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Review

Adiponectin as a potential mediator of the pro-cognitive effects of physical exercise on Alzheimer's disease

Hui-Hui Guo[1, 2], Hai-Ning Ou[1, 3, 4], Jia-Sui Yu[5, 6], Julia Macedo Rosa[5, 6], Douglas Affonso Formolo[5, 6], Tong Cheng[5, 6], Suk-Yu Yau[5, 6, *], Hector Wing Hong Tsang[1, 5, 6, *]

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From the Contents

Abstract

Alzheimer's disease is the primary cause of dementia and imposes a significant socioeconomic burden globally. Physical exercise, as an effective strategy for improving general health, has been largely reported for its effectiveness in slowing neurodegeneration and increasing brain functional plasticity, particularly in aging brains. However, the underlying mechanisms of exercise in cognitive aging remain largely unclear. Adiponectin, a cell-secreted protein hormone, has recently been found to regulate synaptic plasticity and mediate the antidepressant effects of physical exercise. Studies on the neuroprotective effects of adiponectin have revealed potential innovative treatments for Alzheimer's disease. Here, we reviewed the functions of adiponectin and its receptor in the brains of human and animal models of cognitive impairment. We summarized the role of adiponectin in Alzheimer's disease, focusing on its impact on energy metabolism, insulin resistance, and inflammation. We also discuss how exercise increases adiponectin secretion and its potential benefits for learning and memory. Finally, we highlight the latest research on chemical compounds that mimic exercise-enhanced secretion of adiponectin and its receptor in Alzheimer's disease.

Key Words: adiponectin receptor agonists; adiponectin; Alzheimer's disease; amyloid-β; hippocampus; learning and memory; physical exercise; Tau

Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative illnesses that causes dementia in older individuals. It is characterized by the accumulation of amyloid-β (Aβ) and tau pathology in the brain (Knopman et al., 2021; Suresh et al., 2021). Although many pharmacological and non-pharmacological interventions have been implemented, no treatments can halt the neurodegeneration process, possibly owing to an insufficient understanding of the key neuropathology underlying AD.

Physical exercise not only is known to improve mood disorders, metabolic dysregulation, such as obesity, cardiorespiratory fitness, and general health (van der Heijden et al., 2013; Vargas-Terrones et al., 2019; O'Donoghue et al., 2021; Fernández-Rodríguez et al., 2022), but it is also recognized as an effective non-pharmaceutical therapy to treat/prevent AD-associated cognitive impairment involving learning, memory, attention, and executive functions (Russo-Neustadt et al., 1999; Larson et al., 2006; Yau et al., 2014; Duzel et al., 2016; De la Rosa et al., 2020). Emerging animal studies have demonstrated that physical exercise may play a role in reversing memory and learning deficits, possibly through neuroprotective effects promoting adult neurogenesis (Yau, et al., 2014), increasing the levels of hippocampal neurotrophic factors (Russo-Neustadt et al., 1999; Belaya et al., 2020; Wang et al., 2020a), promoting synaptic plasticity and dendritic complexity (Lourenco et al., 2019; Belaya et al., 2020), and ameliorating Aβ oligomer neurotoxicity or tau pathology (Brown et al., 2019; Tan et al., 2021; Zhang et al., 2021). However, how physical exercise elicits neuroprotective effects in the brain remains largely unclear.

The cognitive benefits of physical exercise are linked to activated adiponectin (ADPN) signaling in the brain. ADPN is an adipose-tissue-secreted hormone that is expressed in multiple isoforms as an endocrine messenger in other tissues (Fang and Judd, 2018; Abou-Samra et al., 2020). Studies have shown that ADPN mimetics significantly prevent/treat neurocognitive disorders (Ali et al., 2015, 2021; Badshah et al., 2016; Ng et al., 2021). In this review, we summarize the functions of ADPN signaling in the brain, focusing on the effects of ADPN on the regulation of cognition. We also summarize the potential molecular mechanisms of ADPN in mediating the neuroprotective effects of physical exercise, providing insights into ADPN-based applications in the treatment of AD.

Search Strategy

For this review, we conducted a search on Web of Science and PubMed using keywords, including "Alzheimer's disease," "adiponectin," "exercise or physical activity," "Alzheimer's disease and hippocampus," "adiponectin receptor," "tau and adiponectin," "tau and Alzheimer's disease," "Aβ

[1]Department of Rehabilitation Medicine, The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University, Guangzhou, Guangdong Province, China; [2]Department of Rehabilitation Medicine, Shaoxing People's Hospital, Shaoxing, Zhejiang Province, China; [3]Department of Rehabilitation, the Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, Guangdong Province, China; [4]The Second Institute of Clinical Medicine, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong Province, China; [5]Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong Special Administrative Region, China; [6]Mental Health Research Center, The Hong Kong Polytechnic University, Hong Kong Special Administrative Region, China
***Correspondence to:** Hector Wing Hong Tsang, PhD, hector.tsang@polyu.edu.hk; Suk-Yu Yau, PhD, sonata.yau@polyu.edu.hk.
https://orcid.org/0000-0003-3003-8598 (Hector Wing Hong Tsang); https://orcid.org/0000-0002-7425-6741 (Suk-Yu Yau)

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and Alzheimer's disease," "adiponectin receptor agonists," and terms related to "metabolism," "insulin resistance," and "inflammation" in conjunction with "Alzheimer's disease," or "adiponectin," or "exercise". We included studies deemed most relevant to our topic. Additionally, we identified and incorporated seminal papers contributing to recent advancements in this field. By December 31, 2023, approximately 80% of the references cited were published within the last 5 years.

Adiponectin and Its Receptors

Adiponectin

ADPN, also known as Acrp30, AdipoQ, apM1, and GBP28, exists as three multimeric complexes: a low-molecular-weight form (LMW), a middle-molecular-weight form, and a high-molecular-weight form (HMW). Full-length ADPN can be proteolytically cleaved to a globular ADPN isoform in plasma (Fruebis et al., 2001). These isoforms play different roles in different tissues (Kadowaki and Yamauchi, 2005; Fang and Judd, 2018). Interestingly, ADPN is produced mainly from adipocytes, and its expression levels are inversely proportional to total fat mass and are decreased in type 2 diabetes (Fukuda et al., 2015), cardiovascular diseases (Lei et al., 2022), AD (Teixeira et al., 2013), stroke (Ilhan et al., 2019), traumatic brain injury (Zhang et al., 2022), and cancer (Macleod et al., 2023). At present, ADPN possesses insulin-sensitizing, anti-diabetic, anti-inflammatory, anti-fibrotic, anti-apoptotic, and anti-atherosclerotic properties (Yamauchi et al., 2003; Kadowaki and Yamauchi, 2005; Lihn et al., 2005; Thundyil et al., 2012; Wang and Scherer, 2016) (**Figure 1**). We focus mainly on the functions of ADPN in the brain in this review.

Adiponectin receptor 1

AdipoRs (AdipoR1 and AdipoR2) and T-cadherin are known as ADPN receptors. AdipoRs possess a seven-transmembrane topology with a cytoplasmic N-terminus and an extracellular C-terminus (Yamauchi et al., 2003). AdipoRs are highly homologous and conserved in rodents and humans (Yamauchi et al., 2003, 2007). In general, they modulate the anti-diabetic effects and actions of membrane homeostasis and fluidity (Yamauchi et al., 2014; Ruiz et al., 2022).

AdipoR1 is more prominent in activating AMP-activated protein kinase (AMPK) and has higher expression in skeletal muscle and cardiomyocytes (Yamauchi et al., 2007; Iwabu et al., 2016; Zhu et al., 2022). It is highly dependent on the adaptor proteins Adaptor protein, which contains a pleckstrin homology domain, phosphotyrosine binding domain and leucine zipper motif (APPL1), and endoplasmic reticulum protein 46 and activates protein kinase C and protein casein kinase 2β; therefore, it plays critical roles in lipid oxidation, glucose uptake, insulin sensitivity, and anti-inflammatory effects (Mao et al., 2006; Heiker et al., 2009; Charlton et al., 2010). Additionally, AdipoR1 and AdipoR2 are abundantly expressed in the brain, including the hypothalamus (Kaminska et al., 2020), striatum (Song et al., 2015), pallium (Rastegar et al., 2019), thalamus (Rastegar et al., 2019), brain stem (telencephalon, diencephalon, cerebellum) (Thundyil et al., 2012; Rastegar et al., 2019), hippocampus, and cortex (Thundyil et al., 2012; Song et al., 2015; Bloemer et al., 2018; Rastegar et al., 2019). Evidence has suggested that AdipoR1, not AdipoR2, promotes adult hippocampal neurogenesis (Yau et al., 2014). Moreover, AdipoR1 is involved in the anti-depressant action of ADPN by reducing 5-hydroxy tryptamine transmission in the dorsal raphe nucleus (Li et al., 2021) and the effect of ADPN on dopaminergic neuron activity in the ventral tegmental area (Sun et al., 2019).

Adiponectin receptor 2

The effects of AdipoR2 in the brain are still largely unknown. AdipoR2 is involved mostly in peroxisome proliferator-activated receptor (PPAR)α activation and has high expression levels in the liver (Yamauchi et al., 2007). AdipoR2 is more highly expressed in obese children with nonalcoholic fatty liver disease (Goyal et al., 2023). In a rodent model of posttraumatic stress disorder, AdipoR2 knockout mice presented increased retrieval/expression of contextual fear memories and a lower fear extinction rate (Zhang et al., 2017), suggesting that AdipoR2 could be linked to fear memory.

T-cadherin

Unlike AdipoRs, T-cadherin does not contain an intracellular domain. ADPN binds to T-cadherin to protect the cardiovascular system and promote muscle regeneration by increasing exosome secretion and decreasing cellular ceramides levels (Fukuda et al., 2017; Obata et al., 2018; Tanaka et al., 2019; Nakamura et al., 2020). Whether it works in the brain remains largely unclear and warrants future investigation.

Effects of Adiponectin on Metabolism, Insulin Resistance, Inflammatory Responses, and Neuroprotection Against Alzheimer's Disease

The imbalance of energy metabolism and insulin resistance are the two main causes of the progression of AD pathologies (Steen et al., 2005; Ng et al., 2021). Meanwhile, neuroinflammation is another worthy considerable form of AD (**Figure 2**). They have overlapping pathologies, including deficits in glucose availability, mitochondrial dysfunction, oxidative stress, and low-levels of chronic inflammation. All three pathological changes are contributors to the β-amyloid and Tau hyperphosphorylation in AD as described in **Figure 2.**

Intriguingly, ADPN is known for its role in the regulation of energy metabolism and fatty acid homeostasis, the development of diabetes/obesity, and the modulation of insulin balance and Aβ and Tau pathology in AD (Song and Lee, 2013; Song et al., 2015; Horgusluoglu et al., 2022).

Energy metabolism

Early studies have shown that the peripheral metabolic actions of ADPN rely on the AMPK and PPAR-α pathways via the activation of AdipR1 and AdipoR2, respectively (Yamauchi et al., 2007). Further investigations have shown that ADPN activates the APPL1-live kinase B1-AMPK and CAMKK2-AMPK cascades to increase mitochondrial function and lipid translocation in muscle cells, respectively (Zhou et al., 2009). Adiponectin binds to AdipoR1 mediating mitochondrial function, insulin resistance and exercise endurance, which is dependent on the activation of peroxisome proliferator-activated receptor c coactivator-1α (PGC-1α) and AMPK/ Sirtuin 1 (SIRT1) signaling pathway. PGC-1α is a crucial mitochondrial regulator because it interacts with different transcription factors in different tissues (Rui, 2014; Miller et al., 2019; Rius-Pérez et al., 2020; Suntar et al., 2020; Koh and Kim, 2021). SIRT1 is one of the most studied sirtuins and is an NAD^+-dependent deacetylase and energy status sensor (Chang and Guarente, 2014). In neurons, PGC-1α binds with PPARγ via SIRT1 deacetylation to reduce the expression of β-secretase (BACE1) (Wang et al., 2013). Therefore, ADPN activates AMPK and SIRT1 by increasing PGC-1α activity to elicit its effects on energy metabolism and to decrease toxic Aβ production via the ADPN/AMPK/SIRT1/sterol regulatory element-binding protein 2 (SREBP2) pathway (Shah et al., 2017).

AdipoR levels are significantly decreased in the cortex, hippocampus, and hypothalamus of aged 5×FAD model mice with AD (Pratap and Holsinger, 2020). Consistently, in obese and diabetic human and animal models, the reduced expression of AdipoRs has been verified to lead to metabolic dysfunctions, glucose intolerance, insulin resistance, and spatial learning and memory impairment (Yamauchi et al., 2007; Kim et al., 2017). A recent study revealed that an ADPN receptor agonist has neuroprotective effects on traumatic brain injury and promotes sirtuin 3 transcription by activating the AMPK-PGC-1α pathway (Zhang et al., 2022). The benefits of ADPN in lipid metabolism involve two pathways: (1) ADPN directly regulates acetyl-CoA carboxylase to reduce fatty acid synthesis, and (2) ADPN activates PPARα through AMPK signaling (Schindler et al., 2017). PPARγ is the primary regulator of adipogenesis and controls adipokine gene expression. In adipose tissue, adiponectin mediates the metabolic effects of rosiglitazone in a dependent PPARγ manner (Guo et al., 2017).

Insulin resistance

ADPN regulates insulin resistance and metabolism through various pathways (**Figure 1**). ADPN activates PPARγ effects by activating the AMPK/endothelial nitric oxide synthase (eNOS) and cyclic adenosine monophosphate/protein kinase A signaling pathways to improve insulin sensitivity in diabetic mice (Wong et al., 2011). In skeletal muscle, ADPN depends on APPL1, a central pleckstrin homology (PH) domain, and a COOH-terminal phosphotyrosine-binding domain 1, which interacts with the insulin receptor substrates IRS-1 and IRS-2 to decrease insulin resistance via the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) pathway (Buechler et al., 2010; Liu and Sweeney, 2014). One study showed that ADPN modulates IRS-2 expression and suppresses gluconeogenesis (Awazawa et al., 2011). In brief, ADPN increases glucose uptake and reduces insulin resistance indirectly through the ADPN/APPL1/PI3K/AKT pathway or the ADPN/AMPK/PPARα pathway (Fang and Judd, 2018).

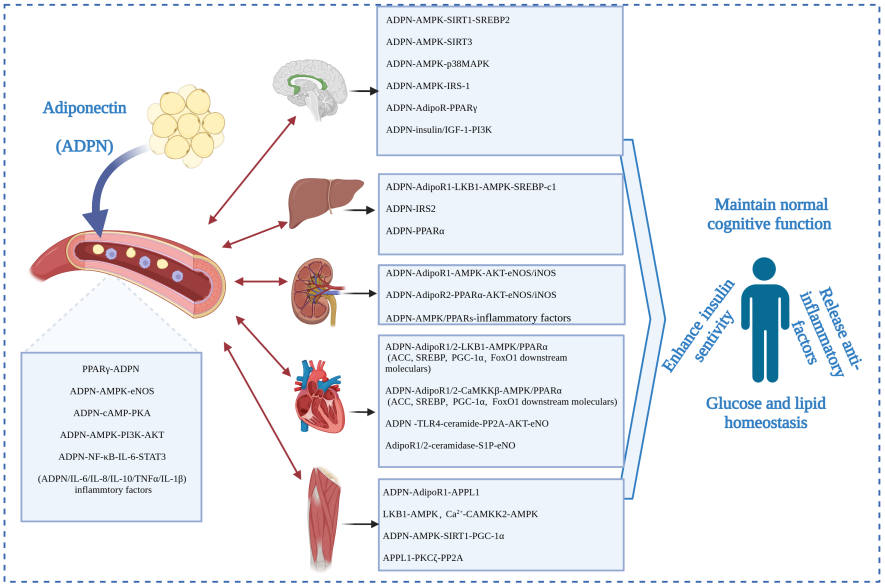

Figure 1 | **The effects of ADPN on metabolism in peripheral organs and related signaling pathways.**
ADPN has regulatory effects on glucolipid metabolism, insulin resistance, and anti-inflammatory effects. It is secreted from adipocytes to blood vessels and then circulated to the brain, liver, kidney, heart, and skeletal muscle. ADPN exerts vascular protective effects via stimulation of the PPARγ pathway, eNOS activation, and AMPK pathways and inhibits inflammatory responses by activating the NF-κB pathway, the IL-6-STAT3 signaling pathway, and some inflammatory factors, such as TNF-α and IL-10. In addition, ADPN targets regulate brain energy metabolism as well as glucose and lipid metabolism through the AMPK pathway, PPARα pathway, P38 MAPK pathway, ceramide pathway, IRS pathway, and insulin/IGF1-PI3K pathway. They also affect skeletal muscle functions through the AdipoR-APPL1, Ca^{2+}-CAMKK2, SIRT1-PGC-1α, and APPL1-PKCζ-PP2A pathways. Created with BioRender.com. ACC: Acetyl-CoA carboxylase; AdipoR1/2: adiponectin receptor 1 and adiponectin receptor 2; AdipoRs: AdipoR1 and AdipoR2; ADPN: adiponectin; AKT: serine/threonine kinase (also called protein kinase B); AMPK: Adenosine monophosphate (AMP)-activated protein kinase; APPL1: adaptor protein containing pleckstrin homology domain, phosphotyrosine binding domain and leucine zipper motif; cAMP: cyclic adenosine monophosphate; eNOS: endothelial nitric oxide synthase; FoxO1: forkhead box O1; IGF-1: Insulin-like growth factor 1; IL-8/IL-10: interleukin-8/10; iNOS: inducible nitric oxide synthase; IRS-1/IRS-2: insulin receptor substrate-1/2; LKB1: live kinase B1; NF-κB: nuclear factor kappa-B; p38MAPK: p38 mitogen-activated protein kinase; PGC-1α: peroxisome proliferator-activated receptor-gamma coactivator-1alpha; PI3K: phosphatidylinositol-3-kinase; PKA: protein kinase A; PKCζ: protein kinase C ζ; PPARα: peroxisome proliferator-activated receptor α; PPARγ: peroxisome proliferator-activated receptor-γ; S1P: sphingosine 1-phosphate; SREBP/SREBP-c1: sterol regulatory element-binding protein/-c1; SREBP2: sterol regulatory element-binding protein 2; STAT3: signal transducer and activator of transcription 3; TLR4: Toll-like receptor 4; TNFα: tumor necrosis factor α.

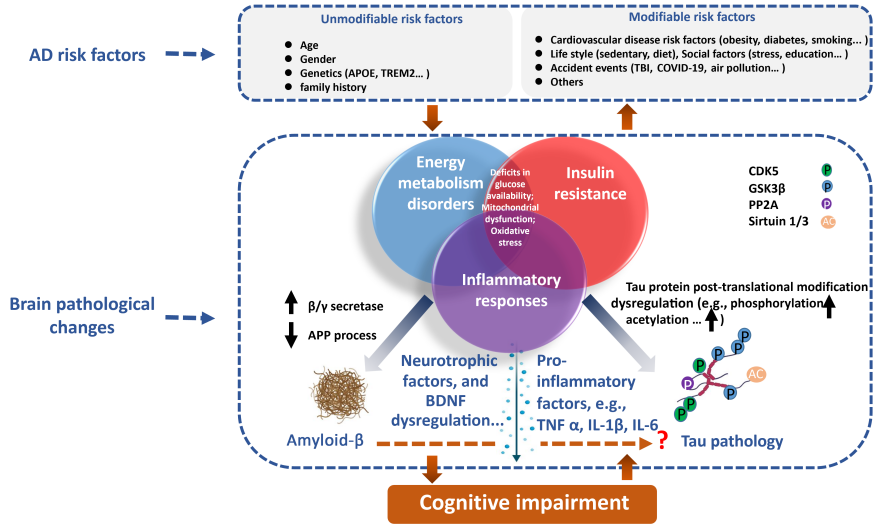

Figure 2 | **The risk factors and mechanisms that could contribute to neuropathology and cognitive impairment in AD.**
Risk factors for developing AD include age, sex, family history, sedentary lifestyle, obesity, smoking, and diet. All these potential risk factors could lead to metabolic disorders, insulin resistance, and inflammatory reactions. Eventually, they promote amyloid-β accumulation, tau pathology (Tau protein is modified with phosphorylation and acetylation by modifying enzymes, such as CDK5, GSK3β, PP2A, and Sirt1/3), and the release of excessive pro-inflammatory cytokines (TNFα, IL-1β, and IL-6). As brain pathology continues to emerge, cognitive deficits consequently appear. Created with BioRender.com. AD: Alzheimer's disease; ADPN: adiponectin; APOE: apolipoprotein E; APP: amyloid precursor protein; BDNF: brain-derived neurotrophic factor; CDK5: cyclin-dependent kinase 5; COVID-19: coronavirus disease 2019; GSK3β: glycogen synthase kinase 3β; IL-1β: interleukin-1β; IL-6: interleukin-6; PPAR: peroxisome proliferator-activated receptor; PP2A: protein phosphatase 2A; Sirt1/3: sirtuin 1/sirtuin 3; TBI: traumatic brain injury; TNFα: tumor necrosis factor α; TREM2: triggering receptor expressed on myeloid cells 2.

Anti-inflammatory effects

ADPN exhibits pro-inflammatory and anti-inflammatory properties, depending on the context of various cells, tissues, and diseases (Choi et al., 2020). As a member of the C1q tumor necrosis factor (TNF) superfamily, ADPN is pivotal for regulating immune responses and directly affects inflammatory cells, such as classically activated macrophages (M1) and alternatively activated macrophages (M2) (Luo and Liu, 2016). These actions act mainly through Toll-like receptor (TLR)-mediated signaling pathways, including the nuclear factor kappa-B (NF-κB) signaling pathway, the interleukin (IL)-4 pathway, and the activation of the extracellular regulated protein kinase (Erk) pathway, the Akt/PI3K pathway, and the AMPK pathway (Luo and Liu, 2016). In innate immune cells, it can negatively regulate Group 2 innate lymphoid cells to elicit anti-thermogenic effects via the AMPK-NF-κB-IL 13/5 pathway (Wang et al., 2021). It can activate plasma B cells and induce the secretion of B-cell-derived peptide (PEPITEM) to inhibit memory T-cell migration (Chimen et al., 2015). In neutrophils, it negatively regulates their function through the AMPK and PI3K/protein kinase B pathways (Luo and Liu, 2016). ADPN can activate dendritic cells via the phospholipase Cγ/c-Jun N-terminal kinase/NF-κB pathways (Luo and Liu, 2016). In adipose tissue, ADPN shows an inverse relationship with TNF-α, IL-6, and C-reactive protein (Devaraj et al., 2008; Feijóo-Bandín et al., 2020; Zaidi et al., 2022). In the cardiovascular system, ADPN suppresses the expression of the inflammatory cytokine TNF-α and induces the anti-inflammatory cytokine IL-10 to modulate inflammation in endothelial cells and macrophages (Fantuzzi, 2008; Li and Wu, 2012; Feijóo-Bandín et al., 2020).

In AD pathology, Aβ aggregation can trigger glial activation, which in turn induces the release of pro-inflammatory cytokines, e.g., IL-1β, IL-6, IL-8, and TNF-α, leading to memory impairment (Rosa et al., 2021; Sellami et al., 2021). ADPN exerts its anti-inflammatory effects via direct and indirect regulation of these inflammatory factors associated with AD pathology. In addition, ADPN can prevent cell death and inhibit the formation of reactive oxygen species in brain endothelial cells (Song et al., 2017). ADPN can also reduce soluble Aβ oligomers and suppress the expression of TNF-α and IL-1β in microglia by activating the AdipoR1/NF-κB signaling pathway (Song et al., 2017; Jian et al., 2019). A recent study revealed that ADPN treatment increased IL-10 expression levels and inhibited abnormal activation of microglia and astroglia to improve memory deficits in 3×Tg-AD mice (Yan et al., 2022). The anti-inflammatory effects of ADPN include the stimulation of NF-κB signaling to decrease the expression of TNF-α (Zaidi et al., 2022), pro-inflammatory IL-6 (Li and Wu, 2012), and C-reactive protein (Devaraj et al., 2008) and the inhibition of Toll-like receptor-mediated NF-κB activation (Devaraj et al., 2008; Li and Wu, 2012; Zaidi et al., 2022). ADPN also suppresses M1 macrophage activation, promotes M2 macrophage proliferation (Luo and Liu, 2016), and induces the production of the anti-inflammatory cytokine IL-10 (Luo and Liu, 2016; Fang and Judd, 2018).

Pro-inflammatory effects

Acting as a pro-inflammatory adipokine, ADPN

can promote TNF-α, IL-6, and C-reactive protein expression in asthma (Choi et al., 2020), rheumatoid arthritis (Li and Wu, 2012; Choi et al., 2020), and inflammatory bowel disease (Peng et al., 2018). The relationships between ADPN, which has pro-inflammatory effects, and AD pathology have not been examined. In summary, ADPN exerts diverse actions on target cells or tissues through various signaling pathways (**Figure 1**). Additionally, the adiponectin/adipoR axis can exert anti-inflammatory properties contributing to neuronal loss and inhibit microglia/macrophage activation through PPARγ (Miao et al., 2021).

Nutritional metabolism

The gut and the gut microbiome are key factors in nutrient absorption and metabolism (Yassine et al., 2023). Growing evidence has shown that alterations in the composition of the gut microbiota can lead to changes in brain function and cognitive behavior (Liu et al., 2020). It is now well established that the gut microbiota regulates the profile of adipokines such as ADPN (Polito et al., 2020). The microbiota–gut–brain axis can influence the onset and progression of AD and is involved in increasing the formation of amyloids, stress granules, and trimethylamine N-oxide and destroying the permeability of the blood–brain barrier (Liu et al., 2020). For example, lipopolysaccharide, a crucial immunoregulatory component of the gut microbiota, significantly induces emic inflammation and neuroinflammation that contributes to the progression of AD (Qian et al., 2021; Brown and Heneka, 2024). Lipopolysaccharide triggers neuroinflammation by activating inflammatory cytokines such as NLRP3, IL-1β, and IL-6 from brain microglia, as well as peripheral immune cells like monocytes, neutrophils, and macrophages (Qian et al., 2021). Consequently, elevated levels of LPS promote the production of Aβ and accelerate tau phosphorylation through these cytokines (Yin et al., 2016). Thus, the microbiota–gut–brain axis controls the degree of ADPN that results in AD via metabolic and immune pathways (**Figure 3**).

Neuroprotection against Alzheimer's disease

As described above, ADPN regulates metabolism, improves insulin sensitivity, and modulates the inflammatory response to reduce AD pathology. ADPN may also prevent and delay the progression of AD through its multiple downstream signaling molecules (**Figure 1**). However, there are also some facts that cannot be ignored. ADPN accumulated in the heart, muscle, and vascular endothelium due to binding to T-cadherin. Therefore, ADPN/T-cadherin controls whole-body glucose metabolism, metabolic inflammation, and insulin sensitivity by exosome (Hug et al., 2004; Kita et al., 2019). ADPN has also cardioprotective functions depending on activating the T-cadherin signaling cascade to regulate molecules in the SMC phenotype and endothelial insulin resistance (Philippova et al., 2012; Frismantiene et al., 2016). ADPN/T-cadherin controls whole-body glucose metabolism, metabolic inflammation, and insulin sensitivity through stimulated exosome secretion (Hug et al., 2004; Kita et al., 2019). Therefore, ADPN has cardioprotective functions through the activation of the T-cadherin signaling cascade to regulate molecules associated with the SMC phenotype and endothelial insulin resistance (Philippova et al., 2012; Frismantiene et al., 2016). T-cadherin alters SMC migration, proliferation, and morphology in the phosphorylated state of glycogen synthase kinase 3β (GSK3β) through the kinase Akt (Frismantiene et al., 2016). It has been suggested that T-cadherin modulates insulin responsiveness and attenuates insulin-induced eNOS activation and angiogenesis via PI3K/Akt/mammalian target of rapamycin (mTOR) signaling in endothelial cells (Philippova et al., 2012). In brief, ADPN/T-cadherin is a noteworthy factor influencing brain function and is worth exploring as T-cadherin downstream signals.

To this end, a recent animal study demonstrated that protein phosphatase 2A (PP2A) activation through treadmill exercise improved cognitive impairments in mice subjected to chronic restraint stress (Zhang et al., 2021). As previously described, physical exercise increases ADPN levels in the hippocampus (Yau et al., 2014). ADPN inhibits the effects of PP2A and subsequently inhibits eNOS via pAMPK-induced forkhead box O1 activation (Kim et al., 2022). In addition, it can also enhance glucose uptake partly by modulating APPL1 and the localization of protein kinase C ζ binding with PP2A (Saito et al., 2016). PP2A plays a central role in tau pathology in the brain (Taleski and Sontag, 2018). Many studies have suggested that PP2A/GSK-3β or PP2A/AKT could lead to tau dephosphorylation in AD (Martin et al., 2013). When PP2A was silenced *in vivo*, Tg2576 mice presented learning and memory deficits, suggesting a critical role for PP2A in AD (Liu et al., 2013). Moreover, PP2A may act on Aβ generation by phosphorylating APP (Liu et al., 2013; Javadpour et al., 2019). For these reasons, interventions for ADPN levels affect brain function and benefit AD patients.

Exercise, Adiponectin, and Alzheimer's Disease in Clinical Studies

Many studies have shown that physical activity can protect against cognitive decline and decrease the risk of developing dementia and AD (Kadowaki and Yamauchi, 2005; Yamauchi et al., 2014; Abou-Samra et al., 2020). For example, in school children, exercise can markedly increase the level of ADPN in association with academic performance (Diaz-Castro et al., 2021). Moreover, one clinical study revealed that menopausal women who are at increased risk for dementia and cognitive decline have decreased plasma ADPN levels and elevated amyloid levels (Wennberg et al., 2016; Baek et al., 2021). Long-term functional fitness could decrease the risk of dementia with depression (Baek et al., 2021). Physical exercise increases serum ADPN levels in humans (**Table 1**; De Franciscis et al., 2017; Cezaretto et al., 2018; Fujita et al., 2018; Gilbert et al., 2018; Trombetta et al., 2018; Beyer et al., 2019; Caunca et al., 2019; Mohorko et al., 2019; Letra et al., 2019; Li et al., 2019, 2022; Sanz et al., 2019; Schön et al., 2019; Xie et al., 2019; Benavente et al., 2020; Feinkohl et al., 2020; Ganguli et al., 2020; Grazioli et al., 2020; Lis et al., 2020; Wen and Tsai, 2020; Baek et al., 2021; Chen et al., 2021; Diaz-Castro et al., 2021; Lopez-Vilaret et al., 2021; van Andel et al., 2021; Alghadir et al., 2022; Liu et al., 2022; Quan et al., 2022; Wittekind et al., 2022), although few studies have shown the negative effects of ADPN on cognitive functions (**Table 1**). In this context, most studies have suggested that increasing ADPN levels through exercise could be an intervention for AD-associated cognitive decline.

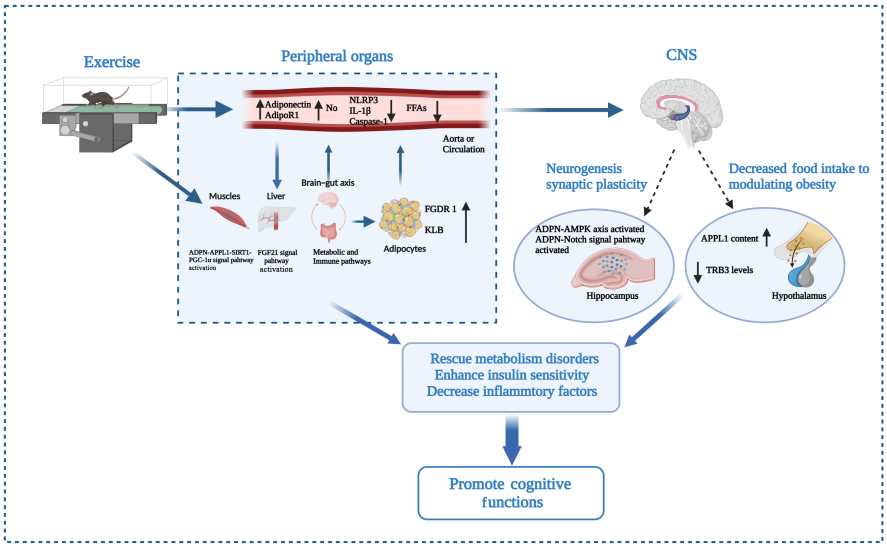

Figure 3 | The molecular mechanisms of exercise-enhanced brain neuroplasticity by enhancing various peripheral factors.

Physical exercise significantly increases ADPN levels and inhibits inflammatory factors in the blood to regulate glucolipid metabolism and insulin sensitivity. Exercise enhances mitochondrial function and oxidative stress by activating the ADPN-SIRT1-PGC-1α signaling pathway in skeletal muscles. In addition, exercise can enhance metabolism and insulin resistance by inducing ADPN signaling in the serum and increasing FGF21 sensitivity in the liver. Physical exercise enhances hippocampal adult neurogenesis and synaptic density and functions through the ADPN-AMPK signaling pathway and ADPN-Notch signaling pathway activation. In the hypothalamus, exercise promotes caloric restriction by increasing APPL1 protein levels and attenuating Drosophila TRB3 levels. Moreover, exercise affects the microbiota and cognition, which links the stimulation of the immune system (NLRP3, IL-1β, and caspase-1) and endocrine signaling, such as the hypothalamus–pituitary–adrenal axis, with the secretion levels of ADPN and the brain–gut–microbiota axis (Liu et al., 2013; Polito et al., 2020). Multiple actions could contribute to the pro-cognitive effects of physical exercise. Created with BioRender.com. CNS: Central nervous system; FFAs: free fatty acids; FGDR1: fibroblast growth factor receptor-1; FGF21: fibroblast growth factor 21; KLB: β-klotho; NLRP3: nucleotide-binding oligomerization domain-like receptor protein 3; TRB3: tribble protein 3.

Table 1 | **Effects of different cognitive deficits models on ADPN levels in clinical studies**

Subject	Gender	Age (yr)	ADPN expression level and main role	Detection method	Highlight (correlation with cognitive function)	Reference
Cognitive aging	Men	69.3	No difference in terms of the relationship between ADPN and age;	Blood	Positive association between high-molecular-weight ADPN and age-related cognitive decline in women but not men	van Andel et al., 2021
	Women	70.3	decreased with age increasing			
Frailty	Men	≥70	lower levels	Blood	Negative between serum ADPN and the percentage of lean mass in men,	Sanz et al., 2019.
	Women				Positive association between serum ADPN and anxiety cognitive decline	
Obesity	Men Women	37±7	ADPN was increased after being treated with the ketogenic diet	Blood	ADPN increased associated with weight loss and cognitive function	Mohorko et al., 2019
Children's cognitive abilities	Male Female	3 to 8	Increased with age increasing	Blood	Positively associated with children's IQ	Li et al., 2018, 2019
Neuro-cognitive disorders	Men Women	≥ 65	Lower levels	Blood	Positive association between ADPN and AD or AD-related disorders	Gilbert et al., 2018
Diabetes and obesity with cognitive decline	Men Women	≥ 65	Decreased with age increasing in younger than 87 years without central obesity	Blood	Positive association between ADPN and cognitive decline	Ganguli et al., 2020
Cognitive impairment	Men Women	≥ 65	Higher leptin/ADPN ratio but not ADPN changed	Blood	Total ADPN and high-molecular-weight ADPN concentrations were each not associated with impairment	Feinkohl et al., 2020
WMLs	Men Women	53 to 85	Lower levels	Blood	Positive association between ADPN and WMLs and cognitive function	Quan et al., 2022
Fatigue	Men Women	50 to 85	Lower levels	Blood	Positive association between ADPN and cognition	Alghadir et al., 2022
Ischemic stroke	Men Women	65.15±9.12	Lower levels	Blood	Positive association between ADPN and ischemic stroke	Li et al., 2022b
Thoracic surgery	Men Women	65 to 81	Higher levels in thoracic paravertebral block combined with general anesthesia	Blood	Positive association between ADPN and cognition with thoracic paravertebral block combined with general anesthesia	Xie et al., 2019
Prediabetes	Men Women	35 to 54	lower levels in participants with prediabetes	Blood	Positive association between ADPN and cognitive impairment	Cezaretto et al., 2018.
Healthy young individuals with acute exercise	Men Women	24.6 ±5.1	After acute exercise, ADPN decreased in the cerebrospinal fluid and increased in serum.	CSF and blood	Positive association between serum ADPN and cognitive impairment	Schön et al., 2019
Postmenopausal women	Women	50 to 66	lower levels	Blood	Positive association between serum ADPN and cognitive function	De Franciscis et al., 2017
Older people with MCI or dementia	Men, Women	60 to 93	High ADPN levels in elderly people with MCI or dementia.	Blood	Negative association between serum ADPN and cerebral WMLs in the elderly with cognitive impairment	Fujita et al., 2018
Practicing exercise in schoolchildren	Male, Female	11.21±0.17 and 11.16±0.18	Higher levels in the exercise group	Blood	Positive association between serum ADPN and academic performance	Diaz-Castro et al., 2021
Bipolar disorder and major depressive disorder	Men, Women	24.6±4.2 and 24.5±3.2	No difference	Blood	No relationship between ADPN and cognitive function within Bipolar	Chen et al., 2021
Dementia	Men, Women	70.88±9.48	No details stated?	Blood	Positive association between serum ADPN and cognitive function	Benavente et al., 2020
Multiple sclerosis	Women	39; 41±2 and 40±3	Aerobic and resistance training can decrease ADPN levels	Blood	Negative association between serum ADPN and Multiple sclerosis with cognitive psychological parameters	Grazioli et al.,
Alzheimer's disease	Men, Women	67.33±8.30 and 68.53±9.08	Higher serum ADPN levels in AD compared to MCI; No changes in CSF	CSF and blood	Positive correlation between CSF levels ADPN and $A\beta_{42}$	Letra et al., 2019
Spinal cord injury	Men, Women	57.1±6.3 and 57.6±6.7	Lower levels	Blood	Positive association between serum ADPN and cognitive function after SCI	Liu et al., 2022
Cognitively normal older adults with insulin resistance	Men, Women	67.4±5.9	Lower levels	Blood	Positive association between serum ADPN and cognitive function	Lopez-Vilaret et al., 2021
Obesity	Women	34.04±5.66 and 34.44±5.77	Lower levels	Blood	Positive association between serum ADPN and cognitive function	Wen and Tsai, 2020
First-episode psychosis	Men Women	34.2±12.5, 37.3±11.2, 32.3±8.4	No difference	Blood	No relationship between ADPN and first-episode psychosis with cognitive function	Lis et al., 2020
Alzheimer's disease	Men Women	63±8.0	No difference	Blood	No relationship between ADPN and AD	Caunca et al., 2019
Obesity	Men Women	68.4±4.8	Lower levels	Blood	Positive association between serum ADPN and cognitive function	Beyer et al., 2019
Dementia in older women with depression	Women	72.55±5.45 and 72.40±3.81	Higher levels	Blood	Positive association between serum ADPN and dementia with depression	Baek et al., 2021
Alzheimer's disease	Men Women	70.10±6.89	Lower levels	Cerebrospinal fluid	Positive association between serum ADPN and AD's cognitive function	Trombetta et al., 2018
Depression	Men Women	57.07±16.26	No difference	Blood	No relationship between ADPN and depression	Wittekind et al., 2022

AD: Alzheimer's disease; ADPN: adiponectin; CSF: cerebrospinal fluid; MCI: mild cognitive impairment; WMLs: white matter lesions.

Possible Mechanisms of the Cognitive Effects of Exercise on Alzheimer's Disease Neuropathology

Amyloid-β accumulation

Aβ accumulation and hyperphosphorylated forms of tau are recognized as the two main causes of AD pathobiology. The Aβ theory has been applied to the development of novel treatment approaches for AD (Jeremic et al., 2021). A cohort study indicated that physical activity reduced the plasma levels of $A\beta_{1-42}$ (Pedrini et al., 2022). It has been reported that exercise can delay or reduce Aβ deposition in the brain (Brown et al., 2019). The beneficial effects of physical exercise could include inhibiting the Aβ generation process, enhancing brain-derived neurotrophic factor (BDNF) production (Brown et al., 2019), modulating APP-cleaved proteases (beta-site APP-cleaving enzyme 1, metalloprotease-10, and sirtuin-1) and increasing the levels of Aβ-degrading enzymes, such as NEP and insulin-degrading enzymes (Brown et al., 2019; Liang et al., 2022). Moreover, physical exercise elicits neuroprotective effects by increasing synaptic transmission, increasing synaptic plasticity, and increasing synaptic growth (Lu et al., 2013). Exercise can also affect the glymphatic system (He et al., 2017), Aβ transport proteins across the blood–brain barrier (Tan et al., 2021), and autophagy (Xu et al., 2022), which eventually decreases Aβ accumulation to protect against the onset of AD (Lu et al., 2013; He et al., 2017; Brown et al., 2019; Liang et al., 2022; Xu et al., 2022).

Tau hyperphosphorylation

Tau is a member of the microtubule-associated protein family, which stabilizes the assembly and function of microtubules (Tapia-Rojas et al., 2019). Tau hyperphosphorylation in the brain leads to neurofibrillary tangles. GSK3 and cyclin-dependent kinase 5 are considered the two main signaling molecules that regulate the phosphorylation of tau protein (Dolan and Johnson, 2010; Li and Gotz, 2017). Aerobic exercise activates the PI3K/AKT/mTOR signaling pathway to suppress the hyperphosphorylation of tau proteins (Xu et al., 2022). GSK3β can be phosphorylated by AKT kinase (Kang and Cho, 2015). A recent animal study indicated that voluntary running wheels increase the total dendritic length by reversing GSK-3β overexpression in newborn hippocampal granule neurons (Llorens-Martín et al., 2016). Conversely, PP2A, the major serine/threonine protein phosphatase, contributes to abnormal phosphorylation of tau protein by dephosphorylating tau (Liu et al., 2005). Exercise can reverse cancerous inhibitors of protein phosphatase 2A (CIP2A), which can inhibit PP2A activity to reduce tau phosphorylation and reverse cognitive deficits (Shentu et al., 2018). PP2A activity is markedly reduced in the cortex and hippocampus in AD patients (Sontag et al., 2004). It is possible that enhancing PP2A activity via exercise could be a promising way to prevent AD-related tau hyperphosphorylation.

Neuroinflammation

Neuroinflammation is a common trigger of AD pathology (Lee et al., 2021). IL-6 is the first myokine discovered to modulate central inflammatory processes that result in neurodegeneration and impaired cognitive function (Marsland et al., 2015). A recent study revealed that regular exercise can reduce IL-6 in the plasma and cortex to improve cognitive function (Belaya et al., 2021). Consistently, resistance exercise decreases the number of Aβ plaques by restoring the levels of IL-1α, IL-4, and IL-6 in APP/PS1 mice (Hashiguchi et al., 2020). IL-6, TNF-α, and IL-1β are other pro-inflammatory factors that can induce neurotoxicity (Marsland et al., 2015; Lee et al., 2021). Exercise can decrease the levels of IL-1β and TNF-α to increase Aβ clearance and increase anti-inflammatory IL-10 to alter AD (Naghibi et al., 2021). Pro-inflammatory NLRP3 is induced by Aβ in microglia both *in vitro* and *in vivo* (Wang et al., 2019; Rosa et al., 2021). Researchers have reported that exercise reduces NLRP3 levels, thereby reducing or delaying the progression of AD (Chimen et al., 2015; Hashiguchi et al., 2020). In addition, physical exercise can also increase anti-inflammatory factor clustering in the brain to improve learning and memory in mice (De Miguel et al., 2021).

Overall, ample evidence shows the pro-cognitive effects of physical exercise. As shown in **Figure 4**, the main mechanisms include maintaining cognitive functions by increasing adult neurogenesis (Yau et al., 2014), restoring synaptic plasticity (Choi et al., 2018a), reducing amyloid and tau pathology, and decreasing neuroinflammation (Valenzuela et al., 2020; Huuha et al., 2022).

Exercise Enhances Adiponectin Signaling

Impaired brain energy metabolism potentially contributes to AD (Cunnane et al., 2020). Exercise and calorie restriction are known to regulate energy metabolism (Cunnane et al., 2020). Exercise regulates glucolipid metabolism and increases angiogenesis and cerebral blood flow (Schön et al., 2019; Cunnane et al., 2020). All of these factors could be helpful in pro-cognitive action.

The hippocampus is the most important anatomical structure for regulating learning, spatial information, and memory processing (Cholvin et al., 2021; Cossart and Khazipov, 2022). ADPN enhances glucose uptake and the glycolytic rate in hippocampal neurons by activating AMPK (Cisternas et al., 2019). Notably, physical exercise directly promotes adult hippocampal neurogenesis through ADPN/AdipoR1/AMPK signaling (Yau et al., 2014) and enhances synaptic function through the ADPN-Notch pathway (You et al., 2021).

ADPN is a critical messenger for peripheral organ cross-talk (Raichle and Mintun, 2006; Abou-Samra et al., 2020). In muscle-specific AdipoR1-knockout mice, ADPN rescues mitochondrial dysfunction and enhances insulin sensitivity by activating AMPK/SIRT1/PGC-1α signaling (Iwabu et al., 2016). Suppression of AdipoR1 decreases exercise endurance (Iwabu et al., 2016). It has also been demonstrated that physical exercise improves insulin resistance through the action of ADPN on the APPL1-SIRT1-PGC-1α pathway, thereby increasing the secretion of the mitochondrial open reading frame of the 12S rRNA (Guo et al., 2020). In addition, acute aerobic exercise increases ADPN levels in serum and muscles and mediates the muscle fatty acid–glucose shift by regulating AMPK phosphorylation (Diniz et al., 2019). Geng et al. (2019) reported that cross-talk among adipose tissues, the liver, and skeletal muscle plays a role in the improvement of metabolic dysfunction caused by exercise.

In high-fat diet-fed mice, voluntary running attenuates NLRP3 inflammasome signaling in the aorta partly through the ADPN/AdipoR1 pathway (Lee et al., 2020). Physical exercise may also restore vascular function by activating ADPN signaling to reduce the level of the inflammatory factor NLRP3 (Lee et al., 2020). Indeed, Rita Polito et al. specifically reported the interplay between exercise and nutrients, the gut microbiota, and ADPN (Peng et al., 2018), suggesting that ADPN could be a mediator of neuroprotection (**Figure 3**).

Effects of Adiponectin and Its Receptor Agonists on Alzheimer's Disease

The process of adult-born neurons (adult neurogenesis) in the hippocampal dentate gyrus plays a crucial role in the cognitive impairment associated with mood disorders and neurodegenerative diseases (Yau et al., 2014). Emerging data suggest that low-molecular-weight ADPN can regulate neural progenitor cell proliferation and differentiation (Yau et al., 2014), dendritic and spine remodeling, and synaptic plasticity (Yau et al., 2014; Ng et al., 2016; Wang et al., 2020b). Targeting ADPN signaling could be a way to improve neurodegeneration in AD.

In recent years, several ADPN agonists have been examined, including ADP355 (Otvos et al., 2011; Pepping et al., 2014), ADP399 (Otvos et al., 2014), Pep 70 (Ma et al., 2017), PEGylated BHD1028 (Lee et al., 2021a), GTDF (Singh et al., 2014), nonapeptide (Os-pep) (Ali et al., 2021), AdipoRon (Choi et al., 2018b; Kim et al., 2018; Lee et al., 2021c; KNg et al., 2021; handelwal et al., 2022), osmotin (Narasimhan et al., 2005; Rawat et al., 2009; Ali et al., 2015; Badshah et al., 2016), and JT003 (Narasimhan et al., 2005; Rawat et al., 2009; Otvos et al., 2011; Otvos et al., 2014; Pepping et al., 2014; Singh et al., 2014; Ma et al., 2017; Lee et al., 2021a) as summarized in **Table 2**. All of these compounds have antidiabetes (Choi et al., 2018b; Kim et al., 2018; Ali et al., 2021), antifibrotic (Ma et al., 2017; Kim et al., 2018), anti-inflammatory (Badshah et al., 2016), and antiatherosclerotic (Narasimhan et al., 2005) functions, as does ADPN. ADP355, ADP399, Pep 70, and PEGylated BHD1028 are peptides that are potential treatments for cancer, brain injury, liver fibrosis, and metabolic disorders, such as type 2 diabetes, obesity, and NAFLD (Otvos et al., 2011, 2014; Ma et al., 2017; Lee et al., 2021a). GTDF and osmotin are plant proteins (Narasimhan et al., 2005; Rawat et al., 2009). GTDF is a natural analog of the flavonoid quercetin, which was originally found in Ulmus wallichiana, whereas osmotin is made from tobacco (Ma et al., 2017). JT003 is the latest peptide for treating nonalcoholic steatohepatitis (Xu et al., 2020). Recent studies have shown that ADPN receptor agonists, including AdipoRon,

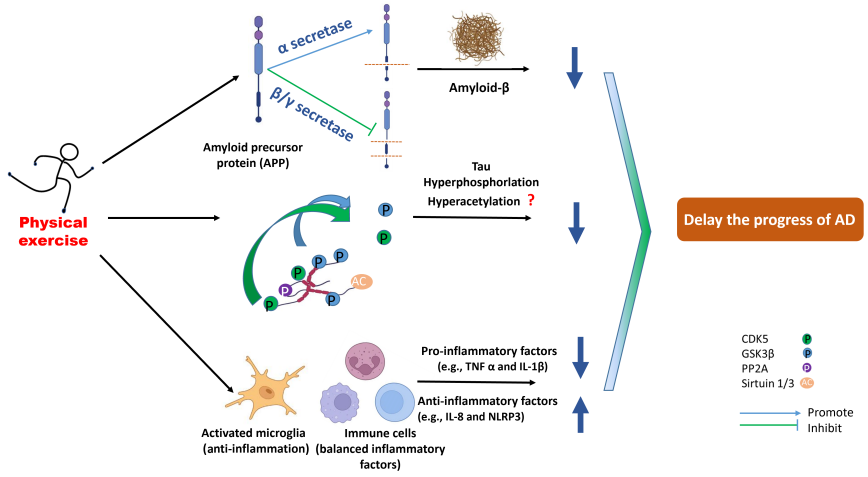

Figure 4 | **Possible mechanisms by which physical exercise halts the progression of AD.**
Exercise can delay the progression of AD and reverse the cognitive impairment associated with AD. Physical exercise decreases amyloid plaque, inhibits tau hyperphosphorylation, and reduces neuroinflammation, thereby delaying the progression of AD. AD: Alzheimer's disease; CDK5: cyclin-dependent kinase 5; GSK3β: glycogen synthase kinase 3β; IL: interleukin; NLRP3: nucleotide-binding oligomerization domain-like receptor protein 3; PP2A: protein phosphatase 2A; TNFα: tumor necrosis factor α.

Table 2 | **ADPN and its receptor agonists**

Compounds	Natures	Target moleculars	Tested subjects	References
ADP355/399	Short peptides	AdipoR1	Breast cancer cell lines; glioblastoma cells; chronic myeloid leukemia cells; Skh1 hairless mice	Otvos et al., 2011, 2014
Pep 70	Short peptides	AdipoR1	HSC-T6 cells; NIH-3T3 cells	Ma et al., 2017
PEGylated BHD1028	Peptides	AdipoR1	C2C12 myotubes	Lee et al., 2021
JT003	Peptides	AdipoR1 and AdipoR2	NAFLD model; hepatoma carcinoma cell line	Xu et al., 2020
nonapeptide (Os-pep)	Peptides	AdipoR1	$A\beta_{1-42}$-induced HT22 cells; Adipo$^{-/-}$ mice; AD mice	Ali et al., 2021
GTDF	Protein	AdipoR1	HEK-293, CHO, C2C12, 3T3L-1 cell-lines; db/db or BKS-db/db mice	Singh et al. 2014
Osmotin	Protein	AdipoR1 and AdipoR2?	Adipo$^{-/-}$ mice; AD mice	Narasimhan et al., 2005; Shah et al., 2017; Yoon et al., 2018
AdipoRon	Small synthetic molecule	AdipoR1 and AdipoR2	db/db mice; Adipor1$^{-/-}$ and Adipor2$^{-/-}$ double-knockout mice	Okada-Iwabu et al., 2013 Abou-Samra et al., 2020

AD: Alzheimer's disease; ADPN: adiponectin; CSF: cerebrospinal fluid; MCI: mild cognitive impairment; WMLs: white matter lesions; GTDF: 6-C-β-d-glucopyranosyl-(2S,3S)-(+)-3′,4′,5,7-tetrahydroxyflavonol.

Osmotin, and Os-pep, have beneficial effects on neurodegenerative diseases (Choi et al., 2016, 2018b; Amin et al., 2017; Shah et al., 2017; Yoon et al., 2018; Schön et al., 2019; Lee et al., 2021c; Ng et al., 2021).

AdipoRon

AdipoRon is an orally active synthetic small-molecule AdipoR agonist that has significant antidiabetic effects by activating the ADPN/AdipoR pathway (Okada-Iwabu et al., 2013; Kim et al., 2018). Emerging data have suggested that AdipoRon could be used as a potential pharmacological inhibitor that reduces neuroinflammation, enhances hippocampal adult neurogenesis, enhances dendritic complexity, and improves learning and memory function (Choi et al, 2018b; Schön et al., 2019; Lee et al., 2021; Chen et al., 2023). ADPN-KO mice exhibit learning and memory deficits as well as increased anxiety-like behaviors and neuroinflammation. AdipoRon counteracts depression behaviors in ADPN-KO mice and attenuates neuroinflammation by interacting with BDNF/TrkB signaling and NF-κB signaling (Li et al., 2022a; Wu et al., 2021). Moreover, AdipoRon can ameliorate Aβ pathologies and neuroinflammation in 5xFAD mice and APP/PS1 mice through the AMPK pathway, which can activate the autophagic/lysosomal system (Ng et al., 2021; Khandelwal et al., 2022). Convergent evidence has suggested that AdipoRon can mimic ADPN's ability to rescue cognitive impairments and elicit neuroprotective effects in AD.

Osmotin

Osmotin is an ADPN homolog from plants. Animal studies have shown its preventive effects on AD, such as ADPN (Shah et al., 2017; Ali et al., 2021). Osmotin attenuates memory impairment, synaptic deficits, tau hyperphosphorylation, and hippocampal neuronal degeneration in $A\beta_{1-42}$-induced and lipopolysaccharide-induced mouse models (Ali et al., 2015; Badshah et al., 2016). The possible neuroprotective mechanisms of osmotin could involve suppressing Aβ production in an AMPK/SIRT1/SREBP2-dependent manner (Shah et al., 2017), reducing neuroinflammation stemming from the TLR4/NFκB signaling pathway (Badshah et al., 2016) and enhancing neurite outgrowth and synaptic complexity through AdipoR1/NgR1 signaling (Shah et al., 2017; Yoon et al., 2018). To date, few studies have indicated the potential value of osmotin therapy in reducing the pathophysiology of neurodegenerative diseases.

ADP355

ADP355, an ADPN-based short peptide, was initially designed as a potential treatment for cancer (Otvos et al., 2011). It is produced on the basis of the beneficial effects of ADPN to prevent obesity-related malignancies (Otvos et al., 2011). ADP335 binds to AdipoRs to mimic the effects of ADPN in the treatment of liver fibrosis, keloids, and skin fibrosis by inhibiting the transforming growth factor-β/Smad and mitogen-activated protein kinase (MAPK)/ERK signaling pathways and activating the functions of macrophages through signal transducer and activator of transcription 3 (STAT3) signaling (Pepping et al., 2014). It is also effective in treating heart failure by preventing cardiomyocyte apoptosis and oxidation and slowing tumor growth by maintaining energy balance and increasing AMPK and STAT3 phosphorylation (Pepping et al., 2014). In addition, it can prevent human immunodeficiency virus protease inhibitor-induced memory impairment in C57BL/6 mice (Pepping et al., 2014). In summary, the peptide ADP355 has antifibrotic, anti-inflammatory, antioxidant, and antiatherosclerotic effects, but there is no direct evidence of its effects on AD. Its relevant biological activity in regulating metabolic changes, lipid metabolism, and neurodegeneration warrants future investigation.

Os-pep

Os-pep is a novel osmotin-derived novel nanopeptide. As mentioned above, osmotin is a plant protein with a homolog of ADPN. However, in its full form, it cannot cross the blood–brain barrier to the brain. Treatment with Os-pep can rescue neuronal insulin resistance and restore synaptic function by activating AdipoR1/AMPK signaling (Ali et al., 2021). These findings suggest that Os-pep is a potential drug for enhancing synaptic impairment in the brain.

Limitations

In this review, there are some limitations that need to be noted. Most of the evidence for these molecular mechanisms is derived from animal models, and sufficient clinical research is lacking. Additionally, the studies and articles we referenced, which were published primarily in English over the past 5–10 years, may introduce publication bias.

Conclusions

Physical exercise is recognized as one of the most feasible and promising nonpharmaceutical interventions to improve neuroplasticity and could be linked to psychological and behavioral changes in AD patients (Yanai and Yoshida, 2019). Although how physical exercise improves the cognitive impairments associated with AD

is still largely unknown, abundant evidence has confirmed that an increase in ADPN levels induced by physical exercise could play a role in preventing AD pathologies. ADPN acts on various peripheral organs and the brain to control the insulin response, glucose and lipid metabolism, and inflammatory reactions. Physical exercise shows promise for decreasing Aβ production, Tau hyperphosphorylation, and the anti-inflammatory response. Because ADPN is the most abundant plasma protein in the human body, the use of recombinant ADPN as a treatment is not feasible in clinical applications. Alternatively, exercise mimetic drugs, such as ADPN-like peptides, may have great potential to reduce tau pathology and Aβ and promote the anti-inflammatory response in the AD brain. However, more studies are needed to demonstrate the promising effects of the abovementioned ADPN mimetics on AD.

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References

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

Alghadir AH, Gabr SA, Almomani M, Almomani F, Tse C (2022) Adiponectin and nitric oxide deficiency-induced cognitive impairment in fatigued home-resident in mature and older adults: a case-control study. Pain Res Manag 2022:7480579.

Ali T, Yoon GH, Shah SA, Lee HY, Kim MO (2015) Osmotin attenuates amyloid beta-induced memory impairment, tau phosphorylation and neurodegeneration in the mouse hippocampus. Sci Rep 5:11708.

Ali T, Rehman SU, Khan A, Badshah H, Abid NB, Kim MW, Jo MH, Chung SS, Lee HG, Rutten BPF, Kim MO (2021) Adiponectin-mimetic novel nonapeptide rescues aberrant neuronal metabolic-associated memory deficits in Alzheimer's disease. Mol Neurodegener 16:23.

Amin FU, Hoshiar AK, Do TD, Noh Y, Shah SA, Khan MS, Yoon J, Kim MO (2017) Osmotin-loadedmagnetic nanoparticles with electromagnetic guidance for the treatment of Alzheimer's disease. Nanoscale 9:10619-10632.

Awazawa M, Ueki K, Inabe K, Yamauchi T, Kubota N, Kaneko K (2011) Adiponectin enhances insulin sensitivity by increasing hepatic IRS-2 expression via a macrophage-derived IL-6-dependent pathway. Cell Metab 13:401-412.

Badshah H, Ali T, Kim MO (2016) Osmotin attenuates LPS-induced neuroinflammation and memory impairments via the TLR4/NFkappaB signaling pathway. Sci Rep 6:24493.

Baek SH, Hong GR, Min DK, Kim EH, Park SK (2021) Effects of functional fitness enhancement through taekwondo training on physical characteristics and risk factors of dementia in elderly women with depression. Int J Environ Res Public Health 18:7961.

Belaya I, Ivanova M, Sorvari A, Ilicic M, Loppi S, Koivisto H, Varricchio A, Tikkanen H, Walker FR, Atalay M, Malm T, Grubman A, Tanila H, Kanninen KM (2020) Astrocyte remodeling in the beneficial effects of long-term voluntary exercise in Alzheimer's disease. J Neuroinflammation 17:271.

Belaya I, Kucháriková N, Górová V, Kysenius K, Hare DJ, Crouch PJ, Malm T, Atalay M, White AR, Liddell JR, Kanninen KM (2021) Regular physical exercise modulates iron homeostasis in the 5xFAD mouse model of Alzheimer's disease. Int J Mol Sci 22: 8715.

Benavente KSK, Palmer RF, Royall DR (2020) Serum adiponectin is related to dementia. J Gerontol A Biol Sci Med Sci 75:779-783.

Beyer F, Kharabian Masouleh S, Kratzsch J, Schroeter ML, Röhr S, Riedel-Heller SG, Villringer A, Witte AV (2019) A metabolic obesity profile is associated with decreased gray matter volume in cognitively healthy older adults. Front Aging Neurosci 11:202.

Bloemer J, Pinky PD, Govindarajulu M, Hong H, Judd R, Amin RH, Moore T, Dhanasekaran M, Reed MN, Suppiramaniam V (2018) Role of adiponectin in central nervous system disorders. Neural Plast 2018:4593530.

Brown BM, Peiffer J, Rainey-Smith SR (2019) Exploring the relationship between physical activity, beta-amyloid and tau: A narrative review. Ageing Res Rev 50:9-18.

Brown GC, Heneka MT (2024) The endotoxin hypothesis of Alzheimer's disease. Mol Neurodegener 19:30.

Buechler C, Wanninger J, Neumeier M (2010) Adiponectin receptor binding proteins--recent advances in elucidating adiponectin signalling pathways. FEBS Lett 584:4280-4286.

Caunca MR, Simonetto M, Alperin N, Elkind MSV, Sacco RL, Wright CB, Rundek T (2019) Measures of adiposity and Alzheimer's disease-related MRI markers: The Northern Manhattan Study. J Alzheimers Dis 70:995-1004.

Cezaretto A, Suemoto CK, Bensenor I, Lotufo PA, de Almeida-Pititto B, Ferreira SRG; ELSA Research Group (2018) Association of adiponectin with cognitive function precedes overt diabetes in the Brazilian Longitudinal Study of Adult Health: ELSA. Diabetol Metab Syndr 10:54.

Chang HC, Guarente L (2014) SIRT1 and other sirtuins in metabolism. Trends Endocrinol Metab 25:138-45.

Charlton HK, Webster J, Kruger S, Simpson F, Richards AA, Whitehead JP (2010) ERp46 binds to AdipoR1, but not AdipoR2, and modulates adiponectin signalling. Biochem Biophys Res Commun 392:234-239.

Chen MH, Hsu JW, Huang KL, Tsai SJ, Su TP, Li CT, Lin WC, Tu PC, Bai YM (2021) World J Biol Psychiatry 22:428-434.

Chen YL, Ma YC, Tang J, Zhang D, Zhao Q, Liu JJ, Tang HS, Zhang JY, He GH, Zhong CH, Wu YT, Wen HR, Ma LQ, Zou CG (2023) Physical exercise attenuates age-related muscle atrophy and exhibits anti-ageing effects via the adiponectin receptor 1 signalling. J Cachexia Sarcopenia Muscle 14:1789-1801.

Chimen M, et al. (2015) Homeostatic regulation of T cell trafficking by a B cell-derived peptide is impaired in autoimmune and chronic inflammatory disease. Nat Med 21:467-475.

Choi HM, Doss HM, Kim KS (2020) Multifaceted physiological roles of adiponectin in inflammation and diseases. Int J Mol Sci 21:1219.

Choi SH, Bylykbashi E, Chatila ZK, Lee SW, Pulli B, Clemenson GD, Kim E, Rompala A, Oram MK, Asselin C, Aronson J, Zhang C, Miller SJ, Lesinski A, Chen JW, Kim DY, van Praag H, Spiegelman BM, Gage FH, Tanzi RE (2018a) Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. Science 361:eaan8821.

Choi SR, Lim JH, Kim MY, Kim EN, Kim Y, Choi BS, Kim YS, Kim HW, Lim KM, Kim MJ, Park CW (2018b) Adiponectin receptor agonist AdipoRon decreased ceramide, and lipotoxicity, and ameliorated diabetic nephropathy. Metabolism 85:348-360.

Cholvin T, Hainmueller T, Bartos M (2021) The hippocampus converts dynamic entorhinal inputs into stable spatial maps. Neuron 109:3135-3148.e7.

Cisternas P, Martinez M, Ahima RS, William Wong G, Inestrosa NC (2019) Modulation of glucose metabolism in hippocampal neurons by adiponectin and resistin. Mol Neurobiol 56:3024-3037.

Cossart R, Khazipov R (2022) How development sculpts hippocampal circuits and function. Physiol Rev 102:343-378.

Cunnane SC, et al. (2020) Brain energy rescue: an emerging therapeutic concept for neurodegenerative disorders of ageing. Nat Rev Drug Discov 19:609-633.

De Franciscis P, Barbieri M, Leo S, Dalise AM, Sardu C, Marfella R, Colacurci N, Paolisso G, Rizzo MR (2017) Serum adiponectin levels are associated with worse cognitive function in postmenopausal women. PLoS One 12:e0186205.

De la Rosa A, Olaso-Gonzalez G, Arc-Chagnaud C, Millan F, Salvador-Pascual A, García-Lucerga C, Blasco-Lafarga C, Garcia-Dominguez E, Carretero A, Correas AG, Viña J, Gomez-Cabrera MC (2020) Physical exercise in the prevention and treatment of Alzheimer's disease. J Sport Health Sci 9:394-404.

De Miguel Z, et al. (2021) Exercise plasma boosts memory and dampens brain inflammation via clusterin. Nature 600:494-499.

Devaraj S, Torok N, Dasu MR, Samols D, Jialal I (2008) Adiponectin decreases C-reactive protein synthesis and secretion from endothelial cells. Arterioscler Thromb Vasc Biol 28:1368-1374.

Diaz-Castro J, Garcia-Vega JE, Ochoa JJ, Puche-Juarez M, Toledano JM, Moreno-Fernandez J (2021) Implementation of a physical activity program protocol in schoolchildren: effects on the endocrine adipose tissue and cognitive functions. Front Nutr 8:761213.

Diniz TA, Aquino Júnior JCJ, Mosele FC, Cabral-Santos C, Lima Junior EA, Teixeira AAS, Lira FS, Rosa Neto JC (2019) Exercise-induced AMPK activation and IL-6 muscle production are disturbed in adiponectin knockout mice. Cytokine 119:71-80.

Dolan PJ, Johnson GV (2010) The role of tau kinases in Alzheimer's disease. Curr Opin Drug Discov Deve 13:595-603.

Duzel E, van Praag H, Sendtner M (2016) Can physical exercise in old age improve memory and hippocampal function? Brain 139: 662–673.

Fang H, Judd RL (2018) Adiponectin regulation and function. Compr Physiol 8:1031-1063.

Fantuzzi G (2008) Adiponectin and inflammation: consensus and controversy. J Allergy Clin Immunol 121:326-30.

Feijóo-Bandín S, Aragón-Herrera A, Moraña-Fernández S, Anido-Varela L, Tarazón E, Roselló-Lletí E, Portolés M, Moscoso I, Gualillo O, González-Juanatey JR, Lago F (2020) Adipokines and inflammation: focus on cardiovascular diseases. Int J Mol Sci 21:7711.

Feinkohl I, Janke J, Slooter AJC, Winterer G, Spies C, Pischon T (2020) Plasma leptin, but not adiponectin, is associated with cognitive impairment in older adults. Psychoneuroendocrinology 120:104783.

Fernández-Rodríguez R, Álvarez-Bueno C, Martínez-Ortega IA, Martínez-Vizcaíno V, Mesas AE, Notario-Pacheco B (2022) Immediate effect of high-intensity exercise on brain-derived neurotrophic factor in healthy young adults: A systematic review and meta-analysis. J Sport Health Sci 11:367-375.

Frismantiene A, Dasen B, Pfaff D, Erne P, Resink TJ, Philippova M (2016) T-cadherin promotes vascular smooth muscle cell dedifferentiation via a GSK3β-inactivation dependent mechanism. Cell Signal 28:516-530.

Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, Bihain BE, Lodish HF (2001) Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad Sci U S A 98:2005-10.

Fujita Y, Toyomoto T, Sakoh-Goshima T, Kohno Y, Okada M, Hamano T, Nakamoto Y (2018) Increased adiponectin is associated with cerebral white matter lesions in the elderly with cognitive impairment. Metab Brain Dis 33:1385-1388.

Fukuda S, Hirata A, Nishizawa H, Nagao H, Kashine S, Kimura T, Inoue K, Fujishima Y, Yamaoka M, Kozawa J, Kitamura T, Yasuda T, Maeda N, Imagawa A, Funahashi T, Shimomura I (2015) Systemic arteriosclerosis and eating behavior in Japanese type 2 diabetic patients with visceral fat accumulation. Cardiovasc Diabetol 14:8.

Fukuda S, Kita S, Obata Y, Fujishima Y, Nagao H, Masuda S, Tanaka Y, Nishizawa H, Funahashi T, Takagi J, Maeda N, Shimomura I (2017) The unique prodomain of T-cadherin plays a key role in adiponectin binding with the essential extracellular cadherin repeats 1 and 2. J Biol Chem 292:7840-7849.

Ganguli M, Beer JC, Zmuda JM, Ryan CM, Sullivan KJ, Chang CH, Rao RH (2020) Aging, diabetes, obesity, and cognitive decline: a population-based study. J Am Geriatr Soc 68:991-998.

Geng L, Liao B, Jin L, Huang Z, Triggle CR, Ding H, Zhang J, Huang Y, Lin Z, Xu A (2019) Exercise alleviates obesity-induced metabolic dysfunction via enhancing FGF21 sensitivity in adipose tissues. Cell Rep 26:2738-2752. e4.

Gilbert T, Roche S, Blond E, Bar JY, Drai J, Cuerq C, Haution-Bitker M, Ecochard R, Bonnefoy M (2018) Association between peripheral leptin and adiponectin levels and cognitive decline in patients with neurocognitive disorders ≥ 65 years. J Alzheimers Dis 66:1255-1264.

Goyal NP, Rosenthal SB, Nasamran C, Behling CA, Angeles JE, Fishbein MH, Harlow KE, Jain AK, Molleston JP, Newton KP, Ugalde-Nicalo P, Xanthankos SA, Yates K, Schork NJ, Fisch KM, Schwimmer JB; NASH Clinical Research Network (2023) Nonalcoholic fatty liver disease risk and histologic severity are associated with genetic polymorphisms in children. Hepatology 77:197-212.

Grazioli E, Nigro E, Cerulli C, Borriello G, Mancini A, Tranchita E, Polito R, Parisi A, Buono P, Daniele A (2020) Case report: concurrent resistance and aerobic training regulate adiponectin expression and disease severity in multiple sclerosis: a case study. Front Neurosci 14:567302.

Guo M, Li C, Lei Y, Xu S, Zhao D, Lu XY (2017) Role of the adipose PPARγ-adiponectin axis in susceptibility to stress and depression/anxiety-related behaviors. Mol Psychiatry 22:1056-1068.

Guo Q, Chang B, Yu QL, Xu ST, Yi XJ, Cao SC (2020) Adiponectin treatment improves insulin resistance in mice by regulating the expression of the mitochondrial-derived peptide MOTS-c and its response to exercise via APPL1-SIRT1-PGC-1α. Diabetologia 63:2675-2688.

Hashiguchi D, Campos HC, Wuo-Silva R, Faber J, Gomes da Silva S, Coppi AA, Arida RM, Longo BM (2020) Resistance exercise decreases amyloid load and modulates inflammatory responses in the APP/PS1 mouse model for Alzheimer's disease. J Alzheimers Dis 73:1525-1539.

He XF, Liu DX, Zhang Q, Liang FY, Dai GY, Zeng JS, Pei Z, Xu GQ, Lan Y (2017) Voluntary exercise promotes glymphatic clearance of amyloid beta and reduces the activation of astrocytes and microglia in aged mice. Frontiers in Molecular Neuroscience 10:1-14.

Heiker JT, Wottawah CM, Juhl C, Kosel D, Mörl K, Beck-Sickinger AG (2009) Protein kinase CK2 interacts with adiponectin receptor 1 and participates in adiponectin signaling. Cell Signal 21:936-42.

Horgusluoglu E, et al. (2022) Integrative metabolomics-genomics approach reveals key metabolic pathways and regulators of Alzheimer's disease. Alzheimers Dement 18:1260-1278.

Hug C, Wang J, Ahmad NS, Bogan JS, Tsao TS, Lodish HF (2004) T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. Proc Natl Acad Sci U S A 101:10308-13.

Huuha AM, Norevik CS, Moreira JBN, Kobro-Flatmoen A, Scrimgeour N, Kivipelto M, Van Praag H, Ziaei M, Sando SB, Wisløff U, Tari AR (2022) Can exercise training teach us how to treat Alzheimer's disease? Ageing Res Rev 75:101559.

Ilhan N, Susam S, Canpolat O, Belhan O (2019) The emerging role of leptin, adiponectin and visfatin in ischemic/hemorrhagic stroke. Br J Neurosurg 33:504-507.

Iwabu M, et al. (2016) Adiponectin and AdipoR1 regulate PGC-1alpha and mitochondria by Ca (2+) and AMPK/SIRT1. Nature 464:1313-1319.

Javadpour P, Dargahi L, Ahmadiani A, Ghasemi R (2019) To be or not to be: PP2A as a dual player in CNS functions, its role in neurodegeneration, and its interaction with brain insulin signaling. Cell Mol Life Sci 76:2277-2297.

Jeremic D, Jiménez-Díaz L, Navarro-López JD (2021) Past, present and future of therapeutic strategies against amyloid-β peptides in Alzheimer's disease: a systematic review. Ageing Res Rev 72:101496.

Jian M, Kwan JS, Bunting M, Ng RC, Chan KH (2019) Adiponectin suppresses amyloid-beta oligomer (AbetaO)-induced inflammatory response of microglia via AdipoR1-AMPK-NF-kappaB signaling pathway. J Neuroinflammation 16:110.

Kadowaki T, Yamauchi T (2005) Adiponectin and adiponectin receptors. Endocr Rev 26:439-451.

Kaminska B, Czerwinska J, Bogacka I, Chojnowska K, Smolinska N, Dobrzyn K, Kiezun M, Zaobidna E, Myszczynski K, Nowakowski JJ, Kaminski T (2020) Sex- and season-dependent differences in the expression of adiponectin and adiponectin receptors (AdipoR1 and AdipoR2) in the hypothalamic-pituitary-adrenal axis of the Eurasian beaver (Castor fiber L.). Gen Comp Endocrinol 298:113575.

Kang EB, Cho JY (2015) Effect of treadmill exercise on PI3K/AKT/mTOR, autophagy, and Tau hyperphosphorylation in the cerebral cortex of NSE/htau23 transgenic mice. J Exerc Nutrition Biochem 19:199-209.

Khandelwal M, Manglani K, Upadhyay P, Azad M, Gupta S (2022) AdipoRon induces AMPK activation and ameliorates Alzheimer's like pathologies and associated cognitive impairment in APP/PS1 mice. Neurobiol Dis 174:105876.

Kim MW, Abid NB, Jo MH, Jo MG, Yoon GH, Kim MO (2017) Suppression of adiponectin receptor 1 promotes memory dysfunction and Alzheimer's disease-like pathologies. Sci Rep 7:12435.

Kim Y, Lim JH, Kim MY, Kim EN, Yoon HE, Shin SJ, Choi BS, Kim YS, Chang YS, Park CW (2018) The adiponectin receptor agonist AdipoRon ameliorates diabetic nephropathy in a model of type 2 diabetes. J Am Soc Nephrol 29:1108-1127.

Kim Y, Lim JH, Kim EN, Hong YA, Park HJ, Chung S, Choi BS, Kim YS, Park JY, Kim HW, Park CW (2022) Adiponectin receptor agonist ameliorates cardiac lipotoxicity via enhancing ceramide metabolism in type 2 diabetic mice. Cell Death Dis 13:282.

Kita S, Maeda N, Shimomura I (2019) Interorgan communication by exosomes, adipose tissue, and adiponectin in metabolic syndrome. J Clin Invest 129:4041-4049.

Knopman DS, Amieva H, Petersen RC, Chételat G, Holtzman DM, Hyman BT, Nixon RA, Jones DT (2021) Alzheimer disease. Nat Rev Dis Primers 7:33.

Koh JH, Kim JY (2021) Role of PGC-1α in the mitochondrial NAD + pool in metabolic diseases. Int J Mol Sci 22:4558.

Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W (2006) Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 144:73-81.

Lee IK, Kim G, Kim DH, Kim BB (2021a) PEG-BHD1028 peptide regulates insulin resistance and fatty acid β-oxidation, and mitochondrial biogenesis by binding to two heterogeneous binding sites of adiponectin receptors, AdipoR1 and AdipoR2. Int J Mol Sci 22:884.

Lee J, Hong J, Umetani M, Lavoy EC, Kim JH, Park Y (2020) Vascular protection by exercise in obesity: inflammasome-associated mechanisms. Med Sci Sports Exerc 52:2538-2545.

Lee S, Cho HJ, Ryu JH (2021b) Innate immunity and cell death in Alzheimer's disease. ASN Neuro13:17590914211051908.

Lee TH, Christie BR, van Praag H, Lin K, Siu PM, Xu A, So KF, Yau SY (2021c) AdipoRon treatment induces a dose-dependent response in adult hippocampal neurogenesis. Int J Mol Sci 22:2068.

Lei X, Qiu S, Yang G, Wu Q (2022) Adiponectin and metabolic cardiovascular diseases: Therapeutic opportunities and challenges. Genes Dis 10:1525-1536.

Letra L, Matafome P, Rodrigues T, Duro D, Lemos R, Baldeiras I, Patrício M, Castelo-Branco M, Caetano G, Seiça R, Santana I (2019) Association between adipokines and biomarkers of Alzheimer's disease: a cross-sectional study. J Alzheimers Dis 67:725-735.

Li C, Gotz J (2017) Tau-based therapies in neurodegeneration: opportunities and challenges. Nat. Rev. Drug Discov 16:863-883.

Li C, Meng F, Garza JC, Liu J, Lei Y, Kirov SA, Guo M, Lu XY (2021) Modulation of depression-related behaviors by adiponectin AdipoR1 receptors in 5-HT neurons. Mol Psychiatry 26:4205-4220.

Li L, Wu LL (2012) Adiponectin and interleukin-6 in inflammation-associated disease. Vitam Horm 90:375-95.

Li N, Yolton K, Lanphear BP, Chen A, Kalkwarf HJ, Braun JM (2018) Impact of early-life weight status on cognitive abilities in children. Obesity (Silver Spring) 26:1088-1095.

Li N, Arbuckle TE, Muckle G, Lanphear BP, Boivin M, Chen A, Dodds L, Fraser WD, Ouellet E, Séguin JR, Velez MP, Yolton K, Braun JM (2019) Associations of cord blood leptin and adiponectin with children's cognitive abilities. Psychoneuroendocrinology 99:257-264.

Li W, Ali T, Zheng C, He K, Liu Z, Shah FA, Li N, Yu ZJ, Li S (2022a) Anti-depressive-like behaviors of APN KO mice involve Trkb/BDNF signaling related neuroinflammatory changes. Mol Psychiatry 27:1047-1058.

Li Z, Zhu M, Meng C, Lin H, Huang L (2022b) Predictive value of serum adiponectin and hemoglobin levels for vascular cognitive impairment in ischemic stroke patients. Pak J Med Sci 38:705-710.

Lihn AS, Pedersen SB, Richelsen B (2005) Adiponectin: action, regulation and association to insulin sensitivity. Obes Rev 6:13-21.

Lis M, Stańczykiewicz B, Pawlik-Sobecka L, Samochowiec A, Reginia A, Misiak B (2020) Assessment of appetite-regulating hormones provides further evidence of altered adipoinsular axis in early psychosis. Front Psychiatry 11:480.

Liu F, Grundke-Iqbal I, Iqbal K, Gong CX (2005) Contributions of protein phosphatases PP1, PP2A, PP2B and PP5 to the regulation of tau phosphorylation. Eur J Neurosci 22:1942-19450.

Liu FJ, Xu HH, Yin Y, Chen YZ, Xie LY, Li HZ, Wang DD, Shi B (2022) Decreased adiponectin levels are a risk factor for cognitive decline in spinal cord injury. Dis Markers 2022:5389162.

Liu GP, Wei W, Zhou X, Shi HR, Liu XH, Chai GS, Yao XQ, Zhang JY, Peng CX, Hu J, Li XC, Wang Q, Wang JZ (2013) Silencing PP2A inhibitor by lenti-shRNA interference ameliorates neuropathologies and memory deficits in tg2576 mice. Mol Ther 21:2247-57.

Liu S, Gao J, Zhu M, Liu K, Zhang HL (2020) Gut microbiota and dysbiosis in Alzheimer's disease: implications for pathogenesis and treatment. Mol Neurobiol 57:5026-5043.

Liu Y, Sweeney G (2014) Adiponectin action in skeletal muscle. Best Pract Res Clin Endocrinol Metab 28:33-41.

Llorens-Martín M, Teixeira CM, Jurado-Arjona J, Rakwal R, Shibato J, Soya H, Ávila J (2016) Retroviral induction of GSK-3β expression blocks the stimulatory action of physical exercise on the maturation of newborn neurons. Cell Mol Life Sci 73:3569-3582.

Lopez-Vilaret KM, Cantero JL, Fernandez-Alvarez M, Calero M, Calero O, Lindín M, Zurrón M, Díaz F, Atienza M (2021) Impaired glucose metabolism reduces the neuroprotective action of adipocytokines in cognitively normal older adults with insulin resistance. Aging (Albany NY) 13:23936-23952.

Lourenco MV, et al. (2019) Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat Med 25:165-175.

Luo Y, Liu M (2016) Adiponectin: A versatile player of innate immunity. J Mol Cell Biol 8:120-128.

Ma L, Zhang Z, Xue X, Wan Y, Ye B, Lin K (2017) A potent peptide as adiponectin receptor 1 agonist to against fibrosis. J Enzyme Inhib Med Chem 32:624-631.

Macleod A, Scheurlen KM, Burton JF, Parks MA, Sumy MSA, Gaskins JT, Galandiuk S (2023) Systemic adiponectin levels in colorectal cancer and adenoma: a systematic review and meta-analysis. Int J Obes (Lond) 47:911-921.

Mao X, Kikani CK, Riojas RA, Langlais P, Wang L, Ramos FJ, Fang Q, Christ-Roberts CY, Hong JY, Kim RY, Liu F, Dong LQ (2006) APPL1 binds to adiponectin receptors and mediates adiponectin signaling and function. Nat Cell Biol 8:516-523.

Marsland AL, Gianaros PJ, Kuan DC, Sheu LK, Krajina K, Manuck SB (2015) Brain morphology links systemic inflammation to cognitive function in midlife adults. Brain Behav Immun 48:195-204.

Martin L, Latypova X, Wilson CM, Magnaudeix A, Perrin ML, Terro F (2013) Tau protein phosphatases in Alzheimer's disease: the leading role of PP2A. Ageing Res Rev 12:39-49.

Miao W, Jiang L, Xu F, Lyu J, Jiang X, He M, Liu Y, Yang T, Leak RK, Stetler RA, Chen J, Hu X (2021) Adiponectin ameliorates hypoperfusive cognitive deficits by boosting a neuroprotective microglial response. Prog Neurobiol 205:102125.

Miller KN, Clark JP, Martin SA, Howell PR, Burhans MS, Haws SA, Johnson NB, Rhoads TW, Pavelec DM, Eliceiri KW, Roopra AS, Ntambi JM, Denu JM, Parks BW, Anderson RM (2019) PGC-1a integrates a metabolism and growth network linked to caloric restriction. Aging Cell 18:e12999.

Mohorko N, Černelič-Bizjak M, Poklar-Vatovec T, Grom G, Kenig S, Petelin A, Jenko-Pražnikar Z (2019) Weight loss, improved physical performance, cognitive function, eating behavior, and metabolic profile in a 12-week ketogenic diet in obese adults. Nutr Res 62:64-77.

Naghibi S, Shariatzadeh Joneydi M, Barzegari A, Davoodabadi A, Ebrahimi A, Eghdami E, Fahimpour N, Ghorbani M, Mohammadikia E, Rostami M, Salari AA (2021) Treadmill exercise sex-dependently alters susceptibility to depression-like behaviour, cytokines and BDNF in the hippocampus and prefrontal cortex of rats with sporadic Alzheimer-like disease. Physiol Behav 241:113595.

Nakamura Y, Kita S, Tanaka Y, Fukuda S, Obata Y, Okita T, Nishida H, Takahashi Y, Kawachi Y, Tsugawa-Shimizu Y, Fujishima Y, Nishizawa H, Takakura Y, Miyagawa S, Sawa Y, Maeda N, Shimomura I (2020) Adiponectin stimulates exosome release to enhance mesenchymal stem-cell-driven therapy of heart failure in mice. Mol Ther 28:2203-2219.

Narasimhan ML, Coca MA, Jin J, Yamauchi T, Ito Y, Kadowaki T, Kim KK, Pardo JM, Damsz B, Hasegawa PM, Yun DJ, Bressan RA (2005) Osmotin is a homolog of mammalian adiponectin and controls apoptosis in yeast through a homolog of mammalian adiponectin receptor. Mol Cell 17:171-180.

Ng RC, Cheng OY, Jian M, Kwan JS, Ho PW, Cheng KK, Yeung PK, Zhou LL, Hoo RL, Chung SK, Xu A, Lam KS, Chan KH (2016) Chronic adiponectin deficiency leads to Alzheimer's disease-like cognitive impairments and pathologies through AMPK inactivation and cerebral insulin resistance in aged mice. Mol Neurodegener 11:71.

Ng RC, Jian M, Ma OK, Bunting M, Kwan JS, Zhou GJ, Senthilkumar K, Iyaswamy A, Chan PK, Li M, Leung KM, Kumar Durairajan SS, Lam KS, Chu LW, Festenstein R, Chung SK, Chan KH (2021) Chronic oral administration of adipoRon reverses cognitive impairments and ameliorates neuropathology in an Alzheimer's disease mouse model. Mol Psychiatry 26:5669-5689.

O'Donoghue G, Blake C, Cunningham C, Lennon O, Perrotta C (2021) What exercise prescription is optimal to improve body composition and cardiorespiratory fitness in adults living with obesity? A network meta-analysis. Obes Rev 22:e13137.

Obata Y, Kita S, Koyama Y, Fukuda S, Takeda H, Takahashi M, Fujishima Y, Nagao H, Masuda S, Tanaka Y, Nakamura Y, Nishizawa H, Funahashi T, Ranscht B, Izumi Y, Bamba T, Fukusaki E, Hanayama R, Shimada S, Maeda N, Shimomura I (2018) Adiponectin/T-cadherin system enhances exosome biogenesis and decreases cellular ceramides by exosomal release. JCI Insight 3:99680.

Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami K, Matsuda K, Yamaguchi M, Tanabe H, Kimura-Someya T, Shirouzu M, Ogata H, Tokuyama K, Ueki K, Nagano T, Tanaka A, Yokoyama S, Kadowaki T (2013) A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. Nature 503:493-9.

Otvos L Jr, Haspinger E, La Russa F, Maspero F, Graziano P, Kovalszky I, Lovas S, Nama K, Hoffmann R, Knappe D, Cassone M, Wade J, Surmacz E (2011) Design and development of a peptide-based adiponectin receptor agonist for cancer treatment. BMC Biotechnol 11: 90.

Otvos L Jr, Knappe D, Hoffmann R, Kovalszky I, Olah J, Hewitson TD, Stawikowska R, Stawikowski M, Cudic P, Lin F, Wade JD, Surmacz E, Lovas S (2014) Development of second generation peptides modulating cellular adiponectin receptor responses. Front Chem 2:93.

Pedrini S, Chatterjee P, Nakamura A, Tegg M, Hone E, Rainey-Smith SR, Rowe CC, Dore V, Villemagne VL, Ames D, Kaneko N, Gardener SL, Taddei K, Fernando B, Martins I, Bharadwaj P, Sohrabi HR, Masters CL, Brown B, Martins RN (2022) The association between Alzheimer's disease-related markers and physical activity in cognitively normal older adults. Front Aging Neurosci 14:771214.

Peng YJ, Shen TL, Chen YS, Mersmann HJ, Liu BH, Ding ST (2018) Adiponectin and adiponectin receptor 1 overexpression enhance inflammatory bowel disease. J Biomed Sci 25:24.

Pepping JK, Otvos L, Surmacz E, Gupta S, Keller JN, Bruce-Keller AJ (2014) Designer adiponectin receptor agonist stabilizes metabolic function and prevents brain injury caused by HIV protease inhibitors. J Neuroimmune Pharmacol 9:388-98.

Philippova M, Joshi MB, Pfaff D, Kyriakakis E, Maslova K, Erne P, Resink TJ (2012) T-cadherin attenuates insulin-dependent signalling, eNOS activation, and angiogenesis in vascular endothelial cells. Cardiovasc Res 93:498-507.

Polito R, Di Meo I, Barbieri M, Daniele A, Paolisso G, Rizzo MR (2020) Adiponectin role in neurodegenerative diseases: focus on nutrition review. Int J Mol Sci 21:9255.

Pratap AA, Holsinger RMD (2020) Altered brain adiponectin receptor expression in the 5XFAD mouse model of Alzheimer's disease. Pharmaceuticals (Basel) 13:150.

Qian XH, Song XX, Liu XL, Chen SD, Tang HD (2021) Inflammatory pathways in Alzheimer's disease mediated by gut microbiota. Ageing Res Rev 68:101317.

Quan H, Yu T, Lin Y, Pan J, Mao B, Wang X, Xie J, Liu X, Zhao Y (2022) Adiponectin levels are associated with white matter lesions (WMLs) and cognitive impairment. Biomed Res Int 18:2022:9943250.

Raichle ME, Mintun MA (2006) Brain work and brain imaging. Annu Rev Neurosci 29:449-476.

Rastegar S, Parimisetty A, Cassam Sulliman N, Narra SS, Weber S, Rastegar M, Viranaicken W, Couret D, Planesse C, Strähle U, Meilhac O, Lefebvre d'Hellencourt C, Diotel N (2019) Expression of adiponectin receptors in the brain of adult zebrafish and mouse: Links with neurogenic niches and brain repair. J Comp Neurol 527:2317-2333.

Rawat P, Kumar M, Sharan K, Chattopadhyay N, Maurya R (2009) Ulmosides A and B: flavonoid 6-C-glycosides from Ulmus wallichiana, stimulating osteoblast differentiation assessed by alkaline phosphatase. Bioorg Med Chem Lett 19:4684-4687.

Rius-Pérez S, Torres-Cuevas I, Millán I, Ortega ÁL, Pérez S (2020) PGC-1α, inflammation, and oxidative stress: an integrative view in metabolism. Oxid Med Cell Longev 2020:1452696.

Rosa JM, Camargo A, Wolin IAV, Kaster MP, Rodrigues ALS (2021) Physical exercise prevents amyloid β1–40-induced disturbances in NLRP3 inflammasome pathway in the hippocampus of mice. Metab Brain Dis 36:351-359.

Rui L (2014) Energy metabolism in the liver. Compr Physiol 4:177-97.

Ruiz M, Devkota R, Panagaki D, Bergh PO, Kaper D, Henricsson M, Nik A, Petkevicius K, Höög JL, Bohlooly-Y M, Carlsson P, Borén J, Pilon M (2022) Sphingosine 1-phosphate mediates adiponectin receptor signaling essential for lipid homeostasis and embryogenesis. Nat Commun 13:7162.

Russo-Neustadt A, Beard RC, Cotman CW (1999) Exercise, antidepressant medications, and enhanced brain derived neurotrophic factor expression. Neuropsychopharmacology 21:679-682.

Saito T, Okada S, Shimoda Y, Tagaya Y, Osaki A, Yamada E, Shibusawa R, Nakajima Y, Ozawa A, Satoh T, Mori M, Yamada M (2016) APPL1 promotes glucose uptake in response to mechanical stretch via the PKCζ-non-muscle myosin IIa pathway in C2C12 myotubes. Cell Signal 28:1694-702.

Sanz B, Arrieta H, Hervás G, Rezola-Pardo C, Ruiz-Litago F, Iturburu M, Gil SM, Rodríguez-Larrad A, Irazusta J (2019) Serum adiponectin is associated with body composition and cognitive and psychological status in older adults living in long-term nursing homes. Exp Gerontol 121:1-9.

Schindler M, Pendzialek M, Grybel KJ, Seeling T, Gürke J, Fischer B, Navarrete Santos A (2017) Adiponectin stimulates lipid metabolism via AMPK in rabbit blastocysts. Hum Reprod 32:1382-1392.

Schön M, Kovaničová Z, Košutzká Z, Nemec M, Tomková M, Jacková L, Máderová D, Slobodová L, Valkovič P, Ukropec J, Ukropcová B (2019) Effects of running on adiponectin, insulin and cytokines in cerebrospinal fluid in healthy young individuals. Sci Rep 9:1959.

Sellami M, Bragazzi NL, Aboghaba B, Elrayess MA (2021) The impact of acute and chronic exercise on immunoglobulins and cytokines in elderly: insights from a critical review of the literature. Front Immunol 12:631873.

Shah SA, Yoon GH, Chung SS, Abid MN, Kim TH, Lee HY, Kim MO (2017) Novel osmotin inhibits SREBP2 via the AdipoR1/AMPK/SIRT1 pathway to improve Alzheimer's disease neuropathological deficits. Mol Psychiatry 22:407-416.

Shentu YP, Huo Y, Feng XL, Gilbert J, Zhang Q, Liuyang ZY, Wang XL, Wang G, Zhou H, Wang XC, Wang JZ, Lu YM, Westermarck J, Man HY, Liu R (2018) CIP2A causes Tau/APP phosphorylation, synaptopathy, and memory deficits in Alzheimer's disease. Cell Rep 24:713-723.

Singh AK, Joharapurkar AA, Khan MP, Mishra JS, Singh N, Yadav M, Hossain Z, Khan K, Kumar S, Dhanesha NA, Mishra DP, Maurya R, Sharma S, Jain MR, Trivedi AK, Godbole MM, Gayen JR, Chattopadhyay N, Sanyal S (2014) Orally active osteoanabolic agent GTDF binds to adiponectin receptors, with a preference for AdipoR1, induces adiponectin-associated signaling, and improves metabolic health in a rodent model of diabetes. Diabetes 63:3530-3544.

Song J, Lee JE (2013) Adiponectin as a new paradigm for approaching Alzheimer's disease. Anat Cell Biol 46:229-234.

Song J, Kang SM, Kim E, Kim CH, Song HT, Lee JE (2015) Adiponectin receptor-mediated signaling ameliorates cerebral cell damage and regulates the neurogenesis of neural stem cells at high glucose concentrations: an in vivo and in vitro study. Cell Death Dis 6:e1844.

Song J, Choi SM, Whitcomb DJ, Kim BC (2017) Adiponectin controls the apoptosis and the expression of tight junction proteins in brain endothelial cells through AdipoR1 under beta amyloid toxicity. Cell Death Dis 8:e3102.

Sontag E, Luangpirom A, Hladik C, Mudrak I, Ogris E, Speciale S, White CL 3rd (2004) Altered expression levels of the protein phosphatase 2A ABalphaC enzyme are associated with Alzheimer disease pathology. J Neuropathol Exp Neurol 63:287-301.

Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, Xu XJ, Wands JR, de la Monte SM (2005) Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease--is this type 3 diabetes? J Alzheimers Dis 7:63-80.

Sun F, Lei Y, You J, Li C, Sun L, Garza J, Zhang D, Guo M, Scherer PE, Lodge D, Lu XY (2019) Adiponectin modulates ventral tegmental area dopamine neuron activity and anxiety-related behavior through AdipoR1. Mol Psychiatry 24:126-144.

Suntar I, Sureda A, Belwal T, Sanches Silva A, Vacca RA, Tewari D, Sobarzo-Sánchez E, Nabavi SF, Shirooie S, Dehpour AR, Xu S, Yousefi B, Majidinia M, Daglia M, D'Antona G, Nabavi SM (2020) Natural products, PGC-1α, and Duchenne muscular dystrophy. Acta Pharm Sin B 10:734-745.

Suresh J, Khor IW, Kaur P, Heng HL, Torta F, Dawe GS, Tai ES, Tolwinski NS (2021) Shared signaling pathways in Alzheimer's and metabolic disease may point to new treatment approaches. FEBS J 288:3855-3873.

Taleski G, Sontag E (2018) Protein phosphatase 2A and tau: an orchestrated 'Pas de Deux'. FEBS Lett 592:1079-1095.

Tan ZX, Dong F, Wu LY, Feng YS, Zhang F (2021) The beneficial role of exercise on treating Alzheimer's disease by inhibiting β-amyloid peptide. Mol Neurobiol 58:5890-5906.

Tanaka Y, Kita S, Nishizawa H, Fukuda S, Fujishima Y, Obata Y, Nagao H, Masuda S, Nakamura Y, Shimizu Y, Mineo R, Natsukawa T, Funahashi T, Ranscht B, Fukada SI, Maeda N, Shimomura I (2019) Adiponectin promotes muscle regeneration through binding to T-cadherin. Sci Rep 9:16.

Tapia-Rojas C, Cabezas-Opazo F, Deaton CA, Vergara EH, Johnson GVW, Quintanilla RA (2019) It's all about tau. Prog Neurobiol 175:54-76.

Teixeira AL, Diniz BS, Campos AC, Miranda AS, Rocha NP, Talib LL, Gattaz WF, Forlenza OV (2013) Decreased levels of circulating adiponectin in mild cognitive impairment and Alzheimer's disease. Neuromol Med 15:115-121.

Thundyil J, Pavlovski D, Sobey CG, Arumugam TV (2012) Adiponectin receptor signaling in the brain. Br J Pharmacol 165:313-327.

Trombetta BA, Carlyle BC, Koenig AM, Shaw LM, Trojanowski JQ, Wolk DA, Locascio JJ, Arnold SE (2018) The technical reliability and biotemporal stability of cerebrospinal fluid biomarkers for profiling multiple pathophysiologies in Alzheimer's disease. PLoS One 13:e0193707.

Valenzuela PL, Castillo-García A, Morales JS, de la Villa P, Hampel H, Emanuele E, Lista S, Lucia A (2020) Exercise benefits on Alzheimer's disease: State-of-the-science. Ageing Res Rev 62:101108.

van Andel M, van Schoor NM, Korten NC, Comijs HC, Heijboer AC, Drent ML (2021) The association between high-molecular-weight adiponectin, ghrelin and leptin and age-related cognitive decline: results from longitudinal aging study Amsterdam. J Gerontol A Biol Sci Med Sci 76:131-140.

van der Heijden MM, van Dooren FE, Pop VJ, Pouwer F (2013) Effects of exercise training on quality of life, symptoms of depression, symptoms of anxiety and emotional well-being in type 2 diabetes mellitus: a systematic review. Diabetologia 56:1210-1225.

Vargas-Terrones M, Barakat R, Santacruz B, Fernandez-Buhigas I, Mottola MF (2019) Physical exercise programme during pregnancy decreases perinatal depression risk: a randomised controlled trial. Br J Sports Med 53:348-353.

Wang L, Luo Y, Luo L, Wu D, Ding X, Zheng H, Wu H, Liu B, Yang X, Silva F, Wang C, Zhang X, Zheng X, Chen J, Brigman J, Mandell M, Zhou Z, Liu F, Yang XO, Liu M (2021) Adiponectin restrains ILC2 activation by AMPK-mediated feedback inhibition of IL-33 signaling. J Exp Med 218:e20191054.

Wang P, Liang Y, Chen K, Yau SY, Sun X, Cheng KK, Xu A, So KF, Li A (2020a) Potential involvement of adiponectin signaling in regulating physical exercise-elicited hippocampal neurogenesis and dendritic morphology in stressed mice. Front Cell Neurosci 14:189.

Wang Q, Hu J, Liu Y, Li J, Liu B, Li M, Lou S (2019) Aerobic exercise improves synaptic-related proteins of diabetic rats by inhibiting FOXO1/NF-κB/NLRP3 inflammatory signaling pathway and ameliorating PI3K/Akt insulin signaling pathway. J Mol Neurosci 9:28-38.

Wang R, Li JJ, Diao S, Kwak YD, Liu L, Zhi L, Büeler H, Bhat NR, Williams RW, Park EA, Liao FF (2013) Metabolic stress modulates Alzheimer's β-secretase gene transcription via SIRT1-PPARγ-PGC-1in neurons. Cell Metab 17:685-94.

Wang R, Tian H, Guo D, Tian Q, Yao T, Kong X (2020b) Impacts of exercise intervention on various diseases in rats. J Sport Health Sci 9:211-227.

Wang ZV, Scherer PE (2016) Adiponectin, the past two decades. J Mol Cell Biol 8:93-100.

Wen HJ, Tsai CL (2020) Effects of acute aerobic exercise combined with resistance exercise on neurocognitive performance in obese women. Brain Sci 10:767.

Wennberg AM, Gustafson D, Hagen CE, Roberts RO, Knopman D, Jack C, Petersen RC, Mielke MM (2016) Serum adiponectin levels, neuroimaging, and cognition in the mayo clinic study of aging. J Alzheimers Dis 53:573-581.

Wittekind DA, Kratzsch J, Biemann R, Mergl R, Riedel-Heller S, Witte V, Villringer A, Kluge M (2022) Association between self-rating depression scores and total ghrelin and adipokine serum levels in a large population-based sample. Front Psychiatry 13:891325.

Wong WT, Tian XY, Xu A, Yu J, Lau CW, Hoo RL, Wang Y, Lee VW, Lam KS, Vanhoutte PM, Huang Y (2011) Adiponectin is required for PPARg-mediated improvement of endothelial function in diabetic mice. Cell Metab 14:104-115.

Wu Z, Chen C, Kang SS, Liu X, Gu X, Yu SP, Keene CD, Cheng L, Ye K (2021) Neurotrophic signaling deficiency exacerbates environmental risks for Alzheimer's disease pathogenesis. Proc Natl Acad Sci U S A 118:e2100986118.

Xie H, Zhou J, Du W, Zhang S, Huang R, Han Q, Guo Q (2019) Impact of thoracic paravertebral block combined with general anesthesia on postoperative cognitive function and serum adiponectin levels in elderly patients undergoing lobectomy. Wideochir Inne Tech Maloinwazyjne 14:538-544.

Xu H, Zhao Q, Song N, Yan Z, Lin R, Wu S, Jiang L, Hong S, Xie J, Zhou H, Wang R, Jiang X (2020) AdipoR1/AdipoR2 dual agonist recovers nonalcoholic steatohepatitis and related fibrosis via endoplasmic reticulum-mitochondria axis. Nat Commun 11:5807.

Xu L, Li M, Wei A, Yang M, Li C, Liu R, Zheng Y, Chen Y, Wang Z, Wang K, Wang T (2022) Treadmill exercise promotes E3 ubiquitin ligase to remove amyloid β and P-tau and improve cognitive ability in APP/PS1 transgenic mice. J Neuroinflammation 19:243.

Yamauchi T, et al. (2003) Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 423:762-769.

Yamauchi T, et al. (2007) Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 13:332-339.

Yamauchi T, Iwabu M, Okada-Iwabu M, Kadowaki T (2014) Adiponectin receptors: a review of their structure, function and how they work. Best Pract Res Clin Endocrinol Metab 28:15-23.

Yan XD, Qu XS, Yin J, Qiao J, Zhang J, Qi JS, Wu MN (2022) Adiponectin ameliorates cognitive behaviors and in vivo synaptic plasticity impairments in 3xTg-AD mice. J Alzheimers Dis 85:343-357.

Yanai H, Yoshida H (2019) Beneficial effects of adiponectin on glucose and lipid metabolism and atherosclerotic progression: mechanisms and perspectives. Int J Mol Sci 20:1190.

Yassine HN, et al. (2023) Nutritional metabolism and cerebral bioenergetics in Alzheimer's disease and related dementias. Alzheimers Dement Alzheimers Dement 19:1041-1066.

Yau SY, Li A, Hoo RL, Ching YP, Christie BR, Lee TM, Xu A, So KF (2014) Physical exercise-induced hippocampal neurogenesis and antidepressant effects are mediated by the adipocyte hormone adiponectin. Proc Natl Acad Sci U S A 111:15810-15815.

Yin F, Sancheti H, Patil I, Cadenas E (2016) Energy metabolism and inflammation in brain aging and Alzheimer's disease. Free Radic Biol Med 100:108-122.

Yoon G, Shah SA, Ali T, Kim MO (2018) The adiponectin homolog osmotin enhances neurite outgrowthand synaptic complexity via AdipoR1/NgR1 signaling in Alzheimer's disease. Mol Neurobiol 55:6673-6686.

You J, Sun L, Wang J, Sun F, Wang W, Wang D, Fan X, Liu D, Xu Z, Qiu C, Chen J, Yan H, Liu B (2021) Role of Adiponectin-Notch pathway in cognitive dysfunction associated with depression and in the therapeutic effect of physical exercise. Aging Cell 20:e13387.

Zaidi H, Aksnes T, Åkra S, Eggesbø HB, Byrkjeland R, Seljeflot I, Opstad TB (2022) Abdominal adipose tissue associates with adiponectin and TNFα in middle-aged healthy men. Front Endocrinol (Lausanne) 13:874977.

Zhang D, Wang X, Wang B, Garza JC, Fang X, Wang J, Scherer PE, Brenner R, Zhang W, Lu XY (2017) Adiponectin regulates contextual fear extinction and intrinsic excitability of dentate gyrus granule neurons through AdipoR2 receptors. Mol Psychiatry 22:1044-1055.

Zhang S, Wu X, Wang J, Shi Y, Hu Q, Cui W, Bai H, Zhou J, Du Y, Han L, Li L, Feng D, Ge S, Qu Y (2022) Adiponectin/AdiopR1 signaling prevents mitochondrial dysfunction and oxidative injury after traumatic brain injury in a SIRT3 dependent manner. Redox Biol 54:102390.

Zhang W, Ou H, Zhang B, Zheng M, Yan L, Chen Y, So KF, Zhang L (2021) Treadmill exercise relieves chronic restraint stress-induced cognitive impairments in mice via activating protein phosphatase 2A. Neurosci Bull 37:1487-1492.

Zhou L, Deepa SS, Etzler JC, Ryu J, Mao X, Fang Q, Liu DD, Torres JM, Jia W, Lechleiter JD, Liu F, Dong LQ (2009) Adiponectin activates AMP-activated protein kinase in muscle cells via APPL1/LKB1-dependent and phospholipase C/Ca2+/Ca2+/calmodulin-dependent protein kinase kinase-dependent pathways. J Biol Chem 284:22426-22435.

Zhu D, Zhang Z, Zhao J, Liu D, Gan L, Lau WB, Xie D, Meng Z, Yao P, Tsukuda J, Christopher TA, Lopez BL, Gao E, Koch WJ, Wang Y, Ma XL (2022) Targeting adiponectin receptor 1 phosphorylation against ischemic heart failure. Circ Res 131:e34-50.

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