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Could exercise hormone irisin be a therapeutic agent against Parkinson's and other neurodegenerative diseases?

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease (AD). The pathologic hallmarks of the disease are the loss of dopaminergic neurons of substantia nigra pars compacta and the presence of intraneuronal alpha synuclein (a-syn) aggregates. Clinical features of PD include motor symptoms such as bradykinesia, rigidity, tremors, postural instability, and gait impairment, and non-motor symptoms such as constipation, orthostatic hypotension, REM sleep disorder, depression and dementia. Currently, there is no disease-modifying therapy for PD. Several human studies have shown that exercise reduces progression of motor symptoms, improves performance on cognitive tasks, and slows functional deterioration. However, regular exercise may not always be feasible in PD patients. Irisin is an exercise-induced myokine involved in metabolism modulation and body fat reduction, but it also crosses the blood-brain barrier and may mediate some of the benefits of exercise in brain function. Recent evidence has shown that irisin could be therapeutically promising in PD as an "exercise-mimicking" intervention. Exogenous irisin administration decreases brain a-syn pathology and loss of dopaminergic neurons, while it improves motor outcomes in preclinical models. Several other neurodegenerative disorders such as AD share common underlying pathogenetic mechanisms with PD such as protein misfolding and aggregation, neuroinflammation, brain metabolic abnormalities, and neuronal loss. Therefore, investigation of irisin as a disease-modifying therapy could be promising for PD and other neurodegenerative disorders including AD.

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease (AD). It has been estimated that globally, 6.1 million individuals were affected in 2016 [1], and it is projected that over 17 million may suffer from PD by 2040 [2]. The disease's symptoms are divided into motor (bradykinesia, rigidity, resting tremor, dysphagia, postural instability, gait freezing) and non-motor (constipation, REM sleep behavior disorder, hyposmia, depression, pain, orthostatic hypotension, and dementia) [3]. Parkinson's disease profoundly impacts the quality of life of patients and their caregivers [4], and has been associated with significant medical costs attributed to medications, hospitalizations and productivity loss [5].

Neurodegeneration in PD is the result of multiple interacting pathological processes that include abnormal a-synuclein (a-syn) aggregation, dysfunction of mitochondria and lysosomes, synaptic transmission abnormalities, and neuroinflammation [6]. Loss of dopaminergic neurons is a well-known characteristic of the disease and is primarily evident in substantia nigra pars compacta, but is also found in the locus coeruleus, nucleus basalis of Meynert, pedunculopontine nucleus, raphe nucleus, dorsal motor nucleus of vagus, caudate nucleus, amygdala and hypothalamus [3,7]. Currently, there is no disease-modifying therapy against neurodegeneration in PD and the available therapies treat only symptoms of the disease.

The mainstay treatment for PD's motor symptoms includes medications that elevate dopamine levels or stimulate dopamine receptors intracerebrally such as levodopa, dopamine agonists, monoamine oxidase B inhibitors and amantadine [3]. Dementia is treated with acetylcholinesterase inhibitors; depression with selective serotonin reuptake inhibitors/serotonin and norepinephrine reuptake inhibitors/tricyclic antidepressants; psychosis with atypical anti-psychotics; sleep disorders with benzodiazepines and melatonin; and fatigue with stimulants such as methylphenidate and modafinil [3].

In addition to medications, physical exercise has been investigated as a possible intervention in PD with promising effects in humans that include reduced decline of postural and gait instability, improved overall mobility, favorable performance on cognitive tasks such as processing speed and cognitive control, and slower deterioration on activities of daily living [8–10]. Evidence from neuroimaging studies suggests that the clinical effects of exercise in PD could be associated with the positive effects of exercise on brain function and structure [9,11]. In a study involving individuals with mild to moderate PD, 3-month aerobic exercise increased ventral striatum activity shown on fMRI during a task involving 75% probability of monetary reward following patients' random selection of one out of four cards [11]. The same study also showed that exercise increased transcranial magnetic stimulation-induced dopamine release in caudate nucleus measured by [11^{C}] raclopride PET [11]. Another study involving mild PD patients showed that 6-month aerobic exercise increased functional connectivity of the right frontoparietal network which was correlated with improved

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measures of fitness [9]. In addition, exercise reduced global brain atrophy [9].

Despite the promising effects of exercise in PD, the molecular mechanisms involved in these benefits are not clear. Studies in preclinical models of PD have provided some insights into the effects of exercise in PD at the molecular level. In a chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD with moderate neurodegeneration, 18-weeks exercise increased striatal antioxidant enzymes [Mn superoxide dismutase (SOD) and Cu–Zn SOD], improved mitochondrial functional indicators in striatum such as the rate of mitochondrial state 3/4 respiration and ATP content, and boosted the neurotrophic factors brain-derived neurotrophic factor (BDNF) in substantia nigra and glial cell line-derived neurotrophic factor (GDNF) in striatum [12]. In a transgenic mouse model expressing a human form of a-syn in all neurons, animals that exercised for 3 months had elevated cortical BDNF, DJ-1 and Hsp70 proteins, and these changes were accompanied by decreased brain a-syn aggregation [13].

In 2002, fibronectin type III domain-containing protein 5 (*FNDC5*), a transmembrane protein, was discovered and shown to be expressed in skeletal muscle, heart, and brain [14]. After a decade, a study showed that in response to exercise in mice, the extracellular component of FNDC5 was released from skeletal muscle into the blood circulation and induced a transition of white adipose tissue (WAT) to adipose tissue with brown adipose tissue (BAT)-like morphology (browning) as well as a thermogenic program dissipating energy as heat [15]. The secretory soluble peptide produced from the proteolytic processing of FNDC5, irisin, is a myokine playing an important role in the modulation of metabolism and body fat reduction, increasing energy expenditure and oxygen consumption while reducing insulinemia [16]. Thus, irisin acting as myokine may present a potential protective effect on the progress of obesity-related conditions [16–27]. Obesity has risen significantly in recent decades, becoming a major global public health concern associated with a variety of diseases including cardiovascular disease, metabolic syndrome, insulin resistance, type 2 diabetes mellitus, cancers and dementia [28–41]. Current data from experiments in rodents suggest that exercise induces significant browning of inguinal WAT. Nevertheless, there is little evidence that this extends to humans, which is attributed mainly to the different fat depots and role of subcutaneous WAT in humans compared with mice [42–44]. Other preclinical studies have shown that irisin exerts a plethora of additional biologic actions such as osteoblast proliferation and differentiation, increase of insulin sensitivity in muscle, and importantly, neuronal differentiation, rescue of synaptic plasticity and improvements in cognition and memory [45–47]. There are many challenges related to irisin's physiology, molecular mechanisms and laboratory determination. Studies are needed to identify the cleavage site of FNDC5 and the related secretase, the molecular mechanism of shedding, the associated mechanism of irisin's passage into the blood-brain barrier (BBB) and its relationship with the regulation of BDNF and neurogenesis in mice [42]. The generation of FNDC5 knockout mice may provide a new tool to study many facets of FNDC5/irisin biology [48]. Nevertheless, irisin has emerged as an important exercise-induced hormone with therapeutic potential across multiple diseases due to its pleiotropic actions.

In a recent study, Kam et al. used the a-synuclein preformed fibril (a-syn PFF) seeding model of PD to investigate the role of the irisin in PD [45]. They leveraged prior knowledge that irisin is induced by exercise not only in humans, but also in mice, and directly administered irisin to their PD model to test whether it can ameliorate the hallmark PD pathology a-syn, and whether it can improve PD-relevant motor outcomes. Initially, the authors used primary cortical cultures treated with a-syn PFF which is shown to induce toxic-for-cells misfolding of endogenous a-syn. It was demonstrated that sustained treatment with various concentrations of irisin starting 1 hour before introduction and continuing during the administration of a-syn PFF, resulted in the reduction of a-syn pathology in a concentration-dependent manner (studied with immunocytochemistry). Additionally, irisin treatment prevented neuronal death when started 1 hour before, 1 or 2 days after, but not 4 or 7 days after a-syn PFF administration. Overall, these findings suggested that irisin has the potential to prevent formation of pathologic a-syn and protect neurons against its toxicity.

Furthermore, to assess the protective role of irisin against dopaminergic neuronal loss in PD in vivo, Kam et al. stereotactically injected a-syn PFF into mice striatum which induces approximately 50% striatal dopaminergic neuron loss within 6 months in the wild type mice [45]. Two weeks after intra-striatal injection of a-syn PFF, researchers injected irisin or control within a vector via the tail vein of mice. Six months after intra-striatal a-syn PFF injection, irisin treatment reduced dopaminergic neuron loss by 35% measured as stereologic counts of tyrosine hydroxylase (TH) and Nissl-stained neurons compared with control. The effect was larger when assessed with immunoblot as it was shown that irisin decreased neuronal loss by 43% measured as levels of TH and by 39% measured as dopamine transporters. Moreover, in mice given irisin, the loss of striatal dopamine and its metabolites 3, 4-dihydroxyphenylacetic acid (DOPAC), homovanilic acid (HVA) and 3-methoxytyramine (3-MT) was inhibited by 87%, 95%, 72% and 70% respectively, as revealed in high-performance liquid chromatography. Interestingly, compared with control, irisin administration through vector in mice decreased insoluble levels of phosphorylated a-syn (p-a-syn) and a-syn, without any effect on soluble monomeric a-syn. In terms of motor outcomes, at 6 months after a-syn PFF intra-striatal injection, irisin improved performance on the pole test which assesses the time for mice to climb down to the bottom of a vertical pole after being placed on the top of it. Similarly, irisin improved performance on grip strength test which assesses peak tension of mice limbs while they are gently being pulled away of a metal grid until they release the handle [45].

To gain insights on the molecular pathways of irisin's effect against a-syn pathology in neurons, proteomic analyses from primary cultures of cortical neurons treated with a-syn PFF in the absence or presence of irisin using liquid chromatography tandem mass spectrometry were performed. Interestingly, compared with control, irisin decreased the a-syn protein itself and opposed a-syn PFF-induced ApoE upregulation. ApoE downregulation by irisin is beneficial since individuals with the e4 allele(s) are not only at an increased risk for AD, but also at a higher risk for earlier PD onset and dementia in PD [49].

After that, the authors asked the question whether irisin's effects on decreasing a-syn pathology could be explained by a block of neuronal internalization and propagation of a-syn [45]. Previous published work showed that biotin-labeled a-syn (biotin-a-syn) PFF is internalized by neurons and induces a-syn pathology similarly to the unlabeled a-syn PFF [50]. Therefore, the authors treated cortical neurons with biotin-a-syn PFF and irisin showing that 50 ng/ml of irisin reduced biotin-a-syn PFF and endogenous a-syn parallelly, 1 and 4 days following treatment. The formation of p-a-syn which is known to start on day 4 was also inhibited by irisin. These findings show that irisin likely intervenes in the processes of internalization of a-syn in neurons and intra-neuronal aggregation.

The authors additionally asked the question whether irisin treatment is associated with lysosome-related degradation of a-syn [45]. It was shown that treatment of cortical neurons with 50 ng/ml irisin starting 1 hour before and continuing during treatment with a-syn-biotin PFF, resulted in decreased a-syn-biotin PFF in the endolysosome-containing fraction, thereby providing evidence that irisin might reduce a-syn pathology by acting in endolysosomes. The authors also showed that a known lysosomal inhibitor (NH_4Cl) inhibits the irisin-induced degradation of a-syn-biotin-PFF but the proteasome inhibitor MG132 does not inhibit degradation. Taken together, these experiments provide important mechanistic evidence that a-syn pathology reduction in neurons by irisin is at least partially endolysosome mediated.

Overall, by showing that irisin decreases a-syn pathology and neuronal loss, and improves motor outcomes in a series of in vitro and in vivo experiments using the a-syn PFF seeding model of PD, Kam et al. provide a possible explanation for the clinical benefits of exercise in

individuals with PD. Importantly, the study offers mechanistic evidence that a-syn pathology amelioration by irisin takes place at least via three pathways which include: downregulation of ApoE4, reduction of a-syn internalization by neurons, and endolysosomal degradation of a-syn [45]. A novelty of this study was that irisin was directly administered to the studied PD model rather than induced by exercise. A previous study in mice implementing cellular pathway analysis showed that irisin injection has similar effects with exercise on brain proteome [51] supporting the idea that irisin administration could be used instead of exercise when the latter is not feasible.

The encouraging findings demonstrated by Kam et al. on the effects of irisin in PD could also be relevant in the context of other neurodegerative disorders such as AD, multiple sclerosis (MS), and Huntington's disease (HD), since these diseases share common underlying pathogenetic mechanisms with PD, such as protein misfolding and aggregation, neuroinflammation, metabolic abnormalities, vascular abnormalities, and neuronal loss [52–54]. The view that investigation of irisin could be promising in the context of other neurodegenerative disorders is supported by clinical studies that have shown exercise-induced improvements in neuropsychiatric, functional and cognitive outcomes across multiple neurodegenerative disorders [55–57]. Interestingly, several preclinical and clinical studies have shown that irisin induces the expression of brain BDNF [58,59], a factor that is also increased following exercise in neurodegenerative disorders [60,61].

In conclusion, given that peripheral irisin itself or factors induced by irisin may cross the BBB [62], exogenous irisin administration could be a promising alternative therapeutic approach to exercise in PD, especially since implementing a frequent exercise regimen in individuals with such a disease might be difficult or even risky. Although the safety and feasibility of exogenous irisin in humans is unknown, the current evidence is supportive of pursuing research towards development and testing of irisin administration for the treatment of PD and other neurodegenerative disorders.

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Declaration of competing interest

None.

References

[1] GBDPsD Collaborators. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018;17(11):939–53.
[2] Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. J Parkinsons Dis 2018;8(s1):S3–8.
[3] Kalia LV, Lang AE. Parkinson's disease. Lancet 2015;386(9996):896–912.
[4] Corallo F, De Cola MC, Lo Buono V, Di Lorenzo G, Bramanti P, Marino S. Observational study of quality of life of Parkinson's patients and their caregivers. Psychogeriatr : the Off J Japan Psychogeriatr Soc 2017;17(2):97–102.
[5] Rodriguez-Blazquez C, Forjaz MJ, Lizan L, Paz S, Martinez-Martin P. Estimating the direct and indirect costs associated with Parkinson's disease. Expert Rev Pharmacoecon Outcomes Res 2015;15(6):889–911.
[6] Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet 2021;397(10291):2284–303.
[7] Bohnen NI, Albin RL, Muller ML, Petrou M, Kotagal V, Koeppe RA, et al. Frequency of cholinergic and caudate nucleus dopaminergic deficits across the predemented cognitive spectrum of Parkinson disease and evidence of interaction effects. JAMA Neurol 2015;72(2):194–200.
[8] Tsukita K, Sakamaki-Tsukita H, Takahashi R. Long-term effect of regular physical activity and exercise habits in patients with early Parkinson disease. Neurology 2022;98(8):e859–71.
[9] Johansson ME, Cameron IGM, Van der Kolk NM, de Vries NM, Klimars E, Toni I, et al. Aerobic exercise alters brain function and structure in Parkinson's disease: a randomized controlled trial. Ann Neurol 2022;91(2):203–16.
[10] Oguh O, Eisenstein A, Kwasny M, Simuni T. Back to the basics: regular exercise matters in Parkinson's disease: results from the National Parkinson Foundation QII registry study. Park Relat Disord 2014;20(11):1221–5.
[11] Sacheli MA, Neva JL, Lakhani B, Murray DK, Vafai N, Shahinfard E, et al. Exercise increases caudate dopamine release and ventral striatal activation in Parkinson's disease. Mov Disord 2019;34(12):1891–900.
[12] Lau YS, Patki G, Das-Panja K, Le WD, Ahmad SO. Neuroprotective effects and mechanisms of exercise in a chronic mouse model of Parkinson's disease with moderate neurodegeneration. Eur J Neurosci 2011;33(7):1264–74.
[13] Zhou W, Barkow JC, Freed CR. Running wheel exercise reduces alpha-synuclein aggregation and improves motor and cognitive function in a transgenic mouse model of Parkinson's disease. PLoS One 2017;12(12):e0190160.
[14] Ferrer-Martínez A, Ruiz-Lozano P, Chien KR. Mouse PeP: a novel peroxisomal protein linked to myoblast differentiation and development. Dev Dynam 2002;224(2):154–67.
[15] Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA, Boström EA, Choi JH, Long JZ, Kajimura S, Zingaretti MC, Vind BF, Tu H, Cinti S, Højlund K, Gygi SP, Spiegelman BM. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 2012;481(7382):463–8.
[16] Stratigou T, Dalamaga M, Antonakos G, Marinou I, Vogiatzakis E, Christodoulatos GS, Karampela I, Papavassiliou AG. Hyperirisinemia is independently associated with subclinical hypothyroidism: correlations with cardiometabolic biomarkers and risk factors. Endocrine 2018;61(1):83–93.
[17] Hroussalas G, Kassi E, Dalamaga M, Delimaris I, Zachari A, Dionyssiou-Asteriou A. Leptin, soluble leptin receptor, adiponectin and resistin in relation to OGTT in overweight/obese postmenopausal women. Maturitas 2008;59:339–49.
[18] Marouga A, Dalamaga M, Kastania AN, Antonakos G, Thrasyvoulides A, Kontelia G, et al. Correlates of serum resistin in elderly, non-diabetic patients with chronic kidney disease. Clin Lab 2013;59:1121–8.
[19] Tsigalou C, Vallianou N, Dalamaga M. Autoantibody production in obesity: is there evidence for a link between obesity and autoimmunity? Curr Obes Rep 2020;9(3):245–54.
[20] Koliaki C, Liatis S, Dalamaga M, Kokkinos A. The implication of gut hormones in the regulation of energy homeostasis and their role in the pathophysiology of obesity. Curr Obes Rep 2020;9(3):255–71.
[21] Vallianou N, Dalamaga M, Stratigou T, Karampela I, Tsigalou C. Do antibiotics cause obesity through long-term alterations in the gut microbiome? A review of current evidence. Curr Obes Rep 2021;10(3):244–62.
[22] Kassi E, Dalamaga M, Hroussalas G, Kazanis K, Merantzi G, Zachari A, Giamarellos-Bourboulis EJ, Dionyssiou-Asteriou A. Adipocyte factors, high-sensitive C-reactive protein levels and lipoxidative stress products in overweight postmenopausal women with normal and impaired OGTT. Maturitas 2010;67(1):72–7.
[23] Dalamaga M, Karmaniolas K, Chamberland J, Nikolaidou A, Lekka A, Dionyssiou-Asteriou A, Mantzoros CS. Higher fetuin-A, lower adiponectin and free leptin levels mediate effects of excess body weight on insulin resistance and risk for myelodysplastic syndrome. Metabolism 2013;62(12):1830–9.
[24] Dionyssiou-Asteriou A, Mantzoros CS. Circulating adiponectin and leptin in relation to myelodysplastic syndrome: a case-control study. Oncology 2007;73(1–2):26–32.
[25] Karampela I, Kandri E, Antonakos G, Vogiatzakis E, Christodoulatos GS, Nikolaidou A, Dimopoulos G, Armaganidis A, Dalamaga M. Kinetics of circulating fetuin-A may predict mortality independently from adiponectin, high molecular weight adiponectin and prognostic factors in critically ill patients with sepsis: a prospective study. J Crit Care 2017;41:78–85.
[26] Papadavid E, Katsimbri P, Kapniari I, Koumaki D, Karamparpa A, Dalamaga M, Tzannis K, Boumpas D, Rigopoulos D. Prevalence of psoriatic arthritis and its correlates among patients with psoriasis in Greece: results from a large retrospective study. J Eur Acad Dermatol Venereol 2016;30(10):1749–52.
[27] Dalamaga M, Crotty BH, Fargnoli J, Papadavid E, Lekka A, Triantafilli M, Karmaniolas K, Migdalis I, Dionyssiou-Asteriou A, Mantzoros CS. B-cell chronic lymphocytic leukemia risk in association with serum leptin and adiponectin: a case-control study in Greece. Cancer Causes Control 2010;21(9):1451–9.
[28] Spyrou N, Vallianou N, Kadillari J, Dalamaga M. The interplay of obesity, gut microbiome and diet in the immune check point inhibitors therapy era. Semin Cancer Biol 2021;73:356–76.
[29] Karampela I, Vallianou N, Magkos F, Apovian CM, Dalamaga M. Obesity, hypovitaminosis D, and COVID-19: the Bermuda triangle in public health. Curr Obes Rep 2022;11(3):116–25.
[30] Paroutoglou K, Papadavid E, Christodoulatos GS, Dalamaga M. Deciphering the association between psoriasis and obesity: current evidence and treatment considerations. Curr Obes Rep 2020;9:165–78.
[31] Dalamaga M, Christodoulatos GS, Karampela I, Vallianou N, Apovian CM. Understanding the co-epidemic of obesity and COVID-19: current evidence, comparison with previous epidemics, mechanisms, and preventive and therapeutic perspectives. Curr Obes Rep 2021;10:214–43.
[32] Tsilingiris D, Vallianou NG, Karampela I, Dalamaga M. Vaccine induced thrombotic thrombocytopenia: the shady chapter of a success story. Metabol Open 2021;11:100101.
[33] Kritis P, Karampela I, Kokoris S, Dalamaga M. The combination of bromelain and curcumin as an immune-boosting nutraceutical in the prevention of severe COVID-19. Metabol Open 2020;8:100066.
[34] Vallianou NG, Tsilingiris D, Kounatidis D, Lempesis IG, Karampela I, Dalamaga M. Sodium-glucose cotransporter-2 inhibitors in obesity and associated cardiometabolic disorders: where do we stand? Pol Arch Intern Med 2022;132.
[35] Dalamaga M, Papadavid E, Basios G, Vaggopoulos V, Rigopoulos D, Kassanos D, Trakakis E. Ovarian SAHA syndrome is associated with a more insulin-resistant profile and represents an independent risk factor for glucose abnormalities in

women with polycystic ovary syndrome: a prospective controlled study. J Am Acad Dermatol 2013;69(6):922–30.
[36] Karampela I, Christodoulatos GS, Dalamaga M. The role of adipose tissue and adipokines in sepsis: inflammatory and metabolic considerations, and the obesity paradox. Curr Obes Rep 2019;8(4):434–57.
[37] Dalamaga M, Pantelaki M, Karmaniolas K, Daskalopoulou K, Migdalis I. Isolation of Leclercia adecarboxylata from blood and burn wound after a hydrofluoric acid chemical injury. Burns 2009;35(3):443–5.
[38] Dalamaga M, Pantelaki M, Karmaniolas K, Matekovits A, Daskalopoulou K. Leg ulcer and bacteremia due to Cedecea davisae. Eur J Dermatol 2008;18(2):204–5.
[39] Ma Y, Ajnakina O, Steptoe A, Cadar D. Higher risk of dementia in English older individuals who are overweight or obese. Int J Epidemiol 2020;49(4):1353–65.
[40] Pedditzi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. Age Ageing 2016;45(1):14–21.
[41] Guo Y, Xu W, Liu F-T, Li J-Q, Cao X-P, Tan L, Wang J, Yu J-T. Modifiable risk factors for cognitive impairment in Parkinson's disease: a systematic review and meta-analysis of prospective cohort studies. Mov Disord : Off J Mov Dis Soc 2019;34(6):876–83.
[42] Maak S, Norheim F, Drevon CA, Erickson HP. Progress and challenges in the biology of FNDC5 and irisin. Endocr Rev 2021;42(4):436–56.
[43] Lempesis IG, Tsilingiris D, Liu J, Dalamaga M. Of mice and men: considerations on adipose tissue physiology in animal models of obesity and human studies. Metabol Open 2022;15:100208.
[44] Dalamaga M, Karmaniolas K, Matekovits A, Migdalis I, Papadavid E. Cutaneous manifestations in relation to immunologic parameters in a cohort of primary myelodysplastic syndrome patients. J Eur Acad Dermatol Venereol 2008;22(5):543–8.
[45] Kam TI, Park H, Chou SC, Van Vranken JG, Mittenbuhler MJ, Kim H, et al. Amelioration of pathologic alpha-synuclein-induced Parkinson's disease by irisin. Proc Natl Acad Sci U S A 2022;119(36):e2204835119.
[46] Rabiee F, Lachinani L, Ghaedi S, Nasr-Esfahani MH, Megraw TL, Ghaedi K. New insights into the cellular activities of Fndc5/Irisin and its signaling pathways. Cell Biosci 2020;10:51.
[47] Lourenco MV, Frozza RL, de Freitas GB, Zhang H, Kincheski GC, Ribeiro FC, et al. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat Med 2019;25(1):165–75.
[48] Kim H, Wrann CD, Jedrychowski M, Vidoni S, Kitase Y, Nagano K, Zhou C, Chou J, Parkman VA, Novick SJ, Strutzenberg TS, Pascal BD, Le PT, Brooks DJ, Roche AM, Gerber KK, Mattheis L, Chen W, Tu H, Bouxsein ML, Griffin PR, Baron R, Rosen CJ, Bonewald LF, Spiegelman BM. Irisin mediates effects on bone and fat via αV integrin receptors. Cell 2018;175(7):1756–68. e17.
[49] Pankratz N, Byder L, Halter C, Rudolph A, Shults CW, Conneally PM, et al. Presence of an APOE4 allele results in significantly earlier onset of Parkinson's disease and a higher risk with dementia. Mov Disord 2006;21(1):45–9.
[50] Mao X, Ou MT, Karuppagounder SS, Kam TI, Yin X, Xiong Y, et al. Pathological alpha-synuclein transmission initiated by binding lymphocyte-activation gene 3. Science 2016;353(6307).
[51] Dehghan F, Zamani S, Barreiro C, Jami MS. Irisin injection mimics exercise effects on the brain proteome. Eur J Neurosci 2021;54(10):7422–41.
[52] Wareham LK, Liddelow SA, Temple S, Benowitz LI, di Polo A, Wellington C, Goldberg JL, He Z, et al. Solving neurodegeneration: common mechanisms and strategies for new treatments. Mol Neurodegener 2022;17(1):23.
[53] Soto C, Pritzkow S. Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. Nat Neurosci 2018;21(10):1332–40.
[54] Kapogiannis D, Avgerinos KI. Brain glucose and ketone utilization in brain aging and neurodegenerative diseases. Int Rev Neurobiol 2020;154:79–110.
[55] López-Ortiz S, Valenzuela PL, Seisdedos MM, Morales JS, Vega T, Castillo-García A, Nisticò R, et al. Exercise interventions in Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. Ageing Res Rev 2021;72:101479.
[56] Dauwan M, Begemann MJH, Slot MIE, Lee EHM, Scheltens P, Sommer IE. Physical exercise improves quality of life, depressive symptoms, and cognition across chronic brain disorders: a transdiagnostic systematic review and meta-analysis of randomized controlled trials. J Neurol 2021;268(4):1222–46.
[57] Ströhle A, Schmidt DK, Schultz F, Fricke N, Staden T, Hellweg R, et al. Drug and exercise treatment of alzheimer disease and mild cognitive impairment: a systematic review and meta-analysis of effects on cognition in randomized controlled trials. Am J Geriatr Psychiatr: Off J Am Assoc Geriatr Psychiatr 2015;23(12):1234–49.
[58] Lourenco MV, Ribeiro FC, Sudo FK, Drummond C, Assunção N, Vanderborght B, Tovar-Moll F, Mattos P, De Felice FG, Ferreira ST. Cerebrospinal fluid irisin correlates with amyloid-β, BDNF, and cognition in Alzheimer's disease. Alzheimers Dement (Amst) 2020;12(1):e12034.
[59] Wrann CD, White JP, Salogiannnis J, Laznik-Bogoslavski D, Wu J, Ma D, Lin JD, Greenberg ME, Spiegelman BM. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell Metabol 2013 Nov 5;18(5):649–59.
[60] Ruiz-González D, Hernández-Martínez A, Valenzuela PL, Morales JS, Soriano-Maldonado A. Effects of physical exercise on plasma brain-derived neurotrophic factor in neurodegenerative disorders: a systematic review and meta-analysis of randomized controlled trials. Neurosci Biobehav Rev 2021;128:394–405.
[61] Huang H, Li W, Qin Z, Shen H, Li X, Wang W. Physical exercise increases peripheral brain-derived neurotrophic factors in patients with cognitive impairment: a meta-analysis. Restor Neurol Neurosci 2021;39(3):159–71.
[62] Wrann CD. FNDC5/irisin - their role in the nervous system and as a mediator for beneficial effects of exercise on the brain. Brain Plast 2015;1(1):55–61.

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