Cellular and Molecular Neurobiology (2023) 43:1551–1571
https://doi.org/10.1007/s10571-022-01272-x

REVIEW PAPER

Cellular and Molecular Regulation of Exercise—A Neuronal Perspective

Ishitha Reddy[1] · Yamini Yadav[1] · Chinmoy Sankar Dey[1]

Received: 4 May 2022 / Accepted: 10 August 2022 / Published online: 20 August 2022

Abstract

The beneficial effects of exercise on the proper functioning of the body have been firmly established. Multi-systemic metabolic regulation of exercise is the consequence of multitudinous changes that occur at the cellular level. The exercise responsome comprises all molecular entities including exerkines, miRNA species, growth factors, signaling proteins that are elevated and activated by physical exercise. Exerkines are secretory molecules released by organs such as skeletal muscle, adipose tissue, liver, and gut as a function of acute/chronic exercise. Exerkines such as FNDC5/irisin, Cathepsin B, Adiponectin, and IL-6 circulate through the bloodstream, cross the blood–brain barrier, and modulate the expression of important signaling molecules such as AMPK, SIRT1, PGC1α, BDNF, IGF-1, and VEGF which further contribute to improved energy metabolism, glucose homeostasis, insulin sensitivity, neurogenesis, synaptic plasticity, and overall well-being of the body and brain. These molecules are also responsible for neuroprotective adaptations that exercise confers on the brain and potentially ameliorate neurodegeneration. This review aims to detail important cellular and molecular species that directly or indirectly mediate exercise-induced benefits in the body, with an emphasis on the central nervous system.

Keywords Exercise · Exerkines · Exercise mimetics · Metabolism · Neuron

Introduction

Physical exercise has time and again been recognized as highly beneficial for the mind and body because of its positive effects on a multitude of organs in the body. Exercise has been defined as—'a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness' (Caspersen et al. 1985).

With an increasing shift toward a sedentary lifestyle, the prevalence of a myriad of metabolic conditions, now categorized as lifestyle disorders, is at an all-time high. Exercise is currently being prescribed as a non-pharmaceutical approach to alleviate symptoms of such metabolic, heart and pulmonary, muscle, bone, and joint disorders and conditions that are seemingly unrelated to metabolism such as cancer, asthma, and depression (Pedersen and Saltin 2006). Studies have shown that exercise also confers cognitive benefits to individuals with neurodegenerative disorders by increasing neurogenesis, improving synaptic plasticity, and reducing neuroinflammation. A vast amount of literature has provided evidence that any form of exercise, aerobic, and resistance training can attenuate cognitive impairment and reduce the risk of developing dementia.

Important to mention is the Randomized control trial (RCT), called 'Preserving Cognition, Quality of Life, Physical Health and Functional Ability in Alzheimer's Disease: the Effect of Physical Exercise (ADEX)' of 2012–2013 that recruited 200 patients with mild AD to understand the effects of moderate to high intensity of exercise on cognition over 16 weeks (Hoffmann et al. 2016). Neuropsychiatric symptoms were found to be less severe after 16 weeks of exercise. The authors opined that exercise might have a dose-dependent effect on cognitive improvement and could be used as an add-on therapy for AD patients (Hoffmann et al. 2016).

When the body undergoes physical exercise, a multitude of cellular and molecular changes occur. The exercise responsome is responsible for tissue and organ crosstalk encompassing nearly every organ system. Cytokines released from skeletal muscles (myokines), adipose tissues

✉ Chinmoy Sankar Dey
csdey@bioschool.iitd.ac.in

[1] Kusuma School of Biological Sciences, Indian Institute of Technology, Delhi, New Delhi 110016, India

(adipokines), liver (hepatokines), and bone (osteokines) have an autocrine/paracrine influence in regulating whole-body metabolism, including the brain (Safdar et al. 2016; Lee et al. 2019). These cytokines, miRNAs, and other metabolites released from various organs in response to exercise that extend multisystemic benefits have been termed as exerkines (Safdar et al. 2016).

Some exerkines have been shown to cross the Blood–brain barrier (BBB) and positively regulate pro-survival and longevity-related signaling pathways in the Central nervous system (CNS). The Insulin-like growth factor-1/Phosphoinositide 3-kinase/AKT (IGF-1/PI3K/AKT) axis and AMP-activated protein kinase/Sirtuin 1/Peroxisome proliferator-activated receptor γ co-activator 1-alpha (AMPK/SIRT1/PGC1α) axis are the main molecular signaling pathways upregulated in response to physical exercise (Lin et al. 2020). These pathways are directly responsible for cell survival and neuroprotective effects in the brain. Understanding the intricacies of these pathways is crucial to understanding the wide-reaching advantages of physical exercise.

While the exact dosage, intensity, and specific regimens of exercise are to be established for each disorder to achieve maximum benefits, researchers are also looking at pharmaceutical approaches that induce exercise-like benefits in the body. Exercise mimetics are drugs that activate signaling pathways and mimic exercise-like conditions at the cellular level. Such drugs could be used to increase endurance in rats by translating changes at the cellular level to physiological adaptations such as increased mitochondrial biogenesis and fiber remodeling of skeletal muscles toward more oxidative type (Narkar et al. 2008) (Fig. 1).

Physiological Responses to Exercise

Skeletal muscle is a highly dynamic tissue that regulates bodily movement. It is one of the major sites for the transport of oxygen and metabolites to other organs and has been extensively studied in connection to exercise physiology. With respect to metabolism, the skeletal muscle fibers can be broadly classified into slow twitch (type I) and fast twitch

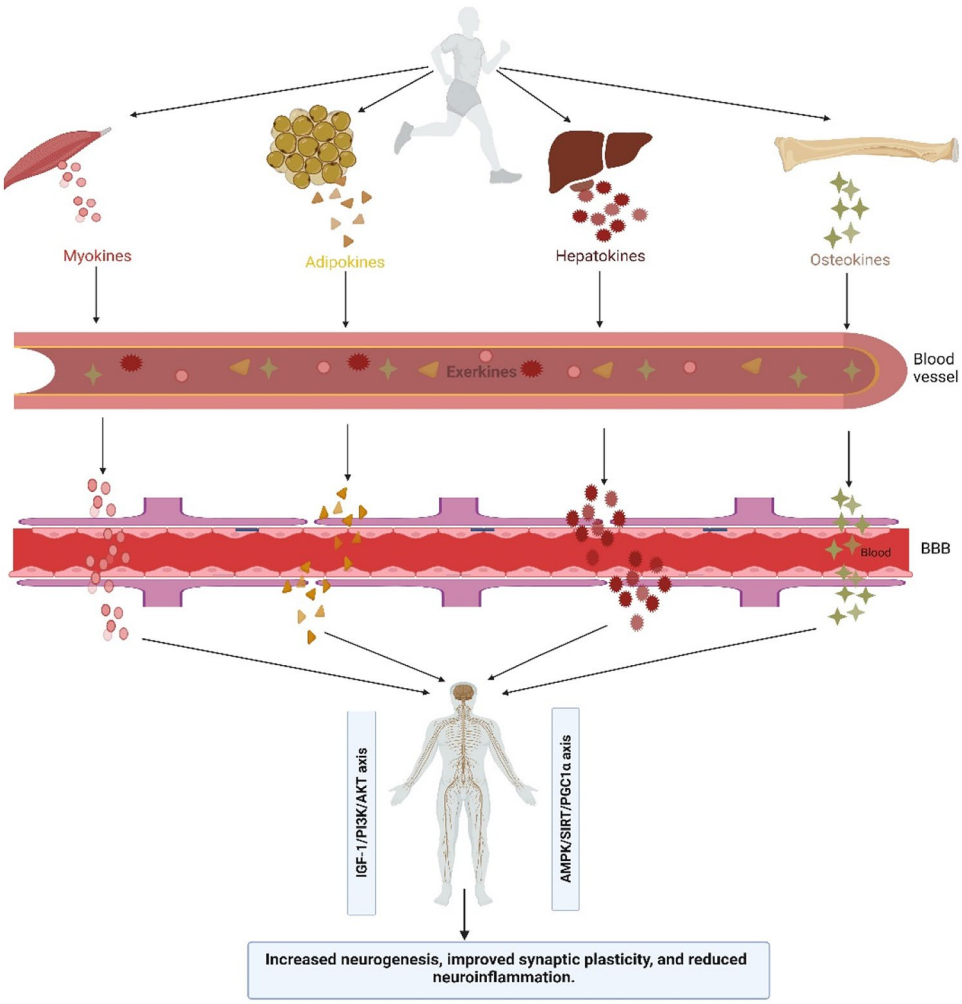

Fig. 1 Schematic representation depicting role of exercise responsome on CNS/brain: During physical exercise, body releases different cytokines from different tissues like skeletal muscles (myokines), adipose tissues (adipokines), liver (hepatokines), and bone (osteokines). These cytokines altogether are known as "exerkines." These exerkines are released in blood and then travel through blood–brain barrier (BBB) and regulate the cellular signaling pathways e.g., IGF-1/PI3K/AKT axis and AMPK/SIRT1/PGC1α axis in CNS/brain causing increased neurogenesis, improved synaptic plasticity, and reduced neuroinflammation. Created with BioRender.com

(type II). In humans, type II fibers are further differentiated into IIa, IIx based on differential myosin heavy chain gene expression (Schiaffino and Reggiani 2011; Talbot and Maves 2016). While type I and IIa are more oxidative, IIx fibers lean toward a glycolytic phenotype. In response to exercise, the skeletal muscle undergoes fiber remodeling to exhibit a higher proportion of oxidative fibers. The more oxidative the fibers are, the higher the mitochondrial content and vascularization. An increase in mitochondrial biogenesis and mitochondrial electron transport chain enzymes is observed in response to exercise (Holloszy and Booth 1976). Rise in glucose uptake and improved insulin sensitivity are also seen in the skeletal muscles of regularly exercising individuals.

Adipose tissue in humans can be classified into White adipose tissue (WAT) and Brown adipose tissue (BAT). While WAT is distributed throughout the body subcutaneously and acts as primary storage for fat, BAT is sparsely distributed and burns energy which is then released as heat (Heinonen et al. 2014). Conclusive evidence for the involvement of BAT has not been obtained, but studies have identified changes in WAT, showing increased mitochondrial activity, glucose uptake, and endocrine capabilities in response to physical exercise (Vidal and Stanford 2020).

The liver is a crucial organ for adapting to exercise-induced changes in skeletal muscles. While the functional capabilities of this organ are vast, one pivotal task it carries out is to meet the metabolic demands of the exercising skeletal muscles, by mobilizing and recycling energy substrates (Trefts et al. 2015).

Evidence is piling up on the multitudinous benefits of exercise in improving cognitive functions. Running can improve hippocampal neurogenesis, synaptic plasticity, memory, and learning capabilities in mice (van Praag et al. 1999). Animal studies have demonstrated marked changes in the hippocampus and neocortex in the form of neural and glial cell proliferation, angiogenesis, and increase in the concentration of neurotransmitters and release of pro-cognitive growth factors such as Brain derived neurotrophic factor (BDNF) and Insulin-like growth factor-1 (IGF-1) (Mandolesi et al. 2018). In animal models of neurodegeneration, motor activity was found to induce neuroprotective effects on the brain (Mandolesi et al. 2018). An exercise-induced upregulation of growth factors such as BDNF, IGF-1, Vascular endothelial growth factor (VEGF) both in the periphery and the CNS; neurotransmitters implicated in neurogenesis such as γ-aminobutyric acid (GABA), dopamine, glutamate, serotonin; transcription factors including sex-determining region Y-box 2 (Sox2), forkhead box O proteins (FoxOs), neuronal differentiation (NeuroD), Kruppel-like factor 9, paired box protein (Pax6), and neurogenin 2 (Neurog2) all of which are involved in neurogenesis has been observed (Kandola et al. 2016). Long-term potentiation (LTP), a form of neural plasticity, was found to be enhanced in the dentate gyrus of the hippocampus of running mice as opposed to sedentary mice (van Praag 2009). Owing to the inaccessibility of the human brain, translating evidence from animal studies to humans, in real-time, is riddled with roadblocks. Nevertheless, similar marker proteins implicated in neurogenesis, neuroinflammation, neuroprotection, and synaptic plasticity have been identified and found to be upregulated upon exercising. A significant increase in brain volume in aged adults who underwent aerobic training regularly for 6 months, as opposed to the control subjects (older non-aerobic exercise group and younger adult group), has been reported (Colcombe et al. 2006).

This affirms the fact that exercise has a multisystemic response in positively regulating metabolic functions, ameliorating symptoms of metabolism-related disorders, and providing neuroprotection to the older population. The molecular and cellular signaling mechanisms regulating such responses to physical exercise are not completely discerned. In the upcoming sections, we will discuss the constituents of exercise responsome, understand the variables associated with exercise, and briefly look at pharmaceutical interventions that mimic exercise-like conditions, exercise mimetics within the body. We will try and understand these signaling mechanisms and the nuances associated with them, from the perspective of the CNS.

The Exercise Responsome

The exercise responsome refers to changes in the molecular profile of tissues and organs when the body undergoes some form of physical exercise (Neufer et al. 2015). It initiates crosstalk between different organs leading to beneficial adaptations.

Based on their involvement, we may classify the exercise responsome into direct and indirect effectors. Indirect effectors include all those factors that are released into the bloodstream from any tissue or organ with the ability to mediate multisystemic benefits of exercise. The term 'exerkines' was coined to describe these circulating species, which may include cytokines, miRNAs, small peptides, and even extracellular vesicles (Safdar et al. 2016). The approach that a therapeutic advantage could be derived from circulating exercise-induced cytokines began when the muscle secretome exerting autocrine, paracrine, and endocrine effects to communicate with other organs were classified as myokines (Pedersen et al. 2003; Pedersen and Febbraio 2012). It has been proposed that myokines could mediate exercise-induced effects that could potentially ameliorate symptoms of lifestyle disorders (Pedersen and Febbraio 2012). Many adipokines, hepatokines, osteokines, and miRNA species have been identified that fit the criteria of exerkines.

Direct effectors include signaling molecules, transcriptional co-activators, and factors, kinases which when acted upon by indirect effectors initiate cellular metabolic changes. These metabolic changes include, as previously discussed, increased glucose uptake, mitochondrial biogenesis, upregulated oxidative phosphorylation which may contribute to neurogenesis, improved synaptic plasticity. These effectors make up the main signaling cascades involved in exercise-mediated adaptations, including the AMPK/SIRT1/PGC1α pathway and the IGF-1/PI3K/AKT pathway.

Ample evidence shows that exerkines released in the periphery can cross the BBB and exert pro-cognitive effects especially in the hippocampus and prefrontal cortex (Lee et al. 2019). The mechanisms governing their regulation are yet to be elucidated.

Exerkines

A diverse range of exerkines is released into the periphery after an acute bout of physical exercise. These circulating species act as messengers by which the brain senses exercise and activates pro-cognitive downstream signaling pathways.

FNDC5/Irisin

When it was first discovered in 2012, irisin was introduced as an exercise-induced myokine—an exerkine, which facilitates browning of adipose tissues, elevates Uncoupling protein 1 (UCP1) in primary fat cells, and improves glucose homeostasis and energy expenditure (Boström et al. 2012). Irisin was proposed to be the secretory form of a transmembrane protein, Fibronectin type III domain-containing protein 5 (FNDC5). FNDC5 was originally classified as a peroxisomal protein, expressed in skeletal muscle, brain, heart, and other tissues of mice (Ferrer-Martínez et al. 2002). When it was discovered, the existence of irisin was called into question and touted to be a myth, much like the Greek goddess Iris. This was in part due to unreliable quantitative methods and non-specificity of antibodies employed and the occurrence of a non-canonical start codon (Albrecht et al. 2015; Raschke et al. 2013). Definitive proof of its existence and circulation induced by exercise was laid when systemic irisin levels were detected at ~3.6 ng/ml in sedentary individuals using state-of-the-art quantitative mass spectrometry (Jedrychowski et al. 2015). Further, elevated levels of irisin [~4.3 ng/ml] following 12 weeks of intense aerobic training were reported (Jedrychowski et al. 2015). A study reported increased *Fndc5* mRNA levels in the skeletal muscles as well as in the hippocampus of exercising mice (Wrann et al. 2013). In addition, gene expression of PGC1α was also upregulated (Wrann et al. 2013).

Irisin is a PGC1α-dependent myokine, i.e., PGC1α's expression in the skeletal muscle of exercising mice induced the secretion of irisin into the bloodstream (Boström et al. 2012). PGC1α is a transcriptional co-activator that mediates the effects of exercise on muscle, brain, and other organs (Boström et al. 2012; Wrann et al. 2013). BDNF, a neurotrophic factor released into the periphery as well as in the brain, is considered indispensable for exercise-related cognitive improvements. Exercise-upregulated PGC1α was found to activate neuronal *Fndc5* gene expression, further positively regulating BDNF in hippocampal neurons (Wrann et al. 2013). Of interest, peripheral delivery of FNDC5 via adenoviral vectors was adequate to induce central expression of *Bdnf* (Wrann et al. 2013). The authors suggested that systemic FNDC5 influences brain health via BDNF possibly by crossing the BBB, opening a way for its therapeutic potential in neurodegenerative disorders (Wrann et al. 2013). Another important study showed that FNDC5/irisin blocks Amyloid β oligomers (AβOs), that accumulate in Alzheimer's disease (AD) brains, from binding to neurons and block their downstream activity implicated in memory failure (Lourenco et al. 2019). The authors divulged into the molecular nuances of FNDC5/irisin's neuroprotective role and concluded that exogenous recombinant irisin activates the cyclic adenosine monophosphate/protein kinase A/cAMP response element-binding protein (cAMP/PKA/CREB) pathway, which is dysregulated in AD patients (Lourenco et al. 2019). Thus, bolstering irisin levels via exercise may indeed ameliorate symptoms of AD. Another research group sought to understand exercise-induced irisin's therapeutic role in cerebral ischemic mice. Important findings were that irisin reduced brain infarction by activating the AKT and Extracellular signal-regulated kinase (ERK)1/2 pathways in the brain implying a much broader role in neuroprotection (Li et al. 2017). Irisin has also been shown to have an anti-inflammatory effect on astrocytes, by lowering the levels of Interleukin-1β (IL-1β) and Interleukin-6 (IL-6), which are otherwise elevated in Amyloid β (Aβ)-induced neuropathology of AD (Wang et al. 2018).

Cathepsin B

Cathepsin B (CTSB) belongs to the papain-like family of cysteine proteases and is involved in the general protein turnover of cells (Cavallo-Medved et al. 2011). Extensive research has implicated the pathological nature of CTSB in cancers and neurodegenerative disorders. CTSB is abundantly expressed in the brain, in comparison to other lysosomal cysteine proteases (Hook et al. 2020). Expression is seen throughout the development of the human brain, from the embryonic to adult stage, implying an important role in neuroprotection possibly by maintaining optimal lysosomal activity. Even so, a myriad of human and animal studies have

shown that CTSB levels are elevated in AD and AD-related disorders, hinting at its involvement in brain pathogenesis (Hook et al. 2020).

Muscle-secreted, exercise-induced CTSB can positively regulate hippocampal functions via BDNF and Doublecortin (DCX) (Moon et al. 2016). They observed that, treadmilling increases plasma CTSB levels in rhesus monkeys and humans and that it crosses the BBB in mice. Knockout (KO) CTSB mice were found to display shortfalls in memory functions as well as hippocampal neurogenesis (Moon et al. 2016). This was a pioneering study that put forward the perspective that CTSB mediates exercise-related cognitive benefits.

The exercise-mediated tendency of CTSB to improve neural health is still at a nascent stage and yet to be extensively characterized. But CTSB is a particularly precarious protein to rely on for its therapeutic abilities. Numerous studies implicate overexpression of CTSB as a contributing factor to malignancies during several cancers including gastric, oesophageal, prostate, breast (Aggarwal and Sloane 2014). Hence, targeting CTSB in cancers may have repercussions on brain health, warranting further research into its molecular and cellular tendencies.

IL-6

IL-6 is a pleiotropic cytokine produced transiently in response to infections or tissue damage and contributes to host defense, through acute phase proteins and hematopoiesis (Tanaka et al. 2014). It has both pro- and anti-inflammatory responses. IL-6 is produced from macrophages, vascular endothelial cells, fibroblasts, with 10–30% of the body's IL-6 coming from adipose tissue (Pedersen et al. 2001).

IL-6 levels were found to rise after a marathon and dropped afterward (Ostrowski et al. 1998). Upon detection of *IL-6* mRNA in muscle biopsies after exercise, it was suggested that IL-6 may be released from skeletal muscles into circulation and that IL-6 possibly induces Interleukin 1 receptor antagonist (IL-1ra) production to inhibit other cytokines (Ostrowski et al. 1998). Tumor necrosis factor (TNF) α, IL-1b were increased moderately, while IL-6 levels rose drastically immediately after a bout of strenuous exercise (Ostrowski et al. 1999). The authors identified that the rise in these pro-inflammatory cytokines is an acute phase response, but not a fully developed whole-body response, as seen in inflammation. The short-lived response may be due to the balance created by the production of cytokine inhibitors as well as anti-inflammatory cytokines, also induced by exercise (Ostrowski et al. 1999). Further, it has been shown that IL-6 production by skeletal muscles in response to exercise is enhanced when glycogen content is low within the contracting muscle suggestive of an energy sensor role for IL-6 (Keller et al. 2001; MacDonald et al. 2003). Subsequent studies have also shown an increase in IL-6 levels after exercise, with a few discrepant studies showing a lack of IL-6 induction, confined only to acute exercise (Catoire and Kersten 2015).

Exercise-induced skeletal muscle IL-6 mediates hepatic gluconeogenesis and lipolysis in adipose tissue. It also helps regulate glucose homeostasis during exercise (MacDonald et al. 2003; Carey et al. 2006). The involvement of AMPK in IL-6 release from skeletal muscle while exercising has been suggested (MacDonald et al. 2003). A strong, positive correlation between IL-6 release and α2-AMPK activity was observed in endurance-trained individuals after a bout of exercise (MacDonald et al. 2003). Another study concluded that IL-6 mediated glucose uptake via enhanced Glucose transporter type 4 (GLUT4) translocation to the cell membrane and found that AMPK is possibly involved in IL-6's role in glucose metabolism (Carey et al. 2006).

Nybo et al. (2002) investigated whether exercise changed IL-6 kinetics in the brain. They found that the brain indeed releases IL-6 transiently in response to prolonged exercise, albeit at a low concentration than that is produced from skeletal muscles. Accordingly, the authors suggested that the role of cerebral IL-6 in glucose homeostasis may be considerably less than that of skeletal muscle IL-6 (Nybo et al. 2002). Rasmussen et al. (2011) performed human and mice studies on brain IL-6 levels and *IL-6* mRNA expression, respectively, after prolonged exercise. The important takeaways were that, human brains release IL-6 while exercising as well as in the recovery period; the mice study showed an inverse relationship between glycogen content and *IL-6* mRNA expression, wherein exercise led to decreased glycogen levels and induced *IL-6* mRNA expression in hippocampus (Rasmussen et al. 2011). While the acute elevation of pro-inflammatory cytokines such as IL-6 has a positive impact on the overall metabolism of the brain, reports indicate that chronic inflammation is detrimental and contributes to neurodegeneration in senescence (Ye and Johnson 1999). Elevated IL-6 has been observed in the hippocampus, cortex, and cerebellum of aged mice in comparison to younger mice (Ye and Johnson 1999). Taking a different approach, the anti- and pro-inflammatory ratio elicited in the hippocampus of aged rats subjected to an aerobic exercise regimen was investigated (Gomes da Silva et al. 2013). A reduction in IL-6/IL-10 and TNF α/IL-10 ratio was detected in the senescent, exercising group as compared to the aged, non-exercising group (Gomes da Silva et al. 2013). The study suggested that a favorable balance between anti- and pro-inflammatory cytokines could be established through physical exercise in aged rats. Elevated levels of IL-6 have been observed after exercise, but the extent to which it contributes to improved brain function is yet to be detailed.

Adiponectin

Adiponectin (ApN) is an adipocytokine released into circulation by adipocytes, produced exclusively in WAT. It plays a crucial role in regulating glucose and lipid metabolism in insulin-responsive tissues of humans and animals. Low levels of circulating ApN have been implicated in obesity and insulin resistance in animal studies. Pleiotropically acting, ApN exerts its beneficial effects on adipose tissue, skeletal muscles, pancreas, liver, kidney, brain, heart, and the vascular system in humans (Abou-Samra et al. 2020).

ApN exerts most, if not all, its metabolic effects through AdipoR1 and AdipoR2 receptors in vivo, where the former is expressed heavily in skeletal muscle and the latter in liver (Yamauchi et al. 2007). The two receptors are different in terms of their signaling inclinations—AdipoR1 activates the AMPK pathway which regulates energy homeostasis specifically by inhibiting anabolic reactions, while AdipoR2 activates Peroxisome proliferator-activated receptor (PPAR) α pathways that are associated with expending energy and inhibiting oxidative stress (Yamauchi et al. 2007). Even though diverging signaling cascades are involved, both the receptors function to ameliorate insulin resistance (Yamauchi et al. 2007). Low molecular weight (LMW) trimers of ApN undergo posttranslational modifications to form Middle molecular weight (MMW) hexamers and the metabolically active, High molecular weight (HMW) multimers, which seem to be a good measure of estimating insulin resistance as well (Krause et al. 2019). HMW ApN can bind to the T-cadherin receptor, a Glycosylphosphatidylinositol-anchored protein (GPI-AP), expressed in abundance in the cardiovascular system (Bloemer et al. 2018).

When ApN was found to cross the BBB in mice, it led to speculation that the hormone also has centrally acting tendencies. Moreover, serum ApN levels are negatively correlated with metabolic syndrome and also appear to be altered in multiple neurological disorders such as ischemic stroke, AD, and Multiple Sclerosis (MS) (Yang et al. 2015). An important seminal study by Kubota et al. (2007) showed that ApN acting through AdipoR can activate AMPK in the hypothalamus of mice, leading to increased food intake and decreased energy dissipation. In conjunction with previous findings that only LMW and MMW were found in Cerebrospinal fluid (CSF) and that all forms can activate AMPK via AdipoR1, the authors suggested that HMW multimers of ApN may be too large to cross the BBB and, LMW trimers and MMW hexamers of ApN may be responsible for their metabolic activities in the CNS (Kubota et al. 2007). A role for ApN in regulating dendritic arborization, spinogenesis, and neurogenesis in the dentate gyrus of the hippocampus was defined, via ApN deficiency and Intracerebroventricular (ICV) infusion of ApN studies in mice by Zhang et al. (2016). Another study using aged ApN KO mice showed that ApN deficiency resulted in cognitive impairments as well as increased Aβ oligomers and hyperphosphorylated tau in the brain (Ng et al. 2016). Substantial neuroinflammation was also identified. ApN deficiency leading to AMPK attenuation and insulin resistance was responsible for AD-like pathologies in the mice (Ng et al. 2016). Yau et al.'s (2014) study showed that 2 weeks of running significantly elevated hippocampal ApN levels, while ApN serum levels were unaffected. The authors opined that the duration of running (2 weeks) may be insufficient to elicit a rise in serum ApN levels or, exercise-induced peripheral ApN simply crossed the BBB and elevated hippocampal levels. They also discovered that ApN partly mediates exercise-induced neurogenesis and antidepressant effects in the brain, possibly via AMPK activation (Yau et al. 2014).

The relationship between exercise and ApN has been widely pursued, because of the metabolic relief both provide. Thus far, results from studies on ApN levels, in response to exercise, have been ambiguous. While chronic, moderate-to-high intensity exercise has led to increased serum levels of ApN in some cases, not all studies are in consensus (Simpson and Singh 2008; Hayashino et al. 2014; Krause et al. 2019). Researchers reckon that interpreting data associated with ApN and exercise is challenging because of various regimens, intensity, and duration of exercise; sex, body composition, and fitness levels of individuals; occurrence of different oligomers of ApN, and call for much more robustly designed exercise trials (Simpson and Singh 2008; Krause et al. 2019; Abou-Samra et al. 2020).

Leptin

Leptin is a pleiotropic adipokine with a central role in energy homeostasis, neuroendocrine regulation, and metabolism. Its concentration in the body is in direct proportion to total body fat mass (Kelesidis et al. 2010). Leptin acts as a sensor for energy reserves in adipose tissue and signals CNS especially the hypothalamus, to regulate food intake and energy expenditure accordingly (Kelesidis et al. 2010). Its anorexigenic effects are exerted through leptin receptors (ObRs), abundantly expressed in the brain, and activation of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) 3 signaling pathway, predominantly (Kelesidis et al. 2010; Triantafyllou et al. 2016). Leptin also acts on peripheral organs where it mediates metabolic functions such as improved glucose sensitivity, browning of adipose tissue, and reduced lipolysis in adipose tissue; increased glucose uptake, increased glycogen synthesis, and lactate formation in skeletal muscles; and reduced hepatic gluconeogenesis (Triantafyllou et al. 2016).

Recombinant leptin replacement therapy has been used to aid leptin-deficient patients to regulate their body weight and energy homeostasis (Izquierdo et al. 2019).

Interestingly, high levels of leptin sans the anorexigenic ability have been observed in obese individuals, a condition called leptin resistance completely thwarting the approach of employing recombinant leptin as a treatment for obesity (Izquierdo et al. 2019). Studies have also shown that hyperleptinemia and leptin resistance lead to insulin resistance and the onset of type 2 diabetes pointing to a major role played by leptin in the pathogenesis of metabolic disorders and a possible crosstalk between insulin and leptin (McNeely et al. 1999; Moonishaa et al. 2017).

Leptin is also synthesized in the brain and has been shown to regulate later developmental processes such as neurogenesis, synaptogenesis, and axonal growth (Bouret 2010; Yook et al. 2019). Leptin gene therapy has been shown to rescue Aβ-induced cognitive impairments in double transgenic APP/PS1 mouse model of AD, which overexpress mutated gene forms of human amyloid precursor protein (hAPP) and prenisilin 1 (PS1), paving a way for leptin-based therapeutics in ameliorating neurodegenerative conditions (Pérez-González et al. 2014).

Several studies aimed to investigate a possible relationship between leptin and exercise, because of the effect both have on general body metabolism. Racette et al.'s (1997) study evaluated plasma leptin levels and abdominal adipose tissue leptin production after a bout of moderate-intensity cycling exercise and no significant changes were reported. Building on the notion that a single bout of exercise does not affect leptin levels, Essig et al. (2000) hypothesized that exercise may decrease peripheral leptin levels, not immediately but after 48 h. They observed that an energy expenditure of 800 or 1500 kcal led to approximately 30% decrease in leptin levels evident only after 48 h (Essig et al. 2000). An extensive meta-analysis study showed that only aerobic exercise led to increased ApN and decreased leptin levels in diabetic and pre-diabetic individuals (Becic et al. 2018).

Importantly, it was observed that hippocampal but not circulatory leptin mediates benefits of a combination of mild exercise and dietary astaxanthin antioxidant including enhancement of adult hippocampal neurogenesis and spatial memory (Yook et al. 2019).

While leptin signaling has been established as an important player in modulating exercise-induced improvements in the brain, its dysregulation—hyperleptinemia and leptin resistance, spells trouble for the whole body—contributes to impairment of energy homeostasis, neurodegeneration, and type 2 diabetes. So, the development of leptin-based therapeutics to combat metabolic disorders may require much deeper background research on leptin signaling in the body and the extent to which exercise-induced leptin is beneficial.

Osteocalcin

Osteocalcin (OCN), a vitamin-K dependent, γ- carboxy glutamic acid (GLA) containing protein is produced abundantly in the bone, specifically by osteoblasts (Price et al. 1976; Hauschka et al. 1989; Mizokami et al. 2017). Circulating OCN occurs as γ- carboxylated OCN and γ- uncarboxylated OCN of which, the uncarboxylated form has been shown to function as a hormone regulating glucose and energy metabolism in the body (Mizokami et al. 2017). Both carboxylated and uncarboxylated forms of OCN are positively associated with improved glucose tolerance in middle-aged men (Hwang et al. 2009). A daily dose of OCN injections administered to wild-type mice exhibits increased insulin secretion, improved insulin sensitivity, and glucose homeostasis as well as a partial restoration of glucose tolerance and insulin sensitivity in High-fat diet (HFD)-fed rats (Ferron et al. 2012).

In addition to regulating whole-body metabolism, OCN can cross the BBB (uncarboxylated form, more efficiently than the carboxylated form), favor post-natal brain development, and positively influence spatial learning and memory in adult mice (Oury et al. 2013). Gpr 158, an orphan class C-G protein coupled receptor (GPCR), expressing in the hippocampal Cornu Ammonis (CA) 3 region, cortex, piriform cortex, retro-splenial area, and ventral tegmental area of the brain, mediates the effects of OCN (Khrimian et al. 2017). They also identified that OCN acting through Gpr 158 is involved in the global trafficking of BDNF vesicles in the brain (Khrimian et al. 2017). There also have been indications that the decrease in OCN levels produced by bone directly correlates with the cognitive decline that comes with aging (Khrimian et al. 2017). Hence, when exogenous OCN was delivered to 14-month-old mice peripherally for 2 months, their hippocampal-dependent memory improved significantly and was found to be comparable to that of 3-month-old mice (Khrimian et al. 2017). The older mice also exhibited significant improvements in spatial learning.

Recent research has shown OCN levels to increase in 3-month-old mice after a single bout of exercise (Mera et al. 2016). OCN levels were also elevated in young women after a 45-min-long exercise regimen (Mera et al. 2016). The authors noted decreased levels of OCN in aging mice, rhesus monkeys, and humans at the same period as their diminishing exercise capacity. Of interest, they observed that OCN levels fail to rise to the same extent as the younger population even after exercise. But, when exogenous OCN was administered to older mice (12- and 15-month-old) with lower circulating OCN levels and exercise capacity, before exercise, not only did it increase peripheral OCN levels by fourfold but also their exercise capacity to that of 3-month-old mice. This led the authors to conclude that exogenous OCN can undo age-related reduction in exercise capacity.

Another study evaluated the levels of OCN, BDNF, and other exerkines such as irisin, CTSB after a bout of High-intensity interval exercise (HIIE) in healthy males (Nicolini et al. 2020). A significant increase in uncarboxylated OCN and BDNF levels was found in the exercising group. The authors found that the levels of uncarboxylated OCN and BDNF are linked and together, help improve exercise-mediated benefits on the brain, in terms of improved neuroplasticity, learning, and memory.

Research linking exercise-mediated effects of the bone hormone, OCN with improved neurological functions albeit promising, is at a nascent stage and worth exploring.

FGF21

Fibroblast growth factor 21 (FGF21), prominently expressed in the liver, but also in adipose tissue, pancreas, skeletal muscle, and brain, is involved in regulating energy metabolism by improving insulin sensitivity, glucose, and lipid homeostasis of the body (Kim et al. 2013; Sa-nguanmoo et al. 2016). A study by Kharitonenkov et al. (2005) depicted that FGF21 reduces circulatory glucose and lipid levels in diabetic rodents, and suggested it to be a novel metabolic regulator and a potential therapeutic agent for diabetes. In humans and rodents, FGF21 is induced by prolonged fasting (Inagaki et al. 2007; Gälman et al. 2008). As part of the adaptive response against starvation, FGF21 crosses BBB and induces hypothalamus-regulated hepatic gluconeogenesis in mice (Liang et al. 2014).

FGF21 is also expressed in the brain and acts on dopaminergic neurons to enhance mitochondrial activity, via induction of SIRT1/PGC1α pathway (Mäkelä et al. 2014). In obese insulin-resistant male rats, FGF21 prevents cognitive impairment, improves synaptic plasticity in the hippocampus, enhances brain mitochondrial activity, and protects against oxidative stress and apoptosis in the brain (Sa-nguanmoo et al. 2016).

In 2013, Kim et al. showed that an acute bout of exercise elevates serum levels of FGF21 in mice as well as humans (Kim et al. 2013). Besides, they also found an increased expression of hepatic FGF21, likely responsible for the elevated FGF21 serum levels (Kim et al. 2013). A study by Liu et al. (2018a) discovered that increased serum FGF21 levels in response to exercise were primarily from the liver. Importantly, their FGF21 KO mice study demonstrated that exercise-induced FGF21 may reduce neuroinflammation and improve synaptic plasticity (Liu et al. 2018a). As can be seen, that exercise-mediated FGF21's involvement in neuroprotection is largely unknown. Further studies in this regard are warranted (Fig. 2).

Other Bioactive Molecules Induced in Response to Exercise

Orexin A

Orexins were discovered in 1998, using a cell-based reporter system that was aimed at identifying peptide ligands for many orphan GPCRs (Sakurai et al. 1998). Orexins, A, and B were then categorized as a novel family of neuropeptides that respond per the nutritional status of the organism (Sakurai et al. 1998). They were found to be highly expressed in the lateral hypothalamus and adjoining areas of the brain involved in the regulation of food intake and energy homeostasis, centrally (Sakurai et al. 1998). The potential involvement of these neuropeptides in the pathology of narcolepsy, wherein, sufficient deficiency of orexin transmission can induce the chronic neurodegenerative disorder, has been widely studied (Ebrahim et al. 2002; De la Herrán-Arita et al. 2011).

Recently, plasma orexin A levels were found to be elevated in response to physical exercise in a study conducted in human subjects (Messina et al. 2016). The authors suggested that the positive correlation between Orexin A and exercise could implicate many roles for this neuropeptide in peripheral adaptations of the body to exercise (Messina et al. 2016). Further studies are mandated to clarify the significance of upregulated Orexin A levels during exercise.

SPARC

Secreted protein acidic and rich in cysteine (SPARC) is a Ca^{2+} binding, matricellular protein that regulates Extracellular matrix (ECM) assembly as well as its organization and is important for cell migration, proliferation, and differentiation (Chlenski et al. 2011). It has also been shown to disassemble and degrade ECM networks (Chlenski et al. 2011). SPARC has been identified in myotubes and muscle fibers, where its production increases during muscle development (So et al. 2014). It is also involved in the inhibition of adipogenesis and regulation of glucose metabolism (So et al. 2014). It has been shown to interact with AMPK and positively contribute to AMPK-regulated glucose metabolism (Song et al. 2010).

In the CNS, SPARC is largely expressed in microglia and a few subcortical astrocytes, where it is involved in the regulation of microglial proliferation and structure, also, it potentially modulates neuro-immune microglial responses after injury (Lloyd-Burton et al. 2013). Upregulation of SPARC has been implicated in many neurological conditions such as AD, ischemia, and gliomas (Jayakumar et al. 2017).

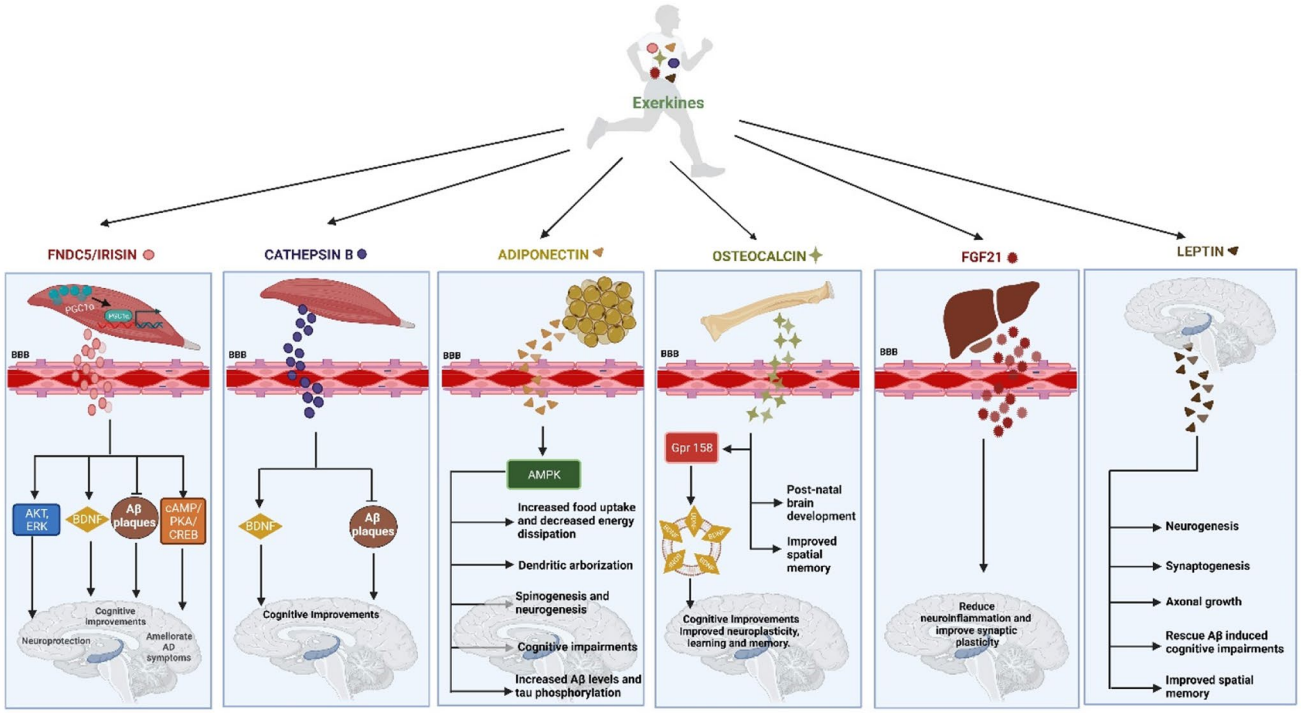

Fig. 2 Exercise-mediated release of various exerkines from different tissues and their effects on hippocampal region of brain: Exercise releases various exerkines like FNDC5/irisin, CTSB, Adiponectin, Osteocalcin, FGF21 from different tissues like skeletal muscles (myokines), adipose tissues (adipokines), liver (hepatokines), and bone (osteokines), respectively. These exerkines cross the BBB and modulate the activities of important signaling molecules such as AKT/ERK, AMPK, cAMP/PKA/CREB, BDNF, and gpr158 which further lead to exercise-induced benefits for brain. Leptin is synthesized and secreted in the brain in response to exercise causing neuroprotection. Created with BioRender.com

SPARC expresses abundantly in the basal lamina and its serum levels were found to be upregulated during cycle ergometer training at Lactate threshold (LT) in a study (Riedl et al. 2010). Another study reported an increase in expression and secretion of skeletal muscle SPARC in mice as well as humans, after a single bout of exercise (Aoi et al. 2013). Further, they observed that SPARC secreted in response to exercise was able to inhibit colon tumorigenesis via apoptosis (Aoi et al. 2013). In a recent study, Songsorn et al. (2017) found that supramaximal exercise failed to affect serum levels of SPARC. The authors opined that duration may be of more significance than the intensity of the exercise, for SPARC serum levels to change (Songsorn et al. 2017).

Musclin

Musclin is a myokine almost exclusively expressed and actively secreted by skeletal muscle (Nishizawa et al. 2004). Another group identified this peptide as Osteocrin, a novel bone-specific protein with an osteoblast-regulatory role (Thomas et al. 2003).

Musclin mRNA levels are controlled by the nutritional status of the organism and were found to be upregulated in insulin-resistant obese mice (Nishizawa et al. 2004). Recombinant musclin was found to attenuate insulin-dependent glucose uptake and glycogen synthesis in muscle cells (Nishizawa et al. 2004). High levels of musclin are implicated in insulin resistance, dysregulation of glucose metabolism, and ultimately the onset of type 2 diabetes (Nishizawa et al. 2004; Liu et al. 2008; Chen et al. 2017a, b).

A 2016 study showed that swimming exercise improves glucose metabolism in HFD-fed rats and downregulates the expression of musclin (Yu et al. 2016). Another group also reported a significant decrease in skeletal muscle-derived-musclin expression, in response to chronic resistance exercise in a type 2 diabetes rat model (Shimomura et al. 2021).

Currently, the underlying mechanisms associated with musclin and insulin resistance, musclin downregulation by physical exercise, and a potential role (if it exists) in neurodegeneration, remain elusive.

METRNL

METRNL is a secreted protein reported by Jørgensen et al. (2012) and Zheng et al. (2016) independently. It is also referred to as cometin, subfatin, and Interleukin 96 for its roles as a neurotrophin, adipokine, and cytokine, respectively

(Zheng et al. 2016). As a neurotrophin, METRNL stimulates neurite growth from sensory neurons, migration of neuroblasts from the subventricular zone in vitro, and promotes neuroprotection of spiral ganglion in vivo (Jørgensen et al. 2012). Acting through PPARγ in the adipose tissue, it promotes white adipocyte differentiation, promotes lipid metabolism, and insulin sensitivity overall (Zheng et al. 2016).

Exercise induces the release of METRNL in skeletal muscles, whose high circulatory levels improve glucose sensitivity in diabetic rats, hinting at a possible role for METRNL in combating metabolic dysregulation (Rao et al. 2014). It has recently been shown that METRNL crosses the BBB and mediates crosstalk between muscle and brain (Berghoff et al. 2021). This suggests that METRNL can be a putative exerkine mediating beneficial effects of exercise in the brain.

The Periphery-Brain Axis of Exercise-Mediated Benefits

In response to physical activity, numerous exerkines are released into circulation which then induce signaling in various organs of the body, including the brain. As previously discussed, the following are some putative exerkines arising in the periphery as well as in the brain, to translate exercise-induced cognitive benefits. Irisin, the cleaved product of FNDC5, is released to the periphery from skeletal muscle in response to exercise (Boström et al. 2012). Peripheral FNDC5 can induce *Bdnf* in the brain, suggesting that it is able to traverse the BBB and induce positive effects on the brain (Wrann et al. 2013). Also, acting directly on the brain, exercise-induced PGC1α can activate neuronal *Fndc5* gene expression, which further increases hippocampal expression of BDNF (Wrann et al. 2013). CTSB, a cysteine protease myokine, has been shown to cross the BBB in mice and regulate hippocampal functionality by increasing the expression of BDNF and DCX (Cavallo-Medved et al. 2011; Moon et al. 2016). IL-6 is released into circulation, most likely by skeletal muscles (Ostrowski et al. 1998). It has been shown to positively regulate glucose homeostasis in the body, possibly involving the energy sensor, AMPK (MacDonald et al. 2003). While the prospect of exercise-induced peripheral IL-6, crossing the BBB and, mediating cognitive benefits is nescient, research shows that IL-6 is released from the brain albeit transiently and in low concentration, in response to prolonged exercise (Nybo et al. 2002). Hippocampal induction of *IL-6* mRNA mediated by prolonged exercise has also been observed (Rasmussen et al. 2011). ApN, arising from adipocytes, has an important role in regulating glucose and lipid homeostasis in the body (Abou-Samra et al. 2020). Studies discerning ApN's exercise responsive nature have been inexplicit with some concurrent and a few others in disagreement (Simpson and Singh 2008; Hayashino et al. 2014; Krause et al. 2019). Running exercise elevates hippocampal ApN and mediates beneficial effects in the brain, likely via AMPK (Yau et al. 2014). Even though significant serum ApN levels were not detected, it could be due to insufficient exercise duration or that peripheral ApN simply crossed the BBB to hippocampus, researchers suggest (Yau et al. 2014). Leptin is another adipokine, with a requisite role in energy metabolism in the periphery, and functions to improve later developmental neurological processes in the brain (Bouret 2010; Triantafyllou et al. 2016; Yook et al. 2019). A study showed that, in response to exercise, hippocampal derived but not systemic leptin in combination with dietary astaxanthin was able to elicit improvements in adult hippocampal neurogenesis and memory (Yook et al. 2019). Peripheral exercise-induced leptin impacting the brain positively is yet to be discovered. OCN, derived from the bone, regulates metabolic activities in the body and contributes to postnatal brain development (Oury et al. 2013). It can cross the BBB and decreased OCN levels directly correlate with age-related cognitive decline (Oury et al. 2013; Khrimian et al. 2017). A correlation between OCN and BDNF levels has been discovered after a bout of high-intensity interval exercise (HIIE), leading to enhanced learning and memory in the brain (Nicolini et al. 2020). The liver-derived metabolic regulator FGF21 is elevated in the serum of mice and humans after an acute bout of exercise (Kim et al. 2013). Exercise-elicited FGF21 has been shown to positively impact the brain in mice (Liu et al. 2018a). Besides these exerkines, a few other, lesser-known molecules have been speculated to contribute to exercise-induced improvements in the brain. Orexins are neuropeptides with roles in energy homeostasis whose serum levels are elevated by exercise (Sakurai et al. 1998; Messina et al. 2016). SPARC is an extracellular matrix regulating protein known to be involved in muscle development, adipogenesis, and microglial proliferation (Lloyd-Burton et al. 2013; So et al. 2014). Serum SPARC was observed to be upregulated by exercise in many studies (Riedl et al. 2010; Aoi et al. 2013). Musclin, another myokine with exercise responsive ability, has been linked with the regulation of glucose metabolism in HFD mice, but a probable neuro-specific role is yet to be elucidated (Yu et al. 2016). METRNL, with neurotrophic and adipokine inclinations, is also released into the periphery by skeletal muscles contributing to better glucose tolerance in diabetic rats (Rao et al. 2014; Zheng et al. 2016). METRNL can traverse the BBB and mediate a crosstalk between muscle and brain, it has recently been shown, suggesting a role in exercise-mediated benefits on the brain (Berghoff et al. 2021). While not all molecular entities that respond to exercise have been designated to cross the BBB and act on the brain, we have discussed those that have such inclinations and some likely candidates whose path of action is yet to be illuminated. Many of these exerkines have been proposed

to activate signaling molecules in the brain, such as, BDNF, SIRT1, PGC1α, and IGF-1, which further turn on downstream signaling pathways that induce positive metabolic changes, neurogenesis, synaptic plasticity in the brain (Lee et al. 2019).

Exercise-Induced Signaling Molecules in the Brain

BDNF

Many of the benefits of exercise are mediated through growth factors, prominent of which is BDNF. Serum BDNF levels increase transiently in response to exercise. Peripheral BDNF release is majorly contributed by vascular endothelial cells, T cells, B cells, monocytes, and skeletal muscle cells (Phillips et al. 2014). Most of the circulatory peripheral BDNF is internalized and stored in platelets, whereas BDNF produced by skeletal muscle cells functions locally at the Neuromuscular junction (NMJ) (Phillips et al. 2014). In mice, BDNF has been shown to cross the BBB (Pan et al. 1998).

BDNF is highly expressed in the hippocampus and cortex and has been associated with the proper functioning and survival of neurons. It has been shown to promote LTP and strengthen neurotransmission (Sleiman and Chao 2015). BDNF also helps alleviate symptoms of Parkinson's by mediating the survival of dopaminergic neurons and strengthening synaptic connections (Sleiman and Chao 2015). Decreased levels of BDNF are seen in many neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and multiple sclerosis (Bathina and Das 2015).

Animal models have shown that exercise induces *Bdnf* mRNA expression in the brain, especially hippocampal dentate gyrus, CA3, and hilus region, and blocking BDNF attenuates exercise-conferred benefits such as improved spatial learning and increased synaptic protein production (Vaynman et al. 2004; Sleiman and Chao 2015). Besides, exerkines such as CTSB, FNDC5/irisin are said to traverse the BBB and activate BDNF as part of their downstream signaling, contributing to neurogenesis and memory enhancement (Liu and Nusslock 2018). In addition to providing evidence that exercise-induced benefits on the brain are mediated by BDNF, a relationship between BDNF and CREB, a protein that has an evolutionarily conserved role in long term memory, has been established (Vaynman et al. 2004). The authors noticed elevated levels of BDNF and phosphorylated CREB in exercising mice (Vaynman et al. 2004). They also observed that exercise via BDNF upregulates mRNA levels of *synapsin 1*, a crucial presynaptic protein that regulates neurotransmitter release, formation of the presynaptic structure, and axonal elongation (Vaynman et al. 2004). Blocking hippocampal BDNF during exercise attenuated CREB and synapsin I expression, hinting that they are downstream effectors of BDNF activity (Vaynman et al. 2004).

BDNF mediates cognitive improvements by binding to Tropomyosin receptor kinase B (TrkB), a single-pass membrane protein highly expressed in the hippocampus. The BDNF-TrkB complex is then internalized into the neuron and thereby serves as a docking site for multiple signaling cascades involving IRS1/2/PI3K/AKT pathway, Mitogen-activated protein kinase/Extracellular signal-regulated kinase (MAPK/ERK) pathway, and Phospholipase C/Diacylglycerol/inositol 1,4,5 trisphosphate (PLC/DAG/IP3) pathway (Bathina and Das 2015; Liu and Nusslock 2018).

While peripheral BDNF has been shown to cross BBB in mice, there have been conflicting results for the same in humans. Since BDNF is produced centrally as well as peripherally in response to exercise, questions like how significant is peripheral BDNF in improving brain health? To what extent can peripheral BDNF influence general metabolism? may be relevant to ponder upon.

AMPK

AMPK was first discovered as an ATP and ADP-dependent kinase inactivating HMG-CoA reductase (Beg et al. 1973), and Acetyl CoA carboxylase (Carlson and Kim 1974). Subsequent studies identified AMP to be a potent allosteric activator of the kinase. The kinase's role is not just confined to these two enzymes but has a broad range of substrates upon which it acts and proceeded to name the kinase based on its allosteric regulator, as AMPK (Hardie et al. 1997). In addition to being allosterically activated by AMP,AMPK is also activated by an upstream kinase by phosphorylation at Thr-172. AMP not only promotes phosphorylation by the upstream kinase but also inhibits dephosphorylation by phosphatases (Hardie 2003). In mammalian cells, LKB1 and Ca^{2+}/Calmodulin-dependent protein kinase kinase (CaMKK) have been identified as the upstream kinases that phosphorylate Thr-172 of AMPK.

AMPK is an important biomolecule in the realm of energy metabolism. As an energy sensor, it retaliates by switching on catabolic pathways that generate energy (ATP), down-regulating anabolic pathways in response to pathological stresses such as hypoxia, ischemia, heat shock as well as physiological stimuli such as physical exercise that may alter the AMP: ATP ratio (Hardie 2003).

AMPK is a heterotrimeric complex composed of a catalytic α subunit and regulatory β, γ subunits. There are two α subunit isoforms, two β, and three γ- isoforms, making up to 12 different possible combinations for the AMPK complex in mammals (Willows et al. 2017).

A 2000 study sought to investigate the activity of human skeletal muscle, isoform-specific in response to high and low intensities of bicycling (Wojtaszewski et al. 2000). They found significant α2-AMPK activation only after high intensity of exercising, while α1-AMPK's exercise-mediated induction did not occur. It was inferred that the activity of α2-AMPK is dependent on the intensity of exercise performed. Since AMPK activation occurs in response to a high AMP: ATP ratio and AMP levels are seemingly high during contractile movement, the authors wanted to know if the exercise-induced α2-AMPK is metabolically significant, by testing its dependency on AMP in comparison to α1-AMPK. They discovered a greater dependency on AMP by α2-AMPK for its activation, strengthening the idea that α2-AMPK is the preferred isoform for metabolic adaptations after a bout of exercise in humans (Wojtaszewski et al. 2000). Another similar study also came to the same conclusions (Kim et al. 2007). An interesting study using β1β2 AMPK knock-out mice discovered that skeletal muscle AMPK is indispensable for maintaining optimal mitochondrial content, and increased insulin-independent glucose uptake during exercise (O'Neill et al. 2011). AMPK's involvement in insulin-sensitizing effects of exercise via mTOR, ApN, and IL-6 has also been identified, analyzed, and discussed (O'Neill 2013). Overall, it may be inferred that AMPK mediates most of the exercise-induced benefits in skeletal muscles.

In the CNS, AMPK plays a similar role in regulating glucose metabolism, mitochondrial function, and biogenesis as well as modulating neurodevelopment, cell polarity, and autophagy in neurons (Rosso et al. 2016). AMPK plays a role in alleviating AD pathogenesis by reducing sphingomyelin levels and regulating Amyloid precursor protein (APP) distribution in lipid rafts, thereby inhibiting amyloidogenesis (Won et al. 2010). AMPK has also been shown to be crucial to maintain optimal neuronal energy levels upon synaptic activation, a parameter that is dysregulated in neurodegenerative disorders (Marinangeli et al. 2018).

While activation of AMPK is neuroprotective, its hyperactivation contributes to the pathogenesis of many brain disorders including AD, brain ischemia, Huntington's (Ronnett et al. 2009; Rosso et al. 2016; Domise et al. 2019). It may be surmised that an optimal level of AMPK needs to be maintained for the proper functioning of the brain, as both under- and over-activation of AMPK seems to be detrimental. It is also worth questioning whether any regimen of physical exercise can hyperactivate AMPK, to avoid any afflictions in the brain.

SIRT1

Sirtuins (SIRTs) are a family of evolutionarily conserved, Nicotinamide adenine dinucleotide $(NAD)^+$ dependent histone deacetylases that are important regulators for cellular senescence, cell proliferation, neuroprotection, stress response, and energy metabolism. In mammals, seven homologs of SIRTs (1–7) exist, of which SIRT1 is a key metabolic sensor, much like AMPK. Its activity is tightly controlled by cellular levels of NAD^+, which in turn is a direct measure of cellular energy status.

SIRT1 is widely expressed in the brain, muscle, liver, heart, pancreas, adipose tissue of humans (Jiao and Gong 2020). SIRT1 has been shown to modulate hepatic gluconeogenesis and fatty acid oxidation, maturation of adipose tissues, and pancreatic insulin secretion in response to nutritional status (Li 2013). Acting in conjunction with AMPK, SIRT1 potentially improves insulin sensitivity overall. SIRT1 can upregulate phosphorylation and activity of AMPK by deacetylating its upstream kinase, LKB1 (Li 2013). On the other hand, AICAR, a synthetic agonist of AMPK can activate SIRT1 by increasing the NAD^+/NADH ratio in cell (Li 2013). Either way, it improves glucose homeostasis, lipid metabolism, and mitochondrial biogenesis in the body.

In the CNS, SIRT1's deacetylase activity has multiple substrates such as FoxO, tumor suppressor p53, PPARγ, PGC1α which are involved in neuroprotection and survival (Paraíso et al. 2013). In recent years, investigating the potential of one SIRT1 activator, resveratrol, capable of inducing numerous cognitive benefits has gained huge momentum (Borra et al. 2005; Sun et al. 2010; Moraes et al. 2020). Also, resveratrol by activating SIRT1 could delay neurodegeneration and cognitive impairment in vivo (Kim et al. 2007). They also observed that SIRT1 deacetylated and activated PGC1α, another important molecule implicated in the regulation of neuronal metabolism (Kim et al. 2007). The authors concluded that PCG1α acting synergistically with SIRT1 mediated neuroprotective actions in their study (Kim et al. 2007).

A single bout of sprint exercise could elicit AMPKα activity and, increase SIRT1 protein expression, likely mediated by AMPKα itself (Guerra et al. 2010). High-intensity interval training was shown to increase SIRT1 activity in human skeletal muscles (Gurd et al. 2010). A connection between exercise, lactate, SIRT1, FNDC5/irisin, and *Bdnf* expression in the hippocampus has been established (El Hayek et al. 2019). They observed that voluntary exercise enhances lactate levels in the body, which then crosses the BBB and induces the gene expression of *Bdnf*. SIRT1 mediates this action of lactate in response to exercise. SIRT1's deacetylase activity induces the transcription of PGC1α and FNDC5/irisin, known to mediate neuro-metabolism and *Bdnf* gene expression, respectively (El Hayek et al. 2019).

SIRT1 induced by exercise potentially influences several metabolic activities in the body, especially the CNS because of its deacetylase activity which can activate

key substrates in energy metabolism including AMPK, PGC1α, and BDNF. Owing to its positive regulation in the brain, the therapeutic potential of SIRT1 in ameliorating neurodegenerative disorders is being widely pursued.

PGC1α

PGC-1α is a transcriptional co-activator touted to be a master regulator of mitochondrial biogenesis, in specific and energy metabolism, overall. PGC1α has multifarious effects when expressed/activated, it regulates adaptive thermogenesis in BAT; increases hepatic gluconeogenesis during fasting state; induces mitochondrial biogenesis and controls fiber switching in skeletal muscle; and controls mitochondrial respiration in cardiac muscle (Lin et al. 2002; Finck and Kelly 2006; Fernandez-Marcos and Auwerx 2011). Naturally, as an important metabolic junction, PGC1α has a wide variety of substrates it acts upon, which include, PPARα, β, γ, Estrogen-related receptors (ERRs), FOXO1, Sox9, retinoid receptors, Nuclear respiratory factor-1 (NRF-1), NRF-2 (Finck and Kelly 2006; Fernandez-Marcos and Auwerx 2011). Besides, PGC1α activity is influenced by important metabolic sensors such as AMPK and SIRT1. PGC1α was identified as a key downstream target for AMPK while regulating GLUT4 and mitochondrial gene expression in skeletal muscles (Jäger et al. 2007). They found that AMPK can phosphorylate PGC1α at Thr-177 and Ser-538 and activate it (Jäger et al. 2007).

Wright et al.'s (2007) study aimed to deduce a signaling cascade involving p38 MAPK, PGC1α behind the robust skeletal muscle mitochondrial biogenesis induced by swimming exercise. Based on their results, they proposed that active p38 MAPK phosphorylates PGC1α which then mediates the initial bout of mitochondrial biogenesis in response to exercise. Subsequently, PGC1α expression is boosted by Activating transcription factor (ATF) 2 and Myocyte enhancer factor (MEF) 2, which then contributes to a second wave of adaptive response to exercise (Wright et al. 2007).

In the brain, PGC1α plays a neuroprotective role against oxidative stress by inducing Reactive oxygen species (ROS)—detoxifying enzymes (St-Pierre et al. 2006). Mediating between the SIRT1-FNDC5/irisin axis, PGC1α can induce the expression of BDNF in the hippocampus of mice, and also contribute to synaptic plasticity and neuroprotection, in response to exercise (Wrann et al. 2013).

PGC1α, as a transcriptional co-activator, is an important metabolic node in the vast network mediating multisystemic, exercise-induced responses and has an exceptional therapeutic prospective in the treatment of metabolic disorders and delaying neurodegeneration.

IGF-1

IGF-1 is a protein, 70 amino acids long, first reported by Salmon and Daughaday in 1957 as a sulfation factor with a function of inducing the incorporation of ^{35}- sulfate in the cartilage of rats (Salmon and Daughaday 1957; Lin et al. 2002; Finck and Kelly 2006; Fernandez-Marcos and Auwerx 2011). Subsequently, it was named somatomedin for its ability to control and mediate the effects of Growth Hormone (GH) aka somatotropin (Laron 2001). Owing to its structural similarity to proinsulin, and for its ability to bind insulin receptor, albeit with a low affinity, it has been called IGF (Laron 2001).

IGF-1 functions as an endocrine, paracrine as well as autocrine hormone whose physiological roles are dependent on the site of its secretion. It is predominantly secreted in the liver, from where it is transported to other tissues via the bloodstream to exert its effects (Laron 2001; Yakar and Adamo 2012). It is also secreted by other organs such as the brain, cartilage where it functions locally (Laron 2001; Wrigley et al. 2017). It acts as an oncogene in an autocrine manner (Laron 2001). While IGF-1 levels are regulated by GH of the pituitary gland, additionally, nutritional status and insulin also govern its secretion (Yakar and Adamo 2012).

In addition to mediating the metabolic and growth-promoting effects of GH, IGF-1 acting through IGF-1 receptor (IGF-1R) triggers PI3K/AKT signaling pathway and MAPK pathways. IGF-1 activation of the PI3K/AKT signaling pathway promotes cell survival by inhibiting pro-apoptotic pathways, glucose uptake, glycogen synthesis, and protein synthesis (Wrigley et al. 2017). MAPK/ERK pathway activation triggers transcription related to cell survival and proliferation (Wrigley et al. 2017).

In the CNS, all major cell types are capable of producing IGF-1, where its expression levels are the highest perinatally, but fall throughout life except for the subventricular zone and dentate gyrus—sites of neurogenesis (Dyer et al. 2016). Contrary to IGF-1, IGF-1R is ubiquitously expressed in the brain indicating a role for peripherally produced IGF-1 in the CNS (Dyer et al. 2016). A large proportion of research supports an essential role for IGF-1 in brain development, adult brain neurogenesis, neuroplasticity, and neuroprotection (Wrigley et al. 2017).

Research discerning the involvement/contribution of IGF-1 in neurodegenerative diseases is contradictory, to say the least. A meta-analysis conducted by Ostrowski et al. (2016) compared plasma, brain, and CSF levels of IGF-1 in animal models of Alzheimer's disease across numerous studies. They also looked at human studies on IGF-1 and AD. The analysis of human studies did not establish a clear-cut relationship between serum IGF-1 levels and AD, important to note—IGF-1 levels were, in most cases dysregulated, either higher or lower than usual. Since there was a

significant variation in serum levels of IGF-1 reported across the studies, the authors opined that serum IGF-1 levels may be personalized and specific to the AD patient. They suggested that treatment for AD patients be done considering their IGF-1 levels besides other factors that may be dysregulated, on an individual basis (Ostrowski et al. 2016).

Building on previous research that serum IGF-1 levels rise in response to exercise, and that exercise-induced neurogenesis and cognitive improvements are mediated by the IGF-1 (besides other growth factors) (Schwarz et al. 1996; Carro et al. 2000), a 2001 study showed that circulating IGF-1 is essential for exercise-mediated neurogenesis in the brain (Trejo et al. 2001). A 3-month intervention aerobic exercise trial conducted on a healthy elderly population provided insights into a connection between exercise, IGF-1 levels, and hippocampal volume (Maass et al. 2016). Regular exercise improved fitness levels and induced positive changes in hippocampal perfusion and volume. In addition, IGF-1 levels correlated positively with hippocampal volume in the exercising elderly population (Maass et al. 2016). Further research on the neuroprotective role of exercise mediated by circulatory IGF-1, at the cellular level, is warranted to understand the level of its indispensability in this context.

Exercise Mimetics

AMPK Agonists

AICAR

AICAR (5-Aminoimidazole 4-carboxamide ribonucleoside) an adenosine analog is converted by adenosine kinase to ZMP (5-aminoimidazole 4-carboxamide ribonucleoside monophosphate) when administered to cells. ZMP is an allosteric activator of rat liver AMPK, much like AMP although to a lesser extent. AICAR activates AMPK without altering the cellular ratio of ATP, ADP, and AMP (Corton et al. 1995). Referred to as Acadesine, this adenosine regulator has implications in the treatment of lymphoblastic leukemia, and Ischemia–reperfusion injury (IRI) (Drew and Kingwell 2008).

AICAR, the AMPK agonist can induce cellular changes mimicking those of exercise, such as improved glucose homeostasis, mitochondrial health, angiogenesis, and lipid metabolism (Guerrieri et al. 2017). Systemic administration of AICAR reduced blood glucose levels and inhibited whole-body lipolysis in type 2 diabetes patients (Boon et al. 2008). AICAR has widely been hailed as an exercise drug after studies showed that it can increase endurance capacity and stimulate OX-PHOS metabolism in sedentary mice (Narkar et al. 2008).

Mice injected with AICAR intraperitoneally exhibited enhanced hippocampal neurogenesis and improved spatial memory, confirming that endurance indeed manifests in improved cognition (Kobilo et al. 2011). Since it has low permeability over BBB, effects mediated by AICAR on the brain are likely mediated by indirect secretory factors (Marangos et al. 1990; Kobilo et al. 2014).

R419

R419 ((*N*-(1-(4-cyanobenzyl) piperidin-4-yl)-6-(4-(4-methoxybenzoyl) piperidine-1-carbonyl) nicotinamide) was first identified as a complex I inhibitor that activates AMPK at doses significantly lower than that of metformin. R419 treatment of obese mice improved their mitochondrial metabolism as evidenced by a decrease in branched-chain amino acids (BCAA) pathway intermediates, substrates catabolized by mitochondria (Jenkins et al. 2013).

Recently, it has been reported that R419 can improve skeletal muscle insulin sensitivity and exercise endurance in HFD-fed obese mice. The study also found that improvement of glucose homeostasis by R419 was independent of AMPK's involvement. Overall, R419 offers a new therapeutic value in improving exercise capacity and ameliorating insulin resistance in obese mice (Marcinko et al. 2015).

AdipoR Agonists

AdipoRon

AdipoRon was discovered as an orally active AdipoR agonist, capable of improving insulin sensitivity in mice (Okada-Iwabu et al. 2013). Much like ApN, it could activate AMPK via AdipoR1 and PPARα pathway via AdipoR2. AdipoRon also improved mitochondrial biogenesis through increased expression of PGC1α. AdipoRon was found to mimic most of the metabolic effects of ApN in vivo (Okada-Iwabu et al. 2013). The same research group later developed muscle-specific human AdipoR1-transgenic mice and exhibited that AdipoRon can act beneficially on human AdipoR1 in terms of improved glucose metabolism and exercise capacity (Iwabu et al. 2021).

It was reported that AdipoRon can cross the BBB and exert ApN mimicking effects on the brain (Ng et al. 2020). Chronic administration of AdipoRon was able to reduce neurotoxic species specific to Alzheimer's disease and confer cognitive and memory improvements to AD mice (Ng et al. 2020). Another study demonstrated that chronic AdipoRon can ameliorate neuro-metabolic dysfunction and cognitive impairment associated with diabetes, enhance hippocampal BDNF levels, and contribute to synaptic plasticity (Lee et al. 2021). The improvements conferred by AdipoRon in

the CNS mimic those observed during exercise, making AdipoRon a newly emerging exercise mimetic.

PPARδ Agonists

GW501516

PPARδ is a ligand-activated transcription factor and nuclear receptor, that plays a key role in energy metabolism (Liu et al. 2018b). Ligand binding induces a conformational change in PPARδ and recruitment of the transcriptional co-activator PGC1α leading to activation of downstream signaling cascades. PPARδ is involved in fatty acid catabolism, glucose homeostasis as well as fiber remodeling in exercising skeletal muscles, where it is abundantly expressed (Luquet et al. 2005). PPARδ is expressed abundantly in the adult brain and spinal cord of rodents. Its expression has been detected in many cell types of CNS including astrocytes, microglia, neurons, endothelial cells (Schnegg and Robbins 2011).

Sznaidman et al. (2003) sought to identify highly selective PPARδ agonists to delve deeper into the physiological roles of the then lesser-known PPARδ. Using combinatorial chemistry and optimizing hits using structure-led design, they reported GW501516 and GW0742 with 1000-fold selectivity to PPARδ over other PPAR subtypes (Sznaidman et al. 2003).

GW501516 was employed by Narkar et al. (2008) in their pioneering exercise mimetics study, along with an AMPK agonist, AICAR. They found that GW501516 and exercise (here, treadmill running) acting synergistically can induce oxidative-type fiber remodeling and increase mitochondrial biogenesis enhancing the running endurance of mice, in comparison to untreated controls (Narkar et al. 2008). While exercise exerts its beneficial effects through the breakdown of proteins, glycolysis, and gluconeogenesis from amino acids, GW501516 promotes fatty acid oxidation via branched-chain amino acid and ketone body pathways, in mice (Chen et al. 2015). It has been reported that GW501516, as a PPARδ agonist has a neuroprotective role in the CNS and delays the onset of neurodegenerative disorders such as Alzheimer's Disease, Parkinson's disease, and spinal cord injury by promoting cell survival (Schnegg and Robbins 2011). It exhibited anti-inflammatory activity by decreasing levels of TNFα and inducible nitric oxide synthase (iNOS) induced by Interferon (IFN) γ in a 3D brain culture system derived from embryonic rat brain, thus demonstrating a neuroprotective role against brain inflammation (Defaux et al. 2009).

Owing to its pro-endurance effects and exploitation in the Sports industry (as Cardarine), GW501516 was added to the prohibited list issued by World Anti-Doping Agency (WADA) in 2009 (World Anti-Doping Agency 2009). Gupta et al.'s (2004) study reported that PPARδ agonists promote adenoma development in the intestines of mice raising concerns of colorectal cancer risk in individuals consuming GW501516. Subsequently, in 2013, WADA issued an alert on GW501516 owing to serious toxicities identified in rodents in pre-clinical studies, and all clinical trials were dropped (Fig. 3).

Conclusion

Leading a sedentary lifestyle spells trouble for the whole body and contributes to type 2 diabetes, obesity, cardiovascular, and neurodegenerative diseases, warranting an immediate change to a more active lifestyle and the inculcation of exercise in one's daily routine. The multitudinous benefits of exercise on different organ systems are well established. Exercise triggers the release of certain molecular entities, now termed as exerkines, from various organs to the periphery. Some of these exerkines can mediate a crosstalk between the periphery and the brain and impart exercise-mediated benefits on the brain. There are also some which are upregulated in the brain directly and mediate positive changes. While the research on molecular and cellular mechanisms underlying exercise-mediated metabolic regulation

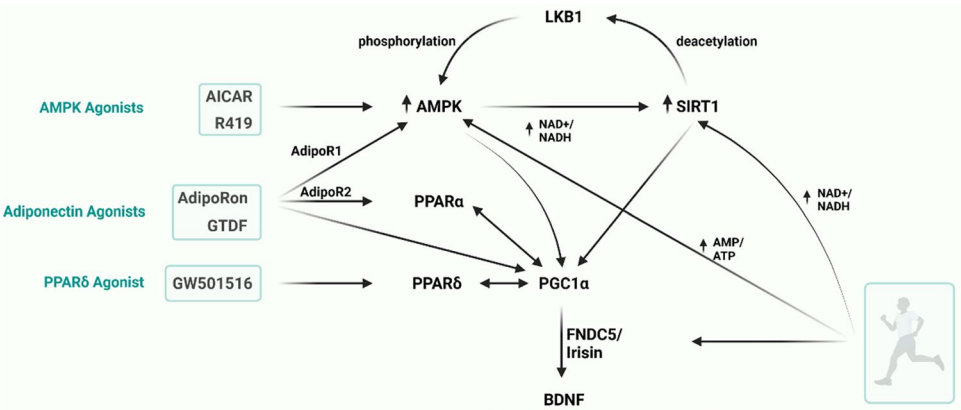

Fig. 3 Exercise mimetics targeting the AMPK-SIRT1-PGC1α-BDNF signaling pathway to enhance cognitive performance. Exercise mimetics such as AICAR, R419, AdipoRon, GTDF, and GW501516 act on signaling molecules involved in translating exercise-mediated benefits on the brain. They target AMPK, PPARα, PPARδ, PGC1α, ultimately converging upon BDNF expression. Created with BioRender.com

is currently at a nascent stage, some of the major metabolic nodes in this vast signaling network have been discerned. The AMPK-SIRT1-PGC1α-BDNF pathway needs to be acknowledged as the main branch point mediating most of the cognitive benefits associated with exercise. Research on bioactive compounds that simulate exercise without having to move a muscle is also underway. Exercise mimetics, as they are called, are a boon to those individuals who would benefit from exercise but are unable to do so. Besides holding a therapeutic value, these drugs can also bring to light unknown signaling molecules in the vast network of exercise signaling. Putative exercise mimetics such as AICAR, GW501516 have been found to have non-specific effects inside cells, and clinical trials have not been very promising. New drugs need to be screened and the transition from bench to bedside needs to be narrowed down to combat metabolic disorders.

Acknowledgements We thank Indian Institute of Technology-Delhi for its support.

Author Contributions CSD and IR conceived the idea; IR and YY wrote the draft of the manuscript; CSD corrected, edited, and reviewed the manuscript; CSD, IR, and YY approved the final version of the manuscript.

Funding I.R is a recipient of Junior Research Fellowship from DBT, Government of India. Y.Y is a recipient of Senior Research Fellowship from DST-INSPIRE, Government of India. C.S.D is supported by a grant from the Science and Engineering Board, Government of India, New Delhi, India CRG/2020/001365.

Data Availability Since this is a review article all the information and publications supporting the conclusions are included in the manuscript.

Declarations

Competing interest The authors declare no competing interests.

Ethical Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

References

Abou-Samra M, Selvais CM, Dubuisson N, Brichard SM (2020) Adiponectin and its mimics on skeletal muscle: insulin sensitizers, fat burners, exercise mimickers, muscling pills … or everything together? Int J Mol Sci 21:2620. https://doi.org/10.3390/ijms21072620

Aggarwal N, Sloane BF (2014) Cathepsin B: multiple roles in cancer. Proteomics Clin Appl 8:427–437. https://doi.org/10.1002/prca.201300105

Albrecht E, Norheim F, Thiede B et al (2015) Irisin—a myth rather than an exercise-inducible myokine. Sci Rep 5:8889. https://doi.org/10.1038/srep08889

Aoi W, Naito Y, Takagi T et al (2013) A novel myokine, secreted protein acidic and rich in cysteine (SPARC), suppresses colon tumorigenesis via regular exercise. Gut 62:882–889. https://doi.org/10.1136/gutjnl-2011-300776

Bathina S, Das UN (2015) Brain-derived neurotrophic factor and its clinical implications. Arch Med Sci AMS 11:1164–1178. https://doi.org/10.5114/aoms.2015.56342

Becic T, Studenik C, Hoffmann G (2018) Exercise increases adiponectin and reduces leptin levels in prediabetic and diabetic individuals: systematic review and meta-analysis of randomized controlled trials. Med Sci 6:97. https://doi.org/10.3390/medsci6040097

Beg ZH, Allmann DW, Gibson DM (1973) Modulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity with cAMP and wth protein fractions of rat liver cytosol. Biochem Biophys Res Commun 54:1362–1369. https://doi.org/10.1016/0006-291x(73)91137-6

Berghoff M, Höpfinger A, Rajendran R et al (2021) Evidence of a muscle-brain axis by quantification of the neurotrophic myokine METRNL (Meteorin-like protein) in human cerebrospinal fluid and serum. J Clin Med 10:3271. https://doi.org/10.3390/jcm10153271

Bloemer J, Pinky PD, Govindarajulu M et al (2018) Role of adiponectin in central nervous system disorders. Neural Plast 2018:4593530. https://doi.org/10.1155/2018/4593530

Boon H, Bosselaar M, Praet SFE et al (2008) Intravenous AICAR administration reduces hepatic glucose output and inhibits whole body lipolysis in type 2 diabetic patients. Diabetologia 51:1893–1900. https://doi.org/10.1007/s00125-008-1108-7

Borra MT, Smith BC, Denu JM (2005) Mechanism of human SIRT1 activation by resveratrol. J Biol Chem 280:17187–17195. https://doi.org/10.1074/jbc.M501250200

Boström P, Wu J, Jedrychowski MP et al (2012) A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 481:463–468. https://doi.org/10.1038/nature10777

Bouret SG (2010) Neurodevelopmental actions of leptin. Brain Res 1350:2–9. https://doi.org/10.1016/j.brainres.2010.04.011

Carey AL, Steinberg GR, Macaulay SL et al (2006) Interleukin-6 increases insulin-stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation in vitro via AMP-activated protein kinase. Diabetes 55:2688–2697. https://doi.org/10.2337/db05-1404

Carlson CA, Kim KH (1974) Regulation of hepatic acetyl coenzyme A carboxylase by phosphorylation and dephosphorylation. Arch Biochem Biophys 164:478–489. https://doi.org/10.1016/0003-9861(74)90058-7

Carro E, Nuñez A, Busiguina S, Torres-Aleman I (2000) Circulating insulin-like growth factor I mediates effects of exercise on the brain. J Neurosci 20:2926–2933. https://doi.org/10.1523/JNEUROSCI.20-08-02926.2000

Caspersen CJ, Powell KE, Christenson GM (1985) Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 100:126–131

Catoire M, Kersten S (2015) The search for exercise factors in humans. FASEB J 29:1615–1628. https://doi.org/10.1096/fj.14-263699

Cavallo-Medved D, Moin K, Sloane B (2011) Cathepsin B: basis sequence: mouse. AFCS-Nat Mol

Chen W, Gao R, Xie X et al (2015) A metabolomic study of the PPARδ agonist GW501516 for enhancing running endurance in Kunming mice. Sci Rep 5:9884. https://doi.org/10.1038/srep09884

Chen W-J, Liu Y, Sui Y-B et al (2017a) Positive association between musclin and insulin resistance in obesity: evidence of a human study and an animal experiment. Nutr Metab 14:46. https://doi.org/10.1186/s12986-017-0199-x

Chen W-J, Liu Y, Sui Y-B et al (2017b) Increased circulating levels of musclin in newly diagnosed type 2 diabetic patients. Diab Vasc Dis Res 14:116–121. https://doi.org/10.1177/1479164116675493

Chlenski A, Guerrero LJ, Salwen HR et al (2011) Secreted protein acidic and rich in cysteine is a matrix scavenger chaperone. PLoS ONE 6:e23880. https://doi.org/10.1371/journal.pone.0023880

Colcombe SJ, Erickson KI, Scalf PE et al (2006) Aerobic exercise training increases brain volume in aging humans. J Gerontol A 61:1166–1170. https://doi.org/10.1093/gerona/61.11.1166

Corton JM, Gillespie JG, Hawley SA, Hardie DG (1995) 5-amino-imidazole-4-carboxamide ribonucleoside. A specific method for activating AMP-activated protein kinase in intact cells? Eur J Biochem 229:558–565. https://doi.org/10.1111/j.1432-1033.1995.tb20498.x

De la Herrán-Arita AK, Guerra-Crespo M, Drucker-Colín R (2011) Narcolepsy and orexins: an example of progress in sleep research. Front Neurol 2:26. https://doi.org/10.3389/fneur.2011.00026

Defaux A, Zurich M-G, Braissant O et al (2009) Effects of the PPAR-beta agonist GW501516 in an in vitro model of brain inflammation and antibody-induced demyelination. J Neuroinflamm 6:15. https://doi.org/10.1186/1742-2094-6-15

Domise M, Sauvé F, Didier S et al (2019) Neuronal AMP-activated protein kinase hyper-activation induces synaptic loss by an autophagy-mediated process. Cell Death Dis 10:221. https://doi.org/10.1038/s41419-019-1464-x

Drew BG, Kingwell BA (2008) Acadesine, an adenosine-regulating agent with the potential for widespread indications. Expert Opin Pharmacother 9:2137–2144. https://doi.org/10.1517/14656566.9.12.2137

Dyer AH, Vahdatpour C, Sanfeliu A, Tropea D (2016) The role of Insulin-Like Growth Factor 1 (IGF-1) in brain development, maturation and neuroplasticity. Neuroscience 325:89–99. https://doi.org/10.1016/j.neuroscience.2016.03.056

Ebrahim IO, Howard RS, Kopelman MD et al (2002) The hypocretin/orexin system. J R Soc Med 95:227–230. https://doi.org/10.1258/jrsm.95.5.227

El Hayek L, Khalifeh M, Zibara V et al (2019) Lactate mediates the effects of exercise on learning and memory through SIRT1-dependent activation of hippocampal Brain-Derived Neurotrophic Factor (BDNF). J Neurosci 39:2369–2382. https://doi.org/10.1523/JNEUROSCI.1661-18.2019

Essig DA, Alderson NL, Ferguson MA et al (2000) Delayed effects of exercise on the plasma leptin concentration. Metabolism 49:395–399. https://doi.org/10.1016/s0026-0495(00)90396-2

Fernandez-Marcos PJ, Auwerx J (2011) Regulation of PGC-1α, a nodal regulator of mitochondrial biogenesis. Am J Clin Nutr 93:884S-S890. https://doi.org/10.3945/ajcn.110.001917

Ferrer-Martínez A, Ruiz-Lozano P, Chien KR (2002) Mouse PeP: a novel peroxisomal protein linked to myoblast differentiation and development. Dev Dyn 224:154–167. https://doi.org/10.1002/dvdy.10099

Ferron M, McKee MD, Levine RL et al (2012) Intermittent injections of osteocalcin improve glucose metabolism and prevent type 2 diabetes in mice. Bone 50:568–575. https://doi.org/10.1016/j.bone.2011.04.017

Finck BN, Kelly DP (2006) PGC-1 coactivators: inducible regulators of energy metabolism in health and disease. J Clin Invest 116:615–622. https://doi.org/10.1172/JCI27794

Gälman C, Lundåsen T, Kharitonenkov A et al (2008) The circulating metabolic regulator fgf21 is induced by prolonged fasting and PPARα activation in man. Cell Metab 8:169–174. https://doi.org/10.1016/j.cmet.2008.06.014

Gomes da Silva S, Simões PSR, Mortara RA et al (2013) Exercise-induced hippocampal anti-inflammatory response in aged rats. J Neuroinflamm 10:61. https://doi.org/10.1186/1742-2094-10-61

Guerra B, Guadalupe-Grau A, Fuentes T et al (2010) SIRT1, AMP-activated protein kinase phosphorylation and downstream kinases in response to a single bout of sprint exercise: influence of glucose ingestion. Eur J Appl Physiol 109:731–743. https://doi.org/10.1007/s00421-010-1413-y

Guerrieri D, Moon HY, van Praag H (2017) Exercise in a pill: the latest on exercise-mimetics. Brain Plast 2:153–169. https://doi.org/10.3233/BPL-160043

Gupta RA, Wang D, Katkuri S et al (2004) Activation of nuclear hormone receptor peroxisome proliferator-activated receptor-delta accelerates intestinal adenoma growth. Nat Med 10:245–247. https://doi.org/10.1038/nm993

Gurd BJ, Perry CGR, Heigenhauser GJF et al (2010) High-intensity interval training increases SIRT1 activity in human skeletal muscle. Appl Physiol Nutr Metab 35:350–357. https://doi.org/10.1139/H10-030

Hardie DG (2003) Minireview: the AMP-activated protein kinase cascade: the key sensor of cellular energy status. Endocrinology 144:5179–5183. https://doi.org/10.1210/en.2003-0982

Hardie DG, Corton J, Ching YP et al (1997) Regulation of lipid metabolism by the AMP-activated protein kinase. Biochem Soc Trans 25:1229–1231. https://doi.org/10.1042/bst0251229

Hauschka PV, Lian JB, Cole DE, Gundberg CM (1989) Osteocalcin and matrix Gla protein: vitamin K-dependent proteins in bone. Physiol Rev 69:990–1047. https://doi.org/10.1152/physrev.1989.69.3.990

Hayashino Y, Jackson JL, Hirata T et al (2014) Effects of exercise on C-reactive protein, inflammatory cytokine and adipokine in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. Metabolism 63:431–440. https://doi.org/10.1016/j.metabol.2013.08.018

Heinonen I, Kalliokoski KK, Hannukainen JC et al (2014) Organ-specific physiological responses to acute physical exercise and long-term training in humans. Physiology 29:421–436. https://doi.org/10.1152/physiol.00067.2013

Hoffmann K, Sobol NA, Frederiksen KS et al (2016) Moderate-to-high intensity physical exercise in patients with Alzheimer's disease: a randomized controlled trial. J Alzheimers Dis 50:443–453. https://doi.org/10.3233/JAD-150817

Holloszy JO, Booth FW (1976) Biochemical adaptations to endurance exercise in muscle. Annu Rev Physiol 38:273–291. https://doi.org/10.1146/annurev.ph.38.030176.001421

Hook V, Yoon M, Mosier C et al (2020) Cathepsin B in neurodegeneration of Alzheimer's disease, traumatic brain injury, and related brain disorders. Biochim Biophys Acta Proteins Proteomics 1868:140428. https://doi.org/10.1016/j.bbapap.2020.140428

Hwang Y-C, Jeong I-K, Ahn KJ, Chung HY (2009) The uncarboxylated form of osteocalcin is associated with improved glucose tolerance and enhanced β-cell function in middle-aged male subjects. Diabetes Metab Res Rev 25:768–772. https://doi.org/10.1002/dmrr.1045

Inagaki T, Dutchak P, Zhao G et al (2007) Endocrine regulation of the fasting response by PPARα-mediated induction of fibroblast growth factor 21. Cell Metab 5:415–425. https://doi.org/10.1016/j.cmet.2007.05.003

Iwabu M, Okada-Iwabu M, Tanabe H et al (2021) AdipoR agonist increases insulin sensitivity and exercise endurance in AdipoR-humanized mice. Commun Biol 4:45. https://doi.org/10.1038/s42003-020-01579-9

Izquierdo AG, Crujeiras AB, Casanueva FF, Carreira MC (2019) Leptin, obesity, and leptin resistance: where are we 25 years later? Nutrients 11:2704. https://doi.org/10.3390/nu11112704

Jäger S, Handschin C, St-Pierre J, Spiegelman BM (2007) AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha. Proc Natl Acad Sci USA 104:12017–12022. https://doi.org/10.1073/pnas.0705070104

Jayakumar AR, Apeksha A, Norenberg MD (2017) Role of matricellular proteins in disorders of the central nervous system. Neurochem Res 42:858–875. https://doi.org/10.1007/s11064-016-2088-5

Jedrychowski MP, Wrann CD, Paulo JA et al (2015) Detection and quantitation of circulating human irisin by tandem mass spectrometry. Cell Metab 22:734–740. https://doi.org/10.1016/j.cmet.2015.08.001

Jenkins Y, Sun T-Q, Markovtsov V et al (2013) AMPK activation through mitochondrial regulation results in increased substrate oxidation and improved metabolic parameters in models of diabetes. PLoS ONE 8:e81870. https://doi.org/10.1371/journal.pone.0081870

Jiao F, Gong Z (2020) The beneficial roles of SIRT1 in neuroinflammation-related diseases. Oxid Med Cell Longev 2020:6782872. https://doi.org/10.1155/2020/6782872

Jørgensen JR, Fransson A, Fjord-Larsen L et al (2012) Cometin is a novel neurotrophic factor that promotes neurite outgrowth and neuroblast migration in vitro and supports survival of spiral ganglion neurons in vivo. Exp Neurol 233:172–181. https://doi.org/10.1016/j.expneurol.2011.09.027

Kandola A, Hendrikse J, Lucassen PJ, Yücel M (2016) Aerobic exercise as a tool to improve hippocampal plasticity and function in humans: practical implications for mental health treatment. Front Hum Neurosci 10:373. https://doi.org/10.3389/fnhum.2016.00373

Kelesidis T, Kelesidis I, Chou S, Mantzoros CS (2010) Narrative review: the role of leptin in human physiology: emerging clinical applications. Ann Intern Med 152:93–100. https://doi.org/10.7326/0003-4819-152-2-201001190-00008

Keller C, Steensberg A, Pilegaard H et al (2001) Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: influence of muscle glycogen content. FASEB J 15:2748–2750. https://doi.org/10.1096/fj.01-0507fje

Kharitonenkov A, Shiyanova TL, Koester A et al (2005) FGF-21 as a novel metabolic regulator. J Clin Invest 115:1627. https://doi.org/10.1172/JCI23606

Khrimian L, Obri A, Ramos-Brossier M et al (2017) Gpr158 mediates osteocalcin's regulation of cognition. J Exp Med 214:2859. https://doi.org/10.1084/jem.20171320

Kim D, Nguyen MD, Dobbin MM et al (2007) SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis. EMBO J 26:3169–3179. https://doi.org/10.1038/sj.emboj.7601758

Kim KH, Kim SH, Min Y-K et al (2013) Acute exercise induces FGF21 expression in mice and in healthy humans. PLoS ONE 8:e0063517. https://doi.org/10.1371/journal.pone.0063517

Kobilo T, Yuan C, van Praag H (2011) Endurance factors improve hippocampal neurogenesis and spatial memory in mice. Learn Mem 18:103–107. https://doi.org/10.1101/lm.2001611

Kobilo T, Guerrieri D, Zhang Y et al (2014) AMPK agonist AICAR improves cognition and motor coordination in young and aged mice. Learn Mem 21:119–126. https://doi.org/10.1101/lm.033332.113

Krause MP, Milne KJ, Hawke TJ (2019) Adiponectin-consideration for its role in skeletal muscle health. Int J Mol Sci 20:1528. https://doi.org/10.3390/ijms20071528

Kubota N, Yano W, Kubota T et al (2007) Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. Cell Metab 6:55–68. https://doi.org/10.1016/j.cmet.2007.06.003

Laron Z (2001) Insulin-like growth factor 1 (IGF-1): a growth hormone. Mol Pathol 54:311–316. https://doi.org/10.1136/mp.54.5.311

Lee THY, Formolo DA, Kong T et al (2019) Potential exerkines for physical exercise-elicited pro-cognitive effects: insight from clinical and animal research, 1st edn. Elsevier Inc., Amsterdam

Lee TH, Ahadullah CBR et al (2021) Chronic AdipoRon treatment mimics the effects of physical exercise on restoring hippocampal neuroplasticity in diabetic mice. Mol Neurobiol. https://doi.org/10.1007/s12035-021-02441-7

Li X (2013) SIRT1 and energy metabolism. Acta Biochim Biophys Sin 45:51–60. https://doi.org/10.1093/abbs/gms108

Li D-J, Li Y-H, Yuan H-B et al (2017) The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia. Metabolism 68:31–42. https://doi.org/10.1016/j.metabol.2016.12.003

Liang Q, Zhong L, Zhang J et al (2014) FGF21 maintains glucose homeostasis by mediating the cross talk between liver and brain during prolonged fasting. Diabetes 63:4064–4075. https://doi.org/10.2337/db14-0541

Lin J, Wu H, Tarr PT et al (2002) Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. Nature 418:797–801. https://doi.org/10.1038/nature00904

Lin J-Y, Kuo W-W, Baskaran R et al (2020) Swimming exercise stimulates IGF1/PI3K/Akt and AMPK/SIRT1/PGC1α survival signaling to suppress apoptosis and inflammation in aging hippocampus. Aging 12:6852–6864. https://doi.org/10.18632/aging.103046

Liu PZ, Nusslock R (2018) Exercise-mediated neurogenesis in the hippocampus via BDNF. Front Neurosci 12:52. https://doi.org/10.3389/fnins.2018.00052

Liu Y, Huo X, Pang XF et al (2008) Musclin inhibits insulin activation of Akt/protein kinase B in rat skeletal muscle. J Int Med Res 36:496–504. https://doi.org/10.1177/147323000803600314

Liu Y, Colby JK, Zuo X et al (2018a) The role of PPAR-δ in metabolism, inflammation, and cancer: many characters of a critical transcription factor. Int J Mol Sci 19:3339. https://doi.org/10.3390/ijms19113339

Liu Y, Yau SY, Wang Y, Xu A (2018b) FGF-21 as a potential mediator for the antidepressant effects of physical exercise. Diabetes 67:2249. https://doi.org/10.2337/db18-2249-PUB

Lloyd-Burton SM, York EM, Anwar MA et al (2013) SPARC regulates microgliosis and functional recovery following cortical ischemia. J Neurosci 33:4468–4481. https://doi.org/10.1523/JNEUROSCI.3585-12.2013

Lourenco MV, Frozza RL, de Freitas GB et al (2019) Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat Med 25:165–175. https://doi.org/10.1038/s41591-018-0275-4

Luquet S, Gaudel C, Holst D et al (2005) Roles of PPAR delta in lipid absorption and metabolism: a new target for the treatment of type 2 diabetes. Biochim Biophys Acta 1740:313–317. https://doi.org/10.1016/j.bbadis.2004.11.011

Maass A, Düzel S, Brigadski T et al (2016) Relationships of peripheral IGF-1, VEGF and BDNF levels to exercise-related changes in memory, hippocampal perfusion and volumes in older adults. Neuroimage 131:142–154. https://doi.org/10.1016/j.neuroimage.2015.10.084

MacDonald C, Wojtaszewski JFP, Pedersen BK et al (2003) Interleukin-6 release from human skeletal muscle during exercise: relation to AMPK activity. J Appl Physiol 95:2273–2277. https://doi.org/10.1152/japplphysiol.00242.2003

Mäkelä J, Tselykh TV, Maiorana F et al (2014) Fibroblast growth factor-21 enhances mitochondrial functions and increases the activity of PGC-1α in human dopaminergic neurons via Sirtuin-1. Springerplus 3:1–12. https://doi.org/10.1186/2193-1801-3-2

Mandolesi L, Polverino A, Montuori S et al (2018) Effects of physical exercise on cognitive functioning and wellbeing: biological and

psychological benefits. Front Psychol 9:509. https://doi.org/10.3389/fpsyg.2018.00509
Marangos PJ, Loftus T, Wiesner J et al (1990) Adenosinergic modulation of homocysteine-induced seizures in mice. Epilepsia 31:239–246. https://doi.org/10.1111/j.1528-1157.1990.tb05371.x
Marcinko K, Bujak AL, Lally JSV et al (2015) The AMPK activator R419 improves exercise capacity and skeletal muscle insulin sensitivity in obese mice. Mol Metab 4:643–651. https://doi.org/10.1016/j.molmet.2015.06.002
Marinangeli C, Didier S, Ahmed T et al (2018) AMP-activated protein kinase is essential for the maintenance of energy levels during synaptic activation. iScience 9:1–13. https://doi.org/10.1016/j.isci.2018.10.006
McNeely MJ, Boyko EJ, Weigle DS et al (1999) Association between baseline plasma leptin levels and subsequent development of diabetes in Japanese Americans. Diabetes Care 22:65–70. https://doi.org/10.2337/diacare.22.1.65
Mera P, Laue K, Ferron M et al (2016) Osteocalcin signaling in myofibers is necessary and sufficient for optimum adaptation to exercise. Cell Metab 23:1078. https://doi.org/10.1016/j.cmet.2016.05.004
Messina G, Di Bernardo G, Viggiano A et al (2016) Exercise increases the level of plasma orexin A in humans. J Basic Clin Physiol Pharmacol 27:611–616. https://doi.org/10.1515/jbcpp-2015-0133
Mizokami A, Kawakubo-Yasukochi T, Hirata M (2017) Osteocalcin and its endocrine functions. Biochem Pharmacol 132:1–8. https://doi.org/10.1016/j.bcp.2017.02.001
Moon HY, Becke A, Berron D et al (2016) Running-induced systemic Cathepsin B secretion is associated with memory function. Cell Metab 24:332–340. https://doi.org/10.1016/j.cmet.2016.05.025
Moonishaa TM, Nanda SK, Shamraj M et al (2017) Evaluation of leptin as a marker of insulin resistance in type 2 diabetes mellitus. Int J Appl Basic Med Res 7:176–180. https://doi.org/10.4103/ijabmr.IJABMR_278_16
Moraes DS, Moreira DC, Andrade JMO, Santos SHS (2020) Sirtuins, brain and cognition: a review of resveratrol effects. IBRO Rep 9:46–51. https://doi.org/10.1016/j.ibror.2020.06.004
Narkar VA, Downes M, Yu RT et al (2008) AMPK and PPARdelta agonists are exercise mimetics. Cell 134:405–415. https://doi.org/10.1016/j.cell.2008.06.051
Neufer PD, Bamman MM, Muoio DM et al (2015) Understanding the cellular and molecular mechanisms of physical activity-induced health benefits. Cell Metab 22:4–11. https://doi.org/10.1016/j.cmet.2015.05.011
Ng RC-L, Cheng O-Y, Jian M et al (2016) Chronic adiponectin deficiency leads to Alzheimer's disease-like cognitive impairments and pathologies through AMPK inactivation and cerebral insulin resistance in aged mice. Mol Neurodegener 11:71. https://doi.org/10.1186/s13024-016-0136-x
Ng RC-L, Jian M, Ma OK-F et al (2020) Chronic oral administration of adipoRon reverses cognitive impairments and ameliorates neuropathology in an Alzheimer's disease mouse model. Mol Psychiatry. https://doi.org/10.1038/s41380-020-0701-0
Nicolini C, Michalski B, Toepp SL et al (2020) A single bout of high-intensity interval exercise increases corticospinal excitability, brain-derived neurotrophic factor, and uncarboxylated osteocalcin in sedentary, healthy males. Neuroscience 437:242–255. https://doi.org/10.1016/j.neuroscience.2020.03.042
Nishizawa H, Matsuda M, Yamada Y et al (2004) Musclin, a novel skeletal muscle-derived secretory factor. J Biol Chem 279:19391–19395. https://doi.org/10.1074/jbc.C400066200
Nybo L, Nielsen B, Pedersen BK et al (2002) Interleukin-6 release from the human brain during prolonged exercise. J Physiol 542:991–995. https://doi.org/10.1113/jphysiol.2002.022285
Okada-Iwabu M, Yamauchi T, Iwabu M et al (2013) A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. Nature 503:493–499. https://doi.org/10.1038/nature12656
O'Neill HM (2013) AMPK and exercise: glucose uptake and insulin sensitivity. Diabetes Metab J 37:1–21. https://doi.org/10.4093/dmj.2013.37.1.1
O'Neill HM, Maarbjerg SJ, Crane JD et al (2011) AMP-activated protein kinase (AMPK) beta1beta2 muscle null mice reveal an essential role for AMPK in maintaining mitochondrial content and glucose uptake during exercise. Proc Natl Acad Sci USA 108:16092–16097. https://doi.org/10.1073/pnas.1105062108
Ostrowski K, Rohde T, Zacho M et al (1998) Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. J Physiol 508(Pt 3):949–953. https://doi.org/10.1111/j.1469-7793.1998.949bp.x
Ostrowski K, Rohde T, Asp S et al (1999) Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. J Physiol 515(Pt 1):287–291. https://doi.org/10.1111/j.1469-7793.1999.287ad.x
Ostrowski PP, Barszczyk A, Forstenpointner J et al (2016) Meta-analysis of serum insulin-like growth factor 1 in Alzheimer's disease. PLoS ONE 11:e0155733. https://doi.org/10.1371/journal.pone.0155733
Oury F, Khrimian L, Denny CA et al (2013) Maternal and offspring pools of osteocalcin influence brain development and functions. Cell 155:228–241. https://doi.org/10.1016/j.cell.2013.08.042
Pan W, Banks WA, Fasold MB et al (1998) Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 37:1553–1561. https://doi.org/10.1016/s0028-3908(98)00141-5
Paraíso AF, Mendes KL, Santos SHS (2013) Brain activation of SIRT1: role in neuropathology. Mol Neurobiol 48:681–689. https://doi.org/10.1007/s12035-013-8459-x
Pedersen BK, Febbraio MA (2012) Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol 8:457–465. https://doi.org/10.1038/nrendo.2012.49
Pedersen BK, Saltin B (2006) Evidence for prescribing exercise as therapy in chronic disease. Scand J Med Sci Sports 16(Suppl 1):3–63. https://doi.org/10.1111/j.1600-0838.2006.00520.x
Pedersen BK, Steensberg A, Schjerling P (2001) Muscle-derived interleukin-6: possible biological effects. J Physiol 536:329–337. https://doi.org/10.1111/j.1469-7793.2001.0329c.xd
Pedersen BK, Steensberg A, Fischer C et al (2003) Searching for the exercise factor: is IL-6 a candidate? J Muscle Res Cell Motil 24:113–119. https://doi.org/10.1023/a:1026070911202
Pérez-González R, Alvira-Botero MX, Robayo O et al (2014) Leptin gene therapy attenuates neuronal damages evoked by amyloid-β and rescues memory deficits in APP/PS1 mice. Gene Ther 21:298–308. https://doi.org/10.1038/gt.2013.85
Phillips C, Baktir MA, Srivatsan M, Salehi A (2014) Neuroprotective effects of physical activity on the brain: a closer look at trophic factor signaling. Front Cell Neurosci 8:170. https://doi.org/10.3389/fncel.2014.00170
Price PA, Otsuka AA, Poser JW et al (1976) Characterization of a gamma-carboxyglutamic acid-containing protein from bone. Proc Natl Acad Sci USA 73:1447. https://doi.org/10.1073/pnas.73.5.1447
Racette SB, Coppack SW, Landt M, Klein S (1997) Leptin production during moderate-intensity aerobic exercise. J Clin Endocrinol Metab 82:2275–2277. https://doi.org/10.1210/jcem.82.7.4037
Rao RR, Long JZ, White JP et al (2014) Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. Cell 157:1279–1291. https://doi.org/10.1016/j.cell.2014.03.065
Raschke S, Elsen M, Gassenhuber H et al (2013) Evidence against a beneficial effect of irisin in humans. PLoS ONE 8:e73680. https://doi.org/10.1371/journal.pone.0073680
Rasmussen P, Vedel J-C, Olesen J et al (2011) In humans IL-6 is released from the brain during and after exercise and paralleled

by enhanced IL-6 mRNA expression in the hippocampus of mice. Acta Physiol 201:475–482. https://doi.org/10.1111/j.1748-1716.2010.02223.x

Riedl I, Yoshioka M, Nishida Y et al (2010) Regulation of skeletal muscle transcriptome in elderly men after 6 weeks of endurance training at lactate threshold intensity. Exp Gerontol 45:896–903. https://doi.org/10.1016/j.exger.2010.08.014

Ronnett GV, Ramamurthy S, Kleman AM et al (2009) AMPK in the brain: its roles in energy balance and neuroprotection. J Neurochem 109(Suppl):17–23. https://doi.org/10.1111/j.1471-4159.2009.05916.x

Rosso P, Fioramonti M, Fracassi A et al (2016) AMPK in the central nervous system: physiological roles and pathological implications. Res Rep Biol 7:1–13

Safdar A, Saleem A, Tarnopolsky MA (2016) The potential of endurance exercise-derived exosomes to treat metabolic diseases. Nat Rev Endocrinol 12:504–517. https://doi.org/10.1038/nrendo.2016.76

Sakurai T, Amemiya A, Ishii M et al (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 92:573–585. https://doi.org/10.1016/s0092-8674(00)80949-6

Salmon WD, Daughaday WH (1957) A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage in vitro. J Lab Clin Med 49:825–836

Sa-nguanmoo P, Tanajak P, Kerdphoo S et al (2016) FGF21 improves cognition by restored synaptic plasticity, dendritic spine density, brain mitochondrial function and cell apoptosis in obese-insulin resistant male rats. Horm Behav 85:86–95. https://doi.org/10.1016/j.yhbeh.2016.08.006

Schiaffino S, Reggiani C (2011) Fiber types in mammalian skeletal muscles. Physiol Rev 91:1447–1531. https://doi.org/10.1152/physrev.00031.2010

Schnegg CI, Robbins ME (2011) Neuroprotective mechanisms of PPARδ: modulation of oxidative stress and inflammatory processes. PPAR Res 2011:373560. https://doi.org/10.1155/2011/373560

Schwarz AJ, Brasel JA, Hintz RL et al (1996) 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 81:3492–3497. https://doi.org/10.1210/jcem.81.10.8855791

Shimomura M, Horii N, Fujie S et al (2021) Decreased muscle-derived musclin by chronic resistance exercise is associated with improved insulin resistance in rats with type 2 diabetes. Physiol Rep 9:e14823. https://doi.org/10.14814/phy2.14823

Simpson KA, Singh MAF (2008) Effects of exercise on adiponectin: a systematic review. Obesity 16:241–256. https://doi.org/10.1038/oby.2007.53

Sleiman SF, Chao MV (2015) Downstream consequences of exercise through the action of BDNF. Brain Plast 1:143–148. https://doi.org/10.3233/BPL-150017

So B, Kim H-J, Kim J, Song W (2014) Exercise-induced myokines in health and metabolic diseases. Integr Med Res 3:172–179. https://doi.org/10.1016/j.imr.2014.09.007

Song H, Guan Y, Zhang L et al (2010) SPARC interacts with AMPK and regulates GLUT4 expression. Biochem Biophys Res Commun 396:961–966. https://doi.org/10.1016/j.bbrc.2010.05.033

Songsorn P, Ruffino J, Vollaard NBJ (2017) No effect of acute and chronic supramaximal exercise on circulating levels of the myokine SPARC. Eur J Sport Sci 17:447–452. https://doi.org/10.1080/17461391.2016.1266392

St-Pierre J, Drori S, Uldry M et al (2006) Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. Cell 127:397–408. https://doi.org/10.1016/j.cell.2006.09.024

Sun AY, Wang Q, Simonyi A, Sun GY (2010) Resveratrol as a therapeutic agent for neurodegenerative diseases. Mol Neurobiol 41:375–383. https://doi.org/10.1007/s12035-010-8111-y

Sznaidman ML, Haffner CD, Maloney PR et al (2003) Novel selective small molecule agonists for peroxisome proliferator-activated receptor delta (PPARdelta)—synthesis and biological activity. Bioorg Med Chem Lett 13:1517–1521. https://doi.org/10.1016/s0960-894x(03)00207-5

Talbot J, Maves L (2016) Skeletal muscle fiber type: using insights from muscle developmental biology to dissect targets for susceptibility and resistance to muscle disease. Wiley Interdiscip Rev Dev Biol 5:518–534. https://doi.org/10.1002/wdev.230

Tanaka T, Narazaki M, Kishimoto T (2014) IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol 6:a016295. https://doi.org/10.1101/cshperspect.a016295

Thomas G, Moffatt P, Salois P et al (2003) Osteocrin, a novel bone-specific secreted protein that modulates the osteoblast phenotype. J Biol Chem 278:50563–50571. https://doi.org/10.1074/jbc.M307310200

Trefts E, Williams AS, Wasserman DH (2015) Exercise and the regulation of hepatic metabolism. Prog Mol Biol Transl Sci 135:203–225. https://doi.org/10.1016/bs.pmbts.2015.07.010

Trejo JL, Carro E, Torres-Aleman I (2001) Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J Neurosci 21:1628–1634. https://doi.org/10.1523/JNEUROSCI.21-05-01628.2001

Triantafyllou GA, Paschou SA, Mantzoros CS (2016) Leptin and hormones: energy homeostasis. Endocrinol Metab Clin N Am 45:633–645. https://doi.org/10.1016/j.ecl.2016.04.012

van Praag H (2009) Exercise and the brain: something to chew on. Trends Neurosci 32:283–290. https://doi.org/10.1016/j.tins.2008.12.007

van Praag H, Christie BR, Sejnowski TJ, Gage FH (1999) Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci USA 96:13427–13431. https://doi.org/10.1073/pnas.96.23.13427

Vaynman S, Ying Z, Gomez-Pinilla F (2004) Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur J Neurosci 20:2580–2590. https://doi.org/10.1111/j.1460-9568.2004.03720.x

Vidal P, Stanford KI (2020) Exercise-induced adaptations to adipose tissue thermogenesis. Front Endocrinol 11:270. https://doi.org/10.3389/fendo.2020.00270

Wang K, Li H, Wang H et al (2018) Irisin exerts neuroprotective effects on cultured neurons by regulating astrocytes. Mediators Inflamm 2018:9070341. https://doi.org/10.1155/2018/9070341

Willows R, Navaratnam N, Lima A et al (2017) Effect of different γ-subunit isoforms on the regulation of AMPK. Biochem J 474:1741–1754. https://doi.org/10.1042/BCJ20170046

Wojtaszewski JF, Nielsen P, Hansen BF et al (2000) Isoform-specific and exercise intensity-dependent activation of 5'-AMP-activated protein kinase in human skeletal muscle. J Physiol 528(Pt 1):221–226. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00221.x

Won J-S, Im Y-B, Kim J et al (2010) Involvement of AMP-activated-protein-kinase (AMPK) in neuronal amyloidogenesis. Biochem Biophys Res Commun 399:487–491. https://doi.org/10.1016/j.bbrc.2010.07.081

World Anti-Doping Agency (2009) The World Anti-Doping CodeThe 2009 Prohibited List. http://www.wada-ama.org/rtecontent/document/2010_P

Wrann CD, White JP, Salogiannnis J et al (2013) Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell Metab 18:649–659. https://doi.org/10.1016/j.cmet.2013.09.008

Wright DC, Han D-H, Garcia-Roves PM et al (2007) Exercise-induced mitochondrial biogenesis begins before the increase in muscle PGC-1alpha expression. J Biol Chem 282:194–199. https://doi.org/10.1074/jbc.M606116200

Wrigley S, Arafa D, Tropea D (2017) Insulin-like growth factor 1: at the crossroads of brain development and aging. Front Cell Neurosci 11:14. https://doi.org/10.3389/fncel.2017.00014

Yakar S, Adamo ML (2012) Insulin-like growth factor 1 physiology: lessons from mouse models. Endocrinol Metab Clin N Am 41:231–247. https://doi.org/10.1016/j.ecl.2012.04.008

Yamauchi T, Nio Y, Maki T et al (2007) Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 13:332–339. https://doi.org/10.1038/nm1557

Yang Y, Hu W, Jiang S et al (2015) The emerging role of adiponectin in cerebrovascular and neurodegenerative diseases. Biochim Biophys Acta 1852:1887–1894. https://doi.org/10.1016/j.bbadis.2015.06.019

Yau SY, Li A, Hoo RLC et al (2014) Physical exercise-induced hippocampal neurogenesis and antidepressant effects are mediated by the adipocyte hormone adiponectin. Proc Natl Acad Sci USA 111:15810–15815. https://doi.org/10.1073/pnas.1415219111

Ye S-M, Johnson RW (1999) Increased interleukin-6 expression by microglia from brain of aged mice. J Neuroimmunol 93:139–148. https://doi.org/10.1016/S0165-5728(98)00217-3

Yook JS, Rakwal R, Shibato J et al (2019) Leptin in hippocampus mediates benefits of mild exercise by an antioxidant on neurogenesis and memory. Proc Natl Acad Sci USA 116:10988–10993. https://doi.org/10.1073/pnas.1815197116

Yu J, Zheng J, Liu XF et al (2016) Exercise improved lipid metabolism and insulin sensitivity in rats fed a high-fat diet by regulating glucose transporter 4 (GLUT4) and musclin expression. Braz J Med Biol Res 49:e5129. https://doi.org/10.1590/1414-431X20165129

Zhang D, Wang X, Lu X-Y (2016) Adiponectin exerts neurotrophic effects on dendritic arborization, spinogenesis, and neurogenesis of the dentate gyrus of male mice. Endocrinology 157:2853–2869. https://doi.org/10.1210/en.2015-2078

Zheng S-L, Li Z-Y, Song J et al (2016) Metrnl: a secreted protein with new emerging functions. Acta Pharmacol Sin 37:571–579. https://doi.org/10.1038/aps.2016.9