45) has shown that 12 weeks of cardiovascular training increases blood flow in the DG, and this increase is correlated with improved rate of learning in a hippocampus-dependent task [51]. In turn, these changes ensure that the enhanced brain function stimulated by exercise can be supported and maintained. In addition, exercise-induced increases in microglia and astrocytes [52], observed in several brain regions, also might help to maintain enhanced brain health and function with exercise. The significance of changes in glia and astrocytes in response to exercise has not been defined and merits further study.

Growth factors are central to the benefits of exercise for the brain

Exercise modulates both plasticity and various supporting systems that participate in maintaining brain function and health. To understand how exercise achieves these effects, the regulatory mechanisms underlying these changes need to be defined. At first glance, it would seem unlikely that common mechanisms could mediate the varied effects of exercise on learning, depression, neurogenesis, angiogenesis and overall brain health. An emerging overarching concept, however, is that exercise increases brain availability of several classes of growth factors that modulate nearly all of the functional endpoints enhanced by exercise.

At present, BDNF, IGF-1 and vascular endothelial-derived growth factor (VEGF) are the principal growth factors known to mediate the effects of exercise on the brain. These growth factors work in concert to produce complementary functional effects, modulating both overlapping and unique aspects of exercise-related benefits in brain plasticity, function and health. Effects of exercise on learning and depression are predominantly regulated by IGF-1 and BDNF, whereas exercise-dependent stimulation of angiogenesis and hippocampal neurogenesis seems to be regulated by IGF-1 and VEGF (Figure 1).

Role of growth factors in exercise-induced benefits in learning and plasticity

Abundant evidence from animal and human research supports the idea that BDNF is essential for hippocampal function, synaptic plasticity, learning, and modulation of depression [53]. In animal studies, exercise increases BDNF in several brain regions, and the most robust and enduring response occurs in the hippocampus [54]. After several days of exercise, BDNF gene and protein production by neurons is increased in all hippocampal subfields, and remains higher for weeks with sustained exercise [15]. Regulation of hippocampal BDNF by exercise is mediated by neurotransmitter systems (reviewed in Refs

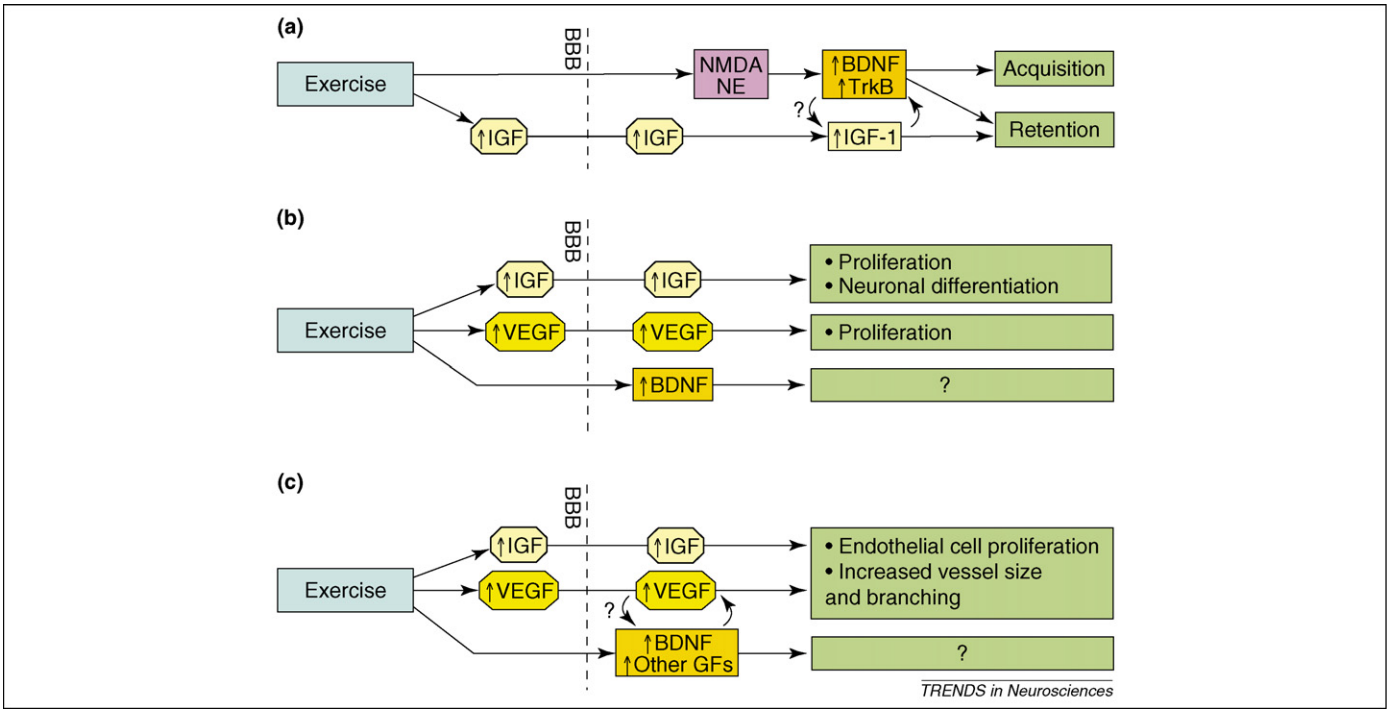

Figure 1. Exercise regulates learning, neurogenesis and angiogenesis through growth factor cascades. Insulin growth factor-1 (IGF-1), brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) derived from central and peripheral sources act in concert to modulate exercise-dependent effects on the brain. **(a)** Exercise enhances learning by induction of BDNF and IGF-1. Neurotransmitters, including NMDA receptors and the noradrenergic (NE) system [54,55], peripheral IGF-1 and possibly centrally derived IGF-1, mediate the induction of hippocampal BDNF with exercise. In turn, BDNF signaling is likely to be a hub for effects of exercise on learning, including acquisition, retention and LTP. **(b)** Exercise stimulates neurogenesis in the hippocampus through the interactive effects of IGF-1 with VEGF. Peripheral IGF-1 and VEGF cross the blood–brain barrier (BBB) and drive enhanced proliferation and survival. **(c)** Exercise stimulates angiogenesis through the effects of IGF-1 and VEGF on endothelial cell proliferation and vessel growth. Peripheral sources of the growth factors (and possibly also central sources) mediate the effects. The role of BDNF in exercise-mediated neurogenesis and angiogenesis has not been directly tested.

[54,55]), by neuroendocrine systems [54], and by IGF-1 [56]. Like BDNF, IGF-1 gene expression is increased in hippocampal neurons in response to exercise, occurring several days after exercise onset [56]. In addition, peripheral circulating levels of IGF-1 are rapidly increased in response to exercise (within 1 h) [57], and the peripheral increase in IGF-1 seems to be essential for exercise-induced neurogenesis [16] and improved memory [56].

Both BDNF signaling and IGF-1 signaling are crucial mechanisms underlying improved learning in response to exercise, as has been established by using blocking antibodies in combination with exercise. BDNF signaling can be blocked with antibodies to TrkB (anti-TrkB), the receptor for BDNF. Intra-hippocampal injection of anti-TrkB attenuates the beneficial effects of exercise on hippocampus-dependent learning, specifically blocking improvements in both the acquisition and the retention of a spatial learning task [6,14]. In addition, anti-TrkB attenuates the exercise-dependent induction of synaptic proteins (e.g. synaptophysin and synapsin) in the hippocampus [6,14]. These results demonstrate that BDNF signaling must be active for the effects of exercise on hippocampal plasticity to manifest.

In parallel, function-blocking antibodies to IGF-1 (anti-IGF-1) also demonstrate that IGF-1 signaling has an essential role in exercise effects on hippocampus-dependent learning and plasticity. Intra-hippocampal injection of anti-IGF-1 prevents enhancement of spatial recall, but not acquisition [56]. In addition, anti-IGF-1 attenuates exercise-dependent induction of synapsin I and blocks exercise-induced activation of the calmodulin kinase II and mitogen-activated protein kinase II (MAPKII) pathways [56] – effects that seem to be mediated by IGF-1-dependent regulation of BDNF signaling [56]. This last study could not differentiate whether the effects were due to a block of peripherally derived or centrally produced IGF-1, and IGF-1 from both sources potentially could be involved.

Much evidence indicates that there are points of convergence between IGF-1 and BDNF signaling. First, IGF-1 increases BDNF signaling in response to exercise. Blocking IGF-1 signaling *in vivo* prevents the induction of hippocampal BDNF in response to exercise and, in parallel, attenuates the exercise-dependent induction of synaptic proteins (e.g. synapsin I) downstream from TrkB signaling [56]. Second, IGF-1 increases neuronal levels of TrkB in hippocampal cultures, thereby increasing BDNF signaling [58] – an effect that might also occur *in vivo*. Third, BDNF, but not IGF-1, modulates the exercise-dependent enhancement of synaptic plasticity mechanisms that are thought to underlie learning and memory. For example, BDNF, similar to exercise, facilitates LTP (reviewed in Ref. [59]) and activates MAPK [60] – a signal transduction pathway that is important for LTP. By contrast, a direct role for IGF-1 in LTP has not been shown, and IGF-1 is only a weak activator of the MAPK pathway in comparison to BDNF [60]. These results suggest that IGF-1 and BDNF work in concert, and that there is a convergence on BDNF signaling as a final common downstream mechanism mediating exercise effects on hippocampal plasticity and learning.

Role of growth factors in exercise-induced benefits in depression

The hippocampus is one brain region implicated in the pathophysiology of depression, and exercise-dependent induction of BDNF in the hippocampus might be a mechanism contributing to the protective and therapeutic effect of exercise on this disorder. This idea is based on the observation that hippocampal infusion of BDNF or overexpression of TrkB receptors produces antidepressant-like effects in preclinical models of behavioral despair [61,62], whereas mice lacking BDNF show impaired antidepressant responses [63]. Furthermore, human genetic studies demonstrate that impaired BDNF availability is associated with susceptibility to depression and other mood disorders [64]. Lastly, evidence indicates that BDNF-mediated TrkB signaling is both sufficient and necessary for antidepressant-like effects in rodents [65]. These data suggest that exercise-dependent induction of hippocampal BDNF might contribute to protective or therapeutic effects of exercise on depression. In addition, exercise and pharmaceutical antidepressants seem to act synergistically to upregulate BDNF in the hippocampus, suggesting that there is a convergent mechanism between these therapeutic interventions [66].

Similar to BDNF, antidepressant effects have been reported for IGF-1: ventricular IGF-1 injection produces antidepressant-like (anxiolytic-like) effects that endure for a week or more [67]. Although the evidence for IGF-1 is not as compelling as that for BDNF, increases in both of these growth factors in the CNS might contribute to anxiolytic or anti-depressant benefits of exercise. The mechanism by which growth factors might have antidepressant effects is largely unknown. It has been recently proposed, however, that neurotrophic factors themselves do not control mood, but rather they facilitate the activity-dependent modulation of networks that are required to induce antidepressant effects [39]. If BDNF signaling does play a central part in exercise-induced benefits in depression, it will be important to determine whether exercise interacts with BDNF polymorphisms, particularly the valine–methionine polymorphism that causes impaired BDNF transport and release [68].

Role of growth factors in exercise effects on neurogenesis and angiogenesis

Whereas IGF-1 and BDNF mediate behavioral improvements with exercise, the interactive effects of IGF-1 with VEGF seem to orchestrate exercise-induced neurogenesis and angiogenesis. Both IGF-1 and VEGF are increased in the periphery by exercise and cross the blood–brain barrier to enter the brain [16,41,69]. Peripheral sources of IGF-1 and VEGF mediate stimulation of neurogenesis and angiogenesis with exercise, as has been demonstrated by using blocking antibodies. For example, blocking either IGF-1 [16] or VEGF [41] signaling (by blocking peripheral growth factor entry to the brain) prevents exercise-induced proliferation of neural precursors in the hippocampus, and blocking IGF-1 partially blocks the survival-promoting effect of exercise on newly generated neural precursors [16] (the effects of anti-VEGF on survival have not been assessed).

In addition to a role in neurogenesis, peripheral IGF-1 is necessary for exercise-induced vessel remodeling in the brain [69], an effect that might be mediated in part by induction of VEGF. Exercise-induced angiogenesis is associated with an increase in brain VEGF mRNA and protein [49]; this increase has potent mitotic activity specific to vascular endothelial cells, affecting proliferation, survival, adhesion, migration and capillary tube formation [70]. A role for BDNF in exercise-dependent neurogenesis or angiogenesis has not been directly tested. We can predict, however, that induction of BDNF participates in increasing proliferation and survival of new neurons because BDNF regulates baseline neurogenesis *in vivo* [71].

Downstream regulation of signal transduction, gene transcription and protein expression

Although it is clear that growth factors and growth factor signaling cascades are central regulatory mechanisms underlying the effects of exercise in the CNS, there is less information on the mechanisms by which these growth factors and other effectors regulate the structural, metabolic and functional endpoints.

It is known that exercise controls signal transduction pathways and gene expression, which then effect downstream change. For example, exercise can activate the MAPK and phosphatidylinositol 3-kinase (PI3K) pathways in neurons [56]; these pathways can augment LTP and production of additional growth factors. In addition, exercise regulates activity of transcription factors such as CREB [72], which is crucial for learning and memory. Furthermore, proteomic and microarray analyses have shown that many classes of proteins, in addition to growth factors, are regulated by exercise [47,48], including those involved in metabolism, inflammation and synaptic plasticity. Lastly, as described above, exercise – through gene and protein expression – controls proliferation of various types of cell in the CNS, including neural progenitors, glia and epithelial cells.

Growth factors orchestrate most, if not all, of the brain responses to exercise through either direct or indirect effects. As the field evolves, these and other downstream effects will be further defined as probable mechanisms that mediate the neuroprotective, structural, metabolic and functional changes elicited by exercise.

Systemic mechanisms: exercise reduces peripheral risk factors

An emerging fundamental concept is that brain health and cognitive function are modulated by the interplay of various central and peripheral factors. Specifically, brain function is compromised by the presence of peripheral risk factors for cognitive decline, including hypertension, hyperglycemia, insulin insensitivity and dyslipidemia – a cluster of features that have been conceptualized as the 'metabolic syndrome' [73]. Of the various aspects of the metabolic syndrome, the most crucial for cognitive function are hypertension and glucose intolerance [73]. A common feature of many of these conditions is systemic inflammation, which contributes to most if not all of the conditions of the metabolic syndrome. Furthermore, systemic inflammation exacerbates CNS inflammation

[74] and correlates with cognitive decline [75,76]. Remarkably, exercise reduces all of these peripheral risk factors, improving cardiovascular health, lipid–cholesterol balance, energy metabolism, glucose use, insulin sensitivity and inflammation [77,78]. Exercise is thus uniquely positioned to improve brain health and function by reducing the peripheral (indirect) risk factors for cognitive decline and, in parallel, by directly enhancing brain health and cognitive function.

The central and peripheral effects of exercise that improve brain health and cognitive function might be mediated through common mechanisms that converge on modulating growth factor signaling. Specifically, exercise can improve growth factor signaling by directly increasing growth factor levels (see above) and by reducing pro-inflammatory conditions, which impair growth factor signaling. The effects on peripheral and central IGF-1 signaling are one example. The presence of pro-inflammatory cytokines impairs insulin–IGF-1 signal transduction and is a mechanism of insulin resistance [79,80]. Peripheral IGF-1 is essential in glucose metabolism, tissue maintenance [57] and cerebrovascular function [81], and a low level of IGF-1 places individuals at risk for cognitive impairment [82]. Exercise increases peripheral IGF-1, leading to improved insulin sensitivity [83], restored insulin–IGF-1 signaling [84] and improved brain health and cognitive function [85]. Furthermore, pro-inflammatory cytokines impair IGF-1 signal transduction in neurons [86,87]. Exercise might counteract the negative effects of this inflammation by acting to restore IGF-1 signaling, because it reduces circulating pro-inflammatory cytokines [88]. In addition to effects on IGF-1 signal transduction, reduction of inflammation by exercise could also improve BDNF signaling in the brain. Inflammation and pro-inflammatory cytokines impair BDNF signaling in neurons, leading to a condition referred to as 'neurotrophin resistance', which is conceptually similar to insulin resistance [87].

Recent data indicate that exercise improves the overall immune condition of the brain, for example, by reducing brain IL-1β (a pro-inflammatory cytokine) in a mouse model of AD [89], and by reducing brain inflammation in response to stroke [90] or peripheral infection [91]. In addition, exercise could attenuate levels of pro-inflammatory cytokine in the brain of individuals with AD by reducing the load of Aβ, which itself has pro-inflammatory effects [92]. Thus, the reduction of peripheral and central inflammation by exercise can serve as a common mechanism to reduce the risk for both diabetes and cognitive decline.

Conclusion and future directions

Human and animal studies indicate that exercise targets many aspects of brain function and has broad effects on overall brain health, resilience, learning and memory, and depression, particularly in elderly populations. Exercise sets into motion an interactive cascade of growth factor signaling that has the net effect of stimulating plasticity, enhancing cognitive function, attenuating the mechanisms driving depression, stimulating neurogenesis and improving cerebrovascular perfusion. IGF-1 signaling converges on BDNF signaling, which might be a hub for effects of exercise on learning and depression. In addition to central mechanisms, exercise reduces several peripheral risk factors for cognitive decline. A common mechanism between many of these peripheral risk factors is inflammation, which interferes with growth factor signaling in the periphery and in the brain. Exercise might improve growth factor signaling by both reducing pro-inflammatory conditions and directly increasing growth factor levels. A unifying concept is that exercise mobilizes growth factor

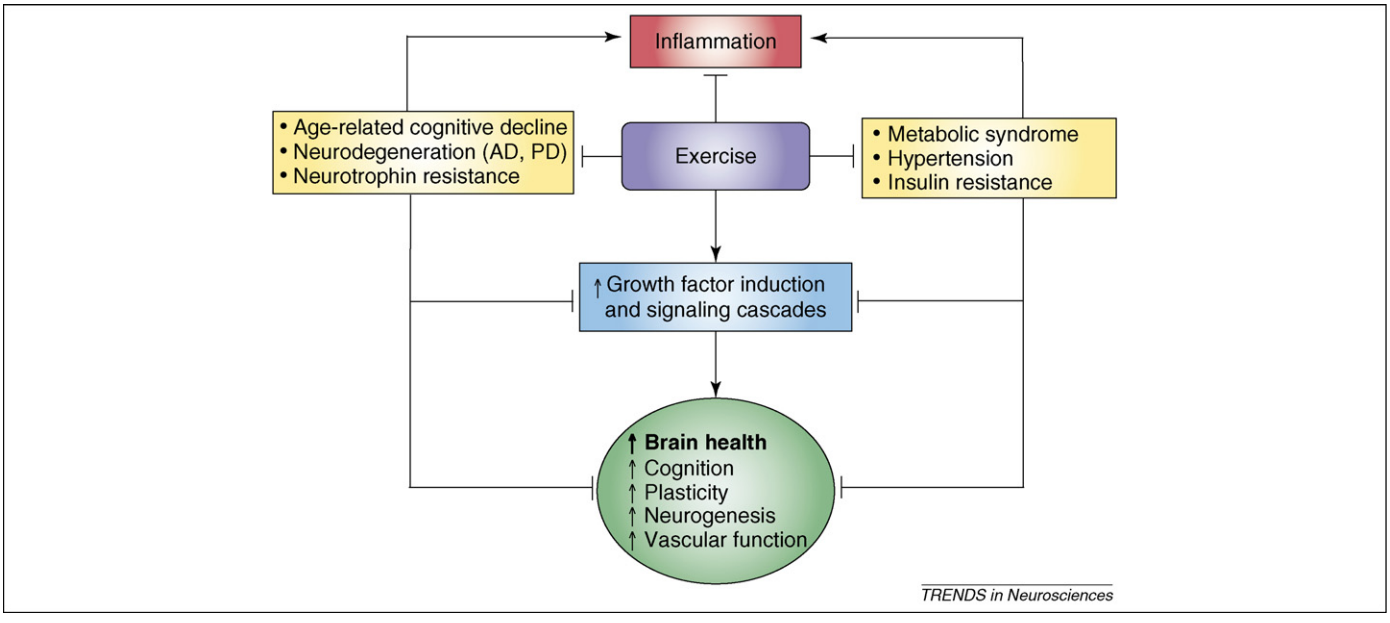

Figure 2. Exercise induces growth factor cascades, a central mechanism mediating exercise-dependent benefits in cognition, synaptic plasticity, neurogenesis and vascular function. In addition, exercise reduces peripheral risk factors for cognitive decline such as hypertension and insulin resistance, components of the metabolic syndrome that converge to increase the risk for brain dysfunction and neurodegeneration. Inflammation, which can impair growth factor signaling, exacerbate the metabolic syndrome and accelerate cognitive decline, is reduced by exercise. Overall, exercise induces growth factor cascades and reduces peripheral risk factors for cognitive decline, all of which converge to improve brain health and function, and to delay the onset of and slow the decline in neurodegenerative diseases including Alzheimer disease (AD) and Parkinson's disease (PD).

cascades – both peripherally and centrally – that act synergistically and drive exercise-mediated brain responses (Figure 2).

Although much progress has been made in animal studies, there is a need for rigorous clinical intervention trials on exercise that are guided by this knowledge from animal models. We can identify three areas where additional research is needed to facilitate translation to clinical trials. First, findings from animal behavioral studies must be translated to humans and, conversely, animal studies must be refined to increase their relevance to humans. Second, the extent, frequency and types of exercise that result in functional benefits must be defined. Third, we need to identify and to target mechanisms by which exercise might act synergistically with key pharmaceuticals to augment improvements observed with either exercise or medication alone. Overall, exercise increases brain health – just as it improves body health – and thus represents an exciting lifestyle intervention technique to improve brain plasticity, function and resistance to neurodegenerative diseases.

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