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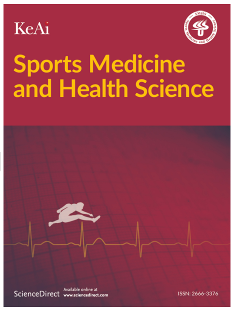

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Exercising the brain: Molecular pathways linking exercise, neuronal mitochondria, and synaptic plasticity

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Abbreviations

AMP	Adenosine monophosphate
ATP	Adenosine triphosphate
LTP	Long-term potentiation
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
NMDA	N-methyl-D-aspartate
MCU	Mitochondrial calcium uniporter
CA	Cornu ammonis
mtDNA	Mitochondrial DNA
E-TCmito	Excitation-mitochondrial transcription coupling
ROS	Reactive oxygen species
TEM	Transmission electron microscope
DG	Dentate gyrus
NR2A	NMDA receptor subunit 2A
NR2B	NMDA receptor subunit 2B
AMPA receptor	α-amino-3-hydroxy-5-methyl-4-isoxazolepropinonic acid receptor (ionotropic glutamate receptor)
CaMKII	calcium/calmodulin-dependent protein Kinase
CREB	cAMP response element-binding protein
AMPK	AMP-activated protein kinase
LEC	Lateral entorhinal cortex
AD	Alzheimer's disease
PAK	AMPK-p21-activated kinase
PGC-1α	Peroxisome proliferator-activated receptor γ coactivator 1α
FNDC5	Fibronectin type III domain-containing protein
SIRT1	Sirtuin 1
PSD-95	Postsynaptic density 95
LDH	lactate dehydrogenase
ERK1/2	Extracellular signal-related kinase 1/2
IL6	Interleukin-6

Abstract:

Regular exercise is the most effective lifestyle intervention to improve cognitive function and reduces the risk of age-related neurodegenerative diseases. However, the underlying mechanisms are not well understood. Accumulating evidence supports that exercise improves mitochondrial structure and function in neurons and enhances synaptic plasticity. We propose that exercise-elicited neuronal activity and the associated cellular cues (e.g., AMP/ATP ratios, calcium influx) activate signaling-transcription regulators, such as AMPK, PGC-1α, SIRT1, to promote mitochondrial remodeling and redox balance, and hence improved synaptic function. In parallel, exerkines, a plethora of humoral factors induced by exercise in peripheral organs/tissues may mediate some of the positive benefits of exercise through endocrine mechanisms. This review focuses on the current evidence and highlights the need of additional mechanistic studies to improve exercise-based interventions to promote the brain health.

Keywords

Exercise; Mitochondria; Synaptic plasticity; Cognitive function; Hippocampus

1. Introduction

Physical activity or regular exercise is the most powerful non-pharmacological strategies to preserve and enhance overall health in humans, including the brain health. Studies have consistently linked effects of exercise to the reduced risk of dementia and mild cognitive impairment [1, 2, 3]. Well-controlled clinical studies have demonstrated measurable cognitive improvements by exercise training in both healthy individuals and those with cognitive impairment [4, 5, 6]. Despite these compelling, profound clinical observations, the cellular and molecular mechanisms through which exercise confers cognitive benefit remain incompletely understood.

Exercise elicits potent systemic stimuli that lead to metabolic and functional adaptations across tissues [7, 8]. Each bout of exercise induces transient physiological signals, and the repetitive cascades of signaling events over time trigger adaptative changes underlying the health benefits. In the central nervous system, regular exercise, particularly endurance exercise, robustly enhances hippocampus-dependent learning and memory [9, 10, 11]. These cognitive benefits are reliant on improvements in activity-dependent synaptic structural and functional changes [12, 13, 14]. Such neuronal activity-dependent modifications are termed as synaptic plasticity, defined by the persistent improvements of synaptic strength in response to neuronal activity [15, 16, 17]. Synaptic plasticity is widely recognized as the foundation of learning and memory, a mechanistic basis through which exercise can enhance or preserve cognitive function.

Accumulating evidence suggests that neuronal mitochondria are key interfaces between exercise, synaptic plasticity and cognitive function [18, 19, 20]. Preclinical studies in rodents show that exercise-induced mitochondrial adaptations coincide with enhanced long-term potentiation (LTP), upregulation of synaptic plasticity markers and improved cognitive performance [21, 22] preferentially in the hippocampus [11], the most important region of the brain for learning and memory. It has been illustrated that neuronal activities in the hippocampus increase significantly during and following exercise [23, 24, 25, 26]. Therefore, it is reasonable to hypothesize that neuronal activities during exercise increase energetic demand, trigger calcium influx, and shift AMP/ATP ratio, activating metabolic sensing cascades.

Over the last two decades, a growing body of work has also highlighted the contribution of exerkines, humoral factors that are secreted by peripheral organs in response to physical activity [27]. Many of these exerkines can cross the blood-brain barrier (BBB) and modulate cognitive function [28], often through engagement of brain-derived neurotrophic factor (BDNF) in the brain, promoting neuronal and neuroglial cell survival and/or neurogenesis [29, 30] as well as synaptic plasticity [31, 32]. The current understanding of specific pathways through which BDNF functions has been extensively covered [33, 34]. However, the role of exerkine in promoting neuronal mitochondrial remodeling and synaptic plasticity is less understood and supported.

In line with the potential role of BDNF, exercise training-induced cognitive improvement may also involve other cellular mechanisms. For example, exercise training promotes the proliferation and functional integration of newborn neurons into learning and memory circuits, called neurogenesis, in the hippocampus [35, 36]. Exercise training also induces angiogenesis and promotes cerebral blood flow, further enhancing oxygen and nutrient delivery to the metabolically active brain regions. However, this review focuses on mitochondria in adult neurons and their functional coupling to synaptic plasticity and cognitive function. We first provide a brief overview of current advances in how exercise influence neuronal mitochondrial function and synaptic plasticity, followed by integration of emerging evidence to build a mechanistic framework through which exercise enhances cognitive function.

2. Exercise impacts neuronal mitochondria and synaptic function

2.1. Overview of neuronal mitochondrial and synaptic transmission

An adult human brain represents 2% of the body weight yet consumes 20% of the body's total energy [37]. The majority of the energy is used to sustain synaptic transmission of the neurons [38]. Adult neurons are highly specialized cells with axonal projections and spines that form synaptic networks, which heavily rely on local energy production [39]. Mitochondrial oxidative phosphorylation is the primary source of ATP in adult neurons. Some mitochondria are located at the soma and many reside at the synaptic terminals, implying a tight functional connection between mitochondrial activity and synaptic function. Rangaraju et al. demonstrated that presynaptic boutons ATP is generated by mitochondria upon acute electrical stimulation of neurons, which is mainly used for synaptic vesicle recycling [40]. Consistent with this finding, Ivannikov et al. showed that higher presynaptic mitochondrial volume is associated with a higher capacity of synaptic vesicle exocytosis, whereas pharmacological inhibition of mitochondrial oxidative phosphorylation reduces synaptosomal ATP level and greatly impairs exocytosis [41]. These findings establish presynaptic mitochondria as active regulators of neurotransmitter release.

Beyond the energy production, mitochondria may also regulate synaptic function through calcium buffering. Calcium influx through voltage-gated ion channels and/or N-methyl-D-aspartate (NMDA) receptors triggers neurotransmitter release and induction of LTP. Mitochondria sequester cytosolic calcium through the mitochondrial calcium uniporter (MCU), which stimulates oxidative phosphorylation for ATP production. In a recently published study, mice with deletion of MCU in the hippocampal neurons in the CA2 area showed more fragmented dendritic mitochondria [42]. In addition, neuronal and synaptic excitation appears to be highly dependent on the mitochondrial DNA (mtDNA) transcription, a mechanism termed excitation-mitochondrial transcription coupling (E-TCmito) [43]. The notion is that synaptic calcium influx drives transcription of mitochondrial genes for the electron transport chain, disruption of which causes a depletion of postsynaptic ATP along with impaired synaptic resilience [43]. Importantly, weakened E-TCmito was found in aging mice, while boosting it in aged mice significantly rescues memory deficit [43]. This study provides a neuronal activity-dependent mitochondrial transcription axis as a fundamental underlying mechanism for the improved synaptic function and cognitive capacity by neuronal activities.

Collectively, available existing evidence suggests that neuronal mitochondria are not only metabolically necessary for neuronal activity, but also regulate calcium dynamics and synaptic strength in response to synaptic demands. Disruption of any of these regulatory steps could impair synaptic function, which is now recognized as a core pathophysiological feature of cognitive aging and neurodegenerative diseases [44, 45, 46, 47, 48]. In a stark constrast, exercise is a well-established lifestyle intervention that enhances mitochondrial fitness and synaptic transmission. Dissecting the molecular cascades and, importantly, the upstream signal activators that regulate neuronal mitochondrial structure and function in response to exercise training remains a major challenge and a promising research direction.

2.2. Exercise and neuronal mitochondria

There are several avenues through which exercise can improve mitochondrial fitness in the brain. Exercise training may increase the volume density of mitochondrial through de novo biogenesis, leading to enhanced mitochondrial respiratory capacity [49, 50, 51, 52, 53, 54]. Exercise training may improve mitochondrial quality by stimulating mitochondrial fission, fusion and mitophagy, optimizing functionality and promoting resilience to cellular stress [55, 56, 57]. The overall impact is that exercise training improves mitochondrial oxidative phosphorylation efficiency while reduces ROS emission, creating a favorable energetic and redox environment in the brain [58, 59]. Considering the importance of exercise training in mitochondrial remodeling in mature neurons, we will review the direct evidence that exercise improves mitochondrial structural and functional integrity in the brain.

Evidence for exercise-induced increase of mitochondrial content in the brain came from studies that measured mitochondrial molecular and functional markers. Steiner et al. demonstrated that eight weeks of treadmill running in mice significantly increased *Pgc-1α*, citrate synthase mRNA and mtDNA copy number in multiple brain regions, including the hippocampus [51]. This finding provides molecular evidence that exercise training may induce mitochondrial biogenesis in the brain. In another study, Zhang et al. showed that, after seven days of treadmill running, mtDNA and protein markers of mitochondrial biogenesis were restored in the rat brain following ischemic injury [53], suggesting that exercise training could serve as therapy. Complementing these findings, one study showed that a single bout of high-intensity exercise, but not low- or moderate-intensity, was sufficient to increase hippocampal *Pgc-1α* mRNA and mtDNA copy number at 12 and 48 hours post-exercise [60]. Up to date, most studies have mainly focused on evidence of increased mitochondrial content after exercise training. Direct structural and functional evidence for exercise training-induced mitochondrial improvements in adult neurons are relatively lacking. One transmission electron microscope (TEM) study showed that four weeks of voluntary running in rats resulted in significant increases of somatic mitochondrial density in both hippocampal CA1 and dentate gyrus (DG) [18]. Rigorous investigations of mitochondrial structure and function in synaptic regions in the hippocampus are much needed.

Some recent studies have also pointed to the improvement of mitochondrial respiratory function in the brain by exercise training. Gusdon et al. reported that treadmill running significantly increased coupled mitochondrial complex I to III enzymatic activity in the brain in aged mice [61]. Interestingly, they showed no change of mitochondrial biogenesis markers in these mice, suggesting that the beneficial effect of exercise may be primarily mediated through enhanced mitochondrial function rather than mitochondrial biogenesis. Another study compared the impacts of treadmill training and voluntary wheel running on mitochondrial bioenergetics in the cortex and cerebellum [62]. Both these exercise modalities resulted in improved respiratory activity and decreased oxidative stress markers with increased OXPHOS complexes I, III and V proteins. Importantly, exercise training has demonstrated consistent restorative effects on hippocampal mitochondrial oxygen consumption, Ca^{2+} retention capacity and reduced ROS generation, along with improved cognitive performance in various disease models, including obesity-induced insulin resistance, chronic stress, PTSD and Alzheimer's disease [63, 64, 65, 66]. These studies provide direct evidence of profound positive impacts of exercise training on mitochondrial bioenergetics within the learning and memory circuit.

Age-related deterioration of mitochondrial quality and redox homeostasis in the hippocampus is increasingly recognized as a contributor to cognitive decline and the onset of neurodegenerative diseases. Exercise training is a lifestyle intervention with great antioxidant efficacy in counteracting this aging-induced cellular dysfunction. Treadmill running in middle-aged rats significantly diminished ROS level and protein carbonyl content in the hippocampus along with upregulation of antioxidant enzymes SOD-1 and GPx [67]. The findings support a mechanism by which exercise training slows down aging by promoting mitochondrial quality in the hippocampus. In fact, even a single session of high-intensity interval exercise enhanced hippocampal antioxidant capacity in rats as shown by increased SOD activity and non-enzymatic total antioxidant capacity measured 24 hours post-exercise [68]. With the repeated bouts of exercise for 6 weeks, healthy young rats demonstrated reduced hippocampal lipid peroxidation and enhanced SOD activity along with reduced proinflammatory cytokines [69]. Collectively, these findings suggest that exercise reduces hippocampal oxidative stress through upregulation of antioxidant defenses and promotion of mitochondrial ROS handling capacity.

2.3. Exercise and synaptic function

A landmark study in 1999 by Van Praag and colleagues first established that voluntary wheel running in mice enhances LTP induced by high frequency stimulation in the DG, but not in the CA1 area [35]. In the same study, they confirmed increased proliferation of neuronal progenitor cells in the DG, implying that neurogenesis may contribute to the enhanced LTP [35]. Later Farmer et al. found that voluntary running reduced the LTP induction threshold upon a weak theta-patterned stimulation, which was completely dependent on NMDA receptors activity [70, 71]. Together , these earlier studies indicate that exercise training-induced LTP is both hippocampal region- and NMDA receptors activity-dependent.

More work has begun to dissect the specific postsynaptic receptor mechanisms underlying exercise-induced facilitation of LTP induction. Vasuta and colleagues demonstrated that an antagonist (NVP-AAM077) with a higher preference for NMDA receptor subunit 2A (NR2A) blocked LTP in runners, but had only a slight effect in sedentary mice. In contrast, NR2B subunit antagonist significantly reduced LTP in both running and sedentary groups, suggesting that exercise training-induced enhancement of LTP is primarily NR2A dependent [72]. However, genetic knockout of NR2A (GluN2A$^{-/-}$ mouse) resulted in impaired performance in the spatial pattern separation, diminished NMDA to ionotropic glutamate (AMPA) receptor current ratios and impaired LTP in the DG [73]. Taken together, these findings establish NR2A as a dominant mechanism in exercise-induced synaptic plasticity in the DG. Mechanistically, NMDA receptor activation permits activity-dependent Ca^{2+} influx, which triggers the induction of LTP [74, 75]. Hence, the subsequent activation of calcium/calmodulin-dependent protein Kinase (CaMKII) may link Ca^{2+} influx to the sustained late-phase LTP and cognitive function enhanced by exercise training. Importantly, exercise training may modulate this signaling axis during the adaptative process. Pharmacological inhibition of CaMKII through intrahippocampal infusion of CaMKII blocker (KN-62) during exercise completely prevent exercise training-induced upregulation of synaptic plasticity markers (e.g., BDNF, CREB), which are key mediators of late-phase LTP related gene transcription and protein synthesis in the hippocampus, while impairing the improvement of memory consolidation induced by voluntary running [76]. To date, a genetic loss-of-function study has not been performed to address the question whether CaMKII is mechanistically required for exercise training-induced LTP.

3. Molecular mechanisms underlying exercise that regulate neuronal mitochondrial

3.1. Local factors

3.1.1. AMPK

AMP-activated protein kinase (AMPK) is a highly conserved cellular energy senor that plays a central role in maintaining metabolic homeostasis in response to energetic stress. Its function in exercise-induced metabolic adaptation has been most extensively studied in skeletal muscle, where contractile activity-induced energetic stress activates AMPK and initiates transcriptional and post-translational programs that govern substrate utilization and mitochondrial and metabolic adaptations [77, 78, 79, 80]. Specifically, exercise-induced AMPK activation orchestrates downstream signaling pathways essential for mitochondrial biogenesis, oxidative metabolism and cellular energy balance [81, 82, 83]. In the central nervous system, there is accumulating evidence that AMPK is highly responsive to exercise. Exercise-induced AMPK phosphorylation has been reported in multiple brain regions, with particularly robust activation observed in the hippocampus [84, 85, 86]. However, the precise mechanisms linking physical activity to neuronal AMPK activation remain elusive. Electrophysiological studies have demonstrated that both acute and chronic exercise transiently enhance hippocampal theta oscillation amplitude and frequency in rodents [23, 25]. High-frequency stimulation can readily activate AMPK, concomitantly with the induction of LTP in the hippocampal neurons [87, 88]. These findings suggest neuronal activity-dependent network oscillations represent a plausible mechanism through which exercise activates AMPK cascades in hippocampal neurons, possibly linking neuronal firing, calcium influx, energetic demand to AMPK activation.

To understand the functional involvement of AMPK activation in the brain, pharmacological approaches have been widely used. Administration of AICAR, an AMPK activator, improves memory consolidation in advanced aging (23-month-old) mice, accompanied by transcriptional upregulation genes associated with energy metabolism and neuronal development in the hippocampus [89]. In young mice (1-month-old), both voluntary wheel running and AICAR treatment for 14 days increased AMPK phosphorylation in the DG, whereas exercise, but not AICAR, also enhanced AMPK activity in the lateral entorhinal cortex (LEC), a major input to the hippocampal trisynaptic circuit via the perforant pathway [90]. Increased AMPK activation in the DG under both conditions correlated with elevated BDNF expression. Microarray analyses further revealed a substantial overlap in exercise-and AICAR-induced gene expression profiles in both the DG and LEC [90]. These studies support the notion that AMPK signaling constitutes a key molecular component of exercise-induced functional remodeling in the hippocampus.

AMPK activation has been implicated in preserving mitochondrial fitness under pathological conditions. In a diabetes-related Alzheimer's disease (AD)-like rat model, AICAR administration provided protection against decreased mitochondrial membrane potential, impaired complex I activity and reduced ATP production [91]. Similar neuroprotective and bioenergetic benefits have been reported with metformin, an indirect AMPK activator that recapitulates several cognitive and mitochondrial adaptations associated with endurance exercise [54, 92, 93]. Apart from direct regulatory impacts of AMPK activation on mitochondrial fitness, a recent study has also shown that AMPK-p21-activated kinase (PAK) signaling is both sufficient and required for trafficking and anchoring mitochondria to presynaptic boutons [45]. However, whether exercise training promotes such a mitochondrial transportation in hippocampal neurons to increase the energy supply remains to be ascertained. Recent work has further highlighted isoform-specific functions of the AMPK catalytic α-subunit in the brain. Neuron-specific deletions of *Ampk*α*2*, but not α*1*, impaired hippocampus-dependent learning and memory in young mice, concomitant with deficits in late-phase LTP [94]. Interestingly, in aged mice, genetic suppression of *Ampk*α*1*, but not α*2*, ameliorated age-associated memory decline, despite no detectable changes in synaptic LTP [95]. These findings underscore a nuanced, age-dependent divergence in AMPK isoform function, suggesting that selective engagement of AMPK may yield distinct cognitive and synaptic modifications across the lifespan. Collectively, while extensive evidence supports a regulatory role for AMPK in mitochondria-mediated neuronal metabolism, synaptic plasticity and cognitive function, direct causal role of AMPK in mediating the beneficial effects of exercise on neuronal mitochondria and synaptic remodeling remain scarce. Addressing this gap represents an important direction for future research.

3.1.2. PGC-1α

Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) was first identified in 1998 as a master regulator of mitochondrial biogenesis and oxidative metabolism [96], driving many years of research in peripheral tissues, such as skeletal muscle, heart and liver [97, 98, 99, 100, 101, 102]. More recently, growing evidence has extended the functional relevance of PGC-1α to the central nervous system, where it has emerged as a key integrator of neuronal activity, energy metabolism and synaptic plasticity. Early mechanistic studies directly demonstrated a cell-autonomous role for PGC-1α in neurons. Genetic knockdown of *Pgc-1*α in developing neurons results in pronounced reduction in dendritic mitochondrial density and ATP availability along with decreased dendritic spine density and impaired expression of synaptic maturation markers [103]. Conversely, in cultured neurons, overexpression of Pgc-1α resulted in increased mitochondrial content, cellular bioenergetic capacity and promoted dendritic spine formation and synaptic differentiation [103]. PGC-1α in vivo is required for maintaining synaptic density in DG granule neurons, highlighting its function in the preservation of synaptic integrity. Mechanistically, PGC-1α has been positioned as a key mediator of neuronal activity-dependent synaptic remodeling via its interaction with BDNF. BDNF is a well-established player in exercise-induced neuroplasticity and is highly expressed in the hippocampus, where it regulates LTP, learning and memory [104, 105]. A provocative study showed that endurance exercise robustly induced hippocampal BDNF expression through a previously unrecognized metabolic-neurotrophic signaling cascade [106]. In this study, *Pgc-1*α-null mice exhibited markedly reduced expression of fibronectin type III domain-containing protein (FNDC5) and failed to upregulate BDNF in response to exercise. These findings identified the PGC-1α-FNDC5 axis as a critical molecular conduit linking metabolic regulation to exercise-induced neurotrophic signaling and synaptic plasticity. Consistently, neuronal overexpression of Pgc-1α conferred a protection against cognitive decline in models of chronic cerebral hypoperfusion, a condition characterized by impaired neuronal energy metabolism and progressive synaptic dysfunction [107]. Transcriptomic and mitochondrial respiratory analyses revealed that Pgc-1α overexpression promoted neuronal oxidative metabolism, respiratory capacity and overall cellular bioenergetic status. These adaptations likely establish a permissive energetic environment that supports synaptic transmission and cognitive resilience under metabolic stress. Together, these findings support a hypothesis in which PGC-1α integrates neuronal activity-dependent signals with metabolic cues to coordinate mitochondrial quantity and quality, thereby sustaining synaptic structure, plasticity and cognitive function.

3.1.3. SIRT1

Sirtuin 1 (SIRT1) is a conserved NAD$^+$-dependent lysine deacetylase that regulate longevity, metabolism, chromatin remodeling and stress response [108, 109]. Its enzymatic activity is responsive to cellular energy status by sensing the intracellular level of NAD$^+$, regulating transcription and post-translational activities [110, 111]. These properties make SIRT1 a potential mediator linking the metabolic fluctuations to adaptive cellular responses in the central nervous system. Consistent with this notion, Steiner et al. reported that 8 weeks of treadmill running in mice resulted in a significant increase of *Sirt1* gene expression along with elevated *Pgc-1α* mRNA and mitochondrial content in multiple brain regions, including the hippocampus [51]. The co-upregulation of *Sirt1* and *Pgc-1α* suggests existence of the regulatory axis that may underlie exercise-induced mitochondrial biogenesis in the hippocampus. This finding is further supported by other studies showing that exercise training increased or restored SIRT1 expression level/activity in the hippocampus in various pathological conditions, often in parallel with enhanced expression of PGC-1α, BDNF and CREB [86, 112, 113, 114, 115]. Collectively, these findings suggest that SIRT1 is a critical molecular node for exercise-induced mitochondrial adaptation and synaptic plasticity in the hippocampus.

The direct evidence that supports SIRT1's role in the brain came from both pharmacological and genetic studies. Activation of SIRT1 significantly increased key mitochondrial biogenesis regulators, including Pgc-1α, Nrf1 and Tfam, accompanied by increased mitochondrial density in the hippocampus, an effect that closely resemble those induced by exercise training [116]. Conversely, genetic knockout of the *Sirt1* gene resulted in impaired hippocampus-dependent cognitive function and reduced synaptic plasticity, as evidenced by diminished LTP in the CA1 region with unchanged basal synaptic transmission [117]. In line with this finding, a recent study showed that exercise-induced increases in SIRT1 were associated with elevated levels of synaptic proteins, synaptophysin and postsynaptic density 95 (PSD-95) [118], further supporting a functional role of SIRT1 in synaptic adaptation. Moreover, neuronal-specific overexpression of SIRT1 in a mouse model of AD led to preserved cognitive function [119], reinforcing its role as a mediator of neuroprotective and synaptic plasticity-related processes in the hippocampus.

Emerging evidence suggests that SIRT1 form a signaling network with AMPK and PGC-1α that play a major function in metabolic regulation in the hippocampus, presumably under the condition of exercise. For example, exercise training has been shown to induce concurrent increases in AMPK activation, SIRT1 and PGC-1α expression in the hippocampus [86, 116]. These findings render a promising hypothesis that AMPK/SIRT1/PGC-1α signaling pathway is responsible for exercise-induced adaptations in the brain and contribute to the neuroprotective effects of exercise.

3.1.4. Redox Signaling

At the physiological level, reactive oxygen species (ROS) have been reported to regulate key synaptic machineries, including NMDA receptors, CaMKII, ERK and CREB, as well as functional changes involved in synaptic plasticity in the hippocampus [120, 121, 122, 123]. Conversely, disruption of redox signaling or excessive ROS accumulation has been shown to be one of the main mechanisms underlying neurodegenerative diseases [124, 125, 126]. Given this critical role of ROS, redox signaling has emerged as a very important bridge linking mitochondria (as mitochondria is the primary resource for producing ROS) to synaptic plasticity. Exercise is increasingly recognized as a potent stimulator of the redox environment in the brain [127, 128]. While acute exercise is well-known to increase ROS production and lead to short-term oxidative stress in many tissues/organs, repetitive bouts of exercise instead promote antioxidant defense system, resulting in improved redox balance. Experimental evidence suggests that, under the natural aging and pathological conditions with high oxidative stress, exercise training greatly attenuates the ROS in the hippocampus concurrent with synaptogenesis and mitigated cognitive decline [129, 130, 131].

In a recent publication, it was demonstrated that eight weeks of treadmill running resulted in increased NRF2 expression and glutathione reductase activity across multiple tissues, including the brain. The induced antioxidant expression were associated with increases of Tfam and Vdac1 in brain samples, suggesting that mitochondrial adaptations underpin improved antioxidant capacity and redox balance by exercise [132].

Collectively, these findings support a promising working hypothesis in which exercise regulates mitochondrial function and resulting balanced redox signaling in the hippocampus to improve synaptic plasticity. The causality of each of these cellular components to the functional outcomes becomes an important area for future research.

3.2. Peripheral factors

3.2.1. Lactate

Lactate has emerged as a molecular link between skeletal muscle contractile activity and cognitive function. During exercise, lactate dehydrogenase (LDH) converts pyruvate in skeletal muscle to lactate, which then enters the circulation and can pass the BBB in a rate-limited manner and taken up by neurons [133, 134, 135]. To date, lactate in the brain has been reported to support the energetic demands of high computational load neuronal processing and long-term memory formation [136, 137]. It has also been speculated to function as a signaling molecule through the G-protein-coupled receptor HCAR1 (GPR81), activating angiogenic (VEGF), neurogenic and neuroprotective grams, modulating neuronal excitability, as well as potentiating NMDA receptor-dependent plasticity [138, 139, 140, 141, 142]. Elevations in circulating lactate from exercise or muscle contractions can drive SIRT1-dependent cerebral BDNF expression [112, 143], and L-lactate infusion has been shown to enhance BDNF expression, mitochondrial biogenesis and antioxidant defenses [144, 145, 146]. Despite the evidence supporting the role of lactate in improving cognitive function, very few studies examined its necessity underlying the exercise training. One recent study has demonstrated that pharmacological blockage of lactate transporter (4-CIN) abolished the beneficial effects of exercise on synaptic markers in the hippocampus and cognitive function [147]. However, the exact downstream signaling mechanisms of lactate in the hippocampus were not examined. Peripherally induced lactate may need to cooperate with exercise-induced signaling networks in the hippocampus, a topic that requires elaborative future research.

3.2.2. FNDC5/Irisin

Emerging evidence supports irisin, a cleaved version of fibronectin type III domain-containing protein 5 (FNDC5), as an important mediator linking exercise to synaptic and cognitive function. Inhibition of FNDC5/irisin signaling significantly attenuated the neuroprotective effects of exercise on synaptic plasticity and cognitive function [148, 149]. Systemic administration of recombinant irisin enhances dendritic length and arborization as well as spine density in the CA1 and CA3 subregions. The administration of exogeneous irisin also augmented the *Pgc-1*α*, Fndc5* and *Bdnf* mRNA in the hippocampus [150]. These findings suggest that circulating irisin can readily cross BBB to exert its effects to promote synaptic structure and function [150]. Mechanistically, irisin has been shown to activate the hippocampal neuronal extracellular signal-related kinase 1/2 (ERK 1/2), of which its activity is required for LTP consolidation and CREB-mediated transcription of synaptic plasticity genes [151]. In addition, *Fndc5* gene has also been shown to be expressed in the hippocampus, along with *Pgc-1*α*,* which can be upregulated by exercise [106], while its protein levels are found to be reduced in the hippocampal tissues of AD patients and mouse models [148]. Global *Pgc-1*$\alpha^{-/-}$ mice have reduced gene expression of *Fndc5 in the brain, and* gain-and loss-of-function experiments showed Fndc5 controls *Bdnf* gene expression in neurons [106]. Therefore, these studies suggest a plausible FNDC5/irisin signaling axis, presumably as an exerkine through regulation of BDNF, underlying the beneficial effects of exercise in the brain.

3.2.3. IL-6

During exercise, circulating IL-6 increases markedly due to the release from skeletal muscle [152, 153, 154]. In addition, IL-6 is produced in the brain during and after prolonged exercise predominantly from hippocampus [155]. IL-6 is mainly considered a pro-inflammatory factor, but exhibits anti-inflammatory effects as a myokine following exercise [156, 157, 158]. Interleukin-6 (IL-6) has been reported to promote the recovery of brain function and cognitive function under disease conditions [159, 160, 161, 162]. Importantly, IL-6 has been shown to regulate synaptic transmission and synaptic plasticity [163, 164, 165, 166]. Consistent with a positive role of IL-6, IL6 also acts as an upstream regulator of bone-derived osteocalcin in response to exercise[167]. Elevation of osteocalcin improved hippocampus-dependent cognition and BDNF expression in the brain [168, 169]. It is worth noticing that chronic IL-6 elevation in the brain drives neuroinflammation through sustained JAK/STAT pathway activation [170], a pattern observed in the brains of Alzheimer's patients [171]. Hence, there may be differential physiological and pathological signaling associated with IL-6, depending on its temporal dynamics and source. More research is warranted to ascertain the precise role of exercise-induced IL-6 in synaptic adaptation.

4. Conclusion

The present review focuses on the evidence of the benefits of regular exercise on brain health, with the impacts on mitochondria in the adult neurons as a promising central cellular mechanism underlying improved synaptic plasticity and cognitive function. Figure 1. summarizes the proposed framework by which exercise-induced signaling pathways discussed in this review.

To date, significant research gaps remain in which the direct causal relationships between these signaling molecules and exercise-induced adaptations are still lacking. Further, the regulation of these signaling molecule remains poorly understood in the adult neurons of the networks fundamental to learning and memory. The emerging signaling pathways and molecules discussed here represent promising targets for preserving cognitive function during natural aging and mitigating the pathogenesis in neurodegenerative diseases. A deeper mechanistic understanding of these signaling networks will facilitate the development of exercise-based interventions to promote the brain health across the lifespan.

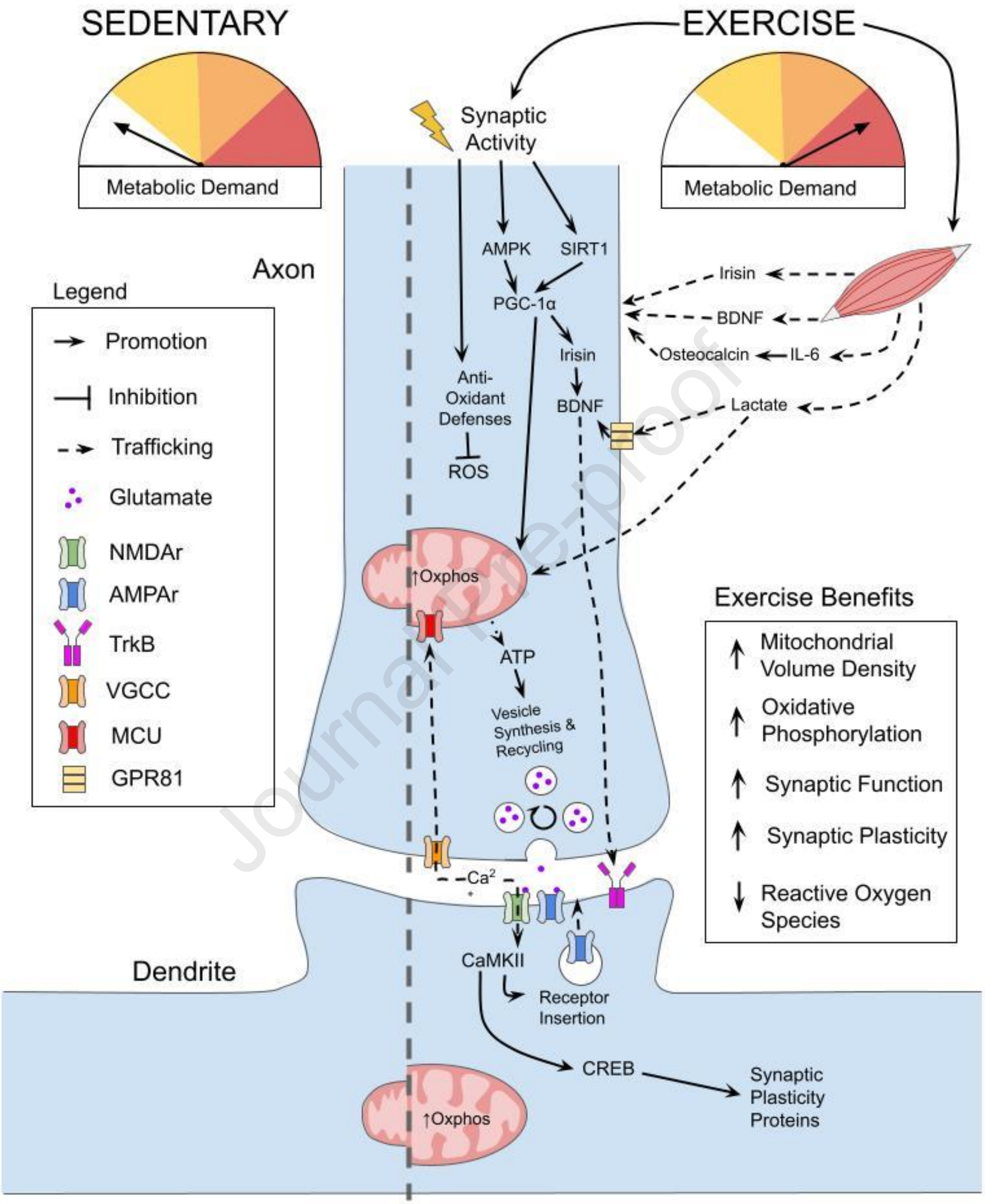
SEDENTARY
Metabolic Demand
EXERCISE
Metabolic Demand
Synaptic Activity
Axon
AMPK
SIRT1
PGC-1α
Irisin
BDNF
Anti-Oxidant Defenses
ROS
Irisin
BDNF
Osteocalcin
IL-6
Lactate
Legend
Promotion
Inhibition
Trafficking
Glutamate
NMDAr
AMPAr
TrkB
VGCC
MCU
GPR81
↑Oxphos
ATP
Vesicle Synthesis & Recycling
Ca2+
CaMKII
Receptor Insertion
Dendrite
CREB
Synaptic Plasticity Proteins
↑Oxphos
Exercise Benefits
↑ Mitochondrial Volume Density
↑ Oxidative Phosphorylation
↑ Synaptic Function
↑ Synaptic Plasticity
↓ Reactive Oxygen Species

Figure 1: Proposed mechanisms underlying exercise-induced neuronal mitochondrial adaptation and improved synaptic plasticity. Exercise increases neuronal activity and metabolic demand within the neurocircuits in the hippocampus, leading to activation of signaling pathways, including AMP-activated protein kinase (AMPK), sirtuin 1 (SIRT1), peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), as well as antioxidant defense. These signaling networks promote mitochondrial remodeling, enhance oxidative phosphorylation (OXPHOS), increase antioxidant defenses, and reduce reactive oxygen species (ROS) production. Improved mitochondrial function promotes ATP production and calcium handling, which facilitate synaptic vesicle recycling and neurotransmitter release at presynaptic terminals. At the postsynaptic terminal, elevated intracellular Ca^{2+} activates Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), which promotes receptor insertion and cAMP response element-binding protein (CREB)-dependent transcription of synaptic plasticity-related proteins. Exercise also stimulates the production and release of exerkines, such as lactate, irisin, interleukin-6 (IL-6), osteocalcin, and brain-derived neurotrophic factor (BDNF). These circulating factors act on the brain through endocrine mechanisms to augment mitochondrial function and synaptic transmission. Collectively, exercise-induced local and peripheral signaling converge on neuronal mitochondria, which serve as an interface to enhance synaptic plastic and cognitive function. **Abbreviations:** AMPK: AMP-activated protein kinase; SIRT1:Sirtuin 1; PGC-1a: Peroxisome proliferator-activated receptor γ coactivator 1α; OXPHOS: Oxidative phosphorylation; ROS: Reactive oxygen species; CaMKII: Ca2+/Calmodulin-dependent protein kinase II; CREB: cAMP response element binding protein; BDNF: Brain derived neurotrophic factor; IL-6: Interleukin-6; NMDAr: N-methyl-D-Aspartate receptor, AMPAr: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, TrkB: Tropomyosin receptor kinase B; VGCC: Voltage-gated calcium channel; MCU: Mitochondrial Ca2+ uniporter; GPR81: G-protein-coupled receptor 81.

CRediT authorship contribution statement

Xuansong Mao: Conceptualization; Writing - original draft; Writing - review & editing; Visualization; Validation. Edward Rygalski: Writing - original draft; Writing - review & editing; Visualization. Zhen Yan: Conceptualization; Writing - review & editing; Visualization; Validation; Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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