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REVIEW

Exercise-Induced Autophagy Ameliorates Motor Symptoms Progressivity in Parkinson's Disease Through Alpha-Synuclein Degradation: A Review

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Abstract: This study reviews the molecular mechanism of exercise-induced autophagy/mitophagy and its possible mechanism in delaying motor symptoms progressivity in Parkinson's disease (PD). Relevant articles obtained from PubMed and EBSCOhost were reviewed. After analyzing the articles, it was found that autophagy can be induced by exercise and can possibly be activated through the AMPK-ULK1 pathway. Mitophagy can also be induced by exercise and can possibly be activated through PINK1/Parkin pathway and AMPK-dependent pathway. Moreover, exercise-induced autophagy can decrease the accumulation of toxic α-synuclein aggregates in PD and therefore can delay motor symptoms progressivity.

Keywords: exercise, autophagy, Parkinson's disease, alpha-synuclein

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease.[1] Over the years, the number of people affected by PD is growing, which is correlated with the increase in life expectancy.[2] PD is related to the loss of dopaminergic neurons of the substantia nigra pars compacta (SNc), which causes progressive motor symptoms.[3] The cardinal motor manifestations are bradykinesia, rigidity and rest tremor.[4] Progressive and worsening mobility impairment in PD has been associated with a decline in the quality of life of a patient.[5]

The pathological hallmark of PD is the presence of Lewy bodies, which mainly consist of α-synuclein aggregates.[6] α-Synuclein aggregates are toxic and could lead to dopaminergic neuron death.[6,7] α-Synuclein aggregates may also self-propagate to healthy neurons, resulting in the progression of neuronal loss.[6,8] Upregulation of autophagy, a cellular system that transports unneeded components to lysosome for degradation, could be neuroprotective in PD by withholding α-synuclein toxicity.[9,10] There are three types of autophagy described in mammals: microautophagy, macroautophagy, and chaperone-mediated autophagy.[11] Of the three, macroautophagy (hereafter referred to as autophagy) is best understood.[12] Furthermore, there is a selective macroautophagy that has specific cytosolic components for degradation such as mitophagy that targeted mitochondrial removal.[11]

Presently, levodopa and other pharmacological dopamine substitution therapies are the mainstays of PD symptomatic treatment.[3] However, long-term use of it is related to several side effects and wearing-off phenomenon.[13,14] Therefore, studies are being done to discover new ways to delay PD progression and improve symptoms using a mechanism different from conventional PD treatment. Among the studied mechanisms are autophagy and mitophagy induction. Autophagy and mitophagy can be induced in several ways; however, this review will only focus on discussing the activation of autophagy and mitophagy via exercise.

Exercise is known to provide a neuroprotective effect in multiple ways such as inducing autophagy, causing neuronal plasticity, employing neurogenesis and decreasing neurodegeneration.[15] Studies have shown that exercise improved

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motor functions in patients with PD compared to sedentary patients with PD and has been proposed to modify the progressive course of PD.[13,16] Thus, to understand more about the effect of exercise-induced autophagy in delaying motor symptoms progressivity in PD, a literature review was conducted. This review aims to elucidate the molecular mechanism of exercise-induced autophagy and/or mitophagy and its correlation with PD pathology.

Methods

Works of literature were searched via advanced search in PubMed and EBSCOhost with the combined keywords: "parkinson", "exercise", "autophagy", "mitophagy", "autophagosome", "synuclein", and "synuclein clearance". The limits apply to the search were original article in vivo studies and those published between 2010 and 2023.

Results and Discussion

PubMed and EBSCOhost were searched for studies published between 2010 and 2023 with the combination of keywords mentioned above. The works of literature were chosen based on the PRISMA 2020 flow diagram as stated in Figure 1. Ten literatures were included.

Molecular Mechanism of Exercise-Induced Autophagy

Exercise resulted in an imbalance of energy demand to energy supply, an increase in the AMP-to-ATP ratio, and an increase in reactive oxygen species (ROS) production.[18] During exercise, ATP consumption increases, which causes the accumulation of intracellular AMP; this then leads to an increase in the AMP-to-ATP ratio, which would then activate AMP-activated protein kinase (AMPK).[18–20] AMPK regulates various metabolic pathways, one of which is autophagy.

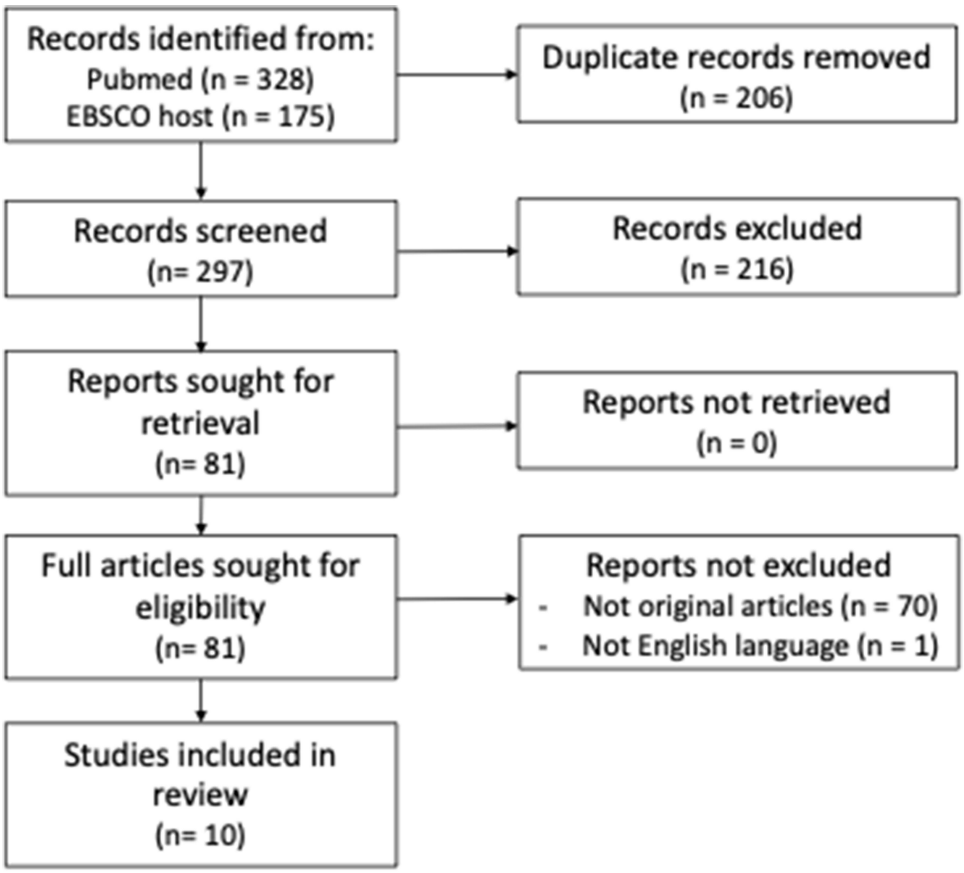

Figure 1 PRISMA 2020 flow diagram of the literature search of this review.
Notes: PRISMA figure adapted from Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Systematic Reviews*. 2022;18:e1230.[17] doi: 10.1002/cl2.1230

Schwalm et al[21] found that in human skeletal muscle, exercise-induced autophagy depends on AMPK activation. Similar findings were seen in the studies by Møller et al[22] and Fritzen et al,[19] which gave insight that AMPK activation in skeletal muscle would then activate Unc-51-like kinase-1 (ULK1) through a site-specific phosphorylation.[19,22] ULK1 is a protein kinase that has a significant role in initiating autophagy.[22] Another important role of AMPK is its ability to inhibit the mammalian target of the rapamycin complex 1 (mTORC1) pathway through phosphorylation on tuberous sclerosis complex 2 (TSC2) and the mTOR binding partner raptor.[23] MTORC1 inhibition is important to initiate the autophagy process.

The next step after the initiation of autophagy is the formation of phagophore, a cytosolic double membrane that will mature into autophagosome. Several in vitro studies showed that upon ULK1 activation, the VPS34 complex is activated. VPS34 complex is a class III phosphoinositide 3-kinase (PI3K) in mammals and can phosphorylate phosphatidylinositol leading to phosphatidylinositol 3-phosphate (PI3P) generation.[24–26] PI3P promotes phagophore expansion through WD-repeat domain phosphoinositide-interacting protein 2 (WIPI2).[27] The final step of autophagosome maturation is microtubule-associated protein 1A/1b-light chain 3 (LC3) lipidation, which refers to the conjugation of phosphatidylethanolamine (PE) to LC3-I forming LC3-PE/LC3-II.[28] Hence, the LC3-II protein is known as a key autophagic marker; it is often measured in studies as indicators of autophagy activity.[18,28] Other autophagic markers commonly measured as indicators of autophagy activity are p62, Beclin1, and LAMP2.[29,30] Autophagosome will then fuse with lysosome, which results in autophagosome's cargo degradation by hydrolase enzymes of lysosome.

Molecular Mechanism of Exercise-Induced Mitophagy

As the powerhouse of cell, mitochondria play a crucial role in the metabolism process of cell. Mitochondrial homeostasis and function need to be controlled at all times, therefore there is a pathway called mitochondrial quality control (MQC). One of the critical pathways of MQC is the phosphatase and tensin homolog-induced putative kinase 1 (PINK1) and Parkin pathway.[31] In healthy mitochondria, PINK1 is cleared from the outer mitochondrial membrane (OMM) by importing it to the inner mitochondrial membrane before it is cleaved and degraded. In dysfunctional mitochondria, PINK1 accumulates in OMM due to its inability to translocate to the inner membrane.[32] Accumulation of PINK1 will then recruit Parkin and initiate the cascade of mitophagy.[31] Exercise could induce mitophagy with the activation of PINK1/Parkin pathway stated above or independently from PINK1/Parkin pathway.

Exercise induces the secretion of irisin, a peptide that is cleaved from fibronectin type III domain-containing protein 5 (FNDC-5). Recently, it has been reported that there is an increase of irisin in the brain tissue of a mice after it was given exercise.[33] Irisin and PINK1/Parkin pathway correlate positively as shown by the study of He et al[34] and Li et al.[35] Therefore, mitophagy is known to be inducible by exercise through the FNDC5/irisin-PINK1/Parkin pathway. However, other study has shown that mitophagy can be induced by exercise independently from the PINK1/Parkin pathway. Seabright et al[36] and Drake et al[37] reported mitophagy regulation via the AMPK-dependent pathway. This pathway is similar to the activation of autophagy mentioned above. The rise of AMP-to-ATP ratio inside the mitochondria will cause mitochondrial energetic stress which then activates mitoAMPK and phosphorylates ULK1 causing the activation of mitophagy cascade.[37]

The Relationship Between Autophagy/Mitophagy and PD Pathology

The progression of PD symptoms is suspected due to the progression of α-synuclein pathology in SNc. α-Synuclein is a small, 140-amino acid presynaptic protein. Physiologically, α-synuclein has a structure of an unfolded monomer or a helix form, with the function of regulating neurotransmitter release in the synaptic terminals.[38] Due to disease-associated mechanisms, both isoforms can misfold and aggregate forming a higher-molecular-weight protofibrils, which can polymerize forming an amyloid fibril found in Lewy bodies of patients with PD.[6] α-Synuclein aggregates are toxic and can lead to dopaminergic neuron death.[6,7]

α-Synuclein aggregates neurotoxicity in PD occurs intracellularly and extracellularly. Intracellularly, α-synuclein aggregates disrupt membrane integrity by creating a pore in the lipid bilayer of the cell membrane which causes in an influx of ions from extracellular space that could lead to cell death.[7] Extracellularly, α-synuclein aggregates are known to activate microglial cells that could then result in an abundant ROS production causing oxidative stress and eventually

neuronal loss. Another thing α-synuclein is believed to be able to do extracellularly is propagate between cells. This implies that the neurotoxicity brought on by α-synuclein aggregate can propagate from one neuron to another, explaining the progression of PD.[7] Furthermore, α-synuclein aggregates can cause disturbance in synaptic transport, causing further dopamine homeostasis disturbance.[39]

Another main cause of neuronal death in PD is mitochondrial dysfunction, which occurs both in sporadic PD and familial PD. In sporadic PD, mitochondrial dysfunction occurs due to the overproduction of ROS as well as the disruptions in the mitochondrial complex activity.[7] In familial PD, mitochondrial dysfunction happens early in the onset of the disease since most of the proteins encoded by PD-related genes are correlated with mitochondrial function.[40]

Therefore, autophagy as a system involved in dysfunctional protein degradation can be beneficial in PD by degrading α-synuclein aggregates. With fewer α-synuclein aggregates, there might be a potential PD motor symptoms' progression delay. In vivo and in vitro studies have shown that autophagy activation contributed to the decrease in α-synuclein aggregates accumulation.[8,41,42] Gao et al[8] demonstrated the improvements of α-synuclein aggregate accumulation in human neural cells treated with α-synuclein fibrils after the intervention. Cells were given small-molecule AMPK activators, and afterward, there were significantly reduced α-synuclein inclusions levels, associated with the changes of key autophagic markers indicating autophagy involvement in the clearance process induced via AMPK activation.[8] By contrast, inhibition of autophagy halted α-synuclein aggregate clearance. This was shown from the studies of Gao et al[8] and Masaracchia et al,[42] which reported that α-synuclein-treated neural cells that were given autophagy inhibitor substances, such as bafilomycin or chloroquine, resulted in the inhibition of α-synuclein aggregate degradation resulting in its accumulation intracellularly.

Besides autophagy, the activation of mitophagy may also be beneficial in delaying PD progression considering that the degradation of dysfunctional mitochondria will reduce the burden of mitochondrial stress inside SNc cells, thus decreasing the accumulation of ROS and increasing the turnover of mitochondrial cells to support mitochondrial homeostasis. Ivankovic et al[43] reported that after the induction of PINK1/Parkin mediated mitophagy in human neuroblastoma SH-SY5Y, transcription factors Nrf2 and TFEB were activated. Nrf2 and TFEB are known to be involved in mitochondrial biogenesis, lysosomal biogenesis, and exert antioxidant effects. Therefore, the induction of mitophagy in PD could possibly protect mitochondria from further oxidative stress damage through its antioxidant effects, and replace dysfunctional mitochondria with newer functional mitochondria through its mitochondrial biogenesis ability.[43]

Because of its effects, autophagy and mitophagy activation becomes a promising therapeutic potential in PD treatment by decreasing α-synuclein aggregates and improving mitochondrial homeostasis. Studies have shown that exercise can induce autophagy/mitophagy in the brain, which leads to neuroprotective effects.[44–47] This review focused on exercise-induced autophagy and mitophagy as a nonpharmacological approach of PD treatment. Figures 2 and 3 conclude a possible mechanism of how exercise-induced autophagy and mitophagy led to motor improvement in PD.

Current Perspective of Exercise-Induced Autophagy and Mitophagy from Experimental Studies

It was evident from animal studies that exercise can lead to a decrease of α-synuclein accumulation, and it was associated with motor function improvements. Although still limited, in recent years, studies are emerging to support the notion that autophagy or mitophagy activation is involved in exerting this beneficial effect. Table 1 summarizes the study findings from five articles.

A study by Koo and Cho in 2017 found that treadmill exercise alleviates dopaminergic neuron loss in animals with PD and it was correlated to autophagy activation. In the study, mice were injected with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and probenecid to induce PD; afterward, the mice were given mild-to-moderate-intensity treadmill exercise for 8 weeks (5 days/week).[48] The results were a significant reduction in α-synuclein levels and dopaminergic neuron loss, along with motor deficits improvements in the PD model mouse compared to the sedentary control. It was also noted that the reduction of α-synuclein is likely due to the increase of autophagic flux, as this was evidenced by the increase of autophagic marker, LC3-II. Afterward, studies by Jang et al,[49] Liu et al,[50] and Jang et al[51] also come up with similar results, in which aerobic exercise increased motoric function, as well as decreased α-synuclein and increased autophagic marker. Although several important autophagy-inducing proteins (eg, AMPK, ULK1) are not measured, these studies are still in line with our

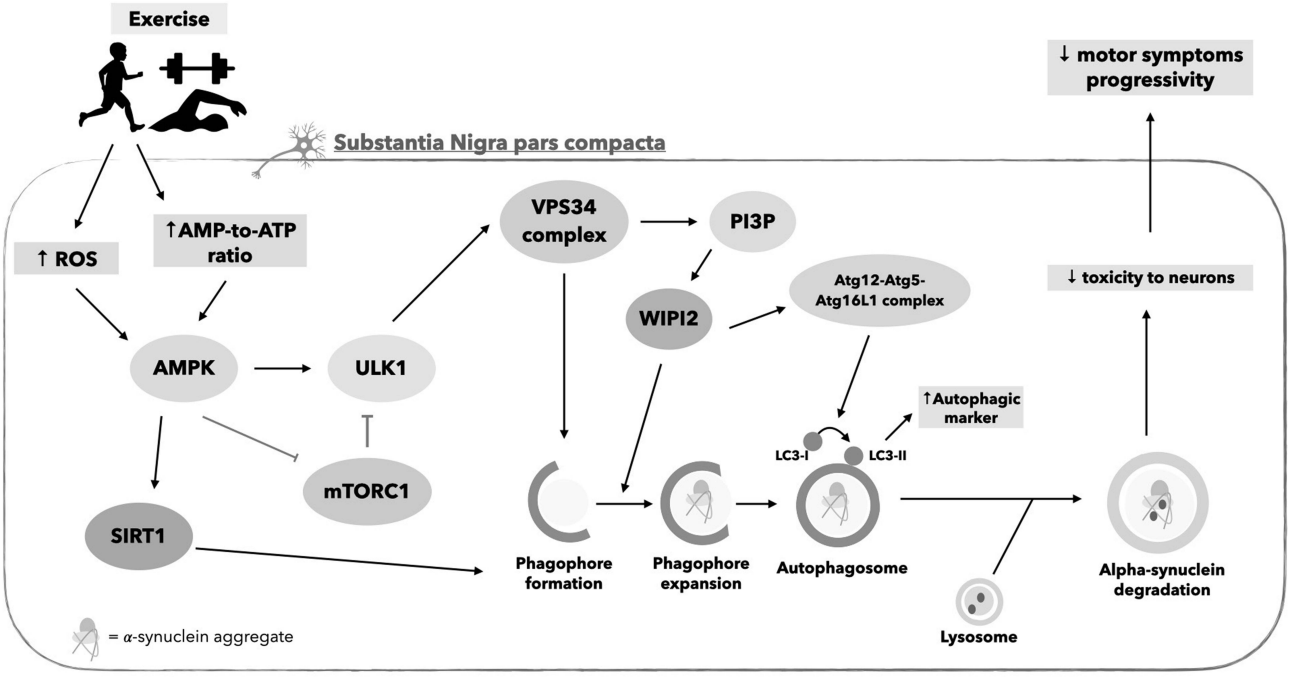

Figure 2 Possible mechanism of exercise-induced autophagy through the AMPK-ULK1 pathway to slow PD progression by decreasing synuclein accumulation.

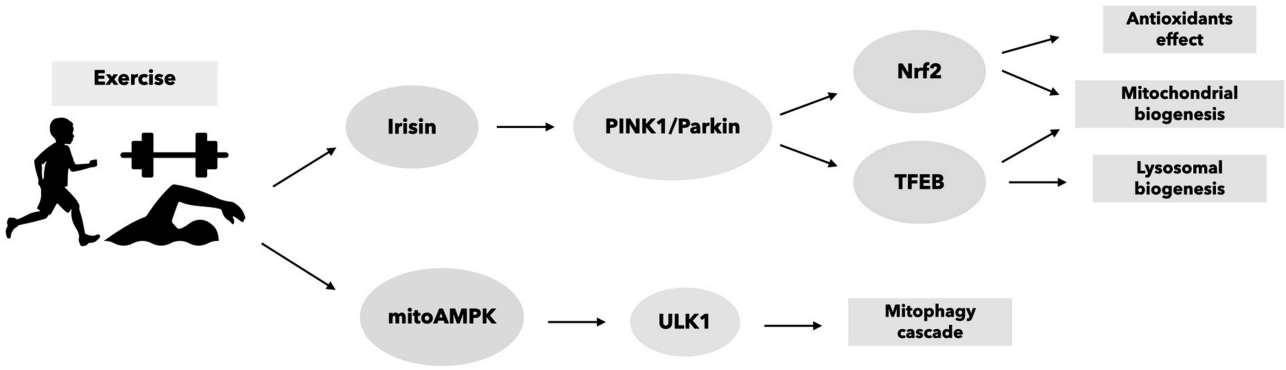

Figure 3 Possible mechanism of exercise-induced mitophagy through the PINK1/Parkin pathway and AMPK-dependent pathway.

propose mechanism of exercise-induced autophagy (Figure 2) because the end-result of autophagy are measured by quantifying several autophagic markers such as LC3-II, Beclin and p62. We also found four other studies that reported the beneficial effect of exercise in PD animal model, ie, alleviating motor deficits and decreasing α-synuclein accumulation; however, the role of autophagy in causing this effect cannot be proven yet from these studies because the autophagic marker was not assessed. The findings of the studies are summarized in Table 2.

As for exercise-induced mitophagy involvement in PD, we found only two studies that discuss this matter. In 2017, a study by Almeida et al[52] found that moderate exercise decreased the accumulation of α-synuclein in rotenone-injected rats and it was associated with the improvement of mitophagy activity. In 2018, Hwang et al[41] also found similar findings, which showed significant improvement of motor behaviour and decreased of α-synuclein accumulation in rotenone-injected rats after exercise, associated with the improvement of mitophagy flux.

Interestingly, there are previous studies that fail to observe an increase in tyrosine hydroxylase (TH) expression in the PD animal model after given exercise, although there is a significant improvement in motoric function.[53,54] These result differences are maybe due to the variation in exercise duration and intensity. It is suggested that exercise with mild intensity and shorter duration might not be sufficient to induce neuroprotective effects. This result emphasizes how

Table 1 Summary of Studies about Exercise Modulate Autophagy and Mitophagy in PD model

Reference	Subject	Intervention for Exercise Group	Outcome
In vivo studies using PD animal model			
Liu et al 2020[50]	Young (3-months), Middle-aged (13-months) and Aged (23-months-old) male rats divided to 5 groups: – Young sedentary group (n=10) – Middle-aged sedentary group (n=12) – Aged sedentary group (n=40) – Middle-aged 6-OHDA-injected group (n=18) – Middle-aged 6-OHDA-injected + exercise group (n=22)	Frequency: 5 days/week for 8 weeks. Intensity: 15–20 m/minute (moderate intensity) Type: Treadmill exercise Time: 14–40 minutes	– ↑ motor function (reduced rotation in apomorphine-injected behavioral rotation test) – SNc and striatum: ↓α-synuclein, ↑TH, ↑LC3-II, ↑Beclin1 protein expression
Hwang et al 2018[41]	8-week-old male mice divided to 3 groups (n = 10 each): – Control group – MPTP-injected group –MPTP-injected + exercise group	Frequency: 5 days/week for 8 weeks Intensity: Mild-to-moderate intensity Type: Treadmill exercise Time: 40 minutes	– ↓ Motor deficit (increase retention time in rota-rod test) – SNc: ↓α-synuclein, ↑TH, ↓PINK1, ↓Parkin, ↓LC3-II/LC3-I ratio, ↓p62 protein expression – Striatum: ↓α-synuclein protein expression
Y. C. Jang et al 2018[49]	7-week-old male mice divided to 3 groups (n = 10 each): – Control group – MPTP-injected group – MPTP-injected + exercise group	Frequency: 5 days/week for 8 weeks Intensity: 10m/min (mild intensity) Type: Treadmill exercise Time: 60 minutes	– ↑ Motor function (increase retention time in rota-rod test) – SNc: ↓α-synuclein, ↑TH, ↑LC3-II, ↓p62, ↑Beclin1, ↑BNIP3 protein expression
Jang, Kwon, Song, Cosio-Lima, and Lee, 2018[51]	7-week-old male mice divided to 4 groups (n = 12 each): – Control group – Exercise group – MPTP-injected group –MPTP-injected + exercise group	Frequency: 5 days/week for 6 weeks Intensity: 10m/min (mild intensity) Type: Treadmill exercise Time: 60 minutes	– ↑ Motor function (decrease time to turn heads from upside to downside and to reach the floor in pole test) – SNc: ↑TH, ↑DAT, ↑Beclin1, ↑BNIP3, ↑LC3-II protein expression
Almeida et al 2017[52]	11-month-old male rats divided to 4 groups (n = 5 each): – Control group – Exercise group –Rotenone-injected group – Rotenone-injected + exercise group	Frequency: 5 days/week for 6 weeks Intensity: Moderate intensity Type: Treadmill exercise Time: 40 minutes	– SNc: ↓α-synuclein, ↑TH, ↑Beclin1, ↑PINK1, ↓LC3-II protein expression
Koo and Cho 2017[48]	7-week-old male mice divided to 3 groups (n = 9 each): – Control group – MPTP-injected group –MPTP-injected + exercise group	Frequency: 5 days/week for 8 weeks Intensity: 10–12m/min (mild-to-moderate intensity) Type: Treadmill exercise Time: 40–60 min	– ↑ Motor function (increase retention time in rota-rod test) – SNc and striatum: ↓α-synuclein, ↑TH, ↑DAT, ↑Beclin1, ↑LC3-II, ↓p62 protein expression

Table 2 Summary of Exercise Effects on Motor Function in PD Model

Reference	Subject	Intervention for Exercise Group	Outcome
In vivo studies using PD animal model			
Koo et al 2017[58]	7-week-old male mice divided to 3 groups (n = 10 each): – Control group – MPTP-injected group – MPTP-injected + exercise group	Frequency: 5 days/week for 8 weeks Intensity: 10m/min (mild intensity) Type: Treadmill exercise Time: 60 minutes	– ↑ Motor function (increase retention time in rota-rod test) – SNc: ↓α-synuclein, ↑TH, ↑DAT protein expression
Shin, Kim, Lee, Ji, and Lim 2017[59]	6-week-old male rats divided to 4 groups (n = 10 each): – Control group – Exercise group –Rotenone-injected group – Rotenone-injected + exercise group	Frequency: 14 consecutive days Intensity: Mild intensity Type: Treadmill exercise Time: 30 minutes	– ↑ Motor function (increase retention time in rota-rod test) – SNc: ↓α-synuclein, ↑TH protein expression – Striatum: ↓α-synuclein protein expression
Jang et al 2017[60]	3-month-old male mice divided to 3 groups (n = 10 each): – Control group – MPTP-injected group –MPTP-injected + exercise group	Frequency: 5 days/week for 8 weeks Intensity: 10m/min (mild intensity) Type: Treadmill exercise Time: 60 minutes	– ↑ Motor function (increase retention time in rota-rod test) – SNc: ↓α-synuclein, ↑TH protein expression
Tuon et al 2012[61]	2-month-old male rats divided to 4 groups (n = 8 each): – Control group – Exercise group –6-OHDA-injected group – 6-OHDA-injected + exercise group	Frequency: 3–4 days/week for 8 weeks Intensity: 13–17 m/min (mild-to-moderate intensity) Type: Treadmill exercise Time: 50 minutes	– ↑ Motor function (reduced rotation in apomorphine-injected behavioral rotation test) – Striatum: ↓α-synuclein protein expression

crucial it is to select the most suitable exercise program in order to realize its benefits. The analysis of animal studies listed in Table 1 shows that the possible exercise regimen to exert neuroprotective effects through exercise-induced autophagy is a mild-to-moderate- or moderate-intensity exercise, 5 days/week, 40 min for each session, and with a minimum of 6-week duration.[51] Nevertheless, to find the best regimen, further studies are still necessary considering that our recommendation is only based on animal studies and very few articles.

To our knowledge, there has not been any human study regarding exercise-induced autophagy/mitophagy in PD. However, there have been several human studies that analyzed the effect of exercise on PD motor symptoms. A Cochrane systematic review by Mehrholz et al[55] stated that treadmill exercise in patients with PD may improve gait speed. A recent meta-analysis and systematic review by Choi et al[13] also showed that aerobic exercise showed a significant effect on motor symptoms and balance in patients with PD in comparison with patients with no exercise regimen. A review by Kim et al[56] identified the recommended exercise regimen for adults with PD from existing literature and guidelines. The exercise regimen recommendation is moderate-intensity exercise, 3–5 days/week, with a duration of 20 min for each session that should gradually progress to 60 min over time. The type of activity should be tailored to the patient's condition and preference; several activity options include walking (overground or treadmill), ergometry, and aquatics (swimming or other aquatic exercises). Overall, this exercise recommendation is similar to the ones we proposed above.

Intriguingly, exercise training given to patients prior to PD onset also resulted in delayed motor symptoms when compared to sedentary control. In a study by Liu et al,[50] rats were given 8 weeks of moderate-intensity treadmill exercise and afterward were administered with 6-OHDA. In the analysis, it was noted that the exercise group in comparison with the sedentary group has an improvement in motor function. Although still inconsistent, several studies involving humans also support the notion that exercise not only improves the symptoms of PD but may also reduce the risk of PD.[57]

Conclusions

Our review shows that autophagy can be induced by exercise and can possibly be activated through the AMPK-ULK1 pathway; moreover, there has been evidence in vivo and in vitro that exercise-induced autophagy could decrease the accumulation of toxic α-synuclein aggregates in PD. Mitophagy can also be induced by exercise via PINK1/Parkin pathway and AMPK-dependent pathway, and can improve mitochondrial homeostasis in PD. There has been evidence of beneficial exercise effects on PD in humans. However, there is currently no human study to back up our proposed molecular mechanism of exercise-induced autophagy/mitophagy, which ameliorates PD motor symptoms. Thus, future research is needed to assess the changes of autophagy and mitophagy process in brain during exercise.

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Disclosure

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