Physical activity and muscle–brain crosstalk

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Abstract | Neurological and mental illnesses account for a considerable proportion of the global burden of disease. Exercise has many beneficial effects on brain health, contributing to decreased risks of dementia, depression and stress, and it has a role in restoring and maintaining cognitive function and metabolic control. The fact that exercise is sensed by the brain suggests that muscle-induced peripheral factors enable direct crosstalk between muscle and brain function. Muscle secretes myokines that contribute to the regulation of hippocampal function. Evidence is accumulating that the myokine cathepsin B passes through the blood–brain barrier to enhance brain-derived neurotrophic factor production and hence neurogenesis, memory and learning. Exercise increases neuronal gene expression of *FNDC5* (which encodes the PGC1α-dependent myokine FNDC5), which can likewise contribute to increased brain-derived neurotrophic factor levels. Serum levels of the prototype myokine, IL-6, increase with exercise and might contribute to the suppression of central mechanisms of feeding. Exercise also increases the PGC1α-dependent muscular expression of kynurenine aminotransferase enzymes, which induces a beneficial shift in the balance between the neurotoxic kynurenine and the neuroprotective kynurenic acid, thereby reducing depression-like symptoms. Myokine signalling, other muscular factors and exercise-induced hepatokines and adipokines are implicated in mediating the exercise-induced beneficial impact on neurogenesis, cognitive function, appetite and metabolism, thus supporting the existence of a muscle–brain endocrine loop.

Physical activity
Any bodily movement produced by skeletal muscles that requires energy expenditure.

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Over the centuries, several philosophers have expressed ideas that are compatible with the existence of a muscle–brain endocrine loop: Friedrich Nietzsche said that "All truly great thoughts are conceived by walking"[1]; Søren Kierkegaard said "I have walked myself into my best thoughts, and I know of no thought so burdensome that one cannot walk away from it"[2]; and Jean-Jacques Rousseau said that "my mind works only with my legs"[3].

Humans developed from tree-dwelling apes to *Homo sapiens* when they started to walk on two legs and became bipedal. Early hominins underwent massive development of skeletal muscle and major changes occurred in their brains in parallel. Noakes and Spedding[4] suggest that these changes rendered *H. sapiens* dependent on physical exercise in order to maintain a healthy brain. In other words, exercise does not just help to develop muscle and physical performance but is essential to activating and increasing the number of neuronal connections. Our Palaeolithic ancestors lived in a world where they had to exercise to chase down meat. Food intake fluctuated depending on the success of a hunt and physical activity alternated between walking and gathering foods and periods of higher-intensity activities such as hunting, running from a predator or fighting for survival. Today's humans often live in an environment where exercise is not an integral part of their daily life and walking has become 'a lost art'. Our life has become a mismatch with our evolutionary past, and our physically inactive lifestyle puts us at risk of developing obesity, diabetes, depression and dementia[5].

Both the historical and evolutionary perspectives suggest a strong link between muscles and the brain. From a scientific perspective, evidence is also now accumulating that moderate-to-vigorous physical activity has many beneficial effects on brain health and cognitive function[6,7]. Together with the well-described robust inverse association between exercise capacity and all-cause mortality[8], physical activity decreases the risk of diseases such as dementia[9–11] and might also be useful in the treatment of this disease[12]. Exercise can lower the rate of cognitive decline in patients with neurodegenerative disorders and in healthy people of all ages[13] and seems to have a positive influence on stress, anxiety and depression[12].

Physical exercise has also been shown to have positive effects on learning, memory and attention[14]; processing speed and executive functions[15]; reaction time and language learning[16]; motor skills and learning[17]; verbal and visuospatial cognitive test results[18]; and academic

REVIEWS

Key points

• Exercise can indirectly be sensed by the brain via adipose tissue (adiponectin) or the liver (fibroblast growth factor 21 and insulin-like growth factor 1).

• Myokines mediate muscle–organ crosstalk to the liver, gut, pancreas, adipose tissue, bone, vascular bed, skin and brain.

• Cathepsin B is an exercise-induced myokine required for exercise-induced improvement in memory and adult neurogenesis.

• Exercise enhances neuronal gene expression of *FNDC5*, the protein product of which might stimulate brain-derived neurotrophic factor in the hippocampus.

• Serum levels of the myokine IL-6 increase with exercise, and this myokine might regulate central mechanisms for food intake.

• Exercise increases muscular expression of kynurenine aminotransferases, which convert blood levels of neurotoxic kynurenine to the neuroprotective kynurenic acid, thereby reducing depression-like symptoms.

Moderate-to-vigorous physical activity
Any activity with an energy expenditure of ≥3 metabolic equivalents (for example, brisk walking); the WHO minimum recommendations are 150 min of moderate-to-vigorous physical activity each week (or 20 min or 10,000 steps on most days of the week) for adults and 60 min of active playing on most days of the week for children and adolescents.

Aerobic exercise
Exercise involving dynamic movements and large muscle groups that predominantly rely on aerobic metabolism for fuelling muscle contractions; examples include jogging, running, swimming and rowing.

Resistance training
Movement performed against a specific external force that is regularly increased during training; examples include weightlifting and exercises using resistance machines.

Exercise training
A subset of physical activity that is planned, structured and repetitive and has a final or intermediate objective of improving or maintaining physical fitness. The terms 'exercise' and 'exercise training' are used interchangeably to refer to the cardiovascular adaptations produced by this specific type of physical activity; a single bout of exercise is referred to as 'acute exercise'.

Myokines
Cytokines or peptides produced by skeletal muscle cells and subsequently released into the circulation, where they exert autocrine, paracrine or endocrine effects in other cells, tissues or organs.

achievement in children and intelligence in adolescents[18]. In addition, exercise improves several basic physiological functions such as sleep[19], appetite[20] and mood[21]. The beneficial effects of muscle activity on cognition have mostly been demonstrated with aerobic exercise; less is known regarding the effects of resistance training. One study reported that resistance training for 8 weeks did not influence cognitive function[22], whereas a meta-analysis reported that resistance exercise training was associated with a significant reduction in depressive symptoms[23].

A review of the literature concluded that a large network of brain areas, equal to 82% of the total grey matter volume, was modifiable by physical activity[24]. The hippocampus, which is involved in memory and learning, is the brain region most affected by exercise. Exercise studies in mice have documented that exercise leads to an increase in the volume of the hippocampus as well as an increase in blood flow to this part of the brain[25]. In particular, exercise influences neurogenesis in the dentate gyrus in the hippocampus[6,7]. In various mouse models, exercise has been shown to increase synapse plasticity as well as to induce morphological changes in dendrites[6,7].

A major question is which peripheral factor or factors enable direct crosstalk between working muscle and brain function, including hippocampal-dependent mood, learning, memory and appetite.

Myokines and other exercise mediators

Robust findings regarding exercise and brain health suggest the existence of a muscle–brain endocrine loop, but it is not entirely clear which peripheral mechanisms elicit these positive effects of exercise. However, the past almost two decades have taught us that skeletal muscle is a secretory organ[26].

Muscle cells are highly metabolically active, and during exercise skeletal muscles communicate with other organs by producing and releasing so-called myokines. The skeletal muscle secretome in humans consists of hundreds of myokines, which are secreted from muscle cells during proliferation and differentiation or in response to muscle contractions. Myokines can exert autocrine, paracrine or endocrine effects[27–33]. Some myokines are involved in energy supply during acute exercise, and repetitive acute bouts are probably involved in mediating adaptation to training in various organs. At rest, myokines are involved in the regulation of muscle proliferation, differentiation

and regeneration[34,35]. Myokines mediate signalling within the muscle and muscle–organ crosstalk to the liver, gut, pancreas, adipose tissue, bone, vascular bed and skin[30,36]. In addition, myokines with an anticancer effect have been identified[37,38].

The skeletal muscle secretome might mediate the effects of exercise on metabolic and cardiovascular health[36] and might be involved in the defence against malignancy[37]. Of particular interest to the present Review is the idea that the muscle secretome might be involved in mediating the beneficial effects of exercise on brain health.

Thus, the exercise-induced beneficial impact on neurogenesis, cognitive function, appetite and metabolism might, at least in part, be mediated by myokine signalling. Other possible mediators of the effects of exercise on the brain include exercise-induced alteration in metabolites[39], non-coding RNAs[40] and hormonal responses as well as changes in muscle enzymes that influence the activity of circulating compounds such as kynurenine[41].

Some investigators have proposed that the sum total of all factors released in response to endurance exercise (including peptides, nucleic acids and metabolites) should be termed 'exerkines'[42]. Many such exerkines are released within extracellular vesicles known as exosomes, which represent subcategories of extracellular vesicles that are released into the circulation with exercise[43]. Exosomes can contain peptides, nucleic acids, microRNA, mRNA and mitochondrial DNA. An acute bout of endurance exercise increases circulating exosomes and might mediate inter-tissue signalling[44].

Together with circulating myokines and other molecules produced and released by skeletal muscles in response to exercise, direct feedback from skeletal muscle through the peripheral nervous system and central nervous system (CNS) to the brain is also involved in muscle-to-brain communication.

The role of BDNF

The neurotrophin known as brain-derived neurotrophic factor (BDNF) seems to be a very important mediator of the effects of exercise on the brain, especially cognition[45]. When rats have access to voluntary exercise, increased BDNF levels are found in the hippocampus compared with mice without such access[46,47]. Wheel running for 6 h was shown to increase *Bdnf* mRNA expression[48] and free access to activity wheels for 1–8 weeks was shown to increase hippocampal *Bdnf* mRNA expression and BDNF protein levels[49–51]. In addition to influencing BDNF concentrations directly, exercise has also been shown to modulate BDNF-linked pathways[52].

Studies have demonstrated that BDNF is mechanistically involved in mediating the exercise-dependent increase in proliferation of hippocampal dentate gyrus cells and that BDNF is required for exercise-induced enhancement of cognitive functions such as memory and learning[53,54].

The release of BDNF from the human brain has been shown to increase with an acute bout of exercise[55,56], suggesting that exercise also mediates central BDNF production in humans. BDNF promotes the growth

and proliferation of cells in the hippocampus, and aerobic exercise training for 3 months has been shown to increase hippocampal volume in healthy individuals and in patients with schizophrenia by 12% and 16%, respectively[57]. BDNF is involved in neuronal differentiation, plasticity, cell survival, hippocampal function and learning[58]. Multiple studies support the idea that BDNF has a dominant role in mediating the effects of physical activity on cognitive changes[59]. However, the underlying mechanisms leading to increased BDNF levels during exercise-induced cardiovascular and muscular activity are unclear.

We showed that BDNF is a contraction-inducible protein in human skeletal muscle that is able to enhance lipid oxidation in skeletal muscle via AMP-activated protein kinase (AMPK) activation[60]. However, we found little indication that muscle-derived BDNF was released from muscle into the bloodstream and thus no evidence that BDNF mediates a direct muscle–brain interaction[60]. The question then remained as to whether exercise provokes muscle-derived circulating factors that can pass through the blood–brain barrier and stimulate BDNF production in the brain.

Cathepsin B and BDNF regulation

In 2016, Moon et al.[61] identified a signalling pathway linking exercising muscle with hippocampal function. They found that in mice, exercise induces elevated systemic levels of a novel myokine, cathepsin B, which promotes hippocampal expression of BDNF and stimulates neurogenesis (FIG. 1a). First, L6 myotubes were treated with the AMPK agonist 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) in an attempt to model the effects of exercise in vitro. Subsequent screening of the culture media for proteins using proteomic and biochemical analyses led to the identification of elevated levels of cathepsin B in conditioned medium derived from skeletal muscle cell cultures treated with the AMPK agonist AICAR[61]. The researchers then demonstrated that running resulted in increased muscular expression of the *Ctsb* gene (which encodes cathepsin B) in mice, which was accompanied by an increase in cathepsin B protein levels in plasma. The findings in rodents were supported by the finding of increased plasma levels of cathepsin B in rhesus macaques as well as in humans following 4 months of treadmill training[61]. The authors also provided evidence that cathepsin B was able to cross the blood–brain barrier in mice[61]. Although cathepsin B application did not affect hippocampal cell proliferation, it led to increased expression of *Bdnf* mRNA and increased BDNF protein levels as well as increases in levels of doublecortin, a protein that has neuroprotective effects as it enhances neuronal migration[61].

To examine whether cathepsin B is directly involved in mediating exercise-induced hippocampal neurogenesis and improvement in hippocampal function, Moon et al.[61] performed studies in *Ctsb*-knockout mice. They found that in wild-type control mice, exercise induced the previously found enhancement of neurogenesis and improvement of spatial memory. However, mice lacking *Ctsb* did not show these effects with voluntary

exercise but demonstrated depression-like symptoms when they were forced to swim[61]. This latter finding is in accordance with the well-known role of hippocampal BDNF in protecting against anxiety and depression[62].

The elegant study by Moon et al.[61] shows that the myokine cathepsin B might be causally involved in mediating the exercise-induced improvement in hippocampal neurogenesis, memory and learning. However, it remains to be shown to what extent this myokine is a determining factor in exercise-induced enhanced cognitive function in humans[61,63].

PGC1α–FNDC5–BDNF pathway

FNDC5 is a membrane protein that is cleaved and secreted into the circulation as the myokine irisin, which is known for its browning effects in white adipose tissue and might also be critical in mediating the effects of physical activity on BDNF protein expression in the brain (FIG. 1b). Exercise induces upregulation of PGC1α in skeletal muscle, and PGC1α has a central role in mediating many of the metabolic effects of exercise locally within the muscle[64]. PGC1α is a transcriptional co-activator of mitochondrial biogenesis and oxidative metabolism in muscle and brown adipose tissue[65]. With exercise, PGC1α expression in muscle increases and stimulates an increase in the expression of FNDC5 and is involved in driving a shift of white adipose tissue into a brown-fat-like phenotype[66].

The group that showed that exercise-induced increased PGC1α expression leads to increased FNDC5 expression[66] later showed that endurance exercise leads to an elevation in *Fndc5* gene expression in the hippocampus of mice[58]. *Pgc1a*^{−/−} mice show reduced *Fndc5* expression in the brain. FNDC5 overexpression in primary cortical neurons stimulates an increase in BDNF expression. By contrast, RNA interference-mediated knockdown of FNDC5 leads to a reduction in *Bdnf* gene expression[66]. Interestingly, increasing systemic levels of irisin by delivery of FNDC5 to the liver via adenoviral vectors led to increased expression of hippocampal *Bdnf*[66].

The critical question is how exercise is sensed by the brain and how muscle can activate the neurological PGC1α–FNDC5–BDNF pathway[67]. The finding that expression of genes with potential neuroprotective functions, such as *BDNF*, is increased in the brain when systemic concentrations of FNDC5 are elevated suggests that the muscle-secreted form of FNDC5 might cross the blood–brain barrier to exert its influence in the CNS — for example, by inducing BDNF expression in the hippocampus — thereby playing a role in neurogenesis and reward-related learning and motivation[58].

Whether exercise leads to increased levels of irisin in the bloodstream is controversial[68]. Some researchers reported that neither acute nor chronic endurance or resistance exercise led to increased FNDC5 expression or circulating concentrations of irisin in healthy men[69]. Another study showed that a bout of acute exercise had no effect on muscle FNDC5 expression, whereas 20 days of high-intensity interval training led to acute increases in muscle expression of FNDC5 in healthy men[70]. Concerns have been expressed regarding the lack of specificity of anti-irisin antibodies[68] used in the above

Browning
Browning can be defined as any substantial increase in the expression of uncoupling protein 1 (UCP1) at the mRNA level occurring in what is normally considered as a white adipose tissue depot. The resulting brown adipocytes that express UCP1 and appear in white adipose tissue are referred to as beige, brite, convertible, ectopic, inducible or recruitable.
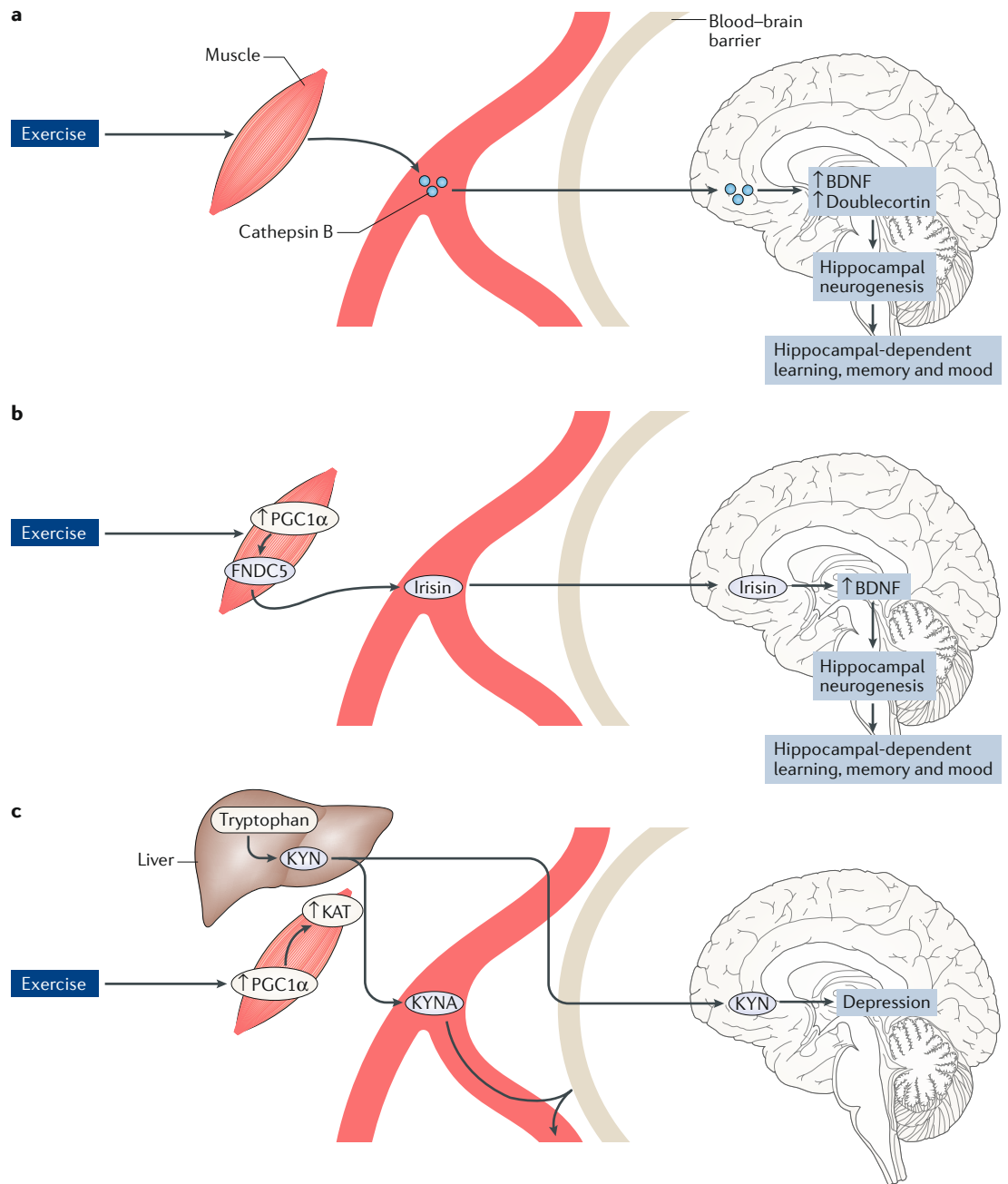
Fig. 1 | **Ways in which exercise might beneficially affect neurogenesis, learning, memory, mood and depression-like symptoms. a** | The myokine cathepsin B is released by skeletal muscle during exercise and might influence neurogenesis, learning, memory and mood. AMP-activated protein kinase (AMPK) activation elicits cathepsin B secretion in skeletal muscle cells. Running increases cathepsin B levels in mouse gastrocnemius muscle, and exercise leads to an increase in levels of the myokine cathepsin B in the plasma of mice, rhesus macaques and humans. In vivo studies provided evidence that, in mice, peripheral cathepsin B crosses the blood–brain barrier. In vitro studies on hippocampal progenitor cells showed that cathepsin B increased both mRNA and protein levels of brain-derived neurotrophic factor (BDNF) as well as doublecortin. These factors are known to be important for neuronal migration and neurogenesis and thereby affect learning, memory and mood. **b** | FNDC5, a membrane protein that is cleaved and secreted into the circulation as the myokine irisin during exercise, might influence BDNF and influence neurogenesis, learning, memory and mood. Exercise in mice and humans induces an upregulation of PGC1α in skeletal muscle. In mice, PGC1α expression in muscle stimulates an increase in the expression of FNDC5. Exercise also leads to a PGC1α-dependent elevation of FNDC5 in the hippocampus of mice. Peripheral delivery of FNDC5 to the liver via adenoviral vectors, resulting in elevated blood levels of irisin, induces expression of BDNF in the hippocampus, suggesting that irisin passes through the blood–brain barrier and induces BDNF expression in the brain, which will lead to enhanced learning, memory and mood. **c** | High levels of the neurotoxic kynurenine (KYN) are associated with depression. Exercise enhances the PGC1α-dependent muscular expression of the enzyme kynurenine aminotransferase (KAT), which converts neurotoxic KYN into neuroprotective kynurenic acid (KYNA), thereby reducing depression-like symptoms. In contrast to KYN, KYNA is not able to pass through the blood–brain barrier. The imbalance between the neuroprotective KYNA and the neurotoxic KYN metabolites has been proposed to be critical for the development of depression.

studies, but a mass spectrometry state-of-the-art method showed that human irisin exists, circulates and is regulated by exercise[71].

Some researchers found that exercise provokes an increase in irisin levels in human plasma[72], and confirmation of these findings would support the possible existence of a muscle–brain endocrine loop. An exercise-induced release of muscle-derived irisin into the blood might provide a link between PGC1α, FNDC5 and hippocampal expression of BDNF. New findings in 2019 suggest a role for FNDC5 and irisin in regulating synaptic function and memory in mouse models of Alzheimer disease[73].

β-Hydroxybutyrate and BDNF

Exercise might also induce increases in BDNF levels by altering the epigenetic markers of the *BDNF* promoters[74]. Physical activity induces multiple metabolic changes, and it is conceivable that an exercise-induced endogenous molecule can serve as a regulator of *BDNF* transcription.

Ketone bodies are markedly increased in the circulation and brain after fasting, dieting and intense exercise[75]. Under conditions of reduced glucose levels, ketone bodies, in the form of β-hydroxybutyrate and acetoacetate, serve as an energy source[75]. Prolonged exercise has been shown to stimulate an increase in β-hydroxybutyrate levels in the blood[75]. β-Hydroxybutyrate crosses the blood–brain barrier, accumulates in the hippocampus and increases the expression of BDNF[76]. Direct application of β-hydroxybutyrate into the brain of rats has been shown to increase the expression of BDNF[76]. Previous work with β-hydroxybutyrate showed that it is an effective neuroprotective agent in experimental models of Huntington disease[77] and Parkinson disease[78], protecting striatal and dopaminergic neurons, respectively.

Taken together, the available evidence suggests that β-hydroxybutyrate provides a link between aerobic exercise and *BDNF* gene expression in the brain.

The sympathetic nervous system and BDNF

Physical exercise is accompanied by the activation of the sympathetic nervous system, which can have multiple effects on peripheral organs, as well as on the brain[79]. β$_2$-Adrenergic stimulation in rats has been shown to reduce expression of inflammatory cytokines and to increase expression of BDNF in the hippocampus[80]. In addition, the noradrenaline reuptake inhibitor, venlafaxine, has been shown to increase expression of BDNF protein in the frontal cortex, which might represent the mechanism whereby venlafaxine improves depression[81].

IL-6 and appetite regulation

Epidemiological studies have shown that IL-6 is implicated in the chronic inflammation that accompanies conditions such as obesity and type 2 diabetes mellitus[30]. The origin of elevated plasma IL-6 levels in these conditions seems to be immune cells located in adipose tissue[82]. Increased systemic IL-6 levels in humans are associated with obesity[83] and the metabolic syndrome[84]. In support of this idea, IL-6 infusion into mice has been shown to impair insulin sensitivity[85], and neutralization

of IL-6 has been shown to lead to an improvement in insulin action in inflammatory murine models[86].

In contrast to the above findings, a large number of studies have identified IL-6 to have a beneficial role in metabolism regulation. IL-6-deficient mice are characterized by whole-body insulin resistance and late-onset obesity[87,88]. Studies in rodents have shown that IL-6 stimulates expansion of pancreatic α-cells in the obese state[89] and promotes enhancement of glucagon-like peptide 1 (GLP1) production and consequently increased insulin secretion[89]. Moreover, IL-6 signalling in murine macrophages and hepatocytes induces anti-inflammatory effects, thereby improving glucose homeostasis[90,91].

Studies in humans clearly show that physiological concentrations of IL-6 have multiple metabolic effects. When IL-6 is infused into healthy humans, it enhances insulin-stimulated glucose uptake[92], stimulates lipolysis and fat oxidation[93] and delays gastric emptying with beneficial effects on postprandial glucose control[94]. Moreover, acute infusion of IL-6 to humans inhibited endotoxin-induced elevation in circulating TNF levels, suggesting an anti-inflammatory effect of IL-6 (REF.[95]). IL-6 infusion into humans also stimulates the production of the anti-inflammatory molecules IL-1 receptor antagonist and IL-10 (REF.[96]).

Interestingly, although IL-6 seems to be released from fat tissue in the obese state, during a bout of exercise IL-6 is released by myocytes, leading to an exponential increase in plasma levels of IL-6; levels are up to 100-fold higher than basal levels immediately after exercise and then return to basal levels within a couple of hours after exercise. Muscle-derived IL-6 is associated with improved insulin sensitivity and fat oxidation[30,97]. The exercise-induced increase in IL-6 is an acute effect mediated by working muscles. The beneficial effects of regular exercise might result from the accumulation of repeated acute bouts of exercise-induced alterations in homeostasis. The signalling pathways for IL-6 differ between muscle cells and macrophages. In macrophages, IL-6 transcription requires activation of the nuclear factor-κB (NF-κB) signalling pathway. In myocytes, IL-6 is regulated by the Ca^{2+}–NFAT (nuclear factor of activated T cells) and glycogen–p38 MAPK (mitogen-activated protein kinase) pathways. Therefore, although IL-6 creates a pro-inflammatory response in macrophages, the contraction-induced activation of IL-6 in muscle cells is independent of NF-κB activation[97].

The role of IL-6 in muscular adaptations to exercise training has been studied extensively. Contracting skeletal muscles produce IL-6 (REF.[98]) in a TNF-independent fashion[99], suggesting that muscle-derived IL-6 has a role in metabolism rather than in inflammation.

Several studies have demonstrated that the release of IL-6 from muscle is regulated by muscle glycogen content and glucose ingestion, as reviewed elsewhere[97]. The exercise-induced increase in plasma IL-6 level is diminished by glucose intake during exercise. In addition, muscular *IL6* mRNA expression[100] and IL-6 protein release from contracting muscle[101] are increased when intramuscular glycogen is low, indicating that IL-6 works as an energy sensor and that muscular IL-6 production

is regulated not only by muscle contractions but also by the energy status of the muscle[100,101].

Several studies have demonstrated that global deletion of *Il6* in mice results in accumulation of adipose tissue[87,88], whereas adeno-associated viral delivery of IL-6 into rat hypothalamus[102] and central overexpression of IL-6 in mice[103,104] are associated with decreased fat content and suppression of body weight gain. These results indicate that IL-6 has an important role in body weight control. IL-6 might cause these effects through regulation of hypothalamic neuropeptides involved in energy homeostasis[104–106].

The absence of muscular IL-6 in male mice results in decreased body weight and reductions in food consumption in response to leptin, suggesting that muscle IL-6 has an impact on the CNS and has a role in mouse metabolism not only during exercise but also in the basal state and in situations in which energy balance is altered[107]. When IL-6 is centrally administered by intracerebroventricular injections in mice, it suppresses feeding and improves glucose tolerance[108]. Of note, although obese mice demonstrate leptin resistance, the ability of IL-6 to inhibit feeding is more pronounced in obese mice than in lean mice[108]. To determine whether the ability of IL-6 to suppress feeding was dependent on the actions of IL-6 centrally in the brain, the researchers injected the same dose of IL-6 intraperitoneally and found no effect on food intake, clearly demonstrating that the observed effect was mediated via the CNS[108]. However, when mice were injected peripherally with a fourfold higher IL-6 concentration than the dose injected centrally, the high dose of IL-6 was associated with a significant reduction in food intake during refeeding. One conclusion from this study is that peripherally derived IL-6 at high concentrations can pass through the blood–brain barrier and suppress feeding in mice. This finding leaves open the possibility that the increases in muscle-derived IL-6 that occur during exercise of high intensity and long duration might inhibit appetite.

Healthy elderly people (aged >70 years) maintain the capacity to produce and release IL-6 in response to dynamic exercise, with no difference compared with younger individuals[109]. Satellite cells derived from humans with insulin resistance demonstrate IL-6 resistance with regard to AMPK activation, but it remains to be shown whether such functional impairments exist with other biological actions of IL-6 or in other subpopulations such as older individuals[110]. In general, lifelong physical activity prevents age-associated insulin resistance in human skeletal muscle myotubes[111].

PGC1α–kynurenine axis

Worldwide, depression and stress are leading causes of disability and negatively influence the quality of life of millions of people. Physical exercise is sometimes prescribed to people suffering from poor mental health[112].

Tryptophan is an essential amino acid critical for protein synthesis, but it also serves as a substrate for the generation of important compounds that have various physiological roles. The best-known fate of tryptophan is its conversion to serotonin (5-hydroxytryptamine), an important neurotransmitter linked with alterations in mood, anxiety or cognition[113]; however, up to 95% of the bioavailable tryptophan is metabolized to kynurenine, which upon accumulation in the CNS can lead to depression and stress[114].

Defects in kynurenine signalling have been noted in mouse models of Alzheimer and Huntington diseases[115,116]. High levels of kynurenine are also found in people with depression[117], and kynurenine might be directly involved in the pathogenesis of depression by inducing death of neuronal cells and neuroinflammation[118]. Kynurenine aminotransferases convert kynurenine to kynurenic acid[119]. Kynurenic acid is neuroprotective and, unlike kynurenine, is not able to cross the blood–brain barrier[119]. An imbalance between the neuroprotective kynurenic acid and the neurotoxic kynurenine metabolites has been proposed to be involved in the development of depression[41].

As mentioned above, exercise leads to upregulation of PGC1α in skeletal muscle cells[64]. Activation of PGC1α leads to an enhancement of processes such as mitochondrial biogenesis, fatty acid oxidation and resistance to muscle atrophy[120,121]. Transgenic murine models with specific PGC1α overexpression in the skeletal muscle demonstrate many of the adaptations to aerobic exercise training such as mitochondrial biogenesis, oxidative metabolism and the formation of slow-twitch muscle fibres[122].

Overexpression of PGC1α in muscle has been shown to have an antidepressant-like effect by reducing entry of neurotoxic kynurenine into the brain[41] (FIG. 1c). Agudelo et al.[41] showed that overexpression of PGC1α in muscle induces a change in kynurenine metabolism leading to protection from stress-induced depression. The authors demonstrated that exercise led to activation of the PGC1α–PPARα–PPARδ pathway, which stimulates the expression of kynurenine aminotransferase within skeletal muscles. High expression of kynurenine aminotransferase led to increased conversion of kynurenine into kynurenic acid. Reduction in plasma kynurenine level protected the animals from stress-induced damage in the brain. Wild-type mice were sensitive to stress-induced depression, whereas transgenic mice with muscle-specific overexpression of PGC1α were resistant to stress-induced depression. Exposure to chronic, mild stress led to a decrease in hippocampal levels of BDNF and increased neuroinflammation in wild-type mice but not in PGC1α transgenic mice[41]. However, although the transgenic mice with muscle-specific PGC1α overexpression were protected from the brain damage, neuroinflammation and depression induced by chronic stress, they did not show overall protection from stress-induced inflammation. In fact, transgenic mice exposed to chronic stress displayed weight loss and increased inflammation in skeletal muscle compared with nonstressed transgenic mice[41].

Exercise training has been shown to increase plasma kynurenic acid levels in rodents[41], and extensive endurance exercise has been shown to increase plasma kynurenic acid levels in humans[123]. Diabetic and obese mice as well as humans with type 2 diabetes mellitus demonstrate reduced muscular expression of PGC1α[124]. The fact that PGC1α shows links with both

insulin resistance and inflammation, and also with the kynurenine pathway, might be of clinical importance. Dysregulation in the PGC1α–kynurenine pathway might explain not only the impaired insulin signalling and inflammation in this disease but also the twofold to threefold increased risk of dementia and depression[125,126].

Increased peripheral FNDC5 levels have been shown to mediate neuroprotective effects by increasing BDNF expression in the brain[58]; however, BDNF levels were unchanged in skeletal muscle-specific PGC1α transgenic mice, which suggests that the FNDC5–BDNF pathway might not be involved in the defence against stress-induced depression.

In the absence of a psychological stress challenge, endurance exercise training is sufficient to activate skeletal muscle kynurenine to kynurenic acid conversion, resulting in considerably elevated circulating kynurenic acid levels[41]. Peripheral kynurenic acid has been shown to possess anti-inflammatory properties[127]. Moreover, kynurenic acid increases energy utilization by activating G protein-coupled receptor GPR35, which stimulates lipid metabolism and anti-inflammatory gene expression in adipose tissue[127]. Kynurenic acid thereby suppresses weight gain in animals fed a high-fat diet, improves glucose tolerance and reduces adipose tissue inflammation[128].

In conclusion, exercised skeletal muscle might positively influence the balance between kynurenine and kynurenic acid by increasing the conversion of kynurenine to kynurenic acid. The fact that kynurenic acid is not able to cross the blood–brain barrier protects the brain from stress-induced kynurenine accumulation, neuroinflammation and changes in synaptic plasticity associated with depression, and kynurenic acid also contributes to an overall improvement in metabolism.

Adipocyte–brain link

Adiponectin is a protein secreted by adipocytes and is primarily produced and released into the circulation from adipose tissue[129]. Studies in rodents have shown that adiponectin is also expressed and released from muscle in association with exercise[129].

Adiponectin has insulin-sensitizing, antidiabetic, anti-inflammatory and antiatherogenic properties[129] as well as neuroprotective effects[130,131]. Adiponectin can pass through the blood–brain barrier and induce increased cell proliferation and decreased depression-like behaviour. Exercise-induced reduction in depression-like behaviour was abrogated in adiponectin-deficient mice via a mechanism that included impairment of AMPK in the hippocampus. These findings suggest that adiponectin is involved in mediating the effect of exercise on hippocampal neurogenesis and depression[130,131]. The discovery of adipokines, such as adiponectin, suggests a direct crosstalk between adipose and brain tissues, which can be modulated by exercise.

Liver–brain link

Similar to muscle and adipose tissue, the liver releases secretory proteins, known in this case as hepatokines, which are involved in metabolism[132,133]. Hepatokines such as fibroblast growth factor 21 (FGF21) and insulin-like growth factor 1 (IGF1) seem to be involved in crosstalk between the liver and brain tissues, and such crosstalk can be modulated by exercise. FGF21 is a hepatokine[134] capable of inducing insulin sensitivity and weight loss[135]. Exercise induces an increase in FGF21 secretion from the human liver, which contributes to an increase in systemic FGF21 levels via a mechanism involving glucagon[136].

Studies in rodents have shown that prolonged fasting stimulates hepatic production of FGF21 via a mechanism that includes activation of the transcription factor PPARα. After production in the liver, FGF21 enters the brain and activates the hypothalamic–pituitary–adrenal axis for release of corticosterone, thereby stimulating hepatic gluconeogenesis[137].

Studies in mice, monkeys and humans show that FGF21 regulates simple sugar intake and preferences for sweet foods via signalling through FGF21 receptors in the paraventricular nucleus of the hypothalamus and correlates with reduced dopamine neurotransmission within the nucleus accumbens[138–140]. FGF21 has also been shown to prevent cognitive decline in obese insulin-resistant rats by improving hippocampal synaptic plasticity and brain FGF21 signalling[141]. Taken together, the available data on FGF21 indicate that exercise causes an increase in circulating FGF21, which crosses the blood–brain barrier and affects metabolic as well as cognitive functions.

The main source of IGF1 is believed to be the liver, but IGF1 has also been shown to be released by contracting muscles, and circulating levels of IGF1 are upregulated by exercise[142,143]. The role of IGF1 in muscle–brain communication is supported by the finding that the effect of physical exercise on upregulation of hippocampal BDNF expression and adult neurogenesis is blocked by neutralizing IGF1 antibodies[144].

Exercise and ageing

Physical exercise offers protection against cognitive decline in ageing[145], but it is not clear whether regular exercise training slows the trajectory of normal ageing by influencing metabolic and vascular risk factors or whether it repetitively boosts brain function, for example, by inducing neurochemical and structural changes in the hippocampus, thereby protecting memory and learning[145].

To what extent the ageing muscle can elicit physiological stimuli capable of inducing sufficient responses in the brain is also unclear. Time course studies in healthy rodents have shown, however, that the age-related loss of skeletal muscle mass and function (sarcopenia) is strongly associated with denervation of myofibres and that exercise can prevent this sarcopenia[121,146–148].

One-third of the hippocampal neurons are subject to exchange[149], with 700 new neurons added in each hippocampus per day in adult humans. This figure corresponds to an annual turnover of 1.75% of the neurons with only a modest decline in this turnover during ageing. Neurons are generated throughout adulthood in both mice and humans[149], suggesting that exercise can positively influence brain hippocampal neurogenesis throughout our lifespan.

Sarcopenia
Derived from the Greek *sarx* ('flesh') and *penia* ('loss'), sarcopenia is the age-induced loss of muscle mass and function that typically manifests as reduced gait speed.

Conclusions

Our understanding of how exercise is sensed by the brain and how hippocampal neurogenesis, cognition, mood and appetite become activated or regulated by muscle has been limited. Findings now suggest the existence of a muscle–brain endocrine loop. Working skeletal muscle secretes myokines or expresses muscle factors that can alter hippocampal function either directly or via an effect on BDNF protein levels. Evidence is accumulating that the myokine cathepsin B, when increased peripherally by exercise, can pass through the blood–brain barrier and enhance BDNF production and hence neurogenesis, memory and learning. Moreover, the PGC1α-dependent myokine irisin, which is released into the circulation by cleavage of FNDC5, might reach the brain and activate the FNDC5–BDNF pathway. The ketone body β-hydroxybutyrate might also provide a link between aerobic exercise and BDNF gene expression in the brain. The myokine IL-6 is produced in muscle and released into the blood with exercise, and plasma levels increase exponentially with exercise duration. IL-6 can pass through the blood–brain barrier, and via central mechanisms it suppresses feeding and improves glucose tolerance. In addition, exercise enhances the PGC1α-dependent muscular expression of the enzyme kynurenine aminotransferase, which induces a beneficial shift in the balance between the neurotoxic kynurenine and the neuroprotective kynurenic acid, thereby reducing depression-like symptoms. Direct muscle-to-brain crosstalk is mediated by myokines and metabolites released by muscle, but exercise is also sensed by the brain indirectly via adipose tissue and the liver. These organs secrete adipokines and hepatokines, which can pass through the blood–brain barrier. The identification of exercise-related factors that have a direct or indirect effect on brain function has the potential to highlight novel therapeutic targets for neurodegenerative diseases and cognitive enhancers for people of all ages. These factors might also be useful as markers to be used for monitoring the amount, intensity and mode of exercise that is required in order to prescribe exercise as a booster of neurological and mental health.

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