

Exerkines and long-term synaptic potentiation: Mechanisms of exercise-induced neuroplasticity

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ABSTRACT

Physical exercise may improve cognitive function by modulating molecular and cellular mechanisms within the brain. We propose that the facilitation of long-term synaptic potentiation (LTP)-related pathways, by products induced by physical exercise (i.e., exerkines), is a crucial aspect of the exercise-effect on the brain. This review summarizes synaptic pathways that are activated by exerkines and may potentiate LTP. For a total of 16 exerkines, we indicated how blood and brain exerkine levels are altered depending on the type of physical exercise (i.e., cardiovascular or resistance exercise) and how they respond to a single bout (i.e., acute exercise) or multiple bouts of physical exercise (i.e., chronic exercise). This information may be used for designing individualized physical exercise programs. Finally, this review may serve to direct future research towards fundamental gaps in our current knowledge regarding the biophysical interactions between muscle activity and the brain at both cellular and system levels.

1. Introduction

The beneficial effect of physical exercise on cognition first appeared in literature in the 1930s (Burpee and Stroll, 1936; Beise and Peaseley, 1937). A search in PubMed with the terms “exercise” AND “cognition” shows how this topic has exploded in the last decades, reaching over one

hundred publications a year in 1998 and over 3000 publications a year in 2020. However, the underlying mechanisms of physical exercise-induced cognitive improvements are still not fully understood, indicating the complexity of the neurophysiological processes that mediate the beneficial effects of physical exercise on the brain (Gomez-Pinilla and Hillman 2013; El-Sayes et al., 2019; Kim et al., 2019). Of critical

Abbreviations: AEP, auditory evoked potentials; AMPA, amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; BDNF, brain-derived neurotrophic factor; CamKII, Ca²⁺-calmodulin-dependent kinase II; cAMP, cyclic adenosine monophosphate; CREB, cAMP-response element binding protein; DAG, diacylglycerol; EEG, electroencephalography; EPSP, excitatory postsynaptic potential; ER, endoplasmic reticulum; ERK, extracellular signal regulated kinase; Erra, estrogen-related receptor- α ; FNDC5, fibronectin type III domain-containing protein 5; fMRI, functional magnetic resonance imaging; fNIRS, functional near-infrared spectroscopy; GABA, γ -aminobutyric acid; GH, growth hormone; IGF-1, insulin-like growth factor-1; IPSP, inhibitory postsynaptic potentials; IP3, inositol 1,4,5 triphosphate; LTD, long-term synaptic depression; LTP, long-term synaptic potentiation; mRNA, messenger-ribonucleic acid; NMDA, N-methyl-D-aspartate receptor; PGC1 α , peroxisome proliferator-activated receptor- γ coactivator 1 α ; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PLC γ , phospholipase C- γ ; 1H-MRS, proton magnetic resonance spectroscopy; SIRT-1, silent information regulator 1; TMS, transcranial magnetic stimulation; TrkB, tropomyosin-receptor kinase-B receptor; VEP, visually-evoked potentials; VIP, vasoactive intestinal peptide.

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importance in this respect is neuroplasticity (Martin et al., 2000; Autio et al., 2020). Neuroplasticity refers to the brain's ability to undergo functional and structural changes in response to external or internal stimuli from the environment or organs in the body (Voss et al., 2017). Currently, there is a vast amount of research showing that neuroplasticity could well be induced by acute (i.e., a single bout) or chronic (i.e., a program of multiple bouts) exposure to physical exercise (Knaepen et al., 2010; Svensson et al., 2015; Vilela et al., 2017; Müller et al., 2020).

At the level of the brain, acute exercise studies in humans have discovered transient changes in neurotransmitter levels like glutamate and γ -aminobutyric acid (GABA) immediately following physical exercise, as measured with proton magnetic resonance spectroscopy ($^1\text{H-MRS}$) (Maddock et al., 2016). Both glutamate and GABA are important neurotransmitters in the mammalian brain and are known to be primary mediators of long-term synaptic potentiation (LTP) and long-term synaptic depression (LTD) through glutamatergic (see Box 1) and GABAergic pathways. LTP and LTD are neuroplastic processes, which respectively cause strengthening or weakening of excitatory synaptic connections within the brain (Lisman, 2001). Both induce changes in the synapse involving a rapid, short-lasting alteration of the function of existing synaptic proteins by processes such as phosphorylation (i.e., early LTP or LTD) and a slower, longer-lasting change in the availability

of synaptic proteins by targeting cell DNA and inducing transcription of new proteins (i.e., late LTP or LTD) (Loprinzi, 2019).

'LTP-like' processes (i.e., the increased efficacy of synaptic neuro-transmission through neural networks) are found in many brain regions, playing a critical role in several domains of cognitive function (Martin et al., 2000). For example, disruption of LTP-like processes in the hippocampal, prefrontal, visual, auditory, and motor cortex were respectively suggested to result in an impairment of episodic memory function (Chen et al., 2000; Barnes, 2003), working memory and executive function (Dallérac et al., 2011), visual (Yeap et al., 2008), auditory (O'Donnell et al., 2004), and motor processing (Frantseva et al., 2008). These disruptions can be found with aging (Barnes, 2003), Alzheimer's disease (Chen et al., 2000), major depression (Normann et al., 2007), and other psychiatric (Frantseva et al., 2008; Yeap et al., 2008) and neurological disorders (Rison and Stanton, 1995; Bliss and Cooke, 2011; Dallérac et al., 2011; Conte et al., 2012). While the direct measurement of LTP requires invasive *in vivo* or *in vitro* electrophysiological tests, LTP-like processes can also be assessed with non-invasive techniques. For example, LTP-like processes in the human motor cortex can be assessed with transcranial magnetic stimulation (TMS) (Frantseva et al., 2008). Furthermore, electroencephalography (EEG) (Kirk et al., 2010) can show LTP-like processes in the visual cortex by measuring visually-evoked potentials (VEP) (Yeap et al., 2008), or in the auditory cortex by

Box 1

The long-term synaptic potentiation process (LTP).

LTP is mediated primarily through glutamatergic pathways. In glutamatergic synapses, a signal in the form of an action potential is transmitted from one neuron to the next by the release of glutamate from the presynaptic neuron and the subsequent activation of glutamatergic amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors in the postsynaptic neuron. Postsynaptic AMPA receptor activation causes influx of Na^+ , depolarizing the postsynaptic membrane, which is measured as an excitatory postsynaptic potential (EPSP) with patch clamp techniques. If many EPSPs from multiple excitatory synapses accumulate, depolarization reaches the threshold for the generation of a new action potential and the neural signal is transmitted. LTP is an activity-dependent process that makes the synapse become more responsive to subsequent stimuli, increasing the chance an action potential will be generated in the postsynaptic neuron. The activity-dependence lies in the fact that repeated excitatory stimulation causes the synaptic connections to become more and more strengthened (Lisman, 2001; Vaynman et al., 2003; Marsden et al., 2010). LTP is likely dependent on the activation of Ca^{2+} -sensing signaling pathways, which is (at least in part) mediated by activation of pre- and postsynaptic N-methyl-D-aspartate (NMDA) receptors. These Ca^{2+} -permeable receptors require membrane depolarization and activation by glutamate to open (Fig. 1). In the *presynaptic neuron*, depolarization of the presynaptic membrane by an action potential first activates voltage-gated Ca^{2+} channels. This facilitates Ca^{2+} -dependent exocytosis of glutamate-containing synaptic vesicles. Consequently, Ca^{2+} influx further increases by the opening of NMDA receptors, which results in the activation of pathways involved in LTP, see section 2. These pathways are mainly thought to involve the increased release of glutamate upon activation by a subsequent action potential. This may result from an increased number of glutamate-containing vesicles available in the reserve pool, an increased number of vesicles being transported from the reserve pool towards the releasable pool, and an increased number of vesicles being released upon Ca^{2+} influx (Loprinzi, 2019). At the *postsynaptic excitatory neuron*, glutamatergic AMPA receptor activation causes influx of Na^+ , depolarizing the postsynaptic membrane. Consequently, NMDA receptors become activated, allowing Ca^{2+} to flow into the cell. Postsynaptic Ca^{2+} -sensing pathways result in the activation of kinases, which through phosphorylation induce an increased activity and number of glutamatergic AMPA receptors. This way, the EPSP level in response to a subsequent release of presynaptic glutamate will be enhanced (Lisman, 2001).

Of note, another form of neural plasticity that is mediated through glutamatergic pathways is long-term synaptic depression (LTD). Similar to LTP, LTD is also activated by Ca^{2+} influx inside the cell. In contrast to LTP, phosphatases and not kinases have the overhand during LTD processes at the excitatory glutamatergic synapse. This results in a weakening of glutamatergic synaptic connections, by for example, internalization of AMPA receptors and a decrease in the number of glutamates containing vesicles (Collingridge et al., 2010). LTD has a low intracellular Ca^{2+} threshold, and is typically induced by a prolonged modest increase in Ca^{2+} . In contrast, the induction of LTP requires a brief, but higher amplitude of intracellular Ca^{2+} increase (Yang et al., 1999). An in between zone is also expected to exist, where the amplitude and/or duration of the Ca^{2+} influx is not sufficient for the induction of neither LTP nor LTD (Lisman, 2001). Several pathways may cause that LTD and not LTP would be induced by a Ca^{2+} increase, as is described in more detail by Collingridge et al. (2010). One influential pathway on LTP/LTD we would like to mention is through inhibitory inputs from GABAergic synapses. GABA receptors are Cl^- channels, which hyperpolarize the postsynaptic membrane upon opening, called inhibitory postsynaptic potentials (IPSP). This may cause membrane depolarization by Na^+ not to reach the threshold for opening of NMDA receptors at the glutamatergic synapse upon AMPA activation and Ca^{2+} levels to remain low (Marsden et al., 2010; Mele et al., 2016). Studies have shown that high GABAergic input causes LTD to be induced more readily. This way, a certain concentration of intracellular Ca^{2+} may induce LTD, when in the absence of GABAergic input it would induce LTP or neither LTP nor LTD (Steele and Mauk, 1999). A detailed discussion on the LTD process and the interplay between LTP and LTD is outside the scope of this review paper, but is described in more detail by others, e.g. (Steele and Mauk, 1999; Yang et al., 1999; Lisman, 2001; Collingridge et al., 2010; Marsden et al., 2010; Mele et al., 2016).

using auditory evoked potentials (AEP) (O'Donnell et al., 2004).

Physical exercise can induce either short- or long-lasting neuroplastic changes in the brain. Early LTP is considered a candidate mechanism for the brain's short-lasting functional changes that occur during and/or immediately following acute exercise (Crabbe and Dishman, 2004; Yanagisawa et al., 2010; Singh et al., 2014b; van Dongen et al., 2016). These functional brain changes can be detected with TMS (Singh et al., 2014b), EEG (Crabbe and Dishman, 2004), functional near-infrared spectroscopy (fNIRS) (Yanagisawa et al., 2010), or functional magnetic resonance imaging (fMRI) (van Dongen et al., 2016). In addition, late LTP processes are likely activated during and/or shortly after the exposure to acute exercise, but measurable structural changes have only been observed following chronic exercise (Colcombe et al., 2006; Erickson et al., 2011; Gonzales et al., 2013; Haeger et al., 2019; Herold et al., 2019).

Importantly, the pathways activated in the process of late LTP also increase the transcription of growth and survival stimulating factors, such as brain-derived neurotrophic factor (BDNF). The transcription of BDNF was shown both after acute exercise and chronic exercise (Venezia et al., 2017). The resulting increased availability of BDNF may, in turn, upregulate pathways of neurogenesis, increasing the number of neurons in the dentate gyrus of the hippocampus (Cho et al., 2013). These newly formed neurons were described to activate LTP processes more easily (Snyder et al., 2001; Van Praag et al., 2002). Without effortful learning, and thus the activation of LTP, these new neurons do not survive more than three weeks (Shors et al., 2012). This might indicate that newly formed neurons are dependent on the survival-promoting factors which are being released during LTP for further maturation and to be hooked up into functional networks (Shors et al., 2012; Denoth-Lippuner and Jessberger, 2021). A successful process of neurogenesis might explain the biochemical and structural brain changes reported in chronic exercise studies such as increases in N-acetyl aspartate, a neurometabolic marker of neuronal integrity (Gonzales et al., 2013) measured with ¹H-MRS, and increases in gray matter volume and white matter microstructural organization (Colcombe et al., 2006) measured with magnetic resonance imaging (MRI). These are interesting findings, as higher levels of N-acetyl aspartate and larger brain volume has been associated with better cognitive functioning in older adults (Fjell and Walhovd, 2010; Cleeland et al., 2019).

In sum, a vast amount of research suggests that both acute and chronic exercise have beneficial effects on the biological mechanisms that mediate neuroplasticity, possibly through a physical exercise-induced enhanced response to LTP induction, which in turn induces functional and structural changes to the brain, improving cognitive function (Erickson et al., 2011; Broadhouse et al., 2020). Yet, how muscle activity eventually results in the facilitation of LTP is still a topic of debate. An increasingly popular explanation for the mechanism of cognitive enhancement following physical exercise is the exerkine hypothesis. Exerkines are all of the peptides, metabolites, and nucleic acids released into the bloodstream during and following physical exercise. Depending on the organ they are being released from, they are called myokines, adipokines, or hepatokines, respectively referring to physical exercise-induced factors released from muscle, adipose tissue, or the liver (Pedersen, 2019). Some of these exerkines may cross the blood-brain barrier (Kastin and Akerstrom, 1999; Carro et al., 2000; Dogrukol-Ak et al., 2003; Higuchi et al., 2007; Oury et al., 2013; Agudelo et al., 2014; Ribeiro et al., 2014; Takimoto and Hamada, 2014; Yau et al., 2014; Li et al., 2015; Moon et al., 2016; Serra-Millàs, 2016; Wrann, 2016). It is plausible to assume that exerkines which crossed the blood-brain barrier can facilitate signaling pathways that regulate the induction of LTP.

In this narrative review, we elucidate the possible role that the physical exercise-induced enhancement of the LTP process by the release of exerkines may play in improving brain functions, while showing how it fits the currently popular view that exerkines are involved in multiple signaling pathways that mediate neuroplasticity. As

a general objective, we aim to generate a framework that structures all relevant information about exerkines that are possibly involved in the regulation of early and late stages of LTP in the human brain. We decided to review existing literature on growth factors, myokines, cytokines, metabolites, hormones, and neuropeptides, including only those that are known to be released or generated during physical exercise and appear to have direct or indirect application for the enhancement of early and/or late LTP (Figs. 1 and 2). We purposefully did not review all exerkines that may cross the blood-brain barrier, as for some of them, empirical evidence suggesting the cellular pathway for the facilitation of LTP is not available, unclear, or conflicting. For every exerkine addressed, we will describe their origin, discuss if the effect is to be expected after acute or chronic exercise and differentiate between cardiovascular or resistance exercise (Table 1). In section two, the process of LTP will be explained in short, focused on the pathways important for discussion in the remainder of the paper. In section three, 16 exerkines of interest will be addressed one by one. We start with growth factors (i.e., brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and growth hormone (GH)), followed by pro- and anti-inflammatory biomarkers (i.e., cytokines and kynurenine), of whom some are myokines. Then, we discuss other myokines (i.e., irisin, cathepsin-B, apelin, and adiponectin) and metabolites (i.e., lactate and β -hydroxybutyrate (BHB)). At last, we describe the remaining exerkines that could not be placed in any of the other groups (i.e., osteocalcin, orexin-A, ghrelin, and vasoactive intestinal peptide (VIP)). In sections four and five, we summarize the most interesting conclusions to be drawn from this comprehensive review paper and propose how this information can be used for future research.

2. Long-term synaptic potentiation

For the sake of clarity, we briefly report the most important intracellular pre- and postsynaptic pathways involved in LTP (Fig. 1). At the *presynaptic* neuron, activation of N-methyl-D-aspartate (NMDA)-type ionotropic glutamate receptors induces Ca^{2+} -triggered autophosphorylation of Ca^{2+} -calmodulin-dependent kinase II (CamKII). In turn, CamKII activates synapsin I by phosphorylation and mediates the transcription of synapsin I via phosphorylation of the transcription factor cyclic adenosine monophosphate (cAMP)-response element binding protein (CREB) (Vaynman et al., 2003; Murray and Holmes, 2011). Synapsin I controls the fraction of synaptic vesicles available for release. After activation of synapsin I, synaptic vesicles from the reserve pool are transferred to the releasable pool. Moreover, elevated synapsin I levels at the presynaptic terminal are thought to increase the rate of synaptic vesicle recycling and formation. This is important to prevent synaptic fatigue due to vesicular rundown on subsequent stimulation (Vaynman et al., 2003; Gerth et al., 2017). In addition, calcium-sensitive adenylyl cyclases activate cAMP-dependent protein kinase A (PKA). PKA is also capable of phosphorylating synapsin I (Chenouard et al., 2020). For a more elaborate overview of presynaptic mechanisms, we refer to the review of Yang and Calakos (2013).

At the *postsynaptic* neuron, NMDA-dependent Ca^{2+} influx also activates CamKII. Here, CamKII phosphorylates amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, making them more easily activated. Also, CamKII enhances surface AMPA receptor levels by inducing exocytosis of internalized receptors in the membrane surface (Lu et al., 2001) and de novo synthesis of AMPA receptors via activation of the transcription factor CREB (Middei et al., 2013). Next, PKA stimulates CamKII activity by inhibiting protein phosphatase-1, it potentiates AMPA receptors by phosphorylation (Roche et al., 1996), and also activates CREB (Winder and Sweatt, 2001).

In addition to NMDA-receptors, several exerkines, such as BDNF and IGF-1, have been found to activate pre- and postsynaptic intracellular pathways with similar effects (Fig. 1). These exerkine-induced pathways can transiently potentiate the response of presynaptic synapsin I or postsynaptic AMPA receptor activity during the activation of a

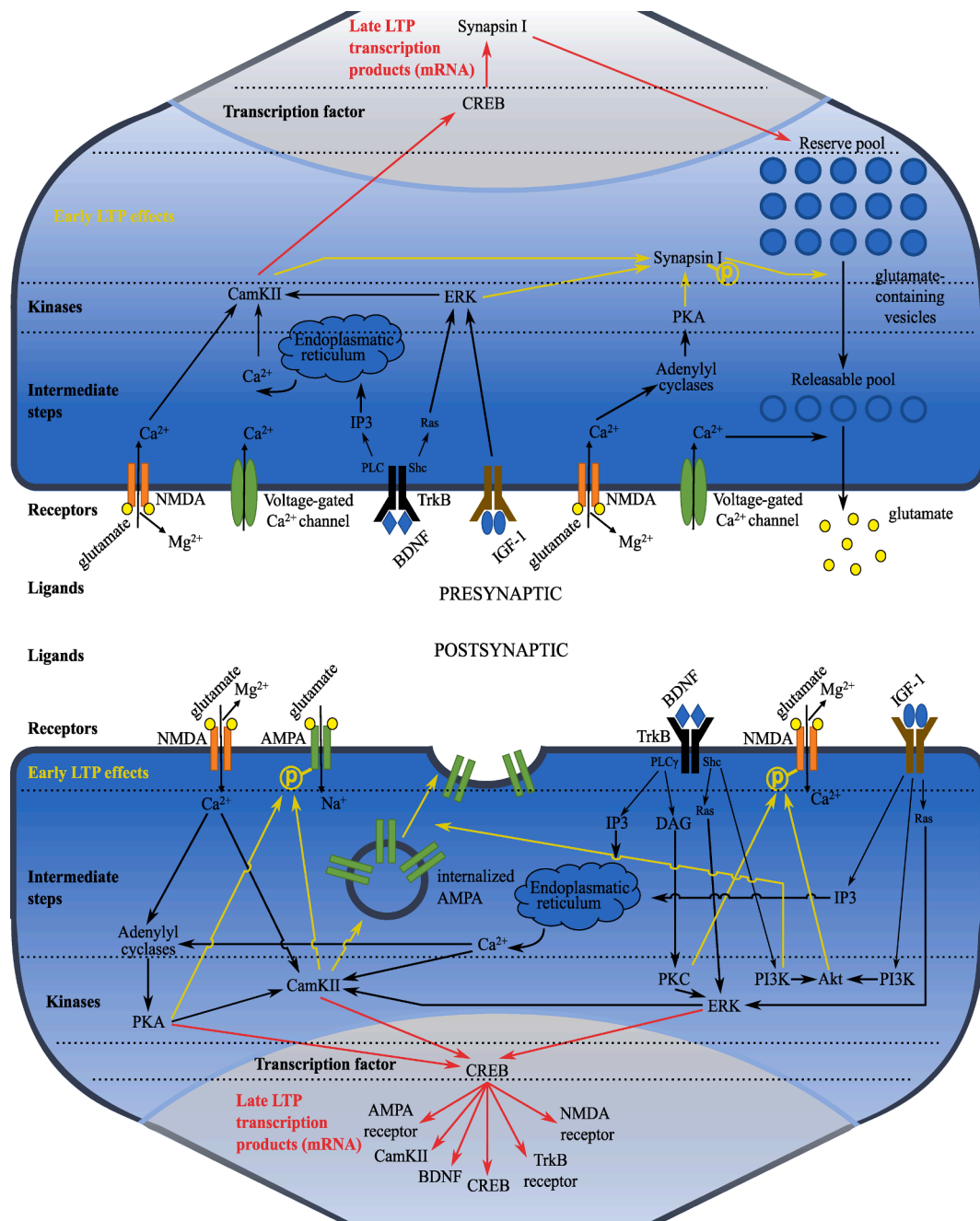


Fig. 1. Visual representation of the early and late LTP pathways in the pre- and post-synaptic excitatory neuron. Abbreviations: Ca²⁺, calcium; AMPA, amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; BDNF, brain-derived neurotrophic factor; CamKII, Ca²⁺-calmodulin-dependent kinase II; CREB, cAMP-response element binding protein; DAG, diacylglycerol; ERK, extracellular signal regulated kinase; IGF-1, insulin-like growth factor-1; IP3, inositol 1,4,5 triphosphate; LTP, long-term synaptic potentiation; mRNA, messenger-ribonucleic acid; NMDA, N-methyl-D-aspartate; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; TrkB, tropomyosin-receptor kinase-B receptor.

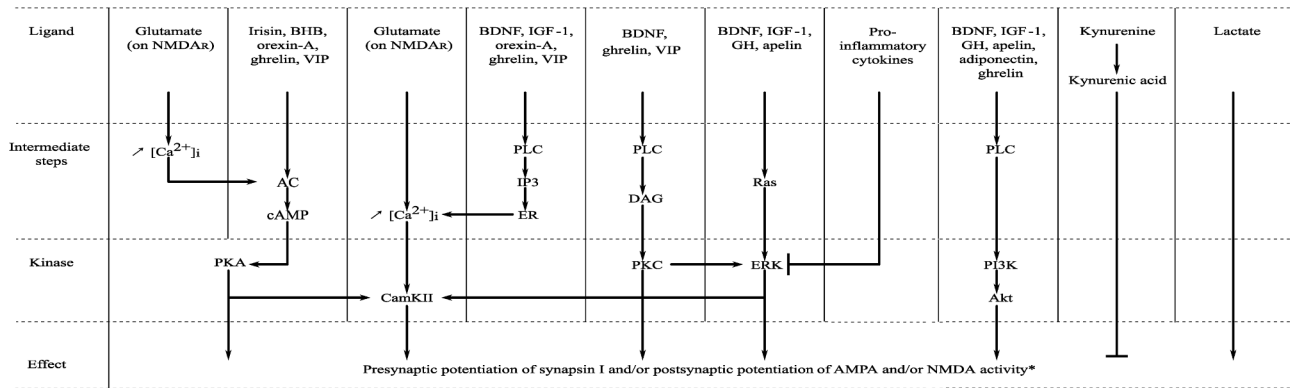
subsequent LTP process by phosphorylation (i.e., early LTP) or by inducing transcription of synapsin I and AMPA receptors by activating the transcription factor CREB (i.e., late LTP) (Vaynman et al., 2003; Prescott et al., 2006; Kim et al., 2010; Murray and Holmes, 2011; Molina et al., 2012; Ribeiro et al., 2014; Wang et al., 2019). Furthermore, some exerkines were reported to indirectly increase the effect of the following LTP induction. For example, by potentiating NMDA receptors, or by inducing transcription or enhancing activity of proteins critical for LTP, like NMDA receptors, downstream products like CamKII and CREB, or BDNF, IGF-1 and their receptors (Fig. 2) (Carro et al., 2001; Vaynman et al., 2003; Ding et al., 2006; Yang et al., 2009; Kim et al., 2010; Molina et al., 2012; Yang et al., 2014; Wang et al., 2019). Other exerkines may

play a regulatory role by modulating synaptic transmission (e.g., kynurenine) (Rózsa et al., 2008; Potter et al., 2010; Demeter et al., 2013; Vécsei et al., 2013) or transcription of other exerkines (e.g., lactate and osteocalcin) (Wrann et al., 2013; Khirmian et al., 2017; Nicolini et al., 2020). These findings underscore how physical exercise may facilitate pathways involved in the LTP process by increasing the circulating levels of these exerkines. We will discuss these exerkine-induced pathways in more detail below.

3. Exerkines with the potential to alter LTP-related pathways

In this section, we will describe the role of 16 different exerkines on

Early LTP



Late LTP

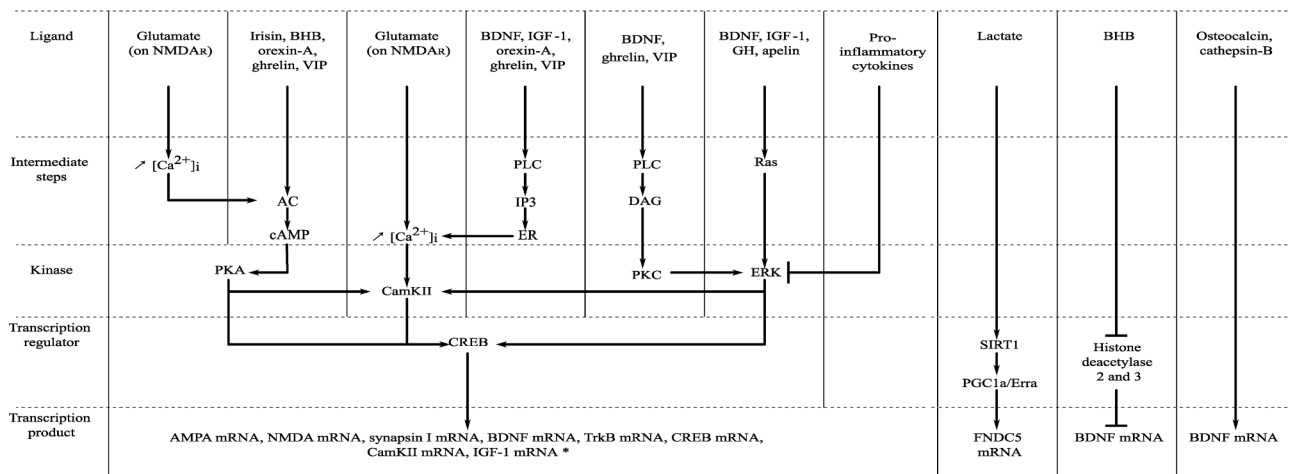


Fig. 2. Schematic overview of the exerkin-mediated pathways associated with early and late LTP in the pre- and postsynaptic excitatory neuron. * Pre- and postsynaptic pathways are not considered separately. In addition, for some of the exerkin, the intermediate steps are currently not completely understood. We refer to the accompanying text for more details. Abbreviations: [Ca²⁺]_i, intracellular calcium concentration; AC, adenylyl cyclase; AMPA, amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; BDNF, brain-derived neurotrophic factor; BHB, β-hydroxybutyrate; CamKII, Ca²⁺-calmodulin-dependent kinase II; cAMP, cyclic adenosine monophosphate; CREB, cAMP-response element binding protein; DAG, diacylglycerol; ER, endoplasmic reticulum; ERK, extracellular signal regulated kinase; Erra, oestrogen-related receptor-α; FND5, fibronectin type III domain-containing protein 5; GH, growth hormone; IGF-1, insulin-like growth factor-1; IP3, inositol 1,4,5 triphosphate; LTP, long-term synaptic potentiation; mRNA, messenger-ribonucleic acid; NMDAR, N-methyl-D-aspartate receptor; PGC1α, peroxisome proliferator-activated receptor-γ coactivator 1α; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; SIRT-1, silent information regulator 1; TrkB, tropomyosin-receptor kinase-B receptor; VIP, vasoactive intestinal peptide.

LTP. These include growth factors, myokines, cytokines, metabolites, hormones, and neuropeptides that are released during physical exercise and have the potential to alter LTP-related pathways. When evidence on the exerkin-mediated facilitation or impairment of LTP-related pathways was not available, unclear or conflicting, the exerkin was not included in this paper, even if the concerned exerkin was known to cross the blood–brain barrier. We will report how the included exerkins are upregulated by physical exercise and the organ of their origin. Furthermore, we will highlight the possible synaptic pathways that they may activate (Fig. 2). Finally, we will discuss if the effect is to be expected after acute or chronic exercise and differentiate between cardiovascular or resistance exercise (Table 1). Findings from both animal and human studies are included. A detailed description of study characteristics including mean age of the subjects, gender of the subjects, healthy/unhealthy study population, fitness level of the subjects, physical exercise duration, physical exercise intensity, and the direction of the (subgroup specific) significant/insignificant changes of the levels of a certain exerkin following acute/chronic cardiovascular/resistance exercise of all physical exercise studies described in this section is provided in Supplementary Table S1 (for blood exerkin levels) and S2 (for

brain exerkin levels). Table 1 can be considered a short summary of Supplementary Table S1 and S2.

3.1. Growth factors

3.1.1. Brain-derived neurotrophic factor (BDNF)

BDNF is recognized as a growth factor with a wide repertoire of neurotrophic and neuroprotective properties in the CNS and the periphery (Knaepen et al., 2010). It can be produced by neurons (Lessmann et al., 2003), astrocytes (Numakawa et al., 2010), and endothelial cells (Wang et al., 2006) within the brain. During physical exercise, an increase in circulating BDNF levels may result from the release of BDNF from skeletal muscle cells or platelets (Antony and Li, 2020; Le Blanc et al., 2020; Farmer et al., 2021). Skeletal muscle cells may synthesize (Matthews et al., 2009) and release BDNF into the circulation (Máderová et al., 2019) in response to physical exercise. Platelets were found to contain 99% of circulating BDNF (Radka et al., 1996). The number of circulating BDNF-containing platelets is increased during physical exercise when the activation of the sympathetic system causes splenic constriction (Ahmadzad and El-Sayed, 2003; Stewart et al., 2003). At

Table 1
Overview of exerkines that influence LTP.

Peripheral versus central measurements:		BLOOD				BRAIN			
Acute versus chronic exercise:		Acute		Chronic		Acute		Chronic	
Cardiovascular (C) versus resistance (R) exercise:		C	R	C	R	C	R	C	R
Growth factors	BDNF	↗ ^{d,f,g}	↗ ^{d,f,g}	↗	↗ ^a	↗	NA	↗	↗
	IGF-1	↔	↗	↔ ^a	↔ ^{a,g}	↗*	X	↗	↗
	GH	↗ ^a	↗ ^a	↗	X	NA	NA	↗	NA
Pro-inflammatory markers	IL-1β, TNFα, IL-6	↗	↗	↔ ^o	↘	↗	NA	↔ ^o	↘
	Kynurenine	↗ ^a	↗	X	↘ ^c	NA	NA	NA	NA
Anti-inflammatory markers	IL-4, IL-10	↗	↗	↗	↗	↗	NA	↗	↗
Myokines [±]	Irisin	↗ ^e	↗	↔ ^{s,a}	↔ ^{a,d,i,w}	NA	NA	↗	NA
	Cathepsin-B	X*	X*	↗*	↗	NA	NA	↗*	X*
	Apelin	↗	↗	↔ ^{a,c,w}	↔ ^{c,w}	NA	NA	NA	NA
	Adiponectin	↔	X	↗ ^w	↗ ^{i,w}	NA	NA	NA	NA
Metabolites	Lactate	↗ ⁱ	↗ ⁱ	NA	NA	↗ ⁱ	NA	↗*	NA
	β-hydroxybutyrate	↗	↗*	↗	↗ ^{s,w}	↗ ^h	NA	↗	NA
Other exerkines [±]	Osteocalcin	↗ ^{a,g}	X	↗	↗	NA	NA	NA	NA
	Orexin-A	↗	NA	↗*	NA	↗	NA	NA	NA
	Ghrelin	↔ ⁱ	↘	↗ ^w	↗	NA	NA	NA	NA
	VIP	↗	NA	↗	NA	NA	NA	NA	NA

The direction of significant changes in exerkine levels were reported as follows: '↗', at least one study found a significant increase and no studies were found that reported significant decreases; '↘' at least one study found a significant decrease and no studies were found that reported significant increases; '↔' inconsistent, with studies indicating both significant increases and decreases. 'X', no significant effect reported by any of the studies found; 'NA', no studies available. '*', was used to mark studies where the arrow's direction was only based on data from 1 study.

It is indicated whether studies have measured these alterations in biomarker levels in peripheral circulation (BLOOD) or behind the blood–brain barrier (BRAIN), after Acute or Chronic exercise, and cardiovascular (C) or resistance (R) exercise. ± All of these factors are considered exerkines. We categorized the exerkines based on how they are most commonly referred to. It should be noted that BDNF, IGF-1, IL-6, etc. can also be considered myokines, as they are to some extent also released from muscle tissue.

Caution is needed when interpreting this table, as findings may be population- or exercise-specific. We refer to the accompanying text and Supplementary Tables 1 and 2 for more details. In addition, letter codes were used to highlight the most important particularities: Significant different results have been reported with 'a', older age (↗ BDNF, IGF-1, kynurenine, irisin, apelin; ↘ GH; X total osteocalcin) or younger age (↘ IGF-1); 'c', conditions such as cancer (↘ kynurenine) or insulin resistance (↘ apelin); 'd', longer exercise duration in minutes (↗ BDNF) or weeks (less than 12 weeks ↗ irisin, greater than 16 weeks ↘ irisin); 'f', higher cardiorespiratory fitness level (↗ BDNF); 'g', female gender (↗ IGF-1) male gender (↗ BDNF, total osteocalcin); 'h', exercise-induced hypoglycemia (↗ β-hydroxybutyrate); 'i', higher exercise intensity (↗ irisin, adiponectin, lactate) or lower intensity (↘ irisin, ↗ ghrelin); 'o', excessive chronic exercise or overtraining (↗ pro-inflammatory factors); 'w', exercise-associated weight loss (↗ irisin, ghrelin, adiponectin; ↘ apelin).

Abbreviations: BDNF, brain-derived neurotrophic factor; IGF-1, insulin-like growth factor-1; IL, interleukin; GH, growth hormone; TNFα, tumor necrosis factor alpha; VIP, vasoactive intestinal peptide.

last, increased shear stress due to acceleration of blood flow during physical exercise causes the release of platelet-derived BDNF (Fujimura et al., 2002). The increased shear stress was also reported in the cerebral vasculature during physical exercise (Jorgensen et al., 1992). However, Pardridge et al. (1994) found that peripherally administered BDNF was rapidly cleared from the systemic circulation and was not able to be delivered to the brain. As was reviewed by Serra-Millàs (2016), the relationship between peripheral and central levels of BDNF remains a topic of discussion. While some studies suggest peripherally administered BDNF may cross the blood–brain barrier or have beneficial effects on central nervous system functioning, several other studies reported blood–brain barrier permeability for BDNF to be poor or absent (Serra-Millàs, 2016). It is possible that the central increases in BDNF availability following physical exercise, as were found in animal studies (see below), merely result from the stimulation of central BDNF synthesis. Other exerkines may be important mediators of this effect. This will be substantiated by pathways of the other exerkines discussed in sections 3.1.2 till 3.5.4, some of whom were found to induce the hippocampal release of BDNF during physical exercise.

3.1.1.1. Pathway. Evidence from studies including animal models suggests that the physical exercise-induced increase of BDNF levels in the brain enhances the response to LTP induction by electrophysiological stimulation (Novkovic et al., 2015; Miao et al., 2021). For example, in wild type and heterozygote BDNF^{+/-} mice, 5 weeks of voluntary physical exercise was found to elevate BDNF levels compared with sedentary controls and enhance LTP activity, measured with in vitro electrophysiological recordings. In the BDNF^{+/-} mice, LTP was initially impaired, but physical exercise restored it to the level of sedentary wild type mice

(Novkovic et al., 2015). Another study reported a dose-dependent enhancement of synaptic responses to electrophysiological stimuli after BDNF administration on slices of the anterior cingulate cortex of male mice in vitro (Miao et al., 2021). BDNF acts via tropomyosin-receptor kinase-B (TrkB) receptors in the postsynaptic density of the excitatory synapse (Figs. 1, 2). TrkB receptors mediate many signaling cascades involved both in early and late LTP (Müller et al., 2020). Specifically, BDNF binding to the TrkB receptor causes dimerization and autophosphorylation of the receptor. Consequently, docking sites for Src homology 2 domain-containing adapter protein (Shc) and phospholipase C-γ (PLCγ) emerge. Shc is coupled with Ras and phosphoinositide 3-kinase (PI3K) signaling cascades. Ras activates extracellular signal regulated kinase (ERK), a member of the mitogen-activated protein kinases (MAPK) that may, in turn, activate several other pathways by phosphorylating its target (Murray and Holmes, 2011). For example, on rat hippocampal slices, inhibition of ERK was found to prevent the phosphorylation of CamKII, which is crucial in the LTP process (Giovannini et al., 2001). ERK also activates CREB (Finkbeiner et al., 1997) and following a physical exercise-induced rise in BDNF, CREB was seen to induce its own gene expression, thereby increasing the number of CREB molecules (Vaynman et al., 2003). Moreover, CREB was found to induce the upregulation of BDNF in response to Ca²⁺ influx in the postsynaptic cell (Shieh and Ghosh, 1999), CamKII during the process of LTP (Giovannini et al., 2001), NMDA receptor transcription following administration of BDNF (Caldeira et al., 2007) and TrkB receptors following physical exercise in response to increased BDNF levels (Vaynman et al., 2003). Ras also promotes the activation of PI3K. In turn, PI3K activates Akt, which counteracts pro-apoptotic proteins, stimulating survival (Murray and Holmes, 2011). Both Ras and PI3K

signaling cascades were found to lead to the phosphorylation of NMDA receptors following administration of BDNF on cultured mouse hippocampi, increasing NMDA receptor open probability (Xu et al., 2006). Furthermore, PI3K was involved in increasing surface AMPA receptor expression during LTP in cultured hippocampal neurons (Man et al., 2003). Results from Vaynman et al. (2003) suggested that the interplay between the TrkB and NMDA receptor signaling cascades is crucial for the CREB-mediated transcription of BDNF, TrkB, CREB and synapsin I mRNA, as blocking of any of these two receptors fully abrogated the physical exercise-induced increases in these transcripts (Vaynman et al., 2003). Next to the Shc induced pathways, PLC γ will promote another pathway starting with the catalyzation of lipids to inositol 1,4,5 triphosphate (IP3). IP3 binds to receptors on the endoplasmic reticulum, triggering calcium release (Yamamoto et al., 2000). This calcium release enhances LTP through activation of the CamKII and PKA mediated pathways similarly as upon activation of NMDA-receptors. Furthermore, IP3 activity is required to keep AMPA receptors clustered at the post-synaptic membrane, as shown on hippocampal slices (Arendt et al., 2010). PLC γ also induces an increase in diacylglycerol (DAG), which regulates protein kinase C (PKC). In turn, PKC might be required for the ERK cascade (Murray and Holmes, 2011) and was found to potentiate AMPA receptors by phosphorylation in cultured neurons during LTP (Roche et al., 1996).

BDNF also binds TrkB receptors at the *presynaptic* neuron of the excitatory synapse (Figs. 1, 2). Here, *in vitro* examination found that ERK signaling activates synapsin I by phosphorylation, targeting synaptic vesicles from the reserve pool toward the releasable pool (Jovanovic et al., 1996). Moreover, BDNF-mediated activation of the PLC/IP3 pathway will increase presynaptic intracellular Ca²⁺-levels. This increases CamKII signaling and results in CREB-mediated transcription of synapsin I. Synapsin I levels were found to increase following cardiovascular exercise, which was abrogated after blocking CamKII (Vaynman et al., 2003; Murray and Holmes, 2011).

3.1.1.2. Acute exercise effect. Both acute cardiovascular and resistance exercise were found to transiently increase circulating BDNF in a *meta-analysis* that included 47 studies on cardiovascular exercise and eight studies on resistance exercise (Dinoff et al., 2017). Dinoff et al. (2017) reported that physical exercise with a duration of more than 30 min induced higher elevations of circulating BDNF than shorter physical exercise bouts. They also found that plasma BDNF measurements increased more in response to physical exercise compared to serum measurements and that studies including more males had greater effect sizes than those where the majority of participants were females. With approximately three-quarters of all participants in the included acute exercise studies being males, subgroup analysis revealed that only in males significant increases in circulating BDNF were found (Dinoff et al., 2017). This might be due to that women already have higher basal serum BDNF levels than men (Glud et al., 2019). It was reported that estrogen levels influence circulating BDNF levels and BDNF signaling pathways (Harte-Hargrove et al., 2013; Dong et al., 2017). Furthermore, Dinoff et al. (2017) found no significant difference in effect sizes associated with age, with most acute exercise studies including young adults. At last, higher cardiorespiratory fitness was associated with greater increases in circulating BDNF (Dinoff et al., 2017).

In the brain, studies in male rats showed that acute voluntary wheel running induced elevated levels of hippocampal BDNF (Oliff et al., 1998; Takimoto and Hamada, 2014).

3.1.1.3. Chronic exercise effect. While Knaepen et al. (2010) concluded in their review that chronic exercise is rather unlikely to elevate basal BDNF concentration in healthy adults, more recent *meta-analyses* did find small effects in favor of a peripheral BDNF rise of baseline levels in response to regular cardiovascular exercise (Szuhany et al., 2015; Dinoff et al., 2016). Moreover, in a systematic review including older adults

with cognitive decline, serum levels of BDNF significantly rose after chronic cardiovascular training (de Assis and de Almondes, 2017). However, this was not confirmed in a more recent *meta-analysis* including older adults with or without cognitive decline (Marinus et al., 2019). The latter *meta-analysis*, including eight resistance training and four combined cardiovascular and resistance training studies, stated that in order to increase baseline BDNF levels, resistance training is an essential component of the physical exercise program in older adults (Marinus et al., 2019). In contrast, the *meta-analysis* of Dinoff et al. (2016), including healthy adults of all ages, did not find an effect of chronic resistance training on resting circulating BDNF levels. Therefore, this effect is probably age-specific (Table 1), although future studies are needed to confirm the inference we make here. Moreover, Dinoff et al. (2016) did not report effect differences dependent on physical exercise intervention characteristics such as duration, frequency, or intensity. In addition, there was no difference between BDNF rises measured in serum or plasma. Finally, age, gender, and body mass index were not related to the effect found after chronic exercise (Dinoff et al., 2016).

Brain levels of BDNF, TrkB and CREB in male rat hippocampus did also increase after chronic cardiovascular (Vaynman et al., 2003; Berchtold et al., 2005; Cassilhas et al., 2012) and resistance training (Tang et al., 2017; Vilela et al., 2017). It was shown that 3 weeks of running resulted in elevated hippocampal BDNF levels until 2 weeks after cessation of physical exercise (Berchtold et al., 2010). In the study of Tang et al. (2017), the resistance trained male diabetic rats showed a higher upregulation of TrkB and CREB genes than cardiovascular trained diabetic rats.

3.1.2. Insulin-like growth factor-1 (IGF-1)

IGF-1 plays a role in enhancing insulin action (Moses et al., 1996), and decreased levels of IGF-1 are associated with age-related sarcopenia (Mak and Rotwein, 2006; Bian et al., 2020). It is secreted both centrally and peripherally and may cross the blood-brain barrier (Carro et al., 2000). The central release has been shown in regions of the brain involved in postnatal neurogenesis, e.g. hippocampus, cerebellum, and olfactory bulb (Wrigley et al., 2017). IGF-1 release in the brain was inconsistently indicated as being regulated by growth hormone (GH) (Furigo et al., 2018) or being GH-independent (Lupu et al., 2001). Peripherally, GH is considered to mediate the main release of IGF1- from the liver (Schwander et al., 1983). During physical exercise, circulating IGF-1 levels were found to increase rapidly in some studies, which indicates it is most likely released from IGF-1 stores and not mediated by GH-induced transcription (Berg and Bang, 2004). It was suggested that muscle cells contain such IGF-1 stores that are released upon muscle contraction (Pedersen, 2019). Furthermore, IGF-1 mRNA expression was found to be upregulated in contracting muscles independently of GH (Berg and Bang, 2004). However, the increase in circulating IGF-1 levels is only inconsistently reported. A possible explanation was given by Carro et al. (2000) who indicated that after acute cardiovascular exercise brain IGF-1 levels increased, while circulating levels did not. They suggested that physical exercise might increase the uptake of IGF-1 in the brain (and other target organs) in association with its release from muscle and liver into the blood stream, keeping circulating IGF-1 levels relatively stable. Depending on the strength of this increased uptake, researchers might find increased, unchanged, or decreased circulating IGF-1 levels after physical exercise (Carro et al., 2000).

3.1.2.1. Pathway. *In vitro* examinations by Zheng and Quirion (2004) and Ding et al. (2006) using hippocampal cultured neurons showed that the IGF-1 receptor shares downstream signaling cascades with the TrkB receptor in pre- and postsynaptic excitatory neurons (Figs. 1, 2). Hence, similarly to BDNF, IGF-1 is thought to activate PI3K/Akt, IP3/CamKII, and Ras/ERK pathways. Zheng and Quirion (2004) indicated IGF-1 causes rapid and sustained activation of Akt signaling, while it

mediated only transient ERK signaling. The inverse was observed for BDNF, i.e. a transient activation of Akt signaling and a sustained activation of ERK signaling. Furthermore, systemic injection of IGF-1 or physical exercise-induced elevations of IGF-1 was found to increase transcription of hippocampal BDNF (Carro et al., 2001; Ding et al., 2006) and IGF-1 (Ding et al., 2006) and intracerebroventricular administration of IGF-1 reversed the age-related decline in the number of NMDA receptors (Sonntag et al., 2000). Blocking the IGF-1 receptor partly disrupted the physical exercise-induced increase of hippocampal BDNF levels and decreased memory recall performance (Ding et al., 2006). To our knowledge, no studies have directly assessed the effect of physical exercise-induced IGF-1 on the increased response to induction of LTP.

3.1.2.2. Acute exercise effect. Several reviews and meta-analyses confirmed that acute resistance exercise may increase circulating IGF-1 (Berg and Bang, 2004; de Alcantara Borba et al., 2020; Gulick et al., 2020), while the findings concerning acute cardiovascular exercise are equivocal (de Alcantara Borba et al., 2020; Gulick et al., 2020).

In the brain, there was evidence to suggest that acute cardiovascular exercise increases IGF-1 levels (Carro et al., 2000). This was not confirmed in a more recent study (Takimoto and Hamada, 2014). To the best of our knowledge, there are only two studies that examined the effect of acute resistance exercise on brain IGF-1 levels and signaling. One studied male rats (Fernandes et al., 2016) while the other used female rats (Kelty et al., 2019). Both failed to find an effect. Fernandes et al. (2016) indicated that this may have been caused by the time of sample collection, which was 24 h after exercise, while circulating IGF-1 levels after acute exercise typically return back to baseline after 15 to 30 min post-exercise (Rubin et al., 2005; West et al., 2009; Rojas Vega et al., 2010; Tsai et al., 2015). Also in the study of Kelty et al. (2019), rats were killed and brain tissue was collected only 24 h after the resistance exercise session.

3.1.2.3. Chronic exercise effect. In a systematic review by Stein and colleagues (2018), circulating levels of IGF-1 were not found to be elevated after chronic cardiovascular exercise in older adults. Only one out of five studies found increased IGF-1 levels after cardiovascular exercise, while one even reported a decrease. This review included only two resistance training studies (Stein et al., 2018). Both of them showed increased IGF-1 levels (Cassilhas et al., 2007; Tsai et al., 2015; Stein et al., 2018). More recent meta-analyses confirmed that IGF-1 may increase following resistance training, but only in women more than 40 years old, while at younger age IGF-1 levels might even decrease following resistance training (Jiang et al., 2020; Ye et al., 2020; Amiri et al., 2021).

Finally, evidence from animal models suggests that physical exercise training had no differential effect on the levels of IGF-1 in the brain as a function of gender. Specifically, it was found that hippocampal IGF-1 levels increased both in male and female rats following chronic cardiovascular training (Ding et al., 2006; Gomes et al., 2009; Wong-Goodrich et al., 2010; Cassilhas et al., 2012) and resistance (Cassilhas et al., 2012; Kelty et al., 2019) exercise.

3.1.3. Growth hormone (GH)

GH is produced by the pituitary gland in response to GH-releasing hormone or somatostatin release from the hypothalamus. Most of the GH release occurs during sleep (Sonntag et al., 2005), but it is also released from the pituitary gland during physical exercise (Galbo, 1993). GH is thought to play a role in the post-exercise repair of tissues and synthesis of new tissues by stimulating protein anabolism. Furthermore, it helps to prepare the individual for future physical exercise bouts by enhancing the synthesis of gluconeogenic and lipolytic enzymes (Galbo, 1993). Decreased GH levels are related to age-related sarcopenia in human subjects (Bian et al., 2020). While studies before

the year 2000 hypothesized that all of the cognitive effects of GH were mediated through its induction of IGF-1-synthesis, since then, some studies have indicated direct effects of GH on cognition (Sonntag et al., 2005).

3.1.3.1. Pathway. In the hippocampus, GH was found to induce dimerization of its receptor upon binding, which in turn activates Janus kinase 2 (JAK2). Activated JAK2 induces signaling cascades including PI3K/Akt and Ras/ERK. Via ERK, GH can also induce CREB activation. These pathways are very similar to the IGF-1 pathways and are shared with some of the BDNF pathways. GH receptor activates these pathways via JAK-mediated phosphorylation of non-receptor tyrosine kinases. In contrast, IGF-1 and BDNF receptors are receptor tyrosine kinases that can phosphorylate signaling molecules by themselves (Lobie et al., 2000). It was shown that a period of daily GH injections facilitated LTP, restored age-related and sleep deprivation-induced alterations in NMDA receptor-dependent synaptic transmission, and enhanced AMPA receptor activity, as shown on CA1 hippocampal slices (Kim et al., 2010; Molina et al., 2012). At last, GH can stimulate neural IGF-1 signaling by inducing its transcription (Furigo et al., 2018). We found no studies that examined the direct link between physical exercise-related increases in GH and the physical exercise-induced facilitation of LTP. Hence, this relationship can only be inferred from models that investigated the effect of GH administration (Kim et al., 2010; Molina et al., 2012).

3.1.3.2. Acute exercise effect. Both acute cardiovascular and resistance exercise were found to induce increases in GH levels in a systematic review (Wideman et al., 2002). It was indicated that this effect occurred both in men and women with similar levels being attained during physical exercise, but the increase from baseline was higher in men, with women having higher baseline GH levels. Older adults of both sexes showed an attenuated GH response to acute exercise. Furthermore, higher intensity of cardiovascular or higher volume of resistance exercise was suggested to induce larger GH increases (Wideman et al., 2002). Furthermore, resistance exercise induced higher acute responses than cardiovascular exercise (Consitt et al., 2007).

3.1.3.3. Chronic exercise effect. A systematic review reported that some studies found increased baseline GH levels after chronic cardiovascular exercise, but not following chronic resistance training (Wideman et al., 2002). The authors indicated that resistance exercise only induces an acute elevation of GH. However, resistance training studies that examine baseline 24 h GH measurements (as is advised) remain scarce (Wideman et al., 2002). In the brain, Blackmore and colleagues provided suggestive findings for the induction of GH signaling and activation of neural precursor cells in the subventricular zone after chronic cardiovascular exercise. They showed that in the absence of GH signaling, by administration of GH antagonist or in GH receptor null female mice, cardiovascular exercise training no longer resulted in the activation of neural precursor cells (Blackmore et al., 2009, 2012).

3.2. Pro- and anti-inflammatory markers

3.2.1. Cytokines

Cytokines play a key role in immune responses. Cytokines such as interleukin-1 β (IL-1 β), IL-2, IL-8, IL-12, IL-15, IL-18, tumor necrosis factor- α (TNF- α), and interferon- γ (IFN- γ) are considered to be markers of pro-inflammatory action. On the contrary, the cytokines IL-4 and IL-10 have anti-inflammatory effects (Dai et al., 2013; Svensson et al., 2015; Agudelo et al., 2018). IL-6 activates both pro-inflammatory and anti-inflammatory processes. It is suggested to have a controlling function in inflammation (Smith and Miles, 2000). Some of these cytokines (e.g. IL-1 β , IL-6, and TNF- α) are known to be released by muscle fibers into the bloodstream and, as such, are expected to play a role in the regulation of physical exercise-induced pro-and anti-inflammatory

processes. Peripheral and central inflammatory levels are linked via blood-borne and neural routes of communication. As a result, peripheral inflammation may activate microglial cells in the brain. These innate immune cells react to inflammatory signals by de novo synthesis of inflammatory cytokines, further increasing inflammation within the brain (Barrientos et al., 2015). Chronic elevation of (neuro-)inflammatory markers has previously been linked to obesity, metabolic syndrome, aging, cognitive decline, and many neurodegenerative disorders like Alzheimer's dementia (Kruse et al., 1993; Cotman et al., 2007; Yudkin, 2007; Sartori et al., 2012; Woods et al., 2012; Su et al., 2019).

Adipose tissue, especially visceral fat, is considered one of the largest contributors to systemic inflammation (Yudkin, 2007; Woods et al., 2012). Furthermore, inflammatory markers are secreted by senescent cells. These are old, damaged cells that, as a protective mechanism, have become locked into cell-cycle arrest to prevent the spread of damage and potential malignant transformation. In association, they exhibit altered secretory activity (Coppé et al., 2010; Hernandez-Segura et al., 2017). The number of these cells gradually increases as we get older (Dimiri et al., 1995). The age-related development of a chronic inflammatory status is also found in the brain (Sartori et al., 2012). Indeed, magnetic resonance spectroscopy studies have shown age-related increases in neuro-inflammatory markers in the brain (i.e., myoinositol and choline) (Glanville et al., 1989; Urenjak et al., 1993). Furthermore, stereological findings have indicated increased numbers of glial cells in the frontal and temporal cortex with age (Terry et al., 1987). These glial cells change into their pro-inflammatory phenotype in older adults (Perry et al., 2007; Cohen and Torres, 2019). It was suggested that these changes underlie, at least in part, the process of age-related cognitive decline (Bourgognon and Cavanagh, 2020).

3.2.1.1. Pathway. The effect of IL-1 β , IL-6 and TNF- α , which are the most studied cytokines, on LTP and learning were recently reviewed by Bourgognon and Cavanagh (2020). They describe that the effect is dependent of the intensity and duration of the inflammatory activity. Low brain cytokine levels may exert beneficial effects, while high or long-lasting elevations are detrimental to the LTP process. The latter is typically reported in older adults and neurodegenerative diseases (Bourgognon and Cavanagh, 2020; Ross et al., 2003). At the cellular level, a non-exhaustive summation of the pathways these cytokines interfere in (probably both in a beneficial or detrimental way depending on their concentration) are: the BDNF and IGF-1 signaling pathways, MAPK pathways both involved in synaptic plasticities such as the postsynaptic ERK pathway and those involved in cell damage or cell death such as c-jun N-terminal kinase (JNK) and p38 pathway, and the presynaptic ERK-mediated phosphorylation of synapsin I that induces glutamate release (Bourgognon and Cavanagh, 2020). As an example, excessively high-intense chronic cardiovascular exercise was found to suppress LTP during in vivo recordings in the hippocampal CA1 area in rats, in association with the increased expression of inflammatory factors IL-1 β and TNF- α and induced activation of microglial cells. In addition, the physical exercise paradigm increased levels of phosphorylated JNK, ERK and p38 (Sun et al., 2017). Other studies on mice reported that the detrimental effect of elevated IL-1 β on LTP could be abrogated by the administration of the anti-inflammatory cytokine IL-10 (Lynch et al., 2004; Lenz et al., 2020). While this study did not examine the effect of physical exercise, other studies have reported the circulating level of IL-10 to increase following cardiovascular exercise, e.g., Gomes da Silva et al. (2013).

3.2.1.2. Acute exercise effect. Acute bouts of cardiovascular and resistance exercise were associated with increased circulating levels of both pro- and anti-inflammatory cytokines (Flynn et al., 2007; Koch, 2010; Johnson et al., 2020). The balance between the pro- and anti-inflammatory response to physical exercise is dependent on several factors, including the individual's health status, intensity or duration of

physical exercise, and glucose availability (Flynn et al., 2007). In addition, pro-inflammatory cytokines may increase less following acute exercise in physical exercise-trained individuals, as was reported after six weeks of cardiovascular training (Fonseca et al., 2021). Overall, the regulation of peripheral inflammation by physical exercise is a complex process and will not be addressed in detail in this review paper. For further reading, we refer to other review articles (Cotman et al., 2007; Woods et al., 2012; Su et al., 2019; Scheffer and Latini, 2020).

At brain levels, both pro- and anti-inflammatory cytokines also increased in response to acute cardiovascular exercise (Packer et al., 2010; Lovatel et al., 2013; Packer and Hoffman-Goetz, 2015; Nogueira et al., 2020). However, the link between physical exercise-induced peripheral and central inflammation is not clear. For example, in a study where IL-6 levels in human plasma and cerebrospinal fluid were measured after acute cardiovascular exercise at 60% of VO₂ max, there was an increase in plasma IL-6 without accompanying cerebrospinal fluid IL-6 increase (Steensberg et al., 2006). A more recent study, using a panel with 92 cytokines and chemokines to measure inflammatory markers in cerebrospinal fluid and plasma reported a modest increase in inflammatory markers in cerebrospinal fluid after acute vigorous intensity exercise (Isung et al., 2021). However, after correction for multiple comparisons, only three cerebrospinal fluid and 12 plasma proteins were significantly changed. In line with Steensberg et al. (2006), changes in cerebrospinal fluid IL-6 levels were nonsignificant (Isung et al., 2021). Steensberg et al. (2006) suggested that IL-6 may not reach the brain via the cerebrospinal fluid, but through alternative routes such as via the hypothalamus, which does not have a blood-brain barrier, via afferent nerves, or from local release by endothelial cells or the pituitary gland (Steensberg et al., 2006).

3.2.1.3. Chronic exercise effect. Chronic cardiovascular and resistance exercises were found to reduce blood and brain pro-inflammatory cytokines and elicit anti-inflammatory effects in an impressive array of human and animal research (Flynn et al., 2007; Gibbons et al., 2014; Kim, 2014; Chupel et al., 2017; Liu et al., 2020; Roh et al., 2020). In humans, findings from resistance exercise studies suggested that lower levels of pre-exercise circulating pro-inflammatory factors were associated with better gains in muscle strength (Forti et al., 2014; Hangelbroek et al., 2018; Grosicki et al., 2020). In contrast to the anti-inflammatory effect of chronic exercise, the cytokine hypothesis of overtraining by Smith states that an inadequate recovery between physical exercise bouts would lead to chronic inflammation, associated with fatigue and depression indicative of overtraining (Smith, 2000). Only a limited amount of human studies investigated the effect of overtraining on pro-inflammatory markers, probably due to ethical considerations (Izquierdo et al., 2009; Main et al., 2009; Main et al., 2010; Halson et al., 2003). Most studies measured inflammatory markers immediately after cardiovascular exercise, which needs to be considered an acute exercise effect in excessively trained human subjects. These studies report increased elevations of pro-inflammatory cytokines following a bout of resistance or cardiovascular exercise in overtrained persons (Izquierdo et al., 2009; Main et al., 2009; Main et al., 2010). We also found one study that reported increased morning pro-inflammatory markers before physical exercise in male cyclists during an intense training program (Halson et al., 2003).

On the brain level, animal studies found that chronic exercise decreased microglial activation in the hypothalamus of obese mice (Barrientos et al., 2011; Yi et al., 2012) and in the hippocampus of aged mice (Kohman et al., 2013). Chronic cardiovascular (Liu et al., 2013; Bobinski et al., 2015) and resistance (Liu et al., 2020) exercise decreased central pro-inflammatory cytokines in male rats, and chronic cardiovascular (Gomes da Silva et al., 2013) and resistance exercise (Liu et al., 2020) increased the level of the anti-inflammatory cytokine IL-10 in the hippocampus of healthy old male rats and frontal cortex of male Alzheimer dementia mice, respectively. In contrast, maximal intensity

cardiovascular exercise on seven consecutive days increased the expression of inflammatory factors IL-1 β and TNF- α in the hippocampus of rats and induced the activation of microglial cells (Sun et al., 2017). In healthy human subjects, observations from a recent study by Isung et al. (2021) showed that chronic exercise has only a small effect on inflammation-related protein levels in the cerebrospinal fluid.

3.2.1.4. Kynurenine. Kynurenine is converted from tryptophan by the enzyme indoleamine 2,3 dioxygenase in the liver (Capuron et al., 2011). Pro-inflammatory cytokines, like IL-1 β , TNF- α and IFN- γ have been shown to upregulate indoleamine 2,3 dioxygenase (Allison et al., 2017). In correspondence with high systemic inflammatory cytokine levels, high circulating kynurenine levels were found to be associated with reduced memory performance (Solvang et al., 2019). During physical exercise, the activity of kynurenine aminotransferase is enhanced. This enzyme converts kynurenine into kynurenic acid, which is unable to cross the blood–brain barrier (Agudelo et al., 2014).

3.2.1.5. Pathway. Within the brain, kynurenine can be metabolized into quinolinic acid by macrophages and microglia, or into kynurenic acid by astrocytes. Quinolinic acid leads to overactivation of NMDA receptors, which contributes to excitotoxic neural damage (Vécsei et al., 2013). Furthermore, it was found to have neuroinflammatory action (Stone and Darlington, 2013). In contrast, kynurenic acid was found to be an antagonist of NMDA and α 7 nicotinic acetylcholine receptors (Potter et al., 2010). The latter receptors exist on presynaptic glutamatergic synapses and increase glutamate release from presynaptic neurons upon activation (Vécsei et al., 2013). Similar to inflammatory cytokines, electrophysiological recordings on rat hippocampal slices in the CA1 region showed that perfusion of low concentrations of kynurenic acid was beneficial, while high concentrations were detrimental for LTP (Rózsa et al., 2008). Only perfusion of low concentrations was found to increase AMPA receptor activity (Prescott et al., 2006). In addition, low concentrations of kynurenic acid preferentially antagonized extrasynaptic NMDA receptors, sparing synaptic NMDA and AMPA receptors, while high concentrations completely antagonized both extrasynaptic and synaptic glutamatergic receptors (Rózsa et al., 2008; Demeter et al., 2013; Vécsei et al., 2013). Kynurenic acid was not found to influence the number of NMDA or AMPA receptors (Potter et al., 2010). Of note, none of these studies examined if physical exercise-induced elevations or reductions of kynurenine, quinolinic acid, or kynurenic acid have an influence on LTP.

3.2.1.6. Acute exercise effect. A recent review paper from Joisten and colleagues (2020) that includes their own work reported the effect of acute and chronic exercise on kynurenine. After acute cardiovascular and resistance exercise, circulating kynurenine levels increased, but this elevation was associated with increased kynurenine aminotransferase and kynurenic acid levels (Joisten et al., 2020). In their own work, Joisten et al. (2020) discovered that the kynurenine aminotransferase pathway was elevated to a higher extent following cardiovascular exercise compared with resistance exercise. From the literature review was derived that kynurenic acid/kynurenine ratios increased immediately and 60 min after cardiovascular and immediately after resistance exercise, and kynurenine levels decreased compared with pre-exercise 60 min after resistance or cardiovascular exercise (Joisten et al., 2020). Another study recently reported that acute sprint interval exercise resulted in increased levels of kynurenine 60 min after physical exercise in old but not in young healthy human subjects. The elevation of kynurenine in older adults was followed by increased levels of kynurenic acid 24 h later (Trepici et al., 2020).

3.2.1.7. Chronic exercise effect. Chronic cardiovascular exercise was also found to upregulate muscle kynurenine aminotransferase activity in mice (Agudelo et al., 2014; Ieraci et al., 2020) and humans (Agudelo

et al., 2014; Allison et al., 2019). Agudelo et al. (2014) showed this resulted in increased conversion of kynurenine into kynurenic acid. One other study confirmed decreased kynurenine levels following cardiovascular exercise in mice that received kynurenine injections (Su et al., 2020). In contrast, most studies in humans have only reported trends of decreased circulating kynurenine levels or no effect after chronic cardiovascular or resistance exercise, as recently reviewed by Joisten et al. (2020) and confirmed in more recent studies (e.g., Isung et al. 2021). However, we found two studies that reported a decrease in circulating kynurenine levels after chronic resistance exercise in breast or pancreatic cancer patients, who had elevated baseline levels compared to healthy subjects (Zimmer et al., 2019; Pal et al., 2021). These results are suggestive to assume kynurenine levels only decrease following chronic exercise in conditions where they were elevated at baseline. In subjects with normal baseline levels, the upregulation of kynurenine aminotransferase activity seems only to keep levels in balance when physical exercise bouts tend to increase kynurenine levels.

3.3. Myokines

3.3.1. Irisin

Irisin was initially best known for turning white adipose tissue into brown adipose tissue (Boström et al., 2012). Furthermore, it was suggested to be a marker for muscle mass (Ruan et al., 2020). Irisin is cleaved from the membrane protein FNDC5. This membrane protein is upregulated after activation of the transcriptional regulators: peroxisome proliferator-activated receptor- γ coactivator 1 α (PGC1 α) and estrogen-related receptor- α (ERR α) (Olesen et al., 2010; Wrann et al., 2013). Physical exercise enhances the PGC1 α /ERR α -induced expression of FNDC5 not only in muscle, but also in the hippocampus (Wrann et al., 2013; Wrann, 2016). It is suggested that peripheral, physical exercise-induced irisin can pass through the blood–brain barrier (Wrann, 2016; Lourenco et al., 2019). Finally, observations from an animal model showed that administration of irisin in the hippocampus increased the response to LTP induction by electrophysiological stimuli (Mohammadi et al., 2019).

3.3.1.1. Pathway. Physical exercise was found to upregulate FNDC5/irisin expression and improve LTP in a mouse Alzheimer's dementia model. Downregulating FNDC5/irisin with lentivirus-mediated short hairpin RNA knockdown centrally or with anti-FNDC5 antibodies peripherally caused LTP not to improve following chronic exercise (Lourenco et al., 2019). Physical exercise-induced irisin was found to increase BDNF levels and is thought to affect neurotransmission and/or regulation of LTP in the brain by stimulating the cAMP/PKA/CREB pathway (Wrann et al., 2013; Lourenco et al., 2019). Greater physical exercise-induced increases of irisin were correlated with higher physical exercise-induced BDNF levels (Nicolini et al., 2020). However, it remains unknown which neuronal receptor induces this pathway after being activated by irisin (Chen and Gan, 2019).

3.3.1.2. Acute exercise effect. A systematic review reported that both acute cardiovascular and acute resistance exercise may induce a transient increase in irisin levels, as the authors found in six out of eight included studies (Rodrigues et al., 2016). The two studies that did not find a significant effect used cardiovascular exercise (Pekkala et al., 2013) (Aydin et al., 2013). Tsuchiya et al. (2015) indicated that resistance exercise induces a larger irisin response than cardiovascular exercise alone or resistance and cardiovascular exercise combined. Kraemer et al. (2014) compared young men with women during the early follicular phase and mid-luteal phase of the menstrual cycle, but did not find any differences. Higher intensity cardiovascular exercise was associated with higher levels of irisin (Daskalopoulou et al., 2014; Huh et al., 2014), but there was no significant difference for age or fitness level (Huh et al., 2014).

3.3.1.3. Chronic exercise effect. Wrann et al. (2013) showed that irisin levels could be increased by chronic cardiovascular exercise both in blood and brain. Multiple animal studies using cardiovascular training confirmed their finding (Wrann, 2016; Uysal et al., 2018; Lourenco et al., 2019; Gruhn et al., 2021). In human studies, we found only two studies that showed increases in irisin levels in men following cardiovascular exercise (Boström et al., 2012; Miyamoto-Mikami et al., 2015) while others indicated no significant effect (Pekkala et al., 2013; Norheim et al., 2014; Kim et al., 2016) and one showed decreases following sprint training in young physically active men (Tsuchiya et al., 2016). Miyamoto-Mikami et al. (2015) found only significant increases in irisin levels in middle-aged/older men and not in the young subgroup. Despite that Wrann (2016) stated that resistance training would probably not induce FNDC5 expression, since resistance exercise was found to activate a different isoform of PCC-1 α than cardiovascular exercise (PCC-1 α 4 instead of PCC-1 α 1), a recent meta-analysis of randomized controlled trials included three resistance training studies which showed significant irisin level increases (Cosio et al., 2021). Furthermore, there were two resistance training studies reporting significant decreases and two reporting nonsignificant effects. Overall, the meta-analysis concluded that the effect of chronic resistance exercise on circulating irisin was a nonsignificant positive trend. However, subgroup analysis showed significant increases for older adults when % body fat decreased during the intervention period and when the intervention was less or equal to 12 weeks. There was a significant decrease when resistance training lasted longer than 4 months or when less than 80% of the sessions were supervised by a professional (Cosio et al., 2021). Both studies with significant decreases had a duration of approximately 6 months, with low intense physical exercise sessions and without progression in intensity (Hecksteden et al., 2013; Scharhag-Rosenberger et al., 2014). Subgroup analysis showed no differences for gender (Cosio et al., 2021). One pilot study reported an increase in circulating irisin in their resistance training group compared to their cardiovascular training group and control group following 8 weeks in obese subjects (Kim et al., 2016).

3.3.2. Cathepsin-B

Cathepsin-B is a lysosomal cysteine protease. During physical exercise, it is released from skeletal muscle cells. Cathepsin-B was found to pass through the blood-brain barrier and induce an increase in brain levels of BDNF. This was associated with improved memory function (Moon et al., 2016). However, cathepsin-B is also suggested to be a major driver for inflammatory brain diseases, neurodegenerative disorders, and brain aging associated with cognitive decline, as reviewed by Hook et al. (2020). Other authors have even advised to search for specific inhibitors of cathepsin-B as a therapeutic approach against neurodegeneration (Nakanishi, 2020).

3.3.2.1. Pathway. Cathepsin-B administration was reported to induce an increase in BDNF mRNA and protein levels on hippocampal progenitor cells in culture (Moon et al., 2016). The downstream signaling cascades that caused transcription of BDNF are currently unknown. A direct effect of physical exercise-induced cathepsin-B on LTP has not yet been investigated.

3.3.2.2. Acute exercise effect. A single bout of high-intensity interval exercise (Nicolini et al., 2020) or resistance exercise (Johnson et al., 2020) did not alter cathepsin-B levels in healthy young male adults.

3.3.2.3. Chronic exercise effect. Evidence for chronic exercise-induced changes in cathepsin-B levels is inconsistent. Moon et al. (2016) showed increased levels after cardiovascular training both peripherally and in the brain, while this was not confirmed by other authors (Gourgouvelis et al., 2018; Mees et al., 2019; Nicolini et al., 2019; Pena et al., 2020). Chronic resistance exercise was found to elevate cathepsin-B mRNA levels in muscle tissue (Norheim et al., 2011) and increase

circulating levels in obese females (Kim and Kang, 2020). Again, other studies only found non-significant trends or no effect in female mice or humans (Pena et al., 2020; Micielska et al., 2021).

3.3.3. Apelin

Apelin is synthesized in many tissues, such as muscle, adipose tissue, and the brain (Masoumi et al., 2018; Wysocka et al., 2018; Halon-Golabek et al., 2019). It was reported to improve glucose homeostasis. Apelin levels were found to be increased in obesity and diabetes mellitus. This is suggested to be a compensatory mechanism to decrease insulin resistance (Boucher et al., 2005; Bertrand et al., 2015). Furthermore, apelin was suggested to be a biomarker for the diagnosis of aging-associated sarcopenia (Vinel et al., 2018). Pro-apelin is cleaved into apelin-36, and then further processed into shorter isoforms. Apelin-13 may represent the adipose tissue-derived isoform. Apelin-13 synthesis was found to be upregulated in adipose tissue of male obese mice (Shin et al., 2013). It is not clear which is the most expressed isoform in muscle tissue, but most researchers use non-specific measurements of apelin (Bae et al., 2019). Muscle-derived apelin might also be able to cross the blood-brain barrier, as intraperitoneal injections have been shown to increase apelin concentrations in the hypothalamus (Higuchi et al., 2007). However, none of the physical exercise studies we found searched for central apelin levels.

3.3.3.1. Pathway. Apelin administration to brain-derived glial cells increased BDNF levels in vitro. Inhibition of the apelin receptor down-regulated BDNF mRNA expression, indicating apelin might promote BDNF-mediated LTP facilitation (Kwak et al., 2019). Another study also found that one week of daily intracerebroventricular injection of apelin increased hippocampal BDNF levels, as measured in vitro 24 h after the last injection on hippocampal slices. In addition, this study also discovered that an antagonist of the TrkB-receptor blocked the ameliorative effect of apelin on memory performance in rats (Shen et al., 2019). Furthermore, apelin has been shown to act via the PI3K and ERK signaling pathways in the hippocampus. The beneficial effect of intracerebroventricular apelin administration on depression and memory of stressed rats was blocked by pretreatment with PI3K or ERK1/2 inhibitors (Li et al., 2016). At last, apelin is considered an anti-inflammatory agent counteracting the elevation of neuroinflammatory markers such as IL-1 β and TNF- α , as occurring following brain injury (Masoumi et al., 2018). No studies searched for a causal link between physical exercise-induced elevations of apelin and the facilitation of LTP.

3.3.3.2. Acute exercise effect. Some studies reported that an acute bout of endurance (Bilski et al., 2016; Son et al., 2019; Dundar et al., 2019a; Kon et al., 2020), sprint interval (Kon et al., 2019), or resistance exercise (Kechyn et al., 2015; Fortunato et al., 2018) significantly increased apelin plasma levels. But levels did not significantly change in other studies (Waller et al., 2019).

3.3.3.3. Chronic exercise effect. A recent meta-analysis from Bae and colleagues (2019), including nine studies, showed that circulating apelin levels increased following physical exercise. They reported that all four studies including participants with a mean age between 50 and 60 years old showed significant increases. In contrast, only one of the five studies including younger adults could replicate these results. Only two studies included resistance exercise, with one reporting non-significant changes and the other reporting a decrease in apelin levels (Bae et al., 2019). In rat studies, apelin levels increased following chronic cardiovascular and resistance exercise (Zhang et al., 2006; Ji et al., 2016; Son et al., 2017; Vinel et al., 2018; Kwak et al., 2019; Sabouri et al., 2020). However, decreases following chronic cardiovascular or resistance exercise were also reported. Some studies in obese women reported declines of (non-isoform specific) apelin levels linked to physical exercise-induced

weight loss (Sheibani et al., 2012; Jang et al., 2019), but physical exercise-induced decreases in apelin levels were more consistently linked to physical exercise-associated improvements of insulin resistance (Krist et al., 2013; Bertrand et al., 2015; Delavar and Heidarianpour, 2016; Otero-Díaz et al., 2018; Kolahdouzi et al., 2019; Nam et al., 2020). Moreover, it was shown that insulin directly drives the upregulation of adipocyte-derived apelin in a state of hyperinsulinemia (Boucher et al., 2005; Yang et al., 2015), while muscle tissue expresses apelin only following physical exercise (Yang et al., 2015). As apelin has a beneficial effect on glucose homeostasis, adipocyte-derived apelin might have a role in limiting insulin resistance when it is already present, while muscle-derived apelin has the potential to prevent it.

3.3.4. Adiponectin

Adiponectin is mainly released from adipose tissue. However, during physical exercise, it is also expressed and released from skeletal muscle (Dai et al., 2013). Circulating adiponectin levels were lower in obese adults (Yang et al., 2002). Adiponectin was found to be able to cross the blood–brain barrier and mediate hippocampal neurogenesis (Yau et al., 2014; Li et al., 2015). Moreover, it is considered an anti-inflammatory marker with beneficial effects on cardiovascular and metabolic disorders (Ouchi and Walsh, 2007).

3.3.4.1. Pathway. Intracerebroventricular injection adiponectin was found to facilitate LTP in anesthetized rats (Pousti et al., 2018). Wang et al. (2019) showed that administration of adiponectin increased AMPA and NMDA surface expression on hippocampal slices. However, the intracellular signaling pathway activated by adiponectin remains unclear. It was suggested that adiponectin might enhance NMDA-receptor function via the PI3K/Akt pathway in the hippocampus (Pousti et al., 2018), as this pathway was activated following intracerebroventricular adiponectin injection in an Alzheimer's rat model (Xu et al., 2018). Furthermore, multiple studies have shown that adiponectin has an anti-inflammatory effect on the brain (Forny-Germano et al., 2019). Although these studies may suggest that adiponectin can mediate the exercise-cognition effect, no studies have currently provided direct evidence that changes in circulating adiponectin levels following physical exercise facilitate LTP.

3.3.4.2. Acute exercise effect. In systematic reviews, acute cardiovascular exercise was found to increase adiponectin levels (Simpson and Singh, 2008; Bouassida et al., 2010). Simpson and Singh (2008) suggested that high-intensity exercise is required for the modulation of adiponectin levels. Bouassida et al. (2010) indicated that increases are only found following physical exercise bouts of less than 60 min. We found only two studies that examined the effect of acute resistance exercise. Both did not show significant changes in adiponectin levels (Mansouri et al., 2011; Ihalainen et al., 2017).

3.3.4.3. Chronic exercise effect. A meta-analysis showed that adiponectin expression increased following chronic cardiovascular exercise, but not following resistance exercise in prediabetic and diabetic adults (Becic et al., 2018). A more recent meta-analysis also reported an overall increase of adiponectin levels following chronic exercise, but only included two studies with resistance exercise. In one of the two studies, resistance exercise induced significant increases in adiponectin levels (Rahimi et al., 2021). However, quite some other studies not included in these meta-analyses did report significant increases in adiponectin levels after chronic resistance exercise (Fatouros et al., 2005; Ihalainen et al., 2017; Galbreath et al., 2018; Montrezol et al., 2019; Park et al., 2019) or combined cardiovascular and resistance exercise protocols (Markofski et al., 2014; Dieli-Conwright et al., 2018a; Dieli-Conwright et al., 2018b; Ghayomzadeh et al., 2020). Of interest, Davis et al. (2015) reported that the combination of cardiovascular and resistance exercise was better at increasing adiponectin levels than resistance exercise alone. This might

be explained by the finding from others that adiponectin increase was linked with fat loss (Bouassida et al., 2010; Christiansen et al., 2010; Kelly et al., 2014).

3.4. Metabolites

3.4.1. Lactate

Acute high-intensity exercise increases muscle-derived lactate levels (Saucedo Marquez et al., 2015; Albesa-Albiol et al., 2019). Next, lactate may cross the blood–brain barrier via monocarboxylate transporters. Interestingly, these transporters were found to be rapidly upregulated during an acute bout of physical exercise (Takimoto and Hamada, 2014). Brain lactate levels were found to remain elevated more than 40 min after vigorously intense physical exercise, while blood lactate levels had already dropped back to baseline (Maddock et al., 2011). Brain lactate can also arise from astrocyte metabolism (Müller et al., 2020). Lactate is transferred via monocarboxylate transporters from astrocytes towards neurons when energy demand is high, such as during memory formation. Pharmacological inhibition of monocarboxylate transporter 2, the transporter that is found on neurons to admit lactate, impairs long-term memory formation (Newman et al., 2011).

3.4.1.1. Pathway. Increased blood lactate levels were found to correlate with circulating BDNF, IGF-1, GH, and VEGF (Schiffer et al., 2011; Salgueiro et al., 2014; Kujach et al., 2020). Furthermore, lactate was found to increase the hippocampal levels of transcriptional coactivator PGC1 α and its transcriptional product, FNDC5/irisin. As described in section 3.3.1, FNDC5/irisin is known to induce BDNF expression (Wrann et al., 2013). Lactate acts by activating silent information regulator 1 (SIRT-1), a class III histone deacetylase (El Hayek et al., 2019). El Hayek et al. (2019) discovered in male mice that SIRT-1 is activated by the NADH molecules that originate from the conversion of lactate back to pyruvate. Moreover, both protein and mRNA levels of SIRT-1 were increased following physical exercise and lactate infusion. The same effect was found after intraperitoneal injections of lactate at concentrations that induced increases in hippocampal lactate levels of the same level as found after physical exercise (El Hayek et al., 2019).

In addition, lactate was found to potentiate active NMDA receptors in cultured cortical neurons, thereby increasing the response of downstream signaling pathways, which are involved in the LTP process (Yang et al., 2014). Lactate can also be used in the tricarboxylic acid cycle to produce intermediates that can be used for de novo synthesis of amino acid neurotransmitters such as glutamate and GABA (Kleppner and Tobin, 2002).

Finally, lactate may also reduce neuroinflammation by changing microglia toward their anti-inflammatory phenotype, see section 3.2.1 (Errea et al., 2016). Lactate causes the addition of a lactyl group to the lysine amino-acid residues in the tails of histone proteins (i.e., histone lactylation) which stimulates genes of the anti-inflammatory phenotype in microglia (Zhang et al., 2019).

Lactate seems to activate several pathways associated with LTP. It can be used as a precursor to the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter GABA (Kleppner and Tobin, 2002), and physical exercise-induced elevations of lactate were reported to cause SIRT-1 activation. The physical exercise-induced activation of PGC1 α and, in turn, FNDC5/irisin, which induces BDNF synthesis, were found to be dependent on SIRT-1 activation (El Hayek et al., 2019). As increased levels of BDNF are linked with the facilitation of LTP, the effect of lactate can be inferred. However, none of these studies examined the direct link between the physical exercise-induced facilitation of LTP and lactate.

3.4.1.2. Acute exercise effect. Both acute high-intensity cardiovascular exercise and resistance exercise are capable of increasing blood lactate levels at intensities above the anaerobic threshold (Saucedo Marquez

et al., 2015; Albesa-Albiol et al., 2019). Animal studies confirmed acute cardiovascular exercise-induced increases in brain lactate levels in the cortex, hippocampus and hypothalamus (Takimoto and Hamada, 2014). In humans, a difference between the carotid artery and jugular vein lactate levels indicated lactate is used within the brain during acute cardiovascular exercise (Ide et al., 1999; 2000). Moreover, magnetic resonance studies showed increased brain lactate levels after high-intensity cardiovascular exercise in the visual cortex (Maddock et al., 2011).

3.4.1.3. Chronic exercise effect. No effect on baseline levels of lactate after chronic exercise is to be expected. However, one study showed that mice with free access to a running wheel for 30 days had higher in vitro hippocampal lactate concentrations than sedentary controls. Therefore, they suggested that lactate accumulates following chronic cardiovascular exercise in the hippocampus of male mice (El Hayek et al., 2019).

3.4.2. β -hydroxybutyrate (BHB)

Ketone bodies, like BHB, are increased in the circulation and brain after fasting, dieting, and prolonged physical exercise (Mitchell et al., 1995). Ketone bodies are produced in the liver. They are used as an energy source under conditions of reduced glucose levels (Mitchell et al., 1995). Similar to lactate, also BHB penetrates the blood–brain barrier through the monocarboxylate transporter (Takimoto and Hamada, 2014). As described in section 3.4.1, the activation of these transporters was found to increase following acute exercise (Takimoto and Hamada, 2014). Of interest, BHB administration was found to improve cognitive function in rats (Murray et al., 2016; Hernandez et al., 2018).

3.4.2.1. Pathway. BHB acts as a direct class I histone deacetylase inhibitor. It prevents the recruitment of histone deacetylase 2 and 3 to the BDNF promoter I. This way, BDNF gene transcription was increased following BHB administration or the elevation of circulating BHB levels after chronic exercise interventions, as was shown on mice and rat hippocampal cultures (Sleiman et al., 2016; Hu et al., 2018; Lan et al., 2018). Moreover, it acts via the cAMP/PKA pathway to activate CREB (Hu et al., 2018). Incubation of hippocampal slices with BHB increased excitatory synaptic transmission, which is related to LTP facilitation (Sleiman et al., 2016). While Sleiman et al. (2016) both reported increased hippocampal BHB levels following physical exercise and facilitation of LTP following administration of BHB on hippocampal slices, they did not directly measure LTP activity following physical exercise.

3.4.2.2. Acute exercise effect. An acute bout of prolonged cardiovascular exercise was found to increase BHB blood (Mitchell et al., 1995; Nybo et al., 2003; Kim et al., 2013) and brain (Nybo et al., 2003; Takimoto and Hamada, 2014) levels in animal and humans (arterial and jugular venous blood level differences). All of these studies used male animals or human subjects. Nybo et al. (2003) reported that the effect was absent when exercising subjects received carbohydrate supplementation. One study showed that acute resistance exercise also increased BHB levels in men (Tsekouras et al., 2009).

3.4.2.3. Chronic exercise effect. In old male mice, BHB serum levels increased following a 4-week physical exercise program in endurance trained, but not in resistance trained animals (Kwak et al., 2021). However, in combination with a low calorie diet, both cardiovascular and resistance training were found to increase BHB levels (Jo et al., 2019; Vieira et al., 2021). Furthermore, elastic band exercise, which was considered a hybrid form of physical exercise between cardiovascular and resistance training, increased BHB serum levels in women with low pre-exercise BHB concentrations (Kwak et al., 2021). Finally, BHB was found to accumulate in the hippocampus of male mice after a chronic cardiovascular exercise program (Sleiman et al., 2016; Lan et al., 2018).

Non-significant trends of increased blood and brain BHB levels after chronic cardiovascular exercise are also reported (Béland-Millar et al., 2020).

3.5. Other exerkinases

3.5.1. Osteocalcin

Osteocalcin is a bone-derived hormone. It is secreted by osteoblasts during bone resorption. It can be found in blood in active (uncarboxylated) and decarboxylated forms (Khrimian et al., 2017). The uncarboxylated form of osteocalcin was found to cross the blood–brain barrier. There, it enhances the synthesis of monoamine neurotransmitters (serotonin and catecholamines), but inhibits the synthesis of GABA. This was found to favor learning in adult mice (Oury et al., 2013). In mice, baseline osteocalcin serum levels were found to decrease with age (Mera et al., 2016). Recent studies in humans also discovered an association between lower levels of osteocalcin and brain atrophy and cognitive performance decline (Puig et al., 2016; Fang et al., 2018). Bradburn and colleagues (2016) reported that lower levels of plasma osteocalcin were only associated with cognitive decline in older women, but not in older men or young adults (Bradburn et al., 2016). However, another study including mainly older women (85% female, 15% male) with cognitive decline did not find an association between cognitive function and total or uncarboxylated osteocalcin (Ross et al., 2018). For more information on the osteocalcin-cognition link, see review papers by Shan et al. (2019) and Nakamura et al. (2020).

3.5.1.1. Pathway. Osteocalcin was shown to bind to the G-protein-coupled receptor (Gpcr158) on cultured hippocampal neurons (Khrimian et al., 2017). Osteocalcin treatment on these cultured hippocampal neurons resulted in an enhancement of hippocampal BDNF and BDNF mRNA expression and fastened trafficking of BDNF-containing vesicles to synapses. The peripheral injection of osteocalcin also improved memory function in old mice (Khrimian et al., 2017). Moreover, greater physical exercise-induced increases in the active, uncarboxylated form of osteocalcin were found to be associated with higher serum BDNF levels in young healthy men (Nicolini et al., 2020). However, no studies examined the direct effect of physical exercise-induced elevations in circulating osteocalcin on LTP activity.

3.5.1.2. Acute exercise effect. The circulating levels of uncarboxylated osteocalcin were found to double during acute cardiovascular exercise in young mice, whereas in older mice, the response was much lower (Mera et al., 2016). In humans, a bout of moderate to high-intensity cardiovascular exercise was found to increase uncarboxylated osteocalcin in males (Levinger et al., 2014a; Nicolini et al., 2020; Smith et al., 2021) and females (Jürimäe et al., 2016; Smith et al., 2021). Smith et al. (2021) reviewed studies with middle-aged and older adults reporting total, uncarboxylated, and carboxylated osteocalcin levels following acute exercise. They described that total osteocalcin levels increased more in middle-aged than in older adults and more in men than in women (Smith et al., 2021). Osteocalcin levels did not change following acute resistance exercise (Levinger et al., 2011; Rogers et al., 2011). The recent systematic review of Smith et al. (2021) only included one study on acute resistance exercise. Hence, more studies are needed to confirm that acute resistance exercise is incapable of increasing circulating osteocalcin.

3.5.1.3. Chronic exercise effect. A meta-analytic study showed that both chronic cardiovascular and resistance exercise were found to increase basal levels of circulating uncarboxylated osteocalcin (Rahimi et al., 2021). In the study of Lester et al. (2009), only resistance exercise or resistance exercise combined with cardiovascular exercise, but not cardiovascular exercise alone, resulted in increased levels of osteocalcin. Furthermore, baseline uncarboxylated osteocalcin levels were positively

associated with muscle strength, which might indicate that chronic resistance exercise is the better approach to induce uncarboxylated osteocalcin (Karlsson et al., 1995; Levinger et al., 2014b).

3.5.2. Orexin-A/Hypocretin-1

Orexin-A is synthesized by neurons in the hypothalamus (Chieffi et al., 2017) or gastro-intestinal tract (Nakabayashi et al., 2003), and by the pancreatic islets (Dall'Aglio et al., 2010). Orexin-A levels are decreased in obese and sedentary humans, whereas high levels are associated with improved cognitive performance (Polito et al., 2020). The origin of the peripheral rise in orexin A levels induced by physical exercise is not well known. However, it has been suggested to be induced by sympathetic nervous system activation (Messina et al., 2016). It may be released in the bloodstream from the pituitary (Tsunematsu and Yamanaka, 2012), leak from cerebrospinal fluid (Chieffi et al., 2017), or diffuse through the blood-brain barrier (Kastin and Akerstrom, 1999).

3.5.2.1. Pathway. Hippocampal orexin-A infusion was reported to enhance the response to LTP induction by electrophysiological stimuli in vivo in anesthetized rats, which was blocked by a specific orexin-A receptor-1 antagonist (Wayner et al., 2004). The same antagonist also decreased LTP in freely moving rats, as measured with two electrodes over the perforant pathway (i.e., the connective route from the entorhinal cortex to the hippocampal formation) (Akbari et al., 2011). In a mouse model in which orexin-producing neurons degenerate by three months of age, in vitro hippocampal LTP magnitude and the level of phosphorylated CREB were decreased. This suggests a role of orexin-A in CREB-mediated transcription (Yang et al., 2013). In vitro electrophysiological recordings with and without administration of orexin receptor 1 + and 2, and PLC and PKA antagonists suggested that orexin-A mediates this effect on LTP by the PLC-pathway via orexin receptor-1 and cAMP/PKA-pathway via orexin receptor-2 (Lu et al., 2016). Currently, a possible link between the physical exercise-induced increase of orexin-A and the facilitation of LTP-related pathways can only be inferred from these models, as no studies exist that examined the direct link between those two.

3.5.2.2. Acute exercise effect. An acute bout of cardiovascular exercise was found to increase circulating orexin-A levels in young sedentary men (Messina et al., 2016) and cerebrospinal fluid levels in animals (Wu et al., 2002; Martins et al., 2004).

3.5.2.3. Chronic exercise effect. We found only one study that showed that chronic cardiovascular exercise increases circulating Orexin-A levels in healthy middle-aged men and men with metabolic syndrome (Monda et al., 2020).

3.5.3. Ghrelin

Ghrelin is mainly produced in the stomach before meals and released into circulation (Cummings et al., 2001). It stimulates appetite and enhances the secretion of GH from the pituitary gland (Kojima et al., 1999). Peripheral ghrelin may cross the blood-brain barrier, but it may also be synthesized in the brain itself (Ribeiro et al., 2014). It has been shown to have neuroprotective properties (Santos et al., 2017) and enhance the response to LTP induction by electrophysiological stimuli in the hippocampus (Diano et al., 2006; Chen et al., 2011).

3.5.3.1. Pathway. Ghrelin binds to the growth hormone secretagogue type 1a receptor in the pituitary (Kojima et al., 1999), where it induces the release of GH (see section 3.1.3) and in the hippocampus (Guan et al., 1997), where it increases memory retention (Diano et al., 2006; Chen et al., 2011). Intraperitoneal injection of ghrelin resulted in hippocampal elevations of IGF-1 and IGF-1 mRNA levels (see Section 3.1.2). In cultured rat hippocampal neurons, Ribeiro et al. (2014) showed that GHS-1a receptors are found on the excitatory synapse. GHS-1a receptor

activation by ghrelin administration resulted in the increase and phosphorylation of AMPA receptors in the postsynaptic density, enhancing excitatory synaptic transmission. This effect was mediated by the PLC/IP₃, PLC/PKC, PLC/PI3K, and cAMP/PKA-pathways (Ribeiro et al., 2014). No studies were found that assessed the influence of physical exercise-induced ghrelin on LTP-related pathways.

3.5.3.2. Acute exercise effect. Autio et al. (2020) recently reviewed the effect of physical exercise on ghrelin levels. They indicated that acute cardiovascular and resistance exercise lowered circulating ghrelin levels in some studies. In contrast, Erdmann et al. (2007) suggested a role of physical exercise intensity, showing increased ghrelin levels after low-intensity cardiovascular exercise below the aerobic threshold. Also Toshinai et al. (2007) showed intensity dependent effects on ghrelin levels in healthy men, with higher intensity physical exercise inducing a greater suppression of ghrelin levels, associated with higher adrenalin and noradrenalin levels.

3.5.3.3. Chronic exercise effect. Chronic cardiovascular and resistance exercise were found to increase baseline plasma ghrelin levels (Ravussin et al., 2001; Martins et al., 2010; Kim et al., 2014; Moraes et al., 2015; Dundar et al., 2019b; Tremblay et al., 2019) and cardiovascular exercise increased 24 h measurements of ghrelin (i.e., the sum of all serum ghrelin levels measured in blood obtained every 20 min for a duration of 24 h) (Leidy et al., 2007). Some authors reported that only those with significant weight loss had increased ghrelin levels after chronic exercise (Leidy et al., 2004; Foster-Schubert et al., 2005; Scheid et al., 2011).

3.5.4. Vasoactive intestinal peptide (VIP)

VIP is a peptide with vasodilatory function, which is secreted by nerve endings in the gastrointestinal tract, heart, lungs, thyroid, urinary bladder, kidney, genital organs, and brain (Said and Mutt, 1970; Henning and Sawmiller, 2001). VIP was found to cross the blood-brain barrier only unidirectionally from blood towards the brain (Dogrukol-Ak et al., 2003). Within the brain, it may potentiate LTP-related pathways (Cunha-Reis and Caulino-Rocha, 2020).

3.5.4.1. Pathway. In the hippocampus, VIP is known to activate the VIP receptor 1, VAPC1, and VIP receptor 2, VAPC2. VAPC1 activated PLC/IP₃ and PLC/PKC-signaling, while VAPC2 induced the cAMP/PKA-pathway in hippocampal CA1 pyramidal cells (Cunha-Reis et al., 2005). In vitro administration of VIP on CA1 cells activated these receptors and resulted in increased synaptic transmission by enhancing NMDA currents (Yang et al., 2009). Inhibition of PKC or PKA attenuated the VIP-mediated enhancement of synaptic transmission (Cunha-Reis et al., 2005). For a review concerning the facilitating action of VIP on LTP and LTP-related pathways, we refer to Cunha-Reis and Caulino-Rocha (2020). However, we found no studies that assessed the direct effect of physical exercise-induced VIP elevations on LTP-related pathways.

3.5.4.2. Acute exercise effect. A bout of cardiovascular exercise until exhaustion, submaximal muscular exercise, and an acute bout of low-intensity cardiovascular exercise of long duration were found to increase circulating VIP levels in men (Galbo et al., 1979; Woie et al., 1986; Rolandi et al., 1988; MacLaren et al., 1995). The acute exercise-associated rise in circulating VIP was suggested to result from the overflow of the peptide at skeletal muscle blood vessels, where it acts as a potent vasodilator (Woie et al., 1986).

3.5.4.3. Chronic exercise effect. A five-day period of physical exercise with calorie deficiency and sleep deprivation induced increases in VIP levels in male military cadets (Øktedalen et al., 1983a, 1983b). However, calorie compensation lowered the VIP increase (Øktedalen et al., 1983a). An eight-week program of low-intensity cardiovascular exercise

did not induce increases in VIP serum levels (Amirazodi et al., 2019).

4. Concluding remarks

This review describes current evidence for the role of exerkinins in mediating the neurophysiological processes leading to LTP that occur in the brain following physical exercise. It is important to note that we only reported a small fraction of all the processes that exerkinins may induce in the brain. Furthermore, we discussed only LTP processes at the glutamatergic excitatory synapse and did not refer in our review to mechanisms and pathways of neurogenesis, LTD-related processes, or processes at the GABAergic inhibitory synapse. Yet, LTP and neurogenesis are somewhat related, as neurogenesis may be boosted by the growth factors that are synthesized in neurons during LTP (Cho et al., 2013), and newly formed neurons appear to depend on LTP for their survival and maturation (Shors et al., 2012; Denoth-Lippuner and Jessberger, 2021). In comparison with LTP and the modulatory effects of exerkinins on pathways at the glutamatergic synapse, evidence for exerkinin effects on LTD or changes in the GABAergic synapse is limited. However, some processes and pathways that were described in this review may also be implicated in up- or downregulation of GABAergic transmission, e.g., studies have reported an effect of lactate on GABA levels (Maddock et al., 2016; Coxon et al., 2018), and of BDNF on GABAergic modulation (Vaz et al., 2011). Furthermore, evidence is still lacking regarding the effect that physical exercise-induced elevations of GABA concentrations in cortical neurons, measured with $^1\text{H-MRS}$, may have on GABAergic neurotransmission (Maddock et al., 2016). On the one hand, lactate may be converted to GABA, which is expected to increase its availability in presynaptic terminals and strengthen GABA-mediated inhibitory control (Kleppner and Tobin, 2002; Maddock et al., 2016). On the other hand, findings generated from studies involving non-invasive brain stimulation methods such as TMS demonstrated an overall downregulation of GABAergic activity following an acute bout of cardiovascular exercise (e.g., Singh et al., 2014a; Mooney et al., 2016; Stavrinou and Coxon, 2017; O'Leary et al., 2018; for a review see Levin et al. 2021).

Although the LTP process has extensively been studied, for example, in relation to neuroplasticity, its relationship with exerkinins needs further exploration. Most studies involve animal models and have investigated the effect of administration of a specific exerkinin on the alteration of LTP-related pathways, but do not offer direct evidence that the physical exercise-induced increase of this exerkinin may also alter LTP-related pathways. More specifically, only for three of the 16 exerkinins presented in this review (BDNF, irisin, and pro-inflammatory cytokines), we found evidence suggesting that the physical exercise-related change in circulating exerkinin levels was associated with the facilitation or impairment of LTP activity. In mice, elevated levels of BDNF (Novkovic et al., 2015) and irisin (Lourenco et al., 2019) following chronic exercise facilitated LTP activity and elevated levels of the pro-inflammatory cytokines TNF- α and IL-1 β following seven days of daily maximal cardiovascular exercise were reported to have detrimental effects on LTP activity (Sun et al., 2017). In other studies, the exerkinin-effect on LTP activity was only reported following in vitro administration of the exerkinin. However, the physical exercise-induced elevation of only four of the 16 exerkinins included in this review (IGF-1, BHB, lactate, and irisin) was found to activate the transcription of one of the exerkinins with known physical exercise-induced facilitatory effect on LTP (i.e., BDNF or irisin). For example, BDNF transcription in rodent brain was associated with physical exercise-induced elevations of IGF-1 (Ding et al., 2006), irisin (Wrann et al., 2013), and BHB (Sleiman et al., 2016) following chronic exercise and with the physical exercise-induced elevation of IGF-1 (Carro et al., 2001) following acute exercise. Furthermore, neural synthesis of irisin was suggested to be an effect of physical exercise-induced elevations in lactate, measured after 30 days of voluntary physical exercise in mice (El Hayek et al., 2019). Of note, physical exercise-induced elevations in irisin were both found to

enhance the response to electrophysiological stimulation of LTP (Lourenco et al., 2019) and to mediate hippocampal BDNF transcription (Wrann et al., 2013). Thus, the facilitatory effect of irisin on LTP activity may be indirect by the induction of a rise in BDNF levels. The circulating levels of the ten remaining exerkinins were found to be altered by physical exercise, but at present, none of the studies measured their role in the physical exercise-induced facilitation of LTP activity. Current evidence about the role of these exerkinins on LTP is mainly derived from studies, in which these exerkinins were administered in vitro and subsequent changes in LTP activity (in case of GH, kynurenine, adiponectin, orexin-A, ghrelin, and VIP) or BDNF levels (in case of cathepsin-B, apelin, and osteocalcin) were found (Wayner et al., 2004; Diano et al., 2006; Róza et al., 2008; Kim et al., 2010; Chen et al., 2011; Molina et al., 2012; Moon et al., 2016; Khirmian et al., 2017; Pousti et al., 2018; Kwak et al., 2019; Cunha-Reis and Caulino-Rocha, 2020; Nicolini et al., 2020).

Of note, there were some inconsistencies in the reported effect of physical exercise on exerkinin levels. Some differences might be due to the discrepancy in the quantification of biomarkers, timing of sample collection, pre-analytic sample processing, the analytical method, and calculation of other factors (Son et al., 2018). As an example, studies have described how BDNF levels may differ between measurements due to circadian variability, the time between blood collection and centrifugation, or whether BDNF was measured in serum or in plasma (Cain et al., 2017; Gejl et al., 2019). Of importance, the time between the last physical exercise bout and sample collection is often not clearly denoted in chronic exercise studies. However, this is critical to differentiate between changes in exerkinin levels that represent acute exercise effects in trained individuals and changes in baseline exerkinin levels as a function of chronic exercise. Acute exercise may transiently change exerkinin levels lasting for minutes up to more than 24 h after physical exercise (Garneau et al., 2020). To accurately measure longer-lasting changes in baseline exerkinin levels induced by chronic exercise, we would advise having at least one, but preferably two or more full rest days between blood sample collection and the last physical exercise bout. Chronic intervention studies should also consider adding follow-up measurements several months after the end of the intervention in order to examine whether exerkinin levels return to their pre-intervention levels or remain elevated.

In addition to the differences in blood sampling methods, there is a large heterogeneity in the physical exercise protocols and study subjects' characteristics, which vary according to the study's objectives. It is interesting to learn which type of physical exercise works best to change a certain exerkinin in a certain population as this may lead to the design of individualized physical exercise protocols. The ultimate goal for individualized physical exercise training is to find a physical exercise protocol that works best to improve performance or prevent a specific type of cognitive or motor deficit in a specific population. In young and healthy older adults, the primary aim may be the improvement or acquisition of certain skills that has been shown to be associated with LTP induction during the memory consolidation phase (e.g., Statton et al., 2015; for a review, see Wannier et al., 2020). For older adults with neurodegenerative disorders or abnormal cognitive decline, physical exercise may have more specific functional/therapeutic goals (e.g., inhibit inflammation or improve cardiovascular function). In the following paragraphs, we will discuss what we can learn from the literature that was summarized in this review paper. As we did not review the link between certain domains of cognitive function and specific exerkinins, our discussion will be limited to the effect of physical exercise and subject characteristics on the release of these exerkinins into circulation. Where possible, the association between these physical exercises and subject characteristics and LTP will be highlighted.

First, different modes of physical exercise (i.e., cardiovascular versus resistance exercise) are expected to activate different regulatory pathways. Kim and colleagues (2019) argued that resistance exercise may be better in promoting the release of myokines, while cardiovascular

exercise may have a greater influence on other exerkines such as adiponectin (Davis et al., 2015; Kim et al., 2019). Compared with resistance exercise, the beneficial effect of cardiovascular exercise on the brain may, to a greater extent, be attributed to improvements in cardiovascular function or changes in energy metabolism, such as increased delivery of nutrients and oxygen (Kim et al., 2019). From our review, it becomes clear that the evidence on exerkine release during and following acute and chronic resistance exercise is limited compared to cardiovascular exercise. Therefore, it is not possible to draw final conclusions. However, it was argued that resistance training is an essential component of the physical exercise program to boost BDNF levels in older (Marinus et al., 2019) and osteocalcin levels in young adults (Lester et al., 2009). Acute or chronic resistance exercise was preferred to boost IGF-1 (de Alcántara Borba et al., 2020; Gulick et al., 2020; Jiang et al., 2020) and acute resistance exercise resulted in larger irisin level increases than cardiovascular exercise (Tsuchiya et al., 2015). In contrast, adiponectin levels were found to increase to a greater extent if physical exercise contained a component of cardiovascular exercise, compared with resistance exercise alone (Davis et al., 2015).

Second, physical exercise intensity was reported to influence the release of exerkines. Acute exercise of higher intensity was associated with higher circulating levels of lactate (Saucedo Marquez et al., 2015; Albesa-Albiol et al., 2019), irisin (Daskalopoulou et al., 2014; Huh et al., 2014) and adiponectin (Simpson and Singh, 2008). While some studies reported that BDNF levels were higher following acute high-intense versus low-intense physical exercise, e.g., Schmolesky et al. (2013), the meta-analysis of Dinoff et al. (2017) only found a nonsignificant positive trend ($p = 0.085$) between BDNF levels and higher physical exercise intensity. In general, the release of exerkines is expected to require a certain physical exercise intensity before protein synthesis is activated. However, higher intensity is not always better. For example, ghrelin levels increased more following low-intense acute exercise compared with high-intense physical exercise in the study of Toshinai et al. (2007). Furthermore, chronic high-intense physical exercise without the necessary recovery periods (i.e., overtraining) was associated with increased levels of pro-inflammatory cytokines, with detrimental effects on LTP (Sun et al., 2017).

Third, longer physical exercise duration was associated with higher levels of BDNF following acute exercise intervention. Also in chronic exercise interventions, the length of the intervention may influence the change in baseline exerkine levels. For example, a meta-analysis reporting the effect of resistance exercise on irisin levels described that irisin levels significantly increased in interventions lasting less than 12 weeks and decreased in physical exercise interventions lasting longer than 16 weeks (Cosio et al., 2021). Two studies had reported decreased irisin levels. Both were not only of long duration (6 months or more), but also used low-intense physical exercise sessions without progression in intensity (Hecksteden et al., 2013; Scharhag-Rosenberger et al., 2014). Hence, it is possible that the physical exercise intensity level, known to affect irisin response (Daskalopoulou et al., 2014; Huh et al., 2014), may have had a higher impact on the irisin levels than the physical exercise duration.

Fourth, age is considered to play an important role in how our body responds to physical exercise. Furthermore, the effect of age is widely studied with respect to LTP. For example, in old compared with young rodents, in vitro radioligand binding studies have shown a significant age-related loss of postsynaptic glutamatergic receptors, especially of the NMDA subtype, which is critical for the LTP process (Kito et al., 1990; Cohen and Müller, 1992). In addition, in vitro electrophysiological studies found LTP induction deficits in hippocampal slices of old rats compared with their younger counterparts (Deupree et al., 1993; Moore et al., 1993). Increasing age is also linked with a decrease in the baseline levels of myokines and growth factors, with BDNF as the cornerstone (Tapia-Arancibia et al., 2008; Erickson et al., 2010; El-Sayes et al., 2019). However, higher physical exercise-induced elevations were found in older adults for IGF-1 following chronic resistance exercise

(Jiang et al., 2020; Ye et al., 2020; Amiri et al., 2021), for irisin following chronic cardiovascular (Miyamoto-Mikami et al., 2015) and resistance exercise (Cosio et al., 2021), and for apelin following chronic cardiovascular exercise (Bae et al., 2019). In contrast, GH (Wideman et al., 2002) and total osteocalcin (Smith et al., 2021) increase following acute exercise were lower in older adults compared with young or middle-aged adults. Furthermore, in the process of aging, persons gradually progress into a more pro-inflammatory state. For example, the pro-inflammatory cytokine IL-1 β was found to be increased in old rats, and the concentration of dentate gyrus IL-1 β was inversely related to the level of hippocampal LTP measured in vivo (Murray and Lynch, 1998). From a mechanistic perspective, chronic inflammation was found to damage neurons and impair neurotrophic factor signaling (Cotman et al., 2007; Bourgognon and Cavanagh, 2020; Scheiblich et al., 2020). Of note, older adults may also be more vulnerable to the pro-inflammatory effects of acute high-intense physical exercise. For example, Trepci et al. (2020) found increased levels of the inflammatory marker kynurenine 60 min after acute sprint interval exercise in old but not in young healthy human subjects (Trepci et al., 2020).

Fifth, gender differences may influence the effect of physical exercise. As with aging, also gender may influence the baseline levels of certain exerkines. As a result, significant pre-to-post physical exercise changes are more easily found in the gender with the lowest baseline levels (Glud et al., 2019). This was reported for BDNF (Dinoff et al., 2017); baseline BDNF levels were found to be influenced by estrogen levels, with women having higher basal serum BDNF levels than men (Harte-Hargrove et al., 2013; Dong et al., 2017; Glud et al., 2019). In addition, we found studies reporting higher acute exercise-induced increases of BDNF (Dinoff et al., 2017) and total osteocalcin (Smith et al., 2021) in men and higher chronic resistance exercise-induced increases of IGF-1 in women (Jiang et al., 2020; Ye et al., 2020; Amiri et al., 2021). It is remarkable to note that the majority of studies were conducted using male human subjects or animals. Therefore, while some studies reported gender-related differences in exerkine responses following physical exercise, gender-related differences are unknown for most of them.

Sixth, it was reported that if the physical exercise intervention induced weight loss, the circulating levels of irisin (Cosio et al., 2021), adiponectin (Bouassida et al., 2010; Christiansen et al., 2010; Kelly et al., 2014), and ghrelin (Leidy et al., 2004; Foster-Schubert et al., 2005; Scheid et al., 2011) increased, while apelin levels of obese women decreased in association with significant weight loss (Sheibani et al., 2012; Jang et al., 2019). However, decreases in apelin levels were more consistently associated with the improvements in insulin sensitivity caused by physical exercise (Krist et al., 2013; Bertrand et al., 2015; Delavar and Heidarianpour, 2016; Otero-Díaz et al., 2018; Kolahdrouzi et al., 2019; Nam et al., 2020). More specifically, it is thought that adipocyte-derived apelin is positively associated with insulin resistance (Boucher et al., 2005; Yang et al., 2015). It remains unclear if the muscle-derived isoform of apelin would also be responsive to changes in insulin sensitivity. Glucose metabolism also plays a role in the release of BHB, with higher levels of BHB found following acute exercise sessions that cause hypoglycemia and long physical exercise sessions without carbohydrate supplementation (Nybo et al., 2003), or in chronic exercise in association with low calorie diet (Jo et al., 2019; Vieira et al., 2021). Importantly, diabetes mellitus and obesity are both also associated with a pro-inflammatory state (Yudkin, 2007; Woods et al., 2012; Pedersen, 2017) which may affect LTP (Murray and Lynch, 1998; Sun et al., 2017; Bourgognon and Cavanagh, 2020). Furthermore, these cardiovascular risk profiles were linked with cognitive decline (Jefferson et al., 2015; Viticchi et al., 2015; Chatterjee et al., 2016) and with structural brain alterations (Cox et al., 2019). Future studies should address whether the cognitive decline in persons with obesity, diabetes mellitus or other cardiovascular risk factors is related to impairments in LTP and the extent by which LTP is compromised by elevated levels of pro-inflammatory cytokines.

5. Future directions

We reviewed a total of 16 different exerkines that were linked to the LTP process. However, the number of myokines currently discovered alone exceeds 600 (Görgens et al., 2015). Researchers should keep exploring the specific bioactivity of exerkines on body systems. Especially, their effect on the central nervous system remains largely undescribed. Unfortunately, technical issues limit the investigation of exerkine effects on the human brain. Only some exerkines can be measured in humans with noninvasive techniques such as ¹H-MRS, e.g., lactate and BHB (Dacko and Lange, 2019). Invasive alternatives that may be used in patient groups, but are not commonly used in research, are cerebrospinal fluid measurements (e.g., Steensberg et al., 2006; Isung et al., 2021) and carotid artery versus jugular vein differences (e.g., Ide et al., 1999; 2000). Hence, most evidence for exerkine changes in the brain arises from animal studies. However, most studies included in this review, which examined the effect of exerkines on LTP, did not measure the physical exercise-induced elevation, but administered the exerkine in vitro on brain slices or by the use of intravenous injections. More clinical and preclinical (physical exercise) research is needed to increase understanding of the effects that exerkines have on the brain and LTP activity. In addition to the exerkines presented in this review, other review papers have presented exerkines that are worth further investigation, as their effect on the LTP process is currently unclear (Woodbury and Ikezu, 2014; Morland et al., 2017; Pedersen, 2019; Autio et al., 2020; Kwon et al., 2020; Scheffer and Latini, 2020).

There is a relatively lower amount of studies examining resistance exercise effects compared with cardiovascular exercise effects. For example, in rodent studies, which are crucial to increase insight into the neurophysiological pathways that are modulated by physical exercise or exerkines, the resistance exercise protocol (most often weighted ladder climbing) is much less used than the cardiovascular exercise protocol (i.e., treadmill running). More specifically, we found only two studies that examined brain exerkine levels after acute resistance exercise (Fernandes et al., 2016; Kelty et al., 2019). In addition, studies comparing resistance and cardiovascular protocols are needed to make final decisions on differences between cardiovascular and resistance exercise effects. These studies comparing both protocols are scarce, e.g., Tang et al. (2017), Joisten et al. (2020), Tsuchiya et al. (2015), Davis et al. (2015), Lester et al. (2009). Also, only for some exerkines there are sufficient high-quality studies to make valuable comparisons in meta-analytic studies, like for BDNF (Dinoff et al., 2016, 2017), IGF-1 (de Alcantara Borba et al., 2020; Gulick et al., 2020; Jiang et al., 2020; Ye et al., 2020; Amiri et al., 2021), and osteocalcin (Rahimi et al., 2021). But again, the reason for this is the limited number of studies using resistance exercise protocols. In sum, we need more clinical and preclinical research to focus on the effect of exerkines following resistance exercise on cognitive improvements and changes in LTP activity. Especially as more and more evidence suggests that resistance exercise might be the preferred physical exercise mode to boost certain of the exerkines (Tsuchiya et al., 2015; Kim et al., 2019; Marinus et al., 2019; de Alcantara Borba et al., 2020; Gulick et al., 2020; Jiang et al., 2020).

This review did not focus on specific disorders that may cause acute or progressive deficits in cognitive function, such as neurodegenerative disorders, stroke, or traumatic brain injury. Yet, more insight into the effect of physical exercise in these specific cases would be of value for rehabilitation practitioners. In addition, certain exerkines may benefit specific domains of cognitive function. This was not discussed in this review, as we focused specifically on the alteration of LTP-related pathways. The combined evaluation of which physical exercise protocol would be most optimal to target specific exerkines and the evaluation of which exerkine could benefit a specific cognitive function may direct researchers towards the design of individualized physical exercise programs that can be implemented as a treatment strategy. Due to the large heterogeneity in possible physical exercise protocols, many more studies will be needed before such physical exercise treatment can be

designed. For example, physical exercise characteristics that should be considered are intensity, duration, frequency, and the amount or size of the muscles used. Also physical exercise type can be further divided into specific sports. While running might be only slightly different from cycling, bigger differences can be expected when using hybrid forms of physical exercise between cardiovascular and resistance training, like elastic band exercises (Kwak et al., 2021), or types of physical exercise that require memorizing movement patterns like dancing (Kimura and Hozumi, 2012) or Tai Chi (Wayne et al., 2014), or a combination of physical and cognitive training (Netz, 2019). At last, increasing insight on the effects of exerkines on our body may lead to the design of pharmacological pills containing exerkines to mimic the effects of physical exercise. This may be especially useful in those unable to perform physical exercise at a sufficient duration and intensity, as recently reviewed by Gubert and Hannan (2021).

6. Summary

We reviewed physical exercise-induced circulating factors (i.e., exerkines) and their effect on LTP-related pathways (Fig. 2). For each of these exerkines we assessed the physical exercise and subject characteristics that influence the alterations of exerkine levels in the circulation and the brain following acute or chronic, cardiovascular or resistance exercise (Table 1). By combining and structuring evidence from a large and rapidly increasing amount of research, this review summarizes what is already sufficiently known and where research is limited. This knowledge may serve to guide researchers towards designing an individualized physical exercise treatment to improve cognitive health. The beneficial effect of physical exercise on cognitive function is only one of the many reasons to promote physical activity for people of all ages, especially in adults with cognitive decline. This is very important in a society that faces the prospect of an aging population.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

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