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Review

All roads lead to Rome — a review of the potential mechanisms by which exerkines exhibit neuroprotective effects in Alzheimer's disease

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Abstract

Age-related neurodegenerative disorders such as Alzheimer's disease (AD) have become a critical public health issue due to the significantly extended human lifespan, leading to considerable economic and social burdens. Traditional therapies for AD such as medicine and surgery remain ineffective, impractical, and expensive. Many studies have shown that a variety of bioactive substances released by physical exercise (called "exerkines") help to maintain and improve the normal functions of the brain in terms of cognition, emotion, and psychomotor coordination. Increasing evidence suggests that exerkines may exert beneficial effects in AD as well. This review summarizes the neuroprotective effects of exerkines in AD, focusing on the underlying molecular mechanism and the dynamic expression of exerkines after physical exercise. The findings described in this review will help direct research into novel targets for the treatment of AD and develop customized exercise therapy for individuals of different ages, genders, and health conditions.

Key Words: Alzheimer's disease; amyloid beta; central nervous system; exerkine; neurodegeneration; neuroinflammation; neuroprotection; oxidative stress; physical exercise; Tau protein

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder whose incidence increases exponentially with age and is currently the most common cause of dementia (accounting for 60–80% of cases) (Scheltens et al., 2021). An epidemiological survey showed that AD was the sixth leading cause of death in the United States between 2000 and 2019, and that the number of deaths attributed to AD rose by 145% during this time period (No authors listed, 2021). It is estimated that there will be over 13.8 million Americans over 65 years old with AD by 2060. AD imposes heavy economic and social burdens. In 2020, care for patients with AD consumed more than 256 billion US dollars and 15.3 billion hours of nursing services provided by over 11 million nurses and family members (No authors listed, 2021).

Physical exercise, an intervention that does not include the use of pharmacological agents, has frequently proven useful in combatting cognitive decline and dysfunction in neurodegenerative diseases and may be associated with a variety of beneficial effects such as upregulation of mitochondrial biogenesis, inhibition of oxidative stress and neuroinflammation, reduction of autophagic impediment, protection of the blood-brain barrier (BBB), and promotion of angiogenesis and neurogenesis (Mahalakshmi et al., 2020). Exercise-elicited neuroprotection is potentially mediated by a series of mechanisms from the molecular level to organ level, and exerkines could be critical regulators involved in this process. A recent report from Horowitz et al. (2020) confirmed that the beneficial effects of exercise on the aging brain [e.g., enhanced neurogenesis and neuronal differentiation, increased brain-derived neurotrophic factor (BDNF) levels, improved spatial learning and memory] can be transferred through systemic plasma administration. This

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surprising therapeutic effect is attributed to the elevated plasma concentration of glycosylphosphatidylinositol specific phospholipase D1, a glycosylphosphatidylinositol-degrading enzyme that cleaves glycosylphosphatidylinositol-anchored substrates, thereby triggering downstream signaling cascades required for exercise-induced benefits. This work highlights the crucial role of exerkines in maintaining brain health.

First introduced by Safdar et al. (2016), the term "exerkines" was originally used to describe a series of exercise-stimulated exosomes that are released into the extracellular environment through autocrine, paracrine, or endocrine processes and enable beneficial crosstalk between various systems, organs, and tissues. Exerkines are believed to mediate many systemic benefits of exercise, including regulation of metabolism and inflammatory responses, exertion of protective effects within the central nervous system (CNS) (e.g., promoting nerve regeneration, strengthening synaptic plasticity, remodeling dendritic morphology), and enhancement of cognitive function (Li et al., 2019). Although the effects of exerkines on AD have not been explored comprehensively, it is likely that bioactive factors promote exercise-induced AD remission in a similar way. Here, we provide an overview of several essential exerkines that are not only released and present at elevated levels in the central or peripheral regions of the body following physical exercise, but also have definite neuroprotective effects in the context of AD. The aforementioned biomolecules can be divided into four categories: growth factors and hormones, enzymes and coenzymes, metabolites, and microRNAs (miRNAs). This review summarizes these four categories and discusses the potential molecular mechanisms underlying their neuroprotective effects and their dynamic expression following physical exercise.

Search Strategy and Selection Criteria

We designed a two-step search strategy to conduct a comprehensive review of the literature regarding exerkines that display anti-AD properties published from July 2020 to March 2021. For the first step, we performed a PubMed search using the term ((exercise) AND (Alzheimer's disease)) AND (English [Language]) to identify potential molecules that are stimulated by physical exercise and involved in neuroprotection in AD. In the second step, candidates identified during the first search, including BDNF, nerve growth factor (NGF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), fibronectin type III domain containing 5 (FNDC5), adiponectin (ADN), kynurenic acid (KYNA), lactate, superoxide dismutase (SOD), glutathione (GSH), neprilysin (NEP), insulin-degrading enzyme (IDE), and miRNA, were used as additional keywords. As an example, the search terms "(brain-derived neurotrophic factor) AND (Alzheimer's disease)" and "(brain-derived neurotrophic factor) AND (exercise)" were used to identify articles related to the association among BDNF, physical exercise, and AD, with a specific focus on the anti-AD mechanism, as well as the dynamics of BDNF expression following physical exercise. Searches for the other candidate exerkines listed above were performed in the same manner as for BDNF. We set the filters to retrieve full-text articles published between 2000 and 2020 and manually confirmed the relevance of each article by scanning the abstracts. We also searched the reference lists of any articles retrieved by the two-step search strategy to identify additional relevant original articles.

Classification of Exercise Paradigms

Human exercise training is routinely categorized into four types according to whether the emphasis is placed on improving endurance, strength, flexibility, or balance (Ketelhut and Ketelhut, 2020; Kramer, 2020). Endurance or aerobic exercise, which promotes endurance performance, cardiovascular function, and metabolic capacity, provides systemic benefits when a sufficient oxygen supply is available. This form of exercise typically involves running, cycling, swimming, or other complex training protocols such as long, slow-distance training, tempo training, interval training, moderate-intensity continuous training, and high-intensity interval training. Strength or resistance exercise promotes the maintenance or development of muscular strength and power and includes weightlifting, sit-ups, push-ups, eccentric or concentric exercise, and isometric exercise. The third type of exercise focuses on flexibility and is designed to enhance joint range of motion and body flexibility by stretching or lengthening specific tendon groups; this form of exercise often involves static or dynamic stretching, proprioceptive neuromuscular facilitation stretching, self-myofascial release, and yoga. Exercises that focus on balance, such as standing on one leg on an unstable surface, enhance the control of body posture and are important for fall prevention (Ketelhut and Ketelhut, 2020; Kramer, 2020). Animal training paradigms such as swimming, wheel running, treadmill training, laddermill climbing, and weightlifting, can be divided into similar categories – the first three are endurance training exercises, while the last two are strength exercises. Of note, animals are rarely subjected to flexibility and balance training; instead, they are permitted to engage in voluntary exercise that allows them to move freely, or are subjected to compulsory exercise that relies on an offensive stimulus to regulate behavior (Arida et al., 2011; Landers et al., 2013). In addition to the categories described above, exercise paradigms can also be classified by factors such as duration (acute or chronic) and intensity (low, medium, or high). However, these classifications vary greatly for a variety of reasons. First, the techniques used to assay the same parameter may not be identical. For example, the most accurate way to measure exercise intensity is to monitor oxygen consumption during exercise and determine the maximal oxygen uptake capacity (VO_2max). Exercises that result in a VO_2max of < 65%, 65–90%, and > 90% are considered low, middle, and high intensity, respectively (Kramer, 2020). However, due to the difficulty in quantifying VO_2max, heart rate, rating of perceived exertion, metabolic equivalents, and specific speeds or watts are used as alternatives for VO_2max, which makes these classifications less uniform (Kramer, 2020). Second, researchers may have their own measurement preferences that result in divergent standards. Taking exercise duration as an example, "long-term" is used to describe training programs ranging from 4 weeks to 21 months in two different studies conducted in the same mouse strain (Belaya et al., 2018; Inoue et al., 2018). Accordingly, the lack of uniform protocols for conducting specific types of exercise intervention can make the outcomes inconsistent and difficult to compare directly.

Pathological Basis of Alzheimer's Disease

Pathological symptoms of AD

As one of the most common neurodegenerative diseases, patients with AD can be roughly classified into a preclinical stage and a dementia stage based on the appearance of canonical pathological symptoms. The dementia stage is further divided into mild, moderate, and severe phases according to the degree of cognitive impairment. In the mild dementia stage, AD is characterized by paroxysmal short-term memory impairment, but long-term memory is less affected. As AD progresses, executive function is increasingly impaired (e.g., deficits in judgment, problem solving, and organization), and this is accompanied by dysfunction in visuospatial skills and language. The development of AD also compromises the maintenance of new information, ultimately depriving patients of their ability to live independently (Tarawneh and Holtzman, 2012). It is worth emphasizing that some preclinical symptoms such as withdrawal, apathy, depression, and heightened anxiety may occur long before the clinical diagnosis of dementia (Atri, 2019). Likewise, the olfactory dysfunction

reportedly precedes the clinical cognitive signs of AD or mild cognitive impairment, and relates the apolipoprotein E-epsilon4 genotype, a pre-symptomatic risk factor for dementia (Graves et al., 1999; Wilson et al., 2009). Of note, the clinical symptoms mentioned above are correlated with pathological changes in the brain. Moderate or severe cortical atrophy (especially in the multimodal association cortices and limbic lobes) and melanin deposition in the locus coeruleus are the two most significant macroscopic changes. At the microscopic scale, the most notable features are the formation of intracellular neurofibrillary tangles (NFTs) and extracellular amyloid plaques, accompanied by other common pathological changes such as granulovacuolar degeneration, the presence of eosinophilic Hirano bodies and dystrophic neurites, the development of cerebral amyloid angiopathy, the emergence of tau-positive neuropil threads, and the loss of neurons and synapses (DeTure and Dickson, 2019).

Pathological mechanism of AD

The pathogenesis of AD is complex and involves multiple interrelated processes. To date, there are four more or less accepted theories of AD pathogenesis that emphasize the potential involvement of beta-amyloid peptide (Aβ) plaques, Tau NFTs, neuroinflammation, and oxidative stress (**Figure 1**).

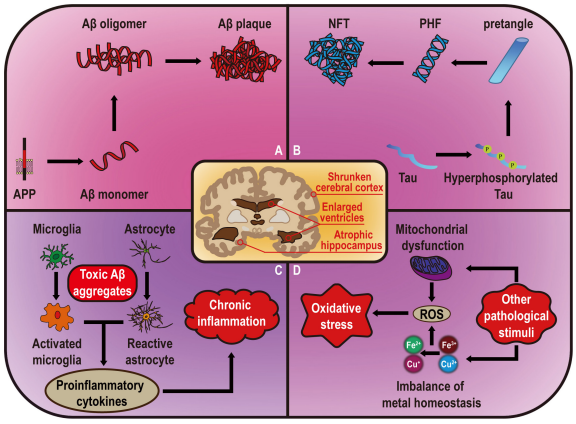

Figure 1 | **Theories regarding the pathogenesis of AD.**
(A) Amyloid-β plaque theory. APP is degraded into Aβ monomers, which then assemble into Aβ oligomers and ultimately pathological Aβ plaques. (B) Tau NFT theory. Abnormal post-translational modification of Tau (especially hyperphosphorylation) promotes Tau-Tau interactions, leading to the sequential formation of tangles, PHFs, and NFTs. (C) Neuroinflammation theory. Quiescent immune cells in the CNS (mainly microglia and astrocytes) can be activated by toxic Aβ aggregates and then secrete a large number of proinflammatory cytokines, leading to chronic inflammation. (D) Oxidative stress theory. Certain pathological stimuli (e.g., Aβ plaques and NFTs) can disrupt metal homeostasis and mitochondrial dysfunction, both of which increase ROS generation and cause neurodegeneration due to oxidative injury. These four mechanisms may work independently or interactively, eventually resulting in AD pathology, including cerebral cortical shrinkage, ventricular enlargement, and hippocampal atrophy. AD: Alzheimer's disease; APP: amyloid precursor protein; Aβ: beta-amyloid peptide; CNS: central nervous system; NFT: neurofibrillary tangle; PHF: paired helical filament; ROS: reactive oxygen species.

Aβ plaque theory

The presence of neurotoxic amyloid plaques, which Aβ forms as a result of a pathological cascade reaction, is considered the gold standard for AD neuropathological diagnosis. Amyloid precursor protein (APP), the precursor of Aβ, is a widely-distributed type I membrane glycoprotein that exists in several isoforms (e.g., APP 751/770, which is mainly expressed in glial cells; and APP 695, which is primarily expressed in neurons) and has various activities, including participating in cell adhesion, providing nutrition, supporting cell growth, and regulating mitochondrial function (Wilkins and Swerdlow, 2017; Zhang et al., 2019a). A diverse range of APP secretases degrade APP in either a non-amyloidogenic or an amyloidogenic manner. Non-amyloidogenic degradation, known as the α-degradation pathway, mainly produces neurotrophic or neuroprotective fragments (e.g., carboxy-terminal α fragments and soluble APP α) and inhibits Aβ formation through cleavage of the Aβ domain within APP. In contrast, the β-degradation pathway generates a variety of neurotoxic Aβ peptides composed of 39–43 amino acids (e.g., $Aβ_{1–40/42}$) through the continuous cleavage activity of β [e.g., β secretase 1 (BACE1)] and γ secretases (Wilkins and Swerdlow, 2017). As the major component of amyloid plaques, $Aβ_{1–42}$ monomers assemble sequentially into oligomeric species, short proto-fibrils, and mature insoluble fibrils. These extracellular, insoluble deposits of fibrous proteins form plaques in multiple brain regions (e.g., the molecular layer of the cerebellum and hippocampus) (Reiss et al., 2018), and thus cause apparent neurotoxicity including axonal dystrophy and transport interruption, mitochondrial dysfunction, autophagic impediment, exaggerated inflammation, and oxidative stress due to activation of astrocytes or microglia, eventually leading to neurodegeneration (Fiala, 2007). Although these amyloid plaques are considered a hallmark of AD pathology, abundant literature also reports a low correlation between fibril burden and cognitive decline, as opposed to the dominant role of low molecular weight Aβ oligomers in AD pathology. Indeed, soluble Aβ oligomers are more cytotoxic to neurons than Aβ fibrils in a myriad of ways. The latest research has confirmed that $Aβ_{1–42}$ tetramers and octamers can embed into the lipid membrane and form marginally conductive pores that disrupt the integrity of cell membranes as well as the homeostasis of intracellular ions (Ciudad et al., 2020). These findings substantiate the amyloid pore hypothesis, which was initially proposed nearly three decades ago (Arispe et al., 1993). Furthermore, other studies have reported that Aβ oligomers can aggravate Tau pathology, oxidative stress, and inflammation, thereby compromising mitochondrial function and synaptic plasticity via diverse downstream effectors (e.g., nicotinic/GABAergic/insulin receptors, prion proteins, pro-inflammatory cytokines) (Lee et al., 2017; Mroczko et al., 2018; Reiss et al., 2018).

Tau NFT theory

Similar to the amyloid plaques mentioned above, NFTs formed of abnormally assembled Tau proteins are another hallmark of AD pathology. Tau is a microtubule-associated protein translated from an alternatively spliced mRNA that generates six Tau isoforms ranging from 352 to 441 amino acids in length. The mature protein contains a projection domain at the amino terminus and a microtubule-binding domain at the carboxyl terminus. Under physiological conditions, Tau is a highly soluble, unfolded protein distributed mainly in the axons of CNS neurons, and plays an indispensable role in the assembly and structural stability of tubulin, thus maintaining normal neuronal physiology (e.g., axonal transport, synaptic function) (Savelieff et al., 2013; Chong et al., 2018). However, following abnormal post-translational modification (e.g., hyper-phosphorylation, glycosylation, ubiquitination, nitration), Tau undergoes conformational changes that promote Tau-Tau interactions and aggregates into paired helical filaments and NFTs that prevent it from binding to microtubules. Tau aggregates first appear in the entorhinal cortex, and gradually spread to the hippocampus and other regions, including the limbic and association cortices (Ballatore et al., 2007; Chong et al., 2018). The neurotoxicity of NFTs may be attributable in part to the loss of Tau's microtubule-stabilizing function, which adversely affects the normal structure and function of the cytoskeleton, thus inevitably resulting in the disruption of axonal transport, synaptic dysfunction, and loss of dendritic structure. Moreover, the accumulation of fibrous aggregates inside neurons also physically blocks normal cellular

functions (Ballatore et al., 2007). Similar to Aβ, small, soluble Tau oligomers (including the 140- and 170-kDa isoforms) may be predominant mediators of AD neurotoxicity and synaptic disorder due to their ability to induce misfolding of endogenous Tau, mitochondrial damage, intracellular Ca^{2+} imbalance, and compromised synaptic plasticity, eventually triggering neurodegeneration (Guerrero-Muñoz et al., 2015; Jouanne et al., 2017; Shafiei et al., 2017). A growing body of evidence shows that Aβ- and Tau-related pathology are not mutually exclusive: formation of an Aβ-Tau complex enhances the sensitivity of Tau to glycogen synthase kinase 3β, which increases Tau phosphorylation and aggravates its pathological effects; in turn, upregulation of Aβ may indirectly contribute to Tau pathology by promoting the expression of Tau-phosphorylating kinases, activating proinflammatory cytokines, and inhibiting degradation of phosphorylated Tau (Ittner and Götz, 2011; Savelieff et al., 2013). Interestingly, it is NFTs rather than Aβ plaques that determine cognitive performance in patients with AD (Nelson et al., 2012).

Neuroinflammation theory

Evidence is accumulating that neuroinflammation plays a critical role in the pathogenesis of AD. For example, immunoproteins and Aβ plaques frequently co-localize. In addition, administration of anti-inflammatory drugs seems to alleviate AD pathology (Rogers et al., 1988; Rich et al., 1995; Mizobuchi and Soma, 2021). A variety of receptors expressed on the surface of microglia and astrocytes, the two glial cell types that are crucial for neuroinflammation, can detect Aβ ligand signals and drive the expression of downstream inflammatory response genes. These receptors can be categorized into different subtypes, including Toll-like receptors 2/4/6/9, which recognize Aβ fibrils signals; receptors for advanced glycoxidation end-products, which detect Aβ oligomer signals; NOD-like receptors, which identify cell damage signals; and others such as scavenger receptor A1, cluster of differentiation (CD) 36 (CD36), CD14, and CD47 (Glass et al., 2010; Heppner et al., 2015). Interestingly, inflammation appears to be a double-edged sword at different stages of AD development. During the acute phase, activated microglia respond to Aβ stimulation by migrating toward Aβ fibrils and subsequently clearing them and other toxic substances via phagocytosis. Meanwhile, extracellular proteases released by microglia (e.g., NEP, IDE, matrix metalloproteinase 9) degrade extracellular soluble Aβ and help counteract AD-related pathology at this early stage (Heneka et al., 2015; Wang and Colonna, 2019). However, prolonged or persistent neuroinflammatory challenges are known to exacerbate AD. The continuous inflammatory response impairs the normal function of microglia and hence reduces their phagocytic capacity, increases the secretion of proinflammatory cytokines, and accelerates the spread and seeding of Aβ aggregates. In addition, chronic exposure to proinflammatory cytokines causes functional and structural neuronal abnormities. The above-mentioned alterations may eventually provoke neuronal degeneration (Heneka et al., 2015; Calsolaro and Edison, 2016; Wang and Colonna, 2019). Furthermore, nuclear factor kappa B (NF-κB) binding sites reportedly exist in the promotor region of APP, presenilin (a component of γ-secretase), and BACE1, implying that these molecules can be upregulated by proinflammatory cytokines and thereby accelerate Aβ pathology (Chami et al., 2012). In addition, upon deregulation of the cyclin-dependent kinase 5/p35 axis, proinflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor α (TNF-α) also increase the proportion of hyper-phosphorylated Tau (Quintanilla et al., 2004).

Oxidative stress theory

An imbalance between the production of reactive oxygen species (ROS) and the defensive effects of antioxidants is called oxidative stress and disrupts the maintenance of normal cellular functions (Pizzino et al., 2017; Tabassum et al., 2020). Abnormal Aβ plaques and Tau proteins cause mitochondrial dysfunction and disrupt transition metal homeostasis, which ultimately promotes the generation of ROS and causes oxidative stress. In turn, oxidative stress mediates Aβ and Tau neurotoxicity, and potentially enhances the Aβ production and aggregation, as well as Tau hyperphosphorylation and polymerization (Zhao and Zhao, 2013; Bhat et al., 2015). Furthermore, oxidative stress triggers neuroinflammation by stimulating proinflammatory cytokine and chemokine activity, and inflammatory responses can activate microglia and astrocytes to produce more ROS (Bhat et al., 2015). Oxidative stress is inseparable from other pathological processes, which together create a complex, vicious circle that aggravates AD pathology.

Exerkines that Potentially Mitigate Alzheimer's Disease

As mentioned above, exerkines are potentially the most important factors mediating the neuroprotective effects of exercise. Physical activity triggers the upregulation of exerkines in diverse tissues that directly or indirectly mitigate AD pathology through a series of biological processes illustrated in **Figure 2**. We classify these exerkines into four categories: growth factors and hormones, enzymes and coenzymes, metabolites, and miRNAs. In this section, we elaborate on the potential roles that exerkines play in ameliorating AD.

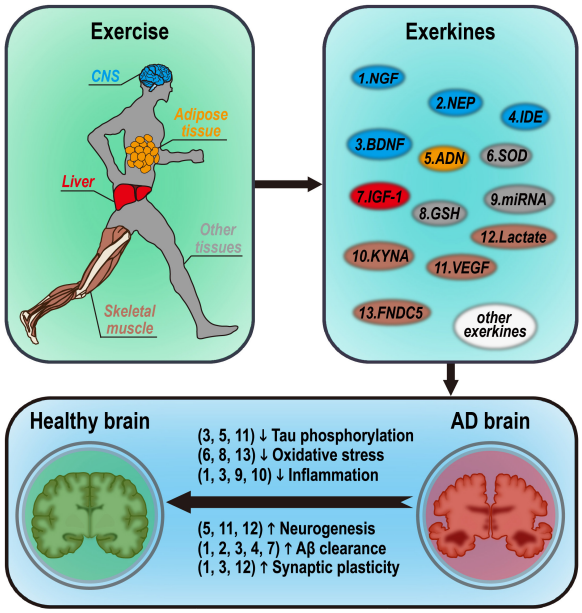

Figure 2 | **How physical exercise may benefit AD brains.**
Physical exercise triggers the release of numerous exerkines from peripheral tissues/organs. Most of these exerkines can permeate through the blood-brain barrier and elicit a variety of biological changes in the central nervous system, such as a reduction in oxidative stress, phosphorylation of Tau, and neuroinflammation, while enhancing Aβ clearance, synaptic plasticity, and neurogenesis. These processes can be neuroprotective and thereby mitigate AD pathology. The exerkines shown in the upper right panel are color-coded to correspond to the main tissue/organ of origin, as shown in the upper left panel. The exerkine numbers shown in the upper right panel correspond with the numbers shown in parentheses in the lower panel, indicating the reported neuroprotective mechanisms of these exerkines with regard to mitigating AD pathology. AD: Alzheimer's disease; ADN: adiponectin; Aβ: beta-amyloid peptide; BDNF: brain-derived neurotrophic factor; CNS: central nervous system; FNDC5: fibronectin type III domain containing 5; GSH: glutathione; IDE: insulin-degrading enzyme; IGF-1: insulin-like growth factor 1; KYNA: kynurenic acid; miRNA: microRNA; NEP: neprilysin; NGF: nerve growth factor; SOD: superoxide dismutase; VEGF: vascular endothelial growth factor.

Growth factors and hormones

Endogenous growth factors and hormones are "canonical" exerkines that are released into the circulation by various secretory tissues/organs in response to physical exercise and mediate exercise-induced neuroprotection by initiating numerous signaling pathways in different brain regions. Generally, these endogenous hormones are divided into different categories based on their origin: myokines are secreted by muscle (e.g., FNDC5), adipokines are secreted by adipose tissue (e.g., ADN), hepatokines are secreted by the liver (e.g., IGF-1), and neurotrophins are secreted by the nervous system (e.g., BDNF).

BDNF

Belonging to the family of neurotrophic factors, mature BDNF (~13.5 kDa) is produced in the endoplasmic reticulum from its precursor pro-BDNF (~26 kDa) through a series of tightly-controlled procedures, including sortilin-dependent folding in Golgi apparatus, carboxypeptidase-E–mediated protein sorting, and intra-/extracellular protease cleavage. Interestingly, signals initiated by mature BDNF and pro-BDNF are mutually antagonistic. BDNF specifically binds to tyrosine-related receptor kinase (Trk) B, triggering intracellular signaling cascades [e.g., the mitogen activated protein kinase (MAPK), phospholipase c γ, and phosphatidylinositol 3-kinase (PI3K) pathways] that promote neuronal survival, the growth of dendritic spines, long-term potentiation (LTP), and synaptogenesis. In contrast, pro-BDNF binds to p75 neurotrophin receptor ($p75^{NTR}$) and elicits neural cell death (Huang and Reichardt, 2001; Lu et al., 2005). Neeper et al. (1995) first reported a positive correlation between physical activity and BDNF expression in the hippocampus and caudate neocortex, which has been supported by subsequent animal and clinical data (**Additional Table 1**) and suggests that physical exercise results in BDNF-associated neurological benefits. Low levels of BDNF have been observed in both serum and postmortem brain samples from patients with AD (Phillips et al., 1991; Ng et al., 2019), suggesting the possible involvement of BDNF in AD pathology. In contrast, activation of BDNF signaling may be closely associated with the beneficial effects of treadmill running on cognitive function (Dao et al., 2013; Koo et al., 2013; Kim et al., 2014; Sim, 2014; Lin et al., 2015; Xiong et al., 2015; Azimi et al., 2018) and emotional health (Rosa et al., 2019) that have been observed in various AD rodent models. Further investigation demonstrated that BDNF can directly restore cognitive dysfunction (especially memory impairment) in animal models of AD, which may involve BDNF-related enhancements of hippocampal neurogenesis, dendritic spine density, and synaptic plasticity (Hsiao et al., 2014; Choi et al., 2018; de Pins et al., 2019). Moreover, the BDNF/NF-κB pathway significantly reduces neuroinflammation in AD transgenic mice by suppressing glial activation and downregulating the proinflammatory cytokines IL-1β, IL-6, and TNF-α, ultimately protecting memory function. Additionally, the BDNF/cyclic AMP response element-binding protein pathway could increase apurinic/apyrimidinic endonuclease 1 expression, thus enhancing DNA-repair capacity and protecting neurons from DNA oxidative damage (Yang et al., 2014c; Fang et al., 2019). Notably, BDNF not only protected neurons from Aβ-induced neurotoxicity *in vitro* and *in vivo* (e.g., increasing cortical neuron survival and choline acetyltransferase activity, mitigating morphological damage to the corpus callosum, and inhibiting miniature excitatory postsynaptic currents, as well as LTP), but also blocked Aβ production by shifting APP degradation to the α-secretase-dependent non-amyloid pathway (Holback et al., 2005; Arancibia et al., 2008; Zeng et al., 2010; Kitiyanant et al., 2012). BDNF was also reported to reduce the phosphorylation of multiple AD-related sites on Tau in neurons through the PI3K-Akt pathway (Elliott et al., 2005). Although no previous study has directly investigated how BDNF knockout would affect the beneficial effects of exercise on AD, some animal studies provide evidence for BDNF's role in AD in response to exercise. For example, strength training decreases the B-cell lymphoma protein 2-associated X protein/B-cell lymphoma protein-2 ratio in an animal model of AD, subsequently attenuating apoptotic signaling and spatial memory impairment through the BDNF/extracellular regulated protein kinases (ERK)/calcium calmodulin-dependent protein kinase II/cyclic AMP response element-binding protein signaling pathway (Martini et al., 2020). Additionally, exogenous application of BDNF partially recapitulates the neurological benefits of exercise in AD. Nigam et al. (2017) demonstrate that wheel running-triggered increases in BDNF expression enhanced α-secretase activity and stimulated the production of soluble APP-α, which prevents β-secretase from degrading APP into $Aβ_{1–40/42}$, in 2xTgAD mice. Additionally, treating SH-SY5Y human neuroblastoma cells with BDNF induces certain phenotypes (e.g., elevation of soluble APP-α and reduction of $Aβ_{1–40/42}$) that reflect the changes seen in *in vivo* models following exercise interventions (Nigam et al., 2017). Similarly, treating adult 5xFAD mice with the chemical P7C3 and Wnt3-overexpressing lentivirus to enhance neurogenesis, as well as with 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside to induce BDNF upregulation in the hippocampus, mimicked exercise-elicited cognitive improvement (Choi et al., 2018).

NGF

NGF, a nerve growth-inducing protein consisting of 118 amino acid residues, was the first neurotrophin discovered, and was originally identified in snake venom and mouse salivary glands (Cohen and Levi-Montalcini, 1956; Cohen, 1960). Located on chromosome 1, the *NGF* gene is translated into a precursor protein called pro-NGF, which is then cleaved into the biologically mature form, a 26-kDa homodimer connected through non-covalent linkage. NGF is expressed at detectable level in neurons and glial cells (e.g., microglia, astrocytes, oligodendrocytes), but its expression level is contingent on both the region of the nervous system and the developmental stage. Interestingly, NGF is also widely expressed by peripheral cells, such as macrophages, platelets, and myocytes. Similar to BDNF, NGF and pro-NGF bind to two different receptors: TrkA and $p75^{NTR}$. NGF has high affinity for TrkA, while its affinity for $p75^{NTR}$ is very low. Activation of TrkA by NGF initiates PI3K- or ERK-dependent signaling, which promotes neuronal survival, whereas pro-NGF binds to $p75^{NTR}$ and stimulates the apoptotic c-Jun N-terminal kinase pathway (Allen et al., 2013; Xu et al., 2016; Canu et al., 2017a). A growing body of evidence from animal and clinical studies has demonstrated that physical exercise upregulates both peripheral and central NGF levels (**Additional Table 1**), suggesting that NGF participates in exercise-induced neurological changes. Unexpectedly, AD pathology is reportedly associated with lowered serum NGF levels but increased NGF synthesis in specific brain regions (Gelfo et al., 2011), which indicates that the release of NGF following physical exercise may be tissue-/organ-specific and could explain why the downstream biological effects of NGF are so variable. NGF plays a pivotal role in neuroprotection by maintaining normal function of the cortical cholinergic system, which is an important neuromodulator indispensable for memory, mood, sleep cycle, and cognition in AD (Ferreira-Vieira et al., 2016). NGF/TrkA signaling is essential for the survival and maturation of cholinergic neurons in the striatum and basal forebrain. NGF reverses cholinergic neuron degeneration in the basal forebrain and attracts their axons in a gradient-dependent manner, thereby stabilizing the rate of cognitive decline in patients with AD (Tuszynski, 2000; Tuszynski et al., 2005; Nagahara et al., 2009). Also, NGF participates in the regulation of synaptic plasticity. NGF/TrkA signaling strictly controls the presynaptic effects and homeostasis of three presynaptic proteins (synapsin

I, synaptosomal-associated protein 25, and α-synuclein) in cholinergic neurons through a protein-degrading mechanism mediated by the ubiquitin-proteasome system. In contrast, NGF withdrawal provokes rapid presynaptic dysfunction and loss of the three aforementioned presynaptic proteins (Latina et al., 2017, 2018). Furthermore, NGF/TrkA signaling favors the non-amyloidogenic APP degradation pathway, consequently inhibiting the formation of neurotoxic Aβ peptides (especially $A\beta_{1-40/42}$). Specifically, NGF promotes TrkA-APP binding, which facilitates APP transportation to the Golgi apparatus, thus hindering the APP-BACE1 interaction. In addition, NGF treatment moderately downregulates BACE1 expression and concurrently upregulates enzymes with α-secretase activity (e.g., disintegrin, metalloprotease-17, metalloprotease-10, and matrix metallopeptidase 9) (Fragkouli et al., 2011; Yang et al., 2014a; Triaca et al., 2016; Xie et al., 2016; Canu et al., 2017b).

VEGF

VEGF is a homodimeric vasoactive glycoprotein that is considered to be a key mediator for angiogenesis and is widely distributed in a variety of cells and tissues, such as macrophages, platelets, astrocytes, white blood cells, and endothelium (Melincovici et al., 2018). The VEGF family contains more than six structurally-related protein members, including VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor. Among them, VEGF-A and -B regulate blood vessel growth, while VEGF-C and -D regulates lymphangiogenesis (Ferrara et al., 2003). VEGF receptors (VEGFRs) mainly comprise the high-affinity tyrosine kinase receptor VEGFR1 and the low-affinity receptor VEGFR2, which has high homology to VEGFR1. Different VEGF subtypes have varying affinities for the VEGFRs: VEGF-B and placental growth factor preferentially bind to VEGFR1, VEGF-C and -D preferentially bind to VEGFR3, and VEGF-A binds to VEGFR1/R2 equally. Notably, VEGF-A and placental growth factor binding to neuropilin 1 increases their affinity for VEGF-R2 (Apte et al., 2019). Breen et al. (1996) reported that a single bout of exercise significantly elevated VEGF mRNA expression in muscle 2- to 4-fold, which may be partly due to a decrease in the intracellular partial pressure of oxygen. Later studies have reported that exercise significantly increases VEGF levels in both the central and peripheral regions of the body (**Additional Table 1**). Interestingly, treadmill exercise in pregnant rats also increases VEGF expression in the prefrontal cortex of their offspring (Aksu et al., 2012). Serum VEGF levels have been observed to decline in AD (Mateo et al., 2007; Huang et al., 2013). The slight increase in hippocampal VEGF levels that occurs in the initial stage of AD disappears rapidly as the disease progresses, and is thus presumably a response to the hypoxia and vascular changes that occur at the onset of AD (Kim and Kim, 2012; Tang et al., 2013). Indeed, the neuroprotective properties of VEGF make it a key participant in the regulation of AD pathology. For example, VEGF restores memory impairment in animal models of AD by enhancing vascular survival and angiogenesis (Wang et al., 2011; Religa et al., 2013). In addition, activation of the caveolin-1/VEGF signaling pathway mediates physical exercise-induced promotion of neurogenesis, dendritic modification, and synaptic plasticity, resulting in the recovery of neurological dysfunction (Zhao et al., 2017; Xie et al., 2019). Moreover, the VEGF-C/VEGFR3 complex is crucial to attenuating neuroinflammation, as it induces M2 microglial polarization and prevents apoptosis (Ju et al., 2019). Additionally, VEGF exposure not only decreases the levels of soluble Aβ peptides and APP-β, but also attenuates the activity of β-secretases in cultured primary neurons or brain slices taken from Tg2576 mice, a transgenic model for AD (Bürger et al., 2009, 2010). Also, administration of exogenous VEGF has been reported to significantly reduce the level of Tau hyper-phosphorylation in AD mice. For instance, intra-hippocampal injections of VEGF-expressing lentiviral particles can reverse the accumulation of hyper-phosphorylated Tau (Salomon-Zimri et al., 2016). Likewise, a substantial decrease in the level of hyper-phosphorylated Tau has been observed in mice treated with the encapsulated VEGF-secreting cells for 3 months (Spuch et al., 2010). Given the above-mentioned benefits (e.g., promoting angiogenesis, neuronal proliferation, and cognitive function and reducing Aβ burden and Tau hyper-phosphorylation), investigators are devising novel strategies to deliver VEGF more effectively and precisely to appropriate neural regions, such as stereotactic transplantation of microcapsules containing VEGF-secreting cells or bone marrow mesenchymal stem cells that express VEGF (Spuch et al., 2010; Antequera et al., 2012; Garcia et al., 2014).

IGF-1

IGF-1 is a 70-amino acid tissue growth factor that is produced following stimulation by growth hormone. It is widely expressed in both the CNS (e.g., cerebellum, olfactory bulb, hippocampus) and peripheral non-neuronal tissues (e.g., liver) (Orrù et al., 2017; Wrigley et al., 2017). Generally, IGF-1 binds to specific receptors on target cells, activates tyrosine kinases, and then phosphorylates certain substrates, including insulin receptor subsets 1/2 and Src-homology/collagen. These phosphorylated substrates are subsequently recognized by second messengers containing SH2 domains (e.g., PI3K), which initiate downstream signaling cascades (e.g., MAPK) that mediate multiple growth factor–induced biological activities (Hakuno and Takahashi, 2018). Studies involving both animal and human subjects have shown that peripheral and central levels of IGF-1 are upregulated by various physical activities, implicating the potential modulatory role of IGF-1 in exercise-elicited neuroprotection (**Additional Table 1**). According to the research conducted in rodents, blockade of IGF-1 signaling may cause a series of pathological changes in AD, including cerebral amyloidosis, Tau phosphorylation deposition, loss of synaptic proteins, and cognitive dysfunction (Carro et al., 2006). IGF-1 is reported to regulate the physiology of neural stem cells (NSCs). For example, it promotes NSC proliferation in the subgranular and subventricular zones in adult mice through the mitogen-activated ERK, or RAS-like protein expressed in many tissues 1/Akt/sex-determining region y-box 2, pathway (Yuan et al., 2015; Mir et al., 2017). Also, IGF-1 induces NSC differentiation through the PI3K/Akt signaling cascade (Yuan et al., 2015). Additionally, IGF-1 modulates inflammatory responses, as restoration of insulin/IGF-1 signaling in the streptozotocin-induced rat model of sporadic AD decreased the expression of multiple proinflammatory cytokines, as well as the severity of neuroinflammation (de la Monte et al., 2017). Moreover, it assists in preventing Aβ toxicity by promoting α-secretase processing of APP and shedding of the amyloid precursor-like protein 1/2 extracellular domain, as well as inhibiting BACE-1 expression through PI3K/Akt or MAPK/ERK signaling (Adlerz et al., 2007; Zhang et al., 2011b). Finally, IGF-1 can prevent Aβ oligomer–induced neuronal death and reduce the Aβ load by enhancing the transport of Aβ carrier proteins to the brain (Carro et al., 2002; Kitiyanant et al., 2012; Hou et al., 2017).

FNDC5

FNDC5, a glycosylated type I membrane protein formerly known as peroxisomal protein, is composed of 209 amino acid residues and contains an N-terminal signal peptide, a type III fibronectin domain, a hydrophobic transmembrane domain, and a C-terminal cytoplasmic tail. Upon cleavage of the C-terminus, the N-terminal fragment of FNDC5, called irisin (112 amino acids), is secreted into the circulation; this exercise-responsive myokine is highly conserved in all mammals (Boström et al., 2012; Schumacher et al., 2013). Both FNDC5 and irisin are expressed ubiquitously throughout the body, including in the skeletal muscle, adipose tissue,

brain, spinal cord, and peripheral nerves (Aydin et al., 2014). Previous studies have shown that FNDC5 expression in muscle, bone, serum, and the hippocampus is uniformly upregulated by physical exercise (**Additional Table 1**). Overexpression of FNDC5 dramatically enhances differentiation of mouse embryonic stem cells into neural precursors and mature neurons, whereas knocking out FNDC5 significantly inhibits neuronal differentiation and maturation of neurons, as well as astrocytes (Hashemi et al., 2013; Forouzanfar et al., 2015).

FNDC5/irisin levels in the brain tissue and cerebrospinal fluid (CSF) of patients with AD are dramatically lower than they are in healthy subjects, and FNDC5/irisin expression levels are inversely associated with AD symptoms in mouse models, suggesting that FNDC5/irisin as a potential biomarker for and regulatory target of AD (Lourenco et al., 2019). Transcription of proliferator-activated receptor-co-activator 1 α (PGC-1α) and estrogen-related receptor α was increased in response to endurance training, which stimulated the synthesis and secretion of FNDC5 (in the form of irisin) (Wrann et al., 2013). Thereafter, irisin permeated through the BBB and ultimately exerted neuroprotective effects by upregulating BDNF expression. Interestingly, increased BDNF expression can trigger a negative feedback signal downregulating FNDC5, thus forming a steady-state regulation loop (Wrann et al., 2013; Azimi et al., 2018; Belviranlı and Okudan, 2018). Taken together, these lines of evidence suggest that the PGC-1α/FNDC5/BDNF axis is crucial for FNDC5/irisin-elicited neuroprotection. In addition, several studies have confirmed that irisin is essential to neural differentiation of mouse embryonic stem cells, affects hippocampal neurogenesis, and induces neuronal proliferation by regulating signal transducer and activator of transcription 3 signaling (Jung et al., 2006; Hashemi et al., 2013; Moon et al., 2013). Irisin also reportedly protects neurons from oxidative stress by activating Akt/ERK1/2 signaling to attenuate the secretion of proinflammatory cytokines (e.g., TNF-α) and exhibits neuroprotective effects by inhibiting ROS–Nod-like receptor family pyrin domain containing 3 inflammatory signals (Annibalini et al., 2017; Peng et al., 2017). Furthermore, many studies have demonstrated that irisin can protect the nervous system against Aβ-induced neurotoxicity. Azimi et al. (2018) showed that moderate treadmill exercise could restore AMP-activated protein kinase (AMPK) activity and PGC-1α/FNDC5/BDNF levels to reduce the spatial learning and memory impairment induced by $A\beta_{1-42}$ injection in rats. In addition, irisin can suppress NF-κB activation by preventing its phosphorylation and loss of IκBα (inhibitor α of NF-κB) in Aβ-exposed astrocytes (Wang et al., 2018). Likewise, increased PGC-1α and FNDC5 expression can offset the influence of $A\beta_{1-42}$ oligomers on neuronal apoptosis in the transformed neuroblastoma cell line Neuro-2a (Xia et al., 2017). Irisin blocks the binding of Aβ oligomers to neurons, thereby alleviating memory and synaptic plasticity impairments resulting from AD. Of note, peripheral injection of FNDC5 can increase hippocampal FNDC5/irisin levels, thus exerting a similar neuroprotective effect (Lourenco et al., 2019).

ADN

ADN is a hormone secreted by fat tissue that was first isolated from rat adipose cells by Scherer and colleagues (Scherer et al., 1995). The 244-amino acid ADN protein has a molecular weight of 30 kDa and contains an N-terminal collagen-like domain and a C-terminal complement factor C1q-like globular domain (Turer and Scherer, 2012). ADN exists in the bloodstream in three major oligomeric complexes, namely the hexamer, trimer, and high-molecular-weight forms (Wang and Scherer, 2016), and is well known to participate in regulation of insulin sensitivity and catabolism of fatty acids and glucose. It is negatively correlated with some risk factors for dementia, such as insulin resistance and type 2 diabetes mellitus (Gustafson, 2010). Three ADN receptors have been identified, including ADN receptor (AdipoR) 1, AdipoR2, and T-cadherin; mouse and human AdipoR1/2 share 95% homology (Yamauchi et al., 2014). Numerous animal and clinical studies have reported the positive regulatory effect of exercise on ADN signaling in the CNS and peripheral tissues, and suggest that exercise may be extremely important for inducing ADN-mediated neurological benefits (**Additional Table 1**). Emerging epidemiological evidence has shown that metabolic abnormalities in the brain or peripheral tissues (e.g., type 2 diabetes mellitus) are a risk factor for dementia (Chatterjee et al., 2016). Previous investigations have confirmed that ADN can improve insulin sensitivity by promoting AMPK phosphorylation (Caselli, 2014), while the activation of AMPK signaling by ADN also enhances hippocampal neurogenesis through the AdipoR1/adaptor protein containing a PH domain, PTB domain, and leucine zipper motif 1/AMPK cascade (Yau et al., 2014, 2018; Yau et al., 2015; Wang et al., 2020). *In vitro*, ADN stimulates the proliferation of adult hippocampal NSCs by activating the p38MAPK/glycogen synthase kinase 3β/β-catenin signaling cascade (Zhang et al., 2011a). In aged ADN-deficient mice, AMPK activity is reduced, and hippocampal insulin resistance is aggravated, eventually triggering AD-like pathological changes, such as spatial memory and learning disorders. In contrast, ADN treatment suppresses glycogen synthase kinase 3β activation, reduces Tau hyper-phosphorylation, and rescues cognitive dysfunction in animal models of AD (Ng et al., 2016; Xu et al., 2018). ADN may also exert neurological benefits by enhancing synaptic plasticity. ADN-knockout mice show synaptic defects (e.g., reduced basal synaptic transmission, increased presynaptic release probability, defective LTP of hippocampal Schaefer collateral pathway), accompanied by cognitive dysfunction in various behavioral tests (e.g., new object recognition, Y-maze test) (Bloemer et al., 2019). Supplementing with ADN restores the hippocampal LTP in 5xFAD mice, a transgenic AD model (Wang et al., 2019). Moreover, ADN serves as a key modulator of neuroinflammation by blocking the inflammatory response of microglia to Aβ oligomers via AdipoR1/AMPK/NF-κB signal transduction; as expected, ADN deficiency enhances microglial activation and aggravates neuroinflammation in AD mice (Jian et al., 2019). Similarly, Acrp30 (a spherical form of ADN) regulates Aβ-evoked inflammatory responses through peroxisome proliferator activated receptor-γ signal transduction, including inducing the M2 phenotype of microglia, downregulating proinflammatory cytokines, and enhancing Aβ clearance by microglia. In addition, Acrp30 attenuates Aβ-induced destruction of the BBB via the AdipoR1/NF-κB axis (Song et al., 2017). Interestingly, long-term oral administration of adiporon (a synthetic AdipoR agonist) stimulates neuronal insulin signal transduction and boosts insulin sensitivity, thereby reducing Aβ levels and plaque deposition. The aforementioned changes help to counteract the loss of neurons and synapses, and ultimately maintain cognitive function and spatial memory in AD mice (Liu et al., 2020).

Enzymes and coenzymes

Aβ-degrading enzymes

Considering that abnormal deposition of Aβ plaque is one of the hallmarks of AD pathogenesis (Tam et al., 2019), alleviating Aβ burden may be the most direct approach to mitigating AD pathology. Inducing the dispersal of Aβ plaques into monomers may be problematic, as the Aβ monomers could go on to form cytolytic pores that are more detrimental to neurons than the plaques themselves. However, rather than directly degrading Aβ plaques, the exerkines discussed above primarily decrease Aβ burden by lowering soluble Aβ monomer production, which prevents both Aβ oligomer formation and deposition. BDNF, NGF, and VEGF can simultaneously reduce β-secretase activity and increase α-secretase activity, thus promoting APP processing by the

non-amyloid pathway which does not favor Aβ monomer formation (Bürger et al., 2010; Triaca et al., 2016; Nigam et al., 2017). IGF-1 enhances expression of the Aβ carrier proteins albumin and transthyretin and promotes the transport of brain Aβ to the CSF, consequently reducing the Aβ burden in the brain (Carro et al., 2002). Notably, NEP and IDE, which are Aβ-degrading enzymes (ADEs), directly cleave Aβ monomers into inactive fragments that lack the capacity to re-aggregate into toxic oligomers or plaques (Zuroff et al., 2017; Sikanyika et al., 2019). Unlike the aforementioned exerkines, these ADEs are often non-secreted factors: NEP is mainly expressed on the cytoplasmic membrane, while IDE is primarily expressed in the cytosol, mitochondria, and peroxisomes (Nalivaeva and Turner, 2019). Nevertheless, we still consider ADEs as belonging to the general exerkine family, given that (i) ADEs can be upregulated by exercise and exert neural benefits in AD by degrading Aβ; and (ii) peripheral supplementation with ADEs affects Aβ aggregation in the CNS (Liu et al., 2009, 2010).

NEP: NEP is a type II integral membrane protein belonging to the M13 zinc metal endopeptidase family. It consists of 742 amino acids and has a molecular weight ranging from 85 to 110 kDa (Malfroy et al., 1988). NEP is widely and highly expressed in various tissues and organs, such as the kidney and brain. In the CNS, NEP is mostly present in pre-synaptic neuronal termini, but can also be detected in activated astrocytes and microglia (Ries and Sastre, 2016). Owing to its extensive enzymatic activities, NEP plays important roles in many biological processes, including the response to inflammatory neuropeptides, bone metabolism, skin aging, and stem cell differentiation (Nalivaeva et al., 2020). To date, research on the exercise-induced regulation of NEP has mainly focused on the CNS. As shown in **Additional Table 2**, physical exercise increases both the expression and enzymatic activity of NEP in the hippocampus and cortex. As a key ADE, NEP benefits the nervous system by degrading Aβ. *In vitro* studies have demonstrated that recombinant NEP can degrade various forms of Aβ (e.g., full-length $Aβ_{1–40}$ and $Aβ_{1–42}$ and truncated $Aβ_{4–15}$), thus preventing Aβ accumulation and neurotoxicity in AD (Oh et al., 2016; Becker et al., 2018). Similarly, *in vivo* studies have confirmed that, in 5xFAD mice, hemizygous NEP deletion aggravates AD-associated behavioral and neuropathological deficits, including impaired spatial working memory, enlarged astrocyte population, enhanced Aβ deposition, and more. In contrast, NEP overexpression in this AD mouse model not only increased Aβ degradation, but also suppressed the increase in BACE1 expression that facilitates the plaque formation, thus reducing the appearance of AD-like phenotypes (Devi and Ohno, 2015; Hüttenrauch et al., 2015). Some studies have reported that peripheral administration of NEP can reduce Aβ levels in both the CNS and peripheral tissues. For instance, Liu et al. (2009) found that overexpression of NEP in the skeletal muscle of an AD mouse strain (3xTg-AD) significantly reduced the Aβ burden in the CNS (soluble Aβ peptide decreased by ~60% and amyloid deposition by ~50%) and improved cognitive function without apparent side effects related to other NEP substrates (e.g., bradykinin, endothelin, angiotensin); this might be due to the clearance of plasma Aβ and alteration of Aβ transport dynamics on the muscle surface. They further found that overexpression of soluble secreted NEP in the same model led to comparable outcomes. Of note, secreted NEP released into the blood stream is undetectable in the CSF, because its large size means that it is unable to cross the BBB (Liu et al., 2010). This suggests that peripheral, rather than intracerebral, NEP mediates the above-mentioned benefits on the nervous system. Interestingly, human NEP overexpressed in AD mice (APP/PS1) by ultrasound-mediated gene transfer of a plasmid encoding the human protein into the skeletal muscle of the mouse model was able to permeate through the BBB and significantly reduced the Aβ load in the brain, which was followed by improvement in spatial learning and memory (Li et al., 2020a). Hence, the clinical use of NEP could be facilitated by accurate, targeted drug delivery methods such as intracerebral injection of recombinant soluble NEP, construction of a BBB-permeable NEP fusion protein with a brain-shuttle module, or hippocampal transplantation of NEP-overexpressing NSCs (Park et al., 2013; Blurton-Jones et al., 2014; Campos et al., 2020).

IDE: IDE, another major enzyme responsible for Aβ degradation, is a zinc-dependent metalloprotease with a molecular weight of 110 kDa. Although insulin is the preferred substrate of IDE, this enzyme can also cleave other peptides (e.g., glucagon, atrial natriuretic peptide, Aβ, transforming growth factor α, IGF1/2) and is widely expressed in almost all types of cells and tissues (e.g., testis, tongue, brain, brown adipose tissue) (Duckworth et al., 1998). Unlike NEP, which exhibits broad substrate specificity, IDE specifically targets β-structure-forming substrates, and thus effectively inhibits the generation of toxic oligomers related to neurodegenerative diseases (Kurochkin et al., 2018). Investigations have shown that exercise can upregulate IDE levels in the hippocampus, cortex, liver, muscle, and adipose tissue of rodents (**Additional Table 2**). According to a clinical study, both the concentration and the activity of membrane-bound IDE were significantly decreased in the hippocampus of patients suffering from mild cognitive impairment with a higher risk of developing AD compared with healthy individuals (Zhao et al., 2007). In contrast, IDE-rich extracellular matrix biomaterials can reduce Aβ peptides aggregation, prevent the formation of amyloid plaques, and inhibit the phosphorylation of Tau protein in an *in vitro* model of AD overexpressing APP695swe (Zhang et al., 2019b). Inducing hyperglycemia with streptozocin in APPSwe/PS1 AD mice significantly lower both IDE and peroxisome proliferator activated receptor-γ levels compared with non-diabetic controls, whereas upregulating IDE by activating the peroxisome proliferator activated receptor-γ/AMPK pathway results in a marked decrease in $Aβ_{1–40}$ and $Aβ_{1–42}$ accumulation and improves spatial learning and recognition (Li et al., 2018). Similarly, overexpression of either drosophila or human IDE in a drosophila model of AD can rescue Aβ-induced neurotoxicity, including reducing retinal photoreceptor apoptosis, mitigating ectopic wing vein phenotype, and reversing the shortened lifespan (Tsuda et al., 2010). Additionally, expression of IDE by brain capillary endothelial cells may mediate Aβ clearance not only via direct degradation but also by efflux transport through the BBB (Ito et al., 2014). Moreover, there is considerable evidence that IDE forms irreversible complexes with α-synuclein and Aβ, thereby preventing the formation of α-synuclein amyloid fibrils and the synthesis of highly toxic soluble Aβ oligomers in its role as a "dead-end chaperone," respectively (Llovera et al., 2008; Sharma et al., 2015).

Antioxidative enzymes or coenzymes

As a key element of AD pathogenesis, oxidative stress is highly related to neuronal death and neurological dysfunction, thereby making antioxidants a potential remedy for AD. By increasing the levels of antioxidative enzymes or coenzymes, exercise intervention may systematically rectify the redox imbalance in AD, and consequently delay the pathological process of AD.

SOD: SOD belongs to a family of metal-containing enzymes that serve as the first line of defense against oxidative stress by catalyzing the conversion of superoxide anions (Zelko et al., 2002). Metal cations (e.g., Cu^{2+}, Zn^{2+}, Mn^{2+}) are essential for maintaining SOD activity, so disruption of metal homeostasis in the CNS is considered a potential cause of endogenous oxidative stress and is closely related to numerous neuropathies (Jomova and Valko, 2011). There are three known subtypes of human SOD: SOD1 is one of the most abundant cytoplasmic enzymes and contains Cu^{2+}/Zn^{2+}; SOD2 is located in mitochondria and contains Mn^{2+}; and SOD3

is a secretory SOD released into the extracellular matrix that is also rich in Cu^{2+}/Zn^{2+} (Zelko et al., 2002; Lewandowski et al., 2019). According to previous animal and clinical studies, both intracellular (SOD1 and SOD2) and extracellular (SOD3) SOD expression levels are significantly elevated by physical exercise (**Additional Table 3**). As the only secreted SOD, SOD3 can enter the circulation, thus exerting systematic antioxidative effects and playing other protective roles. Indeed, in an animal model of ischemia/reperfusion injury, overexpressed pulmonary SOD3 that entered the arterial blood exerted a distal effect on the CNS, including reducing the percentage of damaged cortex area and raising the neurological function score; this might be attributable to SOD3-mediated anti-inflammatory effects, given that SOD3 can suppress hyper-activation of polymorphonuclear neutrophils, and therefore diminish their neurotoxicity, without affecting their migration into the CNS (Mai et al., 2019, 2020). Similarly, tail vein injection of SOD3-overexpressing mesenchymal stem cells clearly alleviated neuronal apoptosis and ischemic stroke in a rat model of ischemia-reperfusion injury (Sun et al., 2019). Additionally, SOD3 is believed to eliminate free radicals, ameliorate neuronal damage, and reduce the cognitive decline associated with senescence in individuals with age-related neurodegenerative disease (Levin, 2005). Specifically, SOD3 alleviates $A\beta_{25-35}$-induced oxidative injury and promotes neuroblastoma cell survival through regulation of the mitochondrial pathway by decreasing levels of ROS, cytochrome c, caspases-3/9, MDA, and cytosolic Ca^{2+} (Yang et al., 2017). In addition, as shown in **Additional Table 3**, the increased expression of intracellular SODs in the CNS also helps combat AD. For example, overexpressing mitochondrial SOD2 in AD transgenic mice reduced oxidative stress (e.g., hippocampal superoxide levels), decreased the ratio of $A\beta_{1-42}/A\beta_{1-40}$ and the number of Aβ plaques, prevented Aβ-induced LTP impairment, and reversed AD-related learning and memory deficits (Dumont et al., 2009; Massaad et al., 2009; Ma et al., 2011). Similarly, SOD1 can rescue APP-induced cerebrovascular endothelial dysfunction, which may cause cerebral blood flow changes and neuronal dysfunction in AD, thereby preventing APP-related premature death in an animal model of AD (Iadecola et al., 1999). In addition, SOD1 treatment reportedly decreases the production of superoxide anions catalyzed by the Cu-Aβ complex in the AD brain in a concentration-dependent manner (Reybier et al., 2016).

GSH: GSH is a tripeptide thiol that is expressed in virtually all cells and is essential for maintaining the redox balance *in vivo*. GSH homeostasis is essential for maintaining the normal activities of various enzymes (e.g., GSH peroxidase, GSH s-transferase) that prevent neurodegeneration (Johnson et al., 2012). In particular, GSH acts as a coenzyme rather than a substrate for some specific enzymes (e.g., glyoxalase, formaldehyde dehydrogenase) that are associated with detoxification and antioxidation (Deponte, 2013; Ken et al., 2014). Also, GSH regulates a variety of cellular processes, including gene expression, replication, protein synthesis, cell proliferation, apoptosis, signal transduction, and the immune response (Wu et al., 2004). A number of clinical and animal studies have shown that physical exercise effectively increases the GSH/GSH persulfide ratio and the GSH content in both the CNS and peripheral tissues (**Additional Table 3**). GSH crosses the BBB by a carrier-mediated mechanism (Kannan et al., 1990). As one of the most important reducing agents *in vivo*, a decrease in GSH expression and the accompanying oxidative damage to neurons are potential hallmarks of early AD in patients with mild cognitive impairment (Bermejo et al., 2008; Mandal et al., 2015). In GSH-depleted primary neurons, Cu^{2+}-induced oxidative stress may lead to DNA damage and activation of p53-programmed cell death (Du et al., 2008). GSH has also been reported to protect brain endothelial cells from peroxide insult, as it inhibits the production of nitric oxide, ROS, and 8-hydroxy-2′-deoxyguanosine, reverses the decrease in tight junction protein expression, and activates the nuclear factor erythroid 2-related factor 2 (a key regulator of antioxidants) signaling pathway (Song et al., 2014). Moreover, GSH exerts neurological benefits by suppressing neuroinflammatory responses. In the AppNL-G-F/NL-G-F mouse model of AD, oral administration of GSH increases the expression level of GSH in the brain, as well as the GSH/GSH persulfide ratio, in a dose-dependent manner, reduces the levels of oxidative stress biomarkers (e.g., 4-hydroxynonenal), inhibits inflammation, as evidenced by blocking the proliferation of microglia and downregulating proinflammatory cytokines, and ultimately reverses behavioral deficits (e.g., cognitive decline, depression-/anxiety-like behaviors) (Izumi et al., 2020). There is also evidence that GSH depletion in cultured human microglia and astrocytes increases Ca^{2+} influx through transient receptor potential cation channel subfamily M member 2, which subsequently activates proinflammatory pathways (e.g., p38MAPK, c-Jun N-terminal kinase, NF-κB) and leads to the release of TNF-α, IL-6, and nitrite ions (Lee et al., 2010). Likewise, GSH deficiency in cultured hippocampal neurons disrupts Ca^{2+} homeostasis, mainly through transient receptor potential cation channel subfamily M member 2 and transient receptor potential cation channel subfamily V member 1, resulting in an increase in cytosolic ROS, mitochondrial dysfunction, and eventually cell apoptosis (Övey İ and Naziroğlu, 2015). Additionally, GSH plays an indispensable role in protecting the brain from the neurotoxicity of amyloid peptides. The age-associated decrease in GSH expression coincides with a gradual reduction in proteolytic tissue plasminogen activator levels and an increase in plasminogen activator inhibitor levels in the brain, which reduce the clearance of amyloid peptides; similarly, blocking GSH synthesis triggers the accumulation of carboxy-terminal fragments of the Aβ precursor protein (Aβ/carboxy-terminal fragments) and aggravates its cytotoxicity (Woltjer et al., 2005; Lasierra-Cirujeda et al., 2013).

Metabolites

As the by-products of metabolic pathways, metabolites are mostly small molecules whose expression levels are influenced by physical exercise. Unlike specialized biological signaling molecules, metabolites also exhibit broad-spectrum neuroprotective effects. For instance, KYNA, which is produced during tryptophan metabolism, can reduce the synthesis of other neurotoxic metabolites, whereas lactate, which is generated by glycolysis, improves neuronal energy supply (Agudelo et al., 2014; Bouzat et al., 2014).

Metabolites of the kynurenine pathway

The kynurenine (KYN) pathway (KP) is one of the most important mechanisms of tryptophan metabolism that converts more than 95% of tryptophan into KYN and its breakdown products. Tryptophan is initially oxidized into KYN by tryptophan dioxygenase or its isozyme indoleamine 2,3-dioxygenase under physiological or pathological (e.g., inflammation) conditions, respectively (Cervenka et al., 2017). Thereafter, KYN is enzymatically degraded either by kynurenine-3-monooxygenase into 3-hydroxykynurenine (3HK), 3-hydroxyanthranilic acid, quinolinic acid, and NAD+ sequentially, or by KYN aminotransferase (KAT) into KYNA (Cervenka et al., 2017). Interestingly, the metabolites of these two branches of the KP seem to play opposite roles in the CNS. For instance, 3HK and quinolinic acid have neurotoxic properties that are central to AD pathogenesis, including promoting Tau phosphorylation and ROS production, destroying the cytoskeleton and BBB, disrupting autophagic flux, inhibiting reuptake of glutamate by astrocytes, and inducing astrocytes to produce proinflammatory factors (Guillemin et al., 2003; Guillemin, 2012). In fact, in drosophila and mouse models of AD, inhibition of 3HK synthesis can effectively alleviate AD-related phenotypes

such as spatial memory deficits, anxiety-related behaviors, neurodegeneration, and synaptic loss, thereby improving life expectancy (Zwilling et al., 2011; Breda et al., 2016). In contrast, KYNA, the only known endogenous inhibitor of all types of glutamate ion channels, is neuroprotective, as it attenuates glutamate excitatoxicity, which contributes to AD pathology (Hilmas et al., 2001; Hynd et al., 2004; Kumar and Babu, 2010). In addition, KYNA modulates Aβ-induced inflammation and reduces the expression of proinflammatory cytokines (e.g., TNF-α, IL-6) in BV-2 microglial cells in its role as an endogenous antagonist of the α7 nicotinic acetylcholine receptor (Steiner et al., 2014). Moreover, as an endogenous antioxidant, KYNA also reduces the production of ROS in the CNS through a mechanism independent of N-methyl-D-aspartate (NMDA) or nicotinic receptor inhibition (Lugo-Huitrón et al., 2011). Additionally, treatment with KYNA reportedly induces the activity and expression of NEP, a metalloproteinase that degrades Aβ deposits in the brain, thus helping offset Aβ-evoked toxicity in AD (Klein et al., 2013; Maitre et al., 2020). Likewise, synthetic KYNA analogs can exert neuroprotection through various anti-AD mechanisms, such as inhibiting the activity of acetyl cholinesterase, scavenging free radicals, blocking NMDA and type 5 metabotropic glutamate receptors, and inhibiting the formation of $A\beta_{1-42}$ fibrils (Deora et al., 2017). However, the relationship between KYNA and AD is somewhat controversial. For example, some investigators have found remarkable decreases in KYNA levels in the plasma, red blood cells, and CSF of patients with AD (Hartai et al., 2007; Sorgdrager et al., 2019), whereas others have reported that the concentration of KYNA in the CSF is significantly increased in patients with AD (González-Sánchez et al., 2020). Also, one study showed that, in addition to promoting nerve cell survival, increased KYNA levels unexpectedly mediated $A\beta_{1-42}$-elicited impairment of NSC plasticity (Papadimitriou et al., 2018). Likewise, excessive blockade of NMDA receptors by abnormal accumulation of endogenous KYNA in the brains of patients with schizophrenia resulted in atrophy of the dorsolateral prefrontal cortex, as well as attention deficit (Kindler et al., 2020). These findings suggest that even a single KP metabolite may play several distinct roles in neurodegeneration, depending on cell/tissue type, brain region, disease, disease phase, and the health status of the subject. Notably, unlike other KP metabolites, KYN and 3HK are the only two intermediate products that can permeate the BBB (Fukui et al., 1991). Hence, decreasing the neurotoxic metabolic flux by reducing KYN and 3HK transport to the CNS may shift the KP to the "safer" branch that produces less 3HK and quinolinic acid and more KYNA. Indeed, various studies confirm that physical exercise can modulate the KP at two key regulatory steps: indoleamine 2,3-dioxygenase and KAT (**Additional Table 4**). Mounting evidence has demonstrated that chronic exercise inhibits abnormal increases in indoleamine 2,3-dioxygenase activity in both the CNS and plasma under pathological conditions (e.g., depression, AD, pancreatic cancer) (Liu et al., 2013; Souza et al., 2017; Pal et al., 2021), whereas exercise-enhanced KAT expression in skeletal muscles induced through a PGC-1α-dependent mechanism results in a decrease in peripheral, and subsequently central, levels of KYN and 3HK (Agudelo et al., 2014, 2019; Schlittler et al., 2016; Allison et al., 2019). Although it remains unclear how and to what extent exercise directly affects key KP enzymes in the CNS, it has been reported that brain-derived kynurenine-3-monooxygenase is activated by systemic inflammation (Connor et al., 2008), while exercise has long been known to exert a broad spectrum of anti-inflammatory effects (Metsios et al., 2020). Also, physical exercise reportedly increases KAT2/4 mRNA levels in the hippocampus of BDNFmet/met mice, a model for various mental disorders such as depression, anxiety, and schizophrenia (Ieraci et al., 2020). Hence, the benefits of exercise to AD brains could be mediated by regulation of the KP both centrally and peripherally, thereby reducing neurotoxic metabolic flux; this warrants further investigation.

Lactate

Lactate is a metabolite of the glycolytic pathway that is generated by conversion from pyruvate by lactate dehydrogenase when the oxygen supply is limited (Valvona et al., 2016). There are two stereo-isomeric forms of lactate: L-lactate and D-lactate (Castillo et al., 2015). Lactate is released into the circulation from muscles during high-intensity exercise and enters the CNS mainly by the action of several monocarboxylate transporters (MCTs). It is then exported from astrocytes by MCT4 or MCT1 and absorbed into neurons by MCT1 or MCT2 (Halestrap, 2013). A variety of exercise paradigms have been demonstrated to effectively induce increases in the blood concentration of lactate. In addition, vigorous exercise causes a significant elevation in brain lactate levels, which may be attributable to the enhanced absorption of available peripheral lactate (**Additional Table 4**). Although lactate used to be regarded as a waste product of metabolism, mounting evidence suggests that it may have neuroprotective effects. Rather than glucose, lactate is the preferred energy source for neuronal metabolism and protects neurons under various pathological conditions such as cerebral ischemia (Bouzat et al., 2014; Castillo et al., 2015; Roumes et al., 2021). Additionally, lactate transport between astrocytes and neurons is essential for maintaining synaptic plasticity (especially LTP of synaptic strength and long-term memory formation), whereas disrupting MCT expression or inhibiting glycogen breakdown in astrocytes leads to memory impairment (Newman et al., 2011; Suzuki et al., 2011). Moreover, brain lactate can enhance angiogenesis and neurogenesis by facilitating NF-κB translocation and increasing the expression of VEGF and basic fibroblast growth factor. Likewise, peripheral L-lactate partially mediates the effects of physical exercise on adult neurogenesis in an MCT2-dependent manner (Zhou et al., 2018; Lev-Vachnish et al., 2019). Also, both exercise-induced accumulation and exogenous administration of L-lactate can increase expression of VEGF-A in the brain (Morland et al., 2017). Similarly, peripheral administration of lactate is closely related to elevated BDNF levels in the circulation and hippocampus, and this relationship may be modulated by the PGC1α/FNDC5 pathway (Schiffer et al., 2011; El Hayek et al., 2019). L-lactate reportedly stimulates the expression of synaptic plasticity-related genes (e.g., ARC, c-FOS, ZIF268) via a mechanism involving NMDA receptor activity and the downstream Erk1/2 signaling cascade in neurons (Yang et al., 2014b). Furthermore, it upregulates TWIK-related potassium channel 1, an ion channel that enhances astrocyte potassium buffering and glutamate clearance, thereby promoting neuronal survival (Banerjee et al., 2016; Ghatak et al., 2016).

miRNAs

miRNAs, endogenous RNAs approximately 20–24 nucleotides in length, regulate the expression of approximately 50% of mammalian protein-coding genes (Krol et al., 2010) and play essential roles in many biological processes, including cell survival, proliferation, differentiation, migration, metabolism, and apoptosis via post-transcriptional regulation (Tony et al., 2015; Leivonen et al., 2017; Ling et al., 2019). In 2018, Dong and colleagues found that voluntary physical exercise significantly inhibited the increase in miR-132 expression seen in the hippocampus of SAMP8 mice (a senescence-accelerated mouse model of AD), as well as reversing the cognitive dysfunction induced by upregulation of miR-132 expression (Dong et al., 2018). A recent report also revealed that physical exercise substantially upregulates miR-129-5p expression in both AD mice and patients, whereas knocking down miR-129-5p attenuates exercise-induced suppression of neuroinflammation and enhanced cognition (Li et al., 2020b). Taken together, these two studies suggest a potential

role for miRNAs in exercise-induced neuroprotection. However, in view of the diversity and wide distribution of miRNAs, few studies have systematically investigated the mechanism by which a specific miRNA mediates exercise-induced neuroprotection. Improta-Caria et al. (2020) first summarized the miRNAs whose expression levels are altered by AD and exercise. They identified seven miRNAs in the CNS (let-7c, miR-7a, miR-15b, miR-103, miR-200b, miR-200c, and miR-504) whose expression is increased by exercise and three (miR-34a, miR-34c, and miR-135a) whose expression is decreased after exercise. In the blood, miR-18b, miR-26a, miR-28, miR-130a, miR-148b, and miR-766 expression levels were decreased, and miR-103, miR-142, miR-181c, miR-214, miR-338, miR-424, and miR-532 expression levels were increased following exercise (Improta-Caria et al., 2020). Later, many of the aforementioned miRNAs were demonstrated to have unique neuroprotective or neurotoxic effects that are central to AD pathogenesis. For example, in SH-SY5Y cells transfected with the APPswe, miR-15b inhibits BACE1 expression and Aβ accumulation by directly targeting the BACE1 mRNA 3′-UTR and reduces APPswe-induced proinflammatory cytokine secretion by suppressing NF-κB (Li and Wang, 2018). The serum and CSF levels of miR-135a and miR-200b in both AD patients and APP/PS1 mice are significantly decreased; miR-135a represses BACE-1 activity and expression, while miR-200b inhibits APP mRNA expression by targeting its 3′-UTR in primary mouse neurons and SH-SY5Y cells (Liu et al., 2014a). However, another study reported that miR-135a inhibited the transcription of thrombospondin 1, and was therefore correlated with an increase in neuronal apoptosis and a decrease in neurite outgrowth; meanwhile, the miR-135a antagonist AM135a prevented neuronal apoptosis and improved spatial learning ability in APP-Tg mice (Chu et al., 2016). Overexpression of miR-200b/c in neurons reportedly reduces Aβ secretion, and intracerebroventricular injection of miR-200b/c in mice alleviates the memory and spatial learning impairment caused by oligomeric Aβ, which may be due to the role of miR-200b/c in promoting insulin signal transduction (Higaki et al., 2018). Also, the abnormally low miR-181c expression seen in SAMP8 mice may lead to an increase in the expression of collapsin response mediator protein 2, whose hyperphosphorylation is an early event in AD, while miR-181c overexpression decreases collapsin response mediator protein 2 abundance (Zhou et al., 2016). According to a clinical study, a decrease in miR-181c-5p serum levels is associated with an increase in Aβ1-40 plasma concentrations, as well as cerebral vulnerability, during the aging process (Manzano-Crespo et al., 2019). miR-214-3p suppresses autophagosome accumulation and reduces hippocampal neuron apoptosis in SAMP8 mice by negatively regulating the expression of Atg12, an important factor promoting caspase-3/7-dependent apoptosis (Zhang et al., 2016). Furthermore, miR-338-5p expression in the hippocampus of 5xFAD mice and AD patients was significantly downregulated by NF-κB signaling, whereas hippocampal overexpression of miR-338-5p in 5xFAD mice may diminish AD pathology, for example by reducing BACE1 and Aβ expression, suppressing neuroinflammation, and restoring long-term synaptic plasticity, as well as learning capacity and memory (Qian et al., 2019). Collectively, a wide variety of miRNAs are involved in exercise-induced neuroprotection in the context of AD, and it is worth pursuing studies of their specific roles and underlying mechanisms in the future.

Conclusion

Physical exercise enhances the expression and/or activity of various factors in the central and peripheral systems through various pathways (**Additional Table 5**). Although some of these factors are not canonical endogenous cytokines, all of these molecules constitute the novel family of exerkines, which potentially mediate exercise-elicited neurological benefits in the context of AD through a variety of mechanisms, including promoting Aβ degradation, inhibiting Tau phosphorylation, and reducing neuroinflammation and oxidative stress. However, there are some challenges that cannot be ignored when applying exercise-based therapy to clinical situations. First, the outcome of this type of intervention is somewhat uncertain and is easily affected by a variety of factors, particularly the exercise paradigm and individual patient characteristics. As mentioned before (see "Introduction"), the variations in exercise protocols (e.g., exercise type, duration, intensity) may lead to them having diverse effects. For example, serum concentrations of BDNF and VEGF in elderly individuals with mild cognitive impairment are increased to a greater extent by acute endurance exercise than by acute resistance exercise (Tsai et al., 2018). Likewise, the impact of voluntary wheel running on increasing hippocampal BDNF expression in elderly people is less significant than in their younger counterparts (Adlard et al., 2005). Second, the changes induced by exerkines are variable and complex, for several possible reasons: (1) Different exerkines elicit non-identical biological alterations at the transcriptional, translational, and post-translational levels. For instance, mature BDNF derived from post-translational modification of pro-BDNF by proteases is neuroprotective, whereas pro-BDNF itself induces the expression of $p75^{NTR}$ and sortilin, subsequently causing neuronal apoptosis in the hippocampus of patients with AD (Fleitas et al., 2018). (2) Different brain regions have potentially divergent sensitivities to the same exerkine. As an example, AdipoR1, which is highly expressed in the medial prefrontal cortex, hippocampus, and amygdala displays a high affinity for globular ADN and mediates ADN-promoted neurogenesis, whereas AdipoR2, whose expression is relatively limited in the hippocampus and certain hypothalamic nuclei, exhibits comparable affinities for both globular and full-length ADN and regulates synaptic function (Liu et al., 2012; Yau et al., 2014; Li et al., 2015; Zhang et al., 2017). (3) Certain exerkines function through secondary signaling cascades, resulting in a much more complex regulatory network. As an example, lactate can exert neuroprotective effects by serving not only as the preferred energy source for neuronal metabolism, but also as a molecular regulator via the silent information regulator 1/PGC1a/FNDC5/BDNF and VEGF signaling pathways (Zhou et al., 2018; El Hayek et al., 2019; Roumes et al., 2021). (4) Exercise training is not suitable for every AD patient. Cognitive decline (particularly impaired spatial learning and memory) may prohibit patients with AD from voluntarily and safely engaging in adequate exercise. In addition, motor dysfunction caused by AD pathology and aging could further jeopardize their ability to exercise (Garvock-de Montbrun et al., 2019). Notably, to date few laboratory biomarkers have been identified that can objectively and accurately reflect the effectiveness of exercise intervention, which further restricts the clinical application of this treatment approach. Despite these difficulties, profiling exerkines still has far-reaching significance. On one hand, unmasking exerkine-regulated molecular processes may assist in devising new targets for treating patients with AD or other neurodegenerative diseases, or for enhancing cognition in healthy people. On the other hand, the dynamic changes in exerkine levels could be used as laboratory biomarkers for monitoring the effectiveness and appropriateness of the clinically prescribed exercise interventions, thus enabling the development of customized exercise therapy for individuals of varied ages, genders, and health states. Moreover, for people who are unable to engage in exercise training, supplementation with appropriate exerkines or treatment with drugs that modulate exerkine levels or are pharmacologically analogous to exerkines may provide anti-neurodegenerative benefits, and these exercise-mimetics could be safer and better targeted than routine drugs or even physical exercise per se. In fact, a few exercise-mimetics are currently available for clinical use. To name a few, agonists of the BDNF/TrkB

signaling cascades include LMDS-1, apelin-13, donepezil, angelica polysaccharide, and safflower yellow (Zheng et al., 2018; Luo et al., 2019; Du et al., 2020; Fan et al., 2020; Pang et al., 2020). Likewise, chemicals used to upregulate NGF are GM6, memantine, propentofylline, lamotrigine, and arginine vasopressin 4–8 (Yamada et al., 1998; Liu et al., 2014b; Zhang et al., 2014, 2020; Yu et al., 2019), and those for IGF-1 include T3D-959, phycocyanin, ginsenoside Rg5, melatonin, and donepezil (Obermayr et al., 2005; Chu et al., 2014; Rudnitskaya et al., 2015; de la Monte et al., 2017; Agrawal et al., 2020). For activating the VEGF pathway, IRL-1620, S38093, sildenafil, and perlecan domain V are frequently applied (Parham et al., 2014; Briyal et al., 2015; Guilloux et al., 2017; Ibrahim et al., 2021), while for stimulating ADN signaling, the homolog osmotin and ADN-mimetic novel nonapeptide (Shah et al., 2017; Yoon et al., 2018; Ali et al., 2021), as well as the AdipoRs agonist AdipoRon (Liu et al., 2020; Sun et al., 2020), are widely used. β-Hydroxybutyrate, γ-hydroxybutyrate, resveratrol, KVN93, perindopril, and naringenin can enhance NEP expression of (Klein et al., 2015; Corpas et al., 2019; Yang et al., 2019; Lee et al., 2020; Messiha et al., 2020; Wu et al., 2020). Similarly, IDE pathways can be initiated by administering metformin, rapamycin, 17β-estradiol, resveratrol, KVN93, perindopril, or naringenin (Zhao et al., 2011; Chen et al., 2019; Corpas et al., 2019; Yang et al., 2019; Lee et al., 2020; Lu et al., 2020; Messiha et al., 2020). Notably, agonists stimulating Nrf2 signal transduction, including FA-97, NXPZ-2, astragalus polysaccharide, and resveratrol, promote the expression of both SOD and IDE (Hui et al., 2018; Wan et al., 2019; Qin et al., 2020; Sun et al., 2020). In conclusion, elucidating the identity, involvement, and underlying molecular mechanism of exerkines will provide novel strategies for treating AD, and is therefore worthy of further investigation.

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Additional files:

Additional Table 1: *Effects of physical exercise on the expression of growth factors and hormones.*

Additional Table 2: *Effects of physical exercise on the expression of Aβ degrading enzymes.*

Additional Table 3: *Effects of physical exercise on the levels of antioxidative enzymes or coenzymes.*

Additional Table 4: *Effects of physical exercise on the levels of metabolites.*

Additional Table 5: *Potential molecular mechanisms underlying the exercise-induced upregulation of exerkines.*

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