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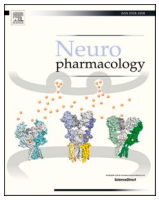

Invited review

How does the skeletal muscle communicate with the brain in health and disease?

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ABSTRACT

Endocrine mechanisms have been largely associated with metabolic control and tissue cross talk in mammals. Classically, myokines comprise a class of signaling proteins released in the bloodstream by the skeletal muscle, which mediate physiological and metabolic responses in several tissues, including the brain. Recent exciting evidence suggests that myokines (e.g. cathepsin B, FNDC5/irisin, interleukin-6) act to control brain functions, including learning, memory, and mood, and may mediate the beneficial actions of physical exercise in the brain. However, the intricate mechanisms connecting peripherally released molecules to brain function are not fully understood. Accumulating findings further indicates that impaired skeletal muscle homeostasis impacts brain metabolism and physiology. Here we review recent findings that suggest that muscle-borne signals are essential for brain physiology and discuss perspectives on how these signals vary in response to exercise or muscle diseases. Understanding the complex interactions between skeletal muscle and brain may result in more effective therapeutic strategies to expand healthspan and to prevent brain disease.

This article is part of the special Issue on 'Cross Talk between Periphery and the Brain'.

1. Introduction

Mounting evidence indicates that the skeletal muscle releases a myriad of signaling molecules induced by contraction, cell proliferation/differentiation, and/or local metabolic processes (Pedersen, 2019). Since the identification of interleukin-6 (IL-6) as a cytokine released in the bloodstream in response to muscle contraction (Starkie et al., 2001; Steensberg et al., 2000; Ullum et al., 1994), several muscle-derived molecules with signaling actions have been identified (Febbraio and Pedersen, 2020). Therefore, the skeletal muscle has now been referred to as an endocrine organ.

Classically, myokines are defined as proteins that transmit messages from the skeletal muscle to several tissues, including adipose tissue, liver, pancreas, bone, and brain (Febbraio and Pedersen, 2020). Here, we propose to expand this concept to other types of molecules, including metabolites such as lactate and ketone bodies, as they are key contributors of muscle-to-brain communication. Together, signals mediated by myokines are essential to maintain proper body metabolism and physiology in response to a changing environment that includes variations in nutrient availability and physical demands, among others. While the endocrine mechanisms triggered by the skeletal muscle to communicate with peripheral tissues have been thoroughly studied for decades, only recently muscle signals targeting the brain began to be further investigated.

A large body of evidence supports the notion that physical exercise improves learning, memory and attention (Cotman and Berchtold, 2002), sleep, appetite regulation and mood (Blundell et al., 2015; Crush et al., 2018; Kelley and Kelley, 2017) in healthy subjects, in addition to correcting disease phenotypes and symptoms in a number of neurological disorders (de Freitas et al., 2020; Mattson, 2012; van Praag et al., 2014). Although exercise directly impacts the brain, there is now considerable body of findings supporting that a muscle-brain cross talk mediates the physiological responses and the beneficial effects of exercise. More recently, the term exerkine has been coined to encompass endocrine factors that are stimulated by physical exercise (Safdar and Tarnopolsky, 2017).

Herein we review recently described roles for muscle-derived molecules in memory, cognition, and mood, and discuss the exciting perspective that harnessing the potential of myokines and exerkines may be key to modulate brain function. Understanding the intricate processes mediating muscle-brain crosstalk may result in strategies to expand health span and to ward off brain disease.

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2. The muscle as an endocrine tissue

The skeletal muscle is amongst the largest organs in the human body and represents an essential component of the locomotor system, being responsible for maintaining postural support, promoting force and power during voluntary movements, and for supporting involuntary actions, such as breathing and reflex (Frontera and Ochala, 2014). The first evidence of the muscle as an endocrine tissue came out when it was described that contracting muscles release signaling molecules, such as cytokines and peptides, that are able to function in autocrine, paracrine, and/or endocrine manners (Pedersen, 2013; Severinsen and Pedersen, 2020).

Interleukin-6 (IL-6) was the first reported myokine released into circulation in response to contractile activity even in the absence of inflammation (Febbraio et al., 2004; Jonsdottir et al., 2000; Keller et al., 2001; Steensberg et al., 2000). The exercise-induced release of IL-6 mediates increases in glucose uptake, lipolysis, and fatty acid oxidation in the muscle, in a process mediated by AMP-activated protein kinase (AMPK) (Carey et al., 2006; Petersen et al., 2005; van Hall et al., 2003), and stimulates hepatic glucose production (Febbraio et al., 2004). Other cytokines, such as interleukin-7 (IL-7), interleukin-15 (IL-15), and leukemia inhibitory factor (LIF), have also been reported to be secreted by the skeletal muscle and to exert metabolic actions (Haugen et al., 2010; Quinn et al., 2002; Spangenburg and Booth, 2006). For instance, overexpression of IL-15 in skeletal muscle reduces adiposity in mice (Quinn et al., 2009). Recent findings also indicate that muscle AMPK signaling is required for adipose tissue expression of DICER, a key enzyme in microRNA biogenesis (Brandão et al., 2020).

Brain-derived neurotrophic factor (BDNF), the most abundant neurotrophin in the brain, has also been described as a myokine. BDNF mRNA levels increases in the muscle of healthy rodents and humans subjected to exercise (Gómez-Pinilla et al., 2001; Matthews et al., 2009; Ogborn and Gardiner, 2009). A recent study showed that muscle-specific deletion of BDNF leads to development of metabolic myopathy and insulin resistance in mice, thereby supporting its key autocrine/paracrine roles as a metabolic regulator (Yang et al., 2019). Recent evidence further supports that muscle-derived BDNF may signal to vascular cells and perivascular adipose depots (Zierold et al., 2021), thereby indicating an endocrine function for this neurotrophin.

The myokine irisin, derived from the membrane precursor fibronectin type III domain-containing protein 5 (FNDC5), and known in to induce BDNF expression in the brain (Wrann et al., 2013), was reported to stimulate thermogenic gene expression in beige adipocytes, facilitating their conversion to brown adipocytes in response to exercise in mice and humans (Bostrom et al., 2012; Jedrychowski et al., 2015; Lee et al., 2014). Irisin further regulates bone mineral density (Colaianni et al., 2015; Kim et al., 2018; Qiao et al., 2016) and synaptic plasticity in the brain (Lourenco et al., 2019; Wrann et al., 2013). Together, these results indicate that the skeletal muscle is an active regulator of body metabolism and physiology.

3. Roles of muscle-derived signals in cognition and mood

While the functions of myokines in regulating peripheral metabolism and physiology have been considerably appreciated, increasing findings propose that these signaling molecules play key roles in neuronal homeostasis in response to physical exercise. A very recent study using tissue specific metabolic labeling followed by proteomics in *Drosophila* identified 51 muscle-secreted proteins in the fly head (Droujinine et al., 2020), suggesting that the pool of secreted factors mediating muscle to brain communication is notably large.

While the nature and mechanisms induced by the pool of myokines that present biological activity in the brain remain to be fully identified, important insights from key molecules have been recently reported. Given its importance for brain functions, BDNF has been substantially investigated in the context of exercise and synapse function. A variety of exercise protocols increase BDNF levels in plasma and the hippocampus of rodents and humans (Oliff et al., 1998; Rasmussen et al., 2009; Seifert et al., 2010; Soya et al., 2007), thus favoring neurogenesis, synaptic plasticity and learning (Lee et al., 2012; Piepmeier and Etnier, 2015; van Praag et al., 1999a; van Praag et al., 1999b). Blocking BDNF binding to its receptor TrkB in the hippocampus attenuates the benefits of exercise on synaptic plasticity and cognition (Vaynman et al., 2004). Moreover, the BDNF Val66Met polymorphism – known for its association with memory and mood impairments (Chen et al., 2006; Egan et al., 2003) – blunts the beneficial effects of exercise in synaptic plasticity and mood, including PGC-1α and FNDC5 expression in the rodent brain (Ieraci et al., 2016). Human subjects carrying the BDNF Val66Met polymorphism do not show increased serum BDNF, nor do they present vascular adaptations, in response to exercise (Kwak et al., 2021; Lemos et al., 2016).

Additional myokines with neuroactive properties have further been identified, including FNDC5/irisin and cathepsin B (CTSB) (Bostrom et al., 2012; Moon et al., 2016). FNDC5/irisin is induced by physical exercise in mice and humans (Bostrom et al., 2012; Jedrychowski et al., 2015). Voluntary running wheel exercise induces FNDC5 expression in the mouse skeletal muscle and brain. Studies in cell cultures and peripheral delivery of FNDC5 via adenoviral vectors in mice suggested that muscle PGC-1α signaling results in FNDC5 expression, irisin release and triggers the expression of BDNF and synaptic plasticity-related genes (e.g. *Arc*, *cFos*, *Zif268*) in hippocampal neurons (Wrann et al., 2013). Intriguingly, muscle contraction induced by electric stimulation in rats induces FNDC5 and BDNF expression in the hippocampus, but not in the stimulated muscle (Maekawa et al., 2018). These results suggest that a FNDC5/irisin-BDNF signaling pathway may contribute to neuronal physiology.

Recently, our group showed that peripheral or brain expression of FNDC5/irisin rescued synaptic plasticity and memory function in mouse models of Alzheimer's disease (AD). We also demonstrated that down-regulating FNDC5 expression blocked the beneficial effects of exercise on synaptic plasticity and memory in this same model (Lourenco et al., 2019). In the AD cerebrospinal fluid, irisin levels directly correlate with BDNF and cognition (Lourenco et al., 2020). Therefore, improving brain FNDC5/irisin levels has emerged as a therapeutic approach to maintain synaptic function and memory in cognitive disorders (Lourenco et al, 2019, 2020).

Although previously known as a key lysosomal protease, CTSB has been further identified as a myokine responding to exercise in mice and humans (Moon et al., 2016). Mice undergoing running wheel exercise had upregulated CTSB mRNA expression in the gastrocnemius muscle and hippocampus, and CTSB protein levels in plasma. Likewise, plasma CTSB levels also increased in rhesus monkeys and humans after 4 months of treadmill exercise. Remarkably, the positive effects of exercise in spatial memory and neurogenesis were abolished in CTSB knockout (KO) mice (Moon et al., 2016). It is thus conceivable that exercise-induced myokines act in concert to stimulate mechanisms of synaptic plasticity, neurogenesis, and cognition.

Muscle-derived signals have further been proposed to regulate mood and emotional behavior. Kynurenine is a tryptophan metabolite that crosses the blood-brain barrier (BBB) and mediates stress-induced depressive-like behavior in mice (Schwarcz et al., 2012). Kynurenine and its metabolites have been correlated with depressive behavior in humans in previous meta-analyses (Marx et al., 2020; Müller and Schwarz, 2007; Pu et al., 2020). Kynurenine is converted to kynurenic acid by kynurenine aminotransferases in several tissues, including liver, immune cells and muscle (Wirthgen et al., 2018). During physical exercise, kynurenine conversion is increased in the skeletal muscle through a signaling mechanism that depends on PGC-1α–PPARα–PPARδ (Agudelo et al., 2014; Allison et al., 2019; Schlittler et al., 2016). Given that kynurenic acid does not efficiently cross the BBB, the muscle likely controls brain availability of kynurenine upon exercise, with potential consequences for serotonin and glutamate neurotransmission (Agudelo

et al., 2014; Schwarcz et al., 2012; Stone et al., 2012).

Importantly, novel pathways of muscle to brain communication have been recently proposed. An elegant study offered proof-of-concept evidence that disturbances in muscle proteostasis, known to develop with aging (Fernando et al., 2019), trigger a long-range communication mechanism to delay age-related declines in retina and brain function in *Drosophila* (Rai et al., 2021). Secretion of the amylase Amyrel by the skeletal muscle results in brain maltose production and reduced the accumulation of polyubiquitinated proteins in the aging brain (Rai et al., 2021). These findings uncover Amyrel as a novel myokine and reveal a novel muscle-to-brain mechanism operating during physiological stress. Given that regulation of brain proteostasis has been regarded as key for higher cognitive and emotional behavior (Longo et al., 2021; Oliveira et al., 2021; Shrestha et al., 2020; Tomaru et al., 2021), it is conceivable that similar mechanisms take place in mammals to drive memory and mood states.

4. Indirect paths from muscle to brain

In complement to muscle-derived molecules that have direct effects in the brain, it is conceivable that muscle-initiated processes trigger indirect consequences to the brain via endocrine and metabolic regulation. Metabolic demands by the skeletal muscle upon exercise promote the liver-mediated synthesis and plasma release of ketone bodies, mainly acetoacetate and D-β-hydroxybutyrate (DBHB). DBHB, for instance, crosses the BBB and accumulates in the hippocampus to stimulate histone acetylation at BDNF promoters and, consequently, BDNF expression (Sleiman et al., 2016). DBHB further controls neuronal metabolism (Marosi et al., 2016) and promotes neurotransmitter release in the hippocampus (Sleiman et al., 2016). Conditions that mimic the exercise-induced energy deprivation, including intermittent fasting and ketogenic diets, trigger similar effects in the brain (Benjamin et al., 2017; Mattson et al., 2018).

Glycosylphosphatidylinositol–specific phospholipase D1 (Gpld1) is a liver-derived enzyme recently described to be released in the bloodstream in response to exercise in mice and humans (Horowitz et al., 2020). Horowitz et al. (2020) reported that intravenous injections of Gpld1 replicate the effects of exercise on hippocampal BDNF expression, neurogenesis, and cognition in aged mice. Although the specific metabolic and/or endocrine signals that may favor liver secretion of Gpld1 remain to be determined, these results pinpoint to Glpd1 as a potent mediator of intertissue communication in a muscle-liver-brain axis.

It is noteworthy that several mechanisms associated with myokine actions in the brain appear to involve BDNF expression. Even though unequivocable evidence that muscle-borne BDNF reaches the brain is lacking, this role can potentially be fulfilled by the action of peripheral myokines and/or metabolites – such as FNDC5/irisin, CTSB, Gpld1 and DBHB – that reach the brain and then promote local BDNF induction (Moon et al., 2016; Sleiman et al., 2016; Wrann et al., 2013).

Fibroblast growth factor 21 (FGF21) is another exercise-induced hepatokine that has neuromodulatory actions in the brain: in the hypothalamus, FGF21 signals to modulate circadian behavior and sugar intake (Bookout et al., 2013; Søberg et al., 2017; Von Holstein-Rathlou et al., 2016); in the hippocampus, it promotes synaptic plasticity, mitochondrial function and cognition (Sa-nguanmoo et al., 2016). Although barely produced by the muscle under physiological conditions, hyperinsulinemia and stress can induce its muscle expression (Hojman et al., 2009; Luo and McKeehan, 2013), with potential consequences to brain function.

Adiponectin, a hormone mostly produced by the adipose tissue (Dai et al., 2013), has further been shown to act in the brain to promote neurogenesis and antidepressant-like effects (Liu et al., 2012; Qi et al., 2004; Yaua et al., 2014). Consistently, peripheral adiponectin levels are reduced in mood disorders (Vuong et al., 2020). Intriguingly, skeletal muscle has been proposed as a source of adiponectin intended for autocrine/paracrine signaling, although major endocrine functions of muscle-derived adiponectin cannot be ruled out (Martinez-Huenchullan et al., 2020).

Recent findings have further proposed the release of extracellular vesicles as an alternative and efficient mechanism to carry over small RNAs, peptides and protein to mediate tissue communication (Safdar and Tarnopolsky, 2018; Trovato et al., 2019; Whitham et al., 2018). Indeed, exercise increases the levels of extracellular vesicles in circulation (Whitham et al., 2018), and the content of muscle-borne vesicles vary with stress (Huang-Doran et al., 2017). Therefore, investigating extracellular vesicle composition and dynamics in response to muscle adaptations might reveal novel potential targets to improve muscle to brain communication in health and disease (Safdar et al., 2016).

In conjunction, exciting observations support the notion that molecules produced by the skeletal muscle upon physiological adaptations control several aspects of brain function and may be relevant approaches to mitigate brain disease. However, a few intriguing questions still need to be addressed. First, whether and how these myokines effectively cross the BBB is not completely clear yet. In addition, some myokines, as is the case for BDNF, FNDC5/irisin and CTSB, are also locally induced in the hippocampus in response to exercise (Lourenco et al., 2019; Wrann et al., 2013). Dissecting the specific roles of local and systemic factors in neuronal function and neuroprotection is warranted to illuminate our understanding of periphery to brain communication. Finally, determining specific target cells and receptors for myokines in the brain will be key to harness the full potential of these myokines as neuromodulators.

5. Muscle-brain axis in energy metabolism

Various signals work collectively to regulate eating behavior and nutrient sensing in mammals (Smeets et al., 2012). In the brain, the hypothalamus is one of the most important centers linked to energy metabolism, notably working as a glucose and hormone sensor (Fioramonti et al., 2017). Systemic glucose levels are detected by specialized neurons that trigger signals locally and to the periphery to maintain homeostasis (Fioramonti et al., 2017; Li et al., 2020; Zhou et al., 2018).

In addition to glucose itself, other metabolites are perceived by the hypothalamus in the regulation of metabolism. Circulating lactate levels are detected and required by the hypothalamus to regulate glucose production, thus supporting glucose homeostasis in rodents (Kokorovic et al., 2009). High-intensity interval exercise interventions or daily injections of L-lactate in mice stimulate the expression of vascular endothelial growth factor (VEGF) and angiogenesis in the cerebral cortex and hippocampus, and this is mediated by the lactate receptor HCAR1 (Morland et al., 2017). This suggests that exercise-induced lactate production directly improves metabolic support to the brain through increased cerebral vascularization.

Carnitine (β-hydroxy-γ-N-trimethylaminobutyric acid) is an amino acid derivative that acts on fatty acid transport for mitochondrial oxidation (Adeva-Andany et al., 2017). Carnitine acetyltransferase (CrAT) is a mitochondrial enzyme that produces carnitine esters, including acetyl-L-carnitine (LAC). Carnitine deficiency has been associated with mitochondrial dysfunction, insulin resistance, and impaired systemic glucose homeostasis (Muoio et al., 2012; Noland et al., 2009). In the brain, LAC induces histone acetylation and expression of glutamate receptors, and drives rapid antidepressant effects (Lau et al., 2017; Nasca et al., 2013). In accordance, reduced levels of LAC in circulation correlate with depressive symptoms (Nasca et al., 2018). Interestingly, muscle-specific deletion of CrAT causes a reduction of 30%–50% in circulating LAC levels (Muoio et al., 2012), suggesting that skeletal muscle is a major source of circulating carnitine esters that modulate brain metabolism, cognition and mood.

Muscle-derived IL-6 has also been reported to control the expression of hypothalamic peptides (Ferrer et al., 2014), to suppress food intake and to reduce body weight in rodents (Shirazi et al., 2013). A recent study demonstrated that, in obese rodents, IL-6 levels are reduced in the

lateral parabrachial nucleus (lPBN), which transmits signals mainly to the medial and lateral hypothalamus. Enhancing IL-6 signaling in the lPBN reduced food intake, increased brown adipose tissue thermogenesis, and improved glucose homeostasis in mice, reinforcing that IL-6 acts in the brain as a key regulator of obesity (Mishra et al., 2019; Timper et al., 2017). Moreover, an acute short-term exercise leading to fatigue transiently suppressed hunger perception and food intake in humans, which associated with increased plasma levels of myokines and hormones, such as IL-6, irisin, nesfatin-1 and ghrelin (Bilski et al., 2020). In contrast, prolonged elevations in brain ketone content increases food intake and alters insulin signaling and glucose homeostasis (Carneiro et al., 2016).

FGF21 further regulates sugar intake and sweet-taste preference by acting on the hypothalamus (Von Holstein-Rathlou et al., 2016), mainly by signaling to glutamatergic neurons via its co-receptor β-klotho in the ventromedial hypothalamus (Jensen-Cody et al., 2020). Notably, FGF21/β-klotho signaling pathway exerts an important regulatory role in metabolic adaptations and feeding behavior (Hill et al., 2019). Therefore, solid evidence demonstrates that several peripherally released molecules signal to the hypothalamus to modulate brain and peripheral energy metabolism.

Disturbances in homeostatic sensors are strongly correlated with metabolic disorders, such as obesity and type 2 diabetes (Cavadas et al., 2016; Moura-Assis et al., 2021). For example, insulin resistance has been markedly linked to diseases of cognition and mood, including AD and depression in humans (Grigolon et al., 2019; Lyra e Silva et al., 2019). Whether and how the noxious impacts of metabolic disease depend on peripheral metabolic impairments or central defects remain to be fully elucidated. Nonetheless, potential insights have already been established.

Notably, inflammatory processes in the central nervous system impair muscle function through hypothalamic-induced adrenal signaling (Braun et al., 2011). Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, with consequent increases in the circulation of corticoid hormones and increased sympathetic tonus, has been reported to impact muscle homeostasis and metabolism (Yiallouris et al., 2019; Zanquetta et al., 2006). For instance, in AD models, hypothalamic targeting by amyloid-β resulted in increased plasma noradrenaline and impaired surface expression of glucose transporter 4 (GLUT4) in the mouse skeletal muscle (Clarke et al., 2015). Defects in HPA axis homeostasis may facilitate muscle atrophy seen in metabolic conditions, such as obesity, and in neurodegenerative diseases characterized by neuroinflammation, such as AD (Batista et al., 2021; Clarke et al, 2015, 2018, 2015; Lourenco et al., 2013). These findings raise the notion that a bidirectional communication takes place and that proper muscle-brain cross talk may be essential for metabolic responsiveness during stress and exercise, and that may be impaired in disease.

6. Does skeletal muscle disease impact the brain?

The key endocrine roles of the skeletal muscle pose the question of whether diseases that distress the muscle could trigger deleterious impacts on brain function. Clinical evidence indicates that humans affected by sarcopenia, a condition of muscle atrophy, present neuroanatomical abnormalities consistent with neurodegeneration (Kwak et al., 2019) and are at increased odds of developing cognitive impairment than matched controls (Chang et al., 2016; Peng et al., 2020). This is consistent with findings demonstrating increased frequency of cognitive decline in older subjects with sarcopenia as compared to those with preserved muscle mass (Cabett Cipolli et al., 2019). Notably, a cross-sectional analysis of a Brazilian cohort in the ELSA-Brasil study revealed that aged subjects with sarcopenia or loss of muscle strength presented impaired cognitive performance (Szlejf et al., 2019b).

Additionally, signs of impaired muscle function associate with worse cognitive and affective states in humans undergoing cognitive decline due to mild cognitive impairment (MCI) or AD (Ohta et al., 2019). A number of observational studies further reported that sarcopenia is associated with increased frequency of depressive states in humans (Chen et al., 2020; Kim et al., 2011; Szlejf et al., 2019a). Conversely, abnormal brain function, cognition, or mood has not been reported in cases of inclusion-body myositis, a sporadic disorder that shares many parallels with AD, such as age-associated onset, and tissue-specific deposition of amyloid-β (Askanas and Engel, 2001; Nogalska et al., 2010).

Muscular dystrophies are genetic diseases that progressively compromise muscle function and frequently associate with cognitive failure. Adults with Duchenne muscular dystrophy present impaired capacity of processing auditory and visual information (Ueda et al., 2017). Accordingly, patients with type 1 myotonic dystrophy present poorer performance in tests of cognition and executive function (Rakocevic-Stojanovic et al., 2014). However, given that such diseases involve mutations in genes often expressed in the brain (Hara et al., 2011), it is not clear whether their cognitive manifestations involve muscle dyshomeostasis rather than being driven by the direct impact of mutations on brain function.

Altogether, these findings indicate that loss of skeletal muscle mass and/or function may render the brain vulnerable to dysfunction and neurological disease. Mechanistically, this connection may have two possible explanations. The first possibility suggests that impaired muscle homeostasis impacts myokine and exerkine production and release, thereby compromising their proper signaling to the brain. The second possibility refers to an indirect effect by which muscle dysfunction harms peripheral metabolic control and immune function (Ferrucci and Fabbri, 2018), with secondary consequences to brain function. The most likely scenario, however, encompasses the combination of both possibilities, resulting in age-linked acceleration of cognitive decline and mood impairment.

7. Tuning muscle-brain cross talk through physical exercise

The molecular scenario of muscle to brain communication raises the prospect that harnessing muscle physiology through exercise might comprise an effective approach to promote brain health. Evidence from randomized trials suggests that it improves memory, processing speed and executive function, notably in children and elderly (Chang et al., 2012; Erickson et al., 2019), and prevent cognitive decline (Beckett et al., 2015; Brasure et al., 2018; Sofi et al., 2011).

A single bout of exercise was shown to rapidly stimulate hippocampal function and connectivity in healthy humans (Suwabe et al., 2018). An interesting study by Colcombe et al. found that prefrontal and parietal cortical activities are increased in fit elderly subjects compared to sedentary volunteers. They also reported that 6 months of aerobic training increased the activity of these brain regions in a second group of aged volunteers (Colcombe et al., 2004).

Some mechanistic insights in humans came from studies showing that healthy elderly individuals undergoing aerobic exercise before an operational memory task exhibited higher plasma levels of BDNF that correlated with higher cognitive performance (Nilsson et al., 2020). Furthermore, 12 months of regular aerobic exercise resulted in increased circulating BDNF, VEGF, and insulin-like growth factor 1 in humans (Voss et al., 2013). Connectivity analyses also supported the notion that exercise training increases temporal (Voss et al., 2013) and hippocampal connectivity and blood flow (Burdette et al., 2010).

In subjects experiencing MCI, exercise mildly improved cognition, metabolic profiles, and specifically increased IGF-1 levels in males (Baker et al., 2010). Subjects who regularly exercise have a reduced risk of developing AD-related neuropathology (Okonkwo et al., 2014) and cognitive decline (Buchman et al., 2012) and, though exercise protocols are rather variable in the literature, at least some training programs have shown beneficial effects for early AD patients (Winchester et al., 2013). It is also noteworthy that multimodal interventions in lifestyle that incorporate physical exercise have shown consistent neuroprotective

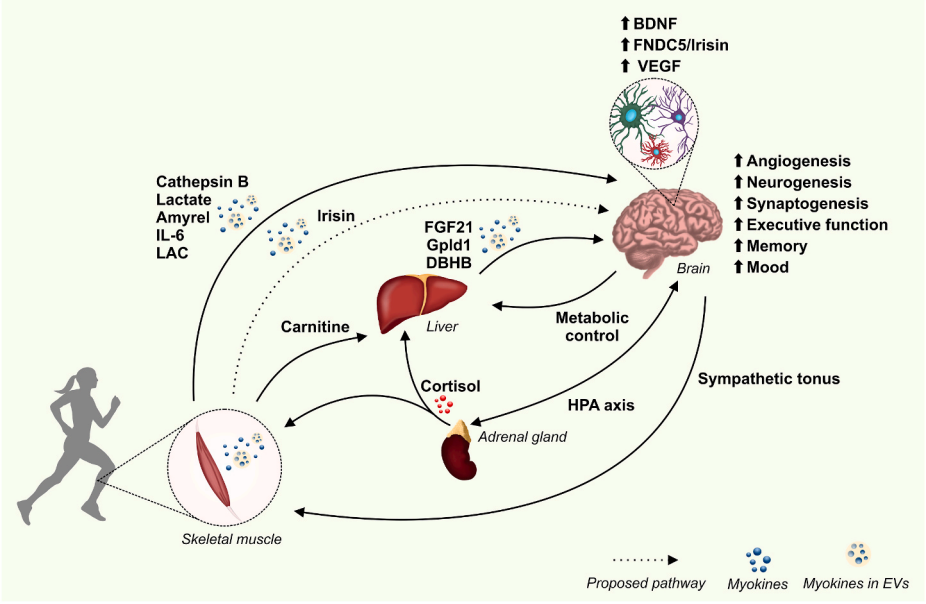

Fig. 1. A model of muscle-brain cross talk. Several myokines, including proteins and metabolites (e.g. cathepsin B, interleukin-6, acetyl-L-carnitine), are released in circulation upon contraction. They may travel as soluble factors or encapsulated in extracellular vesicles (EVs), cross the blood-brain barrier to directly mediate neurotrophic signaling in brain regions relevant for cognitive and executive functions (hippocampus, prefrontal cortex), mood (nucleus accumbens, striatum, prefrontal cortex), and metabolic regulation (hypothalamus). In addition, myokines can also trigger an indirect effect in the brain by signaling to peripheral tissues (e.g. liver), which in turn release molecules (e.g. FGF21, DBHB) that target the brain. In conjunction, muscle-initiated signaling molecules will stimulate the brain actions of neurotrophins, including FNDC5/irisin and BDNF, to facilitate cognitive and emotional regulation. Conversely, the brain controls muscle function and peripheral metabolism by regulating the sympathetic tonus by direct innervation of target tissues and by modulation of cortisol production through the hypothalamic-pituitary-adrenal axis. Proper maintenance of this cross talk, which is facilitated by adequate metabolic control and physical exercise, is essential to preserve brain functions and prevent cognitive decline and mood disorders. A more complete understanding of the intricate mechanisms driving muscle-brain communication may further foster novel therapeutic approaches for memory and mood disorders.

effects in humans at risk for dementia (Kivipelto et al., 2018; Ngandu et al., 2015; Rosenberg et al., 2018). These are encouraging findings that have stimulated replication studies worldwide (Kivipelto et al., 2020).

Physical exercise further reduces the risk of developing MDD in humans (Choi et al., 2019; Schuch et al., 2018). Physical activity/exercise has been shown to attenuate symptoms of depression (Jaworska et al., 2019; Schuch et al., 2016) and has been indicated as an effective adjuvant therapy, especially in mild to moderate MDD (Cleare et al., 2015; Cooney et al., 2013). Together, these results advocate for exercise as a relevant preventative and therapeutic approach for brain disease. Mechanistically, the neuroprotective actions of exercise encompass, at least in part, increases in myokines, although the specific subset of molecules released upon each protocol of exercise (e.g. aerobic vs strength, short vs prolonged; light/moderate vs intense) still remains to be uncovered.

8. Conclusions

In summary, several candidate molecules have now been proposed to mediate muscle-brain communication (Fig. 1), thereby representing powerful alternatives for the prevention or treatment of neurological disorders. Most of these candidates have emerged from studies investigating the endocrine mechanisms of physical exercise. Nonetheless, it is conceivable that proper muscle-to-brain signaling is an essential physiological mechanism that, once disrupted, may contribute to defective endocrine communication, and predispose individuals for brain disease. Which molecules derived from the myokinome that can effectively cross the BBB and display neuroactive roles, as well as how they synergize or antagonize, remain to be uncovered. Additionally, it may be the case that myokines act peripherally to promote metabolic and physiological changes with consequences to the brain (Fig. 1). Thorough investigations of the myokinome identity, as well as the modulatory roles of physical exercise, may result in optimized pharmacological and non-pharmacological applications in the neurological practice.

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