CHAPTER TWO

Exercise and Parkinson's disease

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Abstract

Parkinson's disease (PD) is one of the most common neurodegenerative diseases in the world. Unfortunately, most of the currently used clinical therapies against PD are symptomatic and there is still no remedy can stop disease progression. Collective evidence shows that various kinds of exercise may reduce the risk of PD and do have positive impacts on both motor and nonmotor symptoms of PD. Additionally, exercise can also ameliorate the side effects such as wearing-off and dyskinesia induced by anti-PD therapeutics. In parallel with its benefits in ameliorating clinical symptoms, exercise modulates a range of supporting systems for brain maintenance and plasticity including neurogenesis, synaptogenesis, enhanced metabolism and angiogenesis. Exercise provides all these broad benefits on PD through inhibiting oxidative stress, repairing mitochondrial damage, and promoting the production of growth factors. Moreover, exercise reduces risk of other geriatric diseases such as diabetes, hypertension and cardiovascular disease, which may also contribute to PD pathogenesis. In summary, exercise is increasingly considered to be a complementary strategy to PD medications. In this chapter, we summarize the recent research progress on the beneficial effects of exercise on PD, discuss the underlying mechanisms, and highlight the promising prospects of exercise for antiparkinsonian therapy.

1. Parkinson's disease

As the second most common neurodegenerative disease worldwide, PD typically affects people over the age of 60 with a higher susceptibility in males than females at a ratio of around 3:2 (Kalia & Lang, 2015). It has been reported that almost 1.6 out of 1000 individuals worldwide suffered from PD (Ascherio & Schwarzschild, 2016). Additionally, the number of PD patients is predicted to rise to 9 million by 2030 (Dorsey et al., 2007) and the economic burdens by then will be aggravated to a great extent for patients, their families and society as a whole.

1.1 Clinical symptoms of Parkinson's disease

The primary clinical sign of PD is motor disorders, including bradykinesia, rest tremor, rigidity, postural instability, and dystonia. Bradykinesia, as the most characteristic clinical hallmark of PD, is normally featured by slowness in initiation of voluntary movements with reduced speed and amplitude of repetitive actions, drooling, expressionless face (hypomimia) and micrographia. Motor symptoms start usually from one side of the body and then affect the contralateral side in few years. Despite motor symptoms, nonmotor

symptoms have also been viewed as an integral part of PD and may be caused by disturbances in dopaminergic and nondopaminergic functions. Strong evidence suggests that nonmotor symptoms may serve as earlier disease manifestations for PD, appearing years before the first presence of motor symptoms (Schrag, Horsfall, Walters, Noyce, & Petersen, 2015). Nonmotor symptoms normally include cognitive dysfunction, hyposmia, constipation, rapid eye movement sleep behavioral disorder (RBD), and mood disturbance. About 50%–80% of PD patients at later stage may be affected by PD dementia (PDD), and nearly 30% of the nondemented PD patients still have a risk of suffering from mild cognitive impairment (Aarsland, Zaccai, & Brayne, 2005). This symptom may be much more disabling than motor symptoms. In addition, the pathological course of PD involves the central and peripheral postganglionic autonomic nervous system, leading to the autonomic dysfunction. Orthostatic hypotension is reported to affect 30%–40% of PD patients and may induce hypo-perfusion of the brain to cause dizziness, visual disturbances and cognition impairment (Lahrmann et al., 2006). Moreover, gastrointestinal symptoms, urinary control disturbances and other symptoms such as excessive sweating, salivary secretion and seborrheic keratosis are also common in PD patients.

1.2 Genetic and environmental factors for Parkinson's disease pathologies

PD as an irreversible neurodegenerative disease is pathologically featured by the specific depletion of dopaminergic neurons in the substantia nigra (SN) and the formation of abnormal proteinaceous spherical bodies called Lewy bodies (LBs). While the definite cause of PD and the loss of dopaminergic neurons in SN is still far from being clearly understood, many etiological factors including aging, environmental factors, and genetic factors may account for PD pathogenesis (Ascherio & Schwarzschild, 2016). For examples, traumatic brain injury, pesticide exposure, and reduced physical activity can serve as risk factors for PD pathogenesis. On the contrary, caffeine intake and tea consumption present protective effects against PD. Moreover, over 18 mutant genes including α-synuclein, Parkin, leucine-rich repeat kinase 2, Parkinson disease protein 7, Pink, glucocerebrosidase gene, and others have been reported to cause nigrostriatal degeneration and are closely correlated with PD (Dickson et al., 2009). The combination of different etiological factors may lead to the dysfunction and death of dopaminergic neurons. Various cellular and molecular mechanisms, such as mitochondrial

dysfunction, protein misfolding and aggregation, endoplasmic reticulum stress, oxidative stress, disruption of autophagic catabolism, and the loss of calcium homeostasis, are involved in the pathological process of PD. Except the loss of dopaminergic neurons, the presence of LBs is another typical pathological manifestation of PD. More than 90 proteins have been identified in LBs, among which, α-synuclein is abundant and has been recognized as a key player in PD pathogenesis. Studies have shown that the precursor structures of LBs can change the solubility and binding affinity of α-synuclein, and then lead to the intracellular precipitation. However, LBs are also found in brains of elderly people without PD, instead of being specific for PD.

1.3 Clinical therapy of Parkinson's disease

So far there is still no treatment to stop the progression of PD. Although other medications such as dopamine agonists and monoamine oxidase B inhibitors have also been clinically applied for PD therapy, levodopa remains the most effective and first-line therapeutic agent for the motor symptoms of PD. Previous studies have reported that around 80% of PD patients achieve significant improvement after levodopa treatment (Yahr, Duvoisin, Schear, Barrett, & Hoehn, 1969). However, despite of its promising therapeutic effects, long-term levodopa therapy has serious limitations including the induction of dyskinesia and wearing-off phenomenon. It is necessary to establish an individual medication therapy or combination therapy to prevent or improve these unfavorable side effects of levodopa. Other dopaminergic medications such as dopamine agonists and monoamine oxidase B inhibitors can be combined with levodopa to manage fluctuations or used singly for patients in early stage. Despite of appropriate pharmacological treatment, nonpharmacological therapy such as deep brain electrical stimulation and complementary alternative approaches can be clinically considered when main line medications fail to response properly against motor symptoms of PD. In addition to these conventional therapies, increasing evidence has indicated that exercise or physical therapy might be beneficial to improve both motor- and nonmotor symptoms and enhancing the life quality of PD patients (Cruise et al., 2011; Mak, Wong-Yu, Shen, & Chung, 2017; Reynolds, Otto, Ellis, & Cronin-Golomb, 2016). Furthermore, it is safe and well tolerated when training program is reasonable, which make exercise a promising supplementary therapy to be used to prevent PD development and delay the disease progression.

2. Exercise

2.1 The definition and categories of exercise

Exercise has long been proved to have great benefits on our health and can generally slow down aging, prevent and reduce both morbidity and mortality of many chronic diseases (Booth, Roberts, & Laye, 2012). US Centers for Disease Control and Prevention (CDC) has defined physical activity as "any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level." Exercise is defined as a subcategory of physical activity aimed to improve or maintain one or more components of physical fitness. Although physical activity and exercise may have few differences in definition, they are not distinguished in most of studies. Statistical analysis has revealed that exercise may be beneficial to various chronic diseases including cardiovascular diseases, stroke, diabetes, dementia and osteoporosis (Booth et al., 2012). The increasing risk of these diseases is associated with sedentary lifestyle for long decades and more and more people suffer from and die of chronic diseases. The CDC views physical inactivity as an actual cause of these chronic conditions. Meanwhile, the U.S. Institute of Medicine has regarded exercise as a powerful tool in the prevention of chronic diseases (Booth et al., 2012).

The world health organization (WHO) classifies physical activities into four well-known categories: aerobic, strength, flexibility and balance (WHO Guidelines Approved by the Guidelines Review Committee, 2010). Aerobic activity which is also called endurance activity includes brisk walking, running, bicycling, jumping rope and swimming. Strength activity is aimed at improving muscle strength and cycle ergometer exercise is the most common form. Statistics show that physical activity gives benefits to disease-modifying with clear dose–response relations including intensity, frequency, duration and volume. WHO defined intensity as the rate at which the activity is being performed or the magnitude of the effort required to perform an activity. Moderate-intensity physical activity refers to activity that is performed at 3.0–5.9 times the intensity of rest and vigorous-intensity physical activity refers to that at 6.0 or more. Due to this, walking or hiking outdoors and stair climbing can be viewed as moderate activity, and the others are seen as vigorous. WHO has claimed that 150 min of moderate-intensity aerobic physical activity or 75 min of vigorous-intensity physical activity per week is effective and higher volumes or intensities of physical

activity will bring greater benefits (WHO Guidelines Approved by the Guidelines Review Committee, 2010). Currently, dancing, cycling, walking, tai-chi, yoga, treadmill training are typical forms of exercise have been proved to have positive effects on brain health (Rafferty et al., 2017).

2.2 Exercise and brain health

Growing evidence has implicated that exercise appears to have extensive effects on brain health. Exercise helps to promote neurogenesis, angiogenesis, metabolism of central nervous system (CNS), as well as the release of growth factors, and also modulates inflammation in CNS (Cotman, Berchtold, & Christie, 2007). Intervention studies of both human and rodents have proved that sustained exercise is capable of enhancing learning and memory, ameliorating mental decline resulted by aging and neurodegenerative diseases (Lau, Patki, Das-Panja, Le, & Ahmad, 2011). Moreover, exercise can facilitate synaptic plasticity in the hippocampus, which is essential for spatial learning by enhancing both short-term potentiation and long-term potentiation (LTP) and increasing the levels of synaptic proteins, glutamate receptors, and neurotrophic factors such as insulin-like growth factor-1 (IGF-1) and brain-derived neurotrophic factor (BDNF) (Cotman et al., 2007; LaHue, Comella, & Tanner, 2016; Zigmond & Smeyne, 2014). Besides, exercise also displays neuroprotective and rehabilitative effects. Previous clinical trials have indicated that poststroke therapeutic exercise programs advance functional rehabilitation of those individuals being affected by stroke (Cotman et al., 2007). This protective and therapeutic effect can be also observed in animal models of cerebral ischemia. In addition to stroke, the benefits of exercise mentioned above can also be presented in neurodegenerative diseases. Studies have suggested that exercise is able to delay symptoms onset and reduce risk of suffering from Alzheimer's disease (AD), Huntington's disease and PD (Cotman et al., 2007). Encouragingly, it can also retard the process of these diseases, though it may has started for a few decades. At the same time, improvement in learning and memory along with cognition after exercise are also found in clinical intervention studies (LaHue et al., 2016). In this way, exercise is taken into consideration as one of the therapeutic strategies for neurodegenerative diseases.

3. Exercise and Parkinson's disease

As an inexorable neurodegenerative disease involving problems of movement, cognition and autonomic nervous symptoms, there still remain

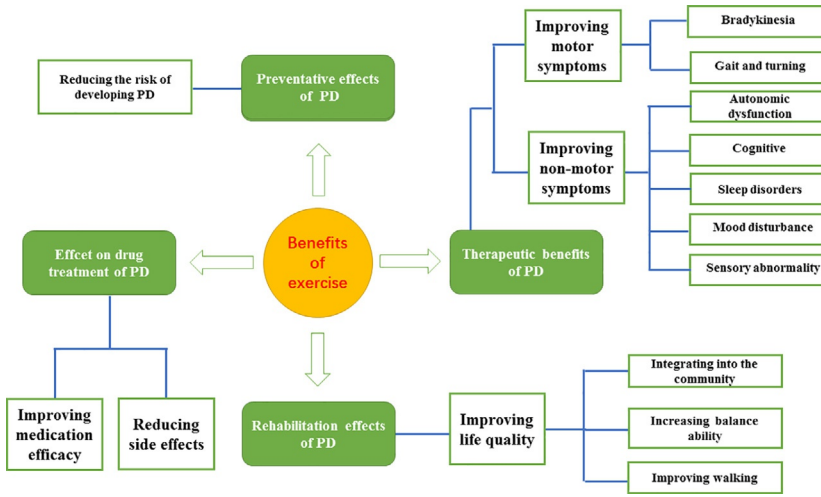

Fig. 1 Exercise has many benefits for Parkinson's disease. Exercise can reduce the risk of Parkinson's disease and improve the motor symptoms. In addition, exercise may improve the non-motor symptoms of the disease, such as cognition, sleep and mood disorders, sensory abnormality, and autonomic dysfunction. Furthermore, exercise also has a beneficial effect on medical treatment of the disease, which can reduce drug side effects and enhance medication efficacy. Moreover, exercise also helps the rehabilitation therapy of the disease.

no effective therapies for PD. In view of the insufficient of pharmacological and neurosurgical treatments, many physicians highly recommend physical therapy serving as an adjunct and complementary to the present treatment of PD (Fig. 1).

3.1 Preventative effects of exercise on Parkinson's disease

Exercise was first reported to be beneficial for PD in 1992 (LaHue et al., 2016). It was found that men who participated in sports had a lower risk of developing PD in an activity-dependent manner (Sasco, Paffenbarger, Gendre, & Wing, 1992). This finding was further confirmed in almost all subsequent epidemiological studies. Among the cancer prevention study II nutrition cohort participants, the risk of developing PD is reduced in patients who are engaged in high-intensity physical activity. Similarly, in the NIH-AARP Diet and Health Study cohort which contained more than 200,000 participants who took part in sustained moderate to severe exercise activity had a 40% lower risk of developing PD than those who were sedentary (LaHue et al., 2016). In the two large prospective cohort studies, the intensity of physical activity is negatively associated with the risk of

developing PD. Studies have shown that intensive exercise is associated with over 60% reduction of PD risk in male (Logroscino, Sesso, Paffenbarger, & Lee, 2006). Using the average level of exercise intensity as a general indicator during their life cycles, the risk of developing PD in male who spent 10 months/year in strenuous activities was 60% lower than those who took 2 months/year (Chen, Zhang, Schwarzschild, Hernan, & Ascherio, 2005). In a 13-year follow-up study in Sweden, people who exercised more than 6 h per week had a 43% reduction in the risk of developing PD (LaHue et al., 2016). This study is particularly important because it shows that, even leisure, occupation, family and commuting activities, can reduce the risk of PD.

Other studies have indicated that physical activity may have a gender bias on PD (LaHue et al., 2016; Logroscino et al., 2006). In a professionals and nurse health follow-up studies, higher levels of exercise can reduce the risk of PD in males, but not females. Similarly, in Swedish national studies, the preventative effects of physical activity against PD are much more obvious in males than in females (Yang et al., 2015). This gender difference suggests that male and female may have different biological responses to physical activity. The long-term metabolic consequences of exercise seem to have greater benefits for men, but epidemiological surveys have found that men and women both benefit from physical activities. Therefore, the low intensity of women's physical exercise in adult may account for gender difference in the risk of PD. However, it is still important to figure out whether the effects of physical activity of same intensity level are different between males and females. It may also reflect some untapped aspects of the pathogenesis of the disease. Further large prospective studies are required to replicate these findings and to explore the implications of this inverse association between exercise and PD.

3.2 Therapeutic benefits of exercise on clinical symptoms of Parkinson's disease

Currently, pharmacological therapies are primarily used for symptomatic control and provide only short-term benefits before the disease progresses to a severe stage. Physical activity and exercise may provide low-cost and universally available aids for current PD therapies. Therefore, studying the effects of physical activity and exercise on PD is imperative.

Previous studies aiming to explore the relationship between PD and exercise have shown that physical exercise can help to delay the disease onset and slow the progression of PD (Cheng et al., 2016; Mak et al., 2017).

In addition, exercise can improve motor impairment, ameliorate cognitive decline, and enhance quality of life. Randomized trials have indicated that a variety of physical activities with various intensities, including treadmill training, dance, and tai-chi improve motor symptoms of PD (Corcos, Comella, & Goetz, 2012; Mak et al., 2017). Several large controlled clinical studies have shown that the continuous exercise can improve the performance of daily activities in the early stage of PD, such as bradykinesia, balance, and turning (Mak et al., 2017).

3.2.1 Therapeutic effects of exercise on motor symptoms of Parkinson's disease

3.2.1.1 Bradykinesia

The predominant feature of PD is motor disorder and the first motor symptom will occur only if the depletion of dopamine at least 60%. Bradykinesia, as the cardinal symptom of PD, presents as slowness of movement associated with declined muscle power and slower walking velocity. All of these changes increase the risk of falling down in PD patients. Muscle weakness could be seen both in the upper and lower limbs. A study found that high intensity quadriceps contractions on an eccentric ergometer 3 days a week show greater improvement in muscle force, bradykinesia, and QoL (quality of life) after training for 12 weeks (Dibble, Foreman, Addison, Marcus, & LaStayo, 2015). After that, another study found that 3-month (two sessions/week) high-speed power-based resistance training is efficacious in the reduction of bradykinesia score both in upper and lower limp measured by UPDRS motor assessment, and can significantly increase the muscular strength and power in patients with mild to moderate PD. Moreover, QoL and physical function are also improved (Ni, Signorile, Balachandran, & Potiaumpai, 2016). Power training is a little superior to conventional resistance training when used to improve physical function, such as balance, walking speed and length, muscle strength and power, etc.

3.2.1.2 Gait and turning performance

In addition to bradykinesia, patients with PD also have difficulties in turning and gait, as shown by the slow turning and freezing of gait (FOG). These motor characteristics also increase the potential risk of falling down for PD patients (Mak et al., 2017). It has been well documented that exercise has beneficial effects to motor symptoms in advanced PD, including improved posture and balance control, gait-related activities, and physical conditions (Mak et al., 2017). Treadmill training is able to improve gait

parameters such as velocity, strides, and step length of PD patients. Thus, it is a good way for gait training. Few studies have shown that after at least 4 weeks training, gait performance is improved in terms of walking speed, step length and support time, and the effect can last for at least 3 months (Mak et al., 2017).

Impaired muscle strength and deficits in functional mobility such as balance ability can also influence gait performance. Thus, physical therapies that combined impairment-level and functional mobility training are required for gait performance improvement. Simultaneously, balance control ability and lower extremity strength have been recognized to have influence in turning performance. And a specific exercise program is designed to emphasize balance and muscle strengthening for turning training. One previous study found that after 12∼30-min specific exercise training for 4–6 weeks, the PD patients' turning performance was greatly improved as compared with the control group (Cheng et al., 2016). As a task-specific training, great improvement could be obtained through practicing functional activity. It is suggested that the concept should be applied in most of the training process aimed to improve walking, up and down the stairs or grasping.

Additionally, the turning-based training exerts benefits on vestibular integration ability of PD patients. Under normal circumstance, vestibular input is required to prepare for turning, and vestibular feedback helps to control axial movements when the head and trunk rotating takes place simultaneously. However, PD patients are usually abnormal in processing visual and vestibular inputs which result in balance disorder. Vestibular function may be also improved through the turning-based treadmill. Improved vestibular function together with strengthened muscle may lead to a better performance in turning after turning-based training. Mechanisms such as increasing neuroplasticity in the basal ganglia system, neuroprotective and neurorestorative capacity induced by intensive exercise may account for the improvement (Cotman et al., 2007). In addition, incremental blood flow and trophic factor along with a strong immune system achieved by exercise can work as an environmental enrichment for neuroplasticity (Allen, Moloney, van Vliet, & Canning, 2015). By improving balance ability and strengthening muscle, exercise has greater fall prevention effects. Falls are leading cause for mortality of older PD patients and will impose great burden to the family and society. In this way, seeking for preventions is urgent. A series of random controlled trials that compared fall rates in older people who received exercise as a single intervention with fall rates in those

randomized to a nonexercise control group (Sherrington et al., 2017). The results provide strong evidence that exercise as a single intervention prevents falls in older people living in the community. Despite this, more work should be performed to establish optimal training strategies in residential care and make the combination of exercise and other fall preventing interventions.

As mentioned above, task-specific training exerts more effects than traditional general exercise in order to improve functional performance of patients suffered from PD. In another study, curved-walking training (CWT), a task-specific training to improve walking ability of PD, was randomly assigned to PD patients who received 12 sessions (each session last for 30 min) of either CWT with a turning-based treadmill or general exercise training for 4–6 week, and the results showed that the CWT group acquire greater improvement in straight-walking speed, cadence and step length than general exercise (Cheng, Yang, Wu, Cheng, & Wang, 2017). Moreover, it provided positive effects on FOG for at least 1 month, suggesting that task-specific training is more effective than traditional general exercise (Cheng et al., 2017).

3.2.2 Therapeutic effects of exercise on nonmotor symptoms of Parkinson's disease

In addition to the classic motor symptoms, nonmotor symptoms, which can occur as the initial symptom and reduce quality of life even in the early stage of disease, are also an important part of PD. Cognitive deficits, mood decline, sleep disorders and pain are common forms of nonmotor symptoms of PD. Statistical data have shown that exercise intervention can also give therapeutic benefits to PD patients with these symptoms (Aarsland et al., 2005; Cruise et al., 2011).

3.2.2.1 Cognitive deficits

Cognitive deficit is one of the most universal complications of PD and up to 50%–80% of PD patients may progress to PDD at the late stage (Aarsland & Kurz, 2010). The prevalence of PDD was estimated at 0.5% in individuals aged more than 65 years old. Cognitive disorders do have great impacts on quality of life and can cost great of their family. Moreover, effective medication is still lack to slow the disease progression. In this way, it is imperative to search for other solutions to manage the cognitive impairment. Previous studies have shown that exercise like dance, treadmill training, etc. could promote the preservation and improvement of cognitive

function in PD patients (Cruise et al., 2011). Though it is well known that exercise is beneficial to brain plasticity, different kinds of exercise have been found selectively affect specific brain regions and functions. Aerobic exercise is proved to have benefits on the superior temporal and parietal prefrontal cortex and transverse tracts between the frontal and parietal lobes and can improve executive function in PD. Judgment, planning, abstraction, problem solving, sequencing, and mental flexibility can be considered as parts of executive function (Cruise et al., 2011), whereas the extent of executive function is still far from these. Trials with moderate intensity and longer decade have reported an improvement on attention and memory, restored processing speeds, and better performances on verbal fluency and spatial working memory as well. Moreover, long-term and high-frequency training along with specific training such as tango and treadmill training can produce better improvements in cognition. The imaging studies have shown that different exercise trainings may produce different patterns of brain activation, selectively affecting specific brain regions' functions (Maidan et al., 2017). PD participants in the treadmill training (TT) + virtual reality (VR) that targets motor and cognitive aspects of safe ambulation arm has lower activation than the TT arm in Brodmann area 10 and the inferior frontal gyrus, while the TT arm has lower activation than TT + VR in the cerebellum and middle temporal. Reducing activation in these regions can be considered as a return toward normal values through the enhancement in the efficiency of cognitive networks.

3.2.2.2 Sleep disorders

Sleep disorders are also one of the most common nonmotor symptoms of PD. The prevalence of sleep disorders in PD ranges from 40% to 80% (Frazzitta et al., 2015). The most common sleep disorders of PD patients include insomnia, excessive daytime sleepiness, RBD, restless leg syndrome and nocturnal. Sleep disorder in PD might be the consequences of neurodegenerative changes such as damage to specific nuclei and neurotransmitters related to sleep control. Unfortunately, the use of dopaminergic medication can also result in sleep disorders. Previous studies have already suggested that the increase of dopaminergic therapy has negative impacts on sleep quality of patients with PD (Frazzitta et al., 2015). In addition, sleep disorders are usually correlated with mood disturbance and cognitive deficits, leading to the decreased quality of life. The pharmacological treatments used for improving sleep quality are proved to have limited effect. Several alternative approaches such as repetitive transcranial magnetic stimulation

are also ineffective (Frazzitta et al., 2015). Under these circumstances, more efficient treatments are needed to address this problem.

Previous studies have documented that regular exercise with moderate intensity truly improves the quality of sleep. The benefits of this chronic exercise appear to be uniform for both younger and older participants, although the effect on sleep-onset latency in elderly is weaker (Kredlow, Capozzoli, Hearon, Calkins, & Otto, 2015; Reynolds et al., 2016). And the weaker effect in elderly may be age dependent. Acute exercise has also been proved to be beneficial on several sleep disorders. Acute exercise is found to result in a decrease in rapid eyes movement sleep without significant effects on total sleep time, slow-wave sleep, sleep onset latency and sleep efficiency (Kredlow et al., 2015). The therapeutic benefits of acute exercise on sleep depend on the exercise time of the day. Three to eight hours before bed time is better. Regular exercise has limited benefits on total sleep time and sleep efficiency, a medium beneficial effect on sleep onset latency, and a moderate beneficial effect on sleep quality. The therapeutic benefits of exercise on sleep are also related to the duration, showing the longer exercise would yield better outcomes. Most of these studies prove that exercise exhibits benefits on improving sleep disorder (Kredlow et al., 2015), but the specific benefits of exercise on sleep disorders in PD are still rarely investigated. Further studies are still needed to elucidate the potential effects of exercise on PD patients' sleep disorders.

3.2.2.3 Mood disturbance

Mood disturbance mainly refers to depression and anxiety, which disturbs the PD patients much earlier than motor-symptoms, causing great burden to the patients and their caregivers. It is estimated that about 20%–40% of individuals with PD may suffer from depression (Reynolds et al., 2016). Ordinarily, depression in PD will cause problems with emotional well-being, social communication and daily activity, meanwhile it may aggravate other symptoms. Anxiety is another element of mood disturbance of PD, it often manifests as fear of falling or fear of crowded places due to freezing of gait (Pontone et al., 2009). So far, there is no specific treatment of PD aiming at ameliorating mood disturbance. Some studies have shown that certain selective serotonin reuptake inhibitors, dual reuptake inhibitors, and dopamine agonists may improve depression in PD, but it may be accompanied by some treatment-related side effects (Richard et al., 2012). In this case, there is an urgent need to search for other means to effectively tackle the mood disturbance. Increasing lines of evidence have confirmed that moderate

aerobic exercise several times a week has positive impact on depression and anxiety (Reynolds et al., 2016). It has been shown to improve mood in healthy older population (Reynolds et al., 2016). Regardless of the basal level of depression, both aerobic and resistance training reduce depression. When compared with pharmacological therapy for depression, exercise is equally effective after 16 weeks of treatment. Many studies confirm that at least moderate aerobic activity for 20–45 min several times a week may exhibit benefits on reduction of depression symptoms relative to nonexercise (Reynolds et al., 2016). In addition, patients who have no improvement after using antidepressant medication feel better after aerobic exercise (30–45 min sessions, 5 days/week) (Reynolds et al., 2016). Functional MRI reward task imaging showed that habitual aerobic exercise can enhance ventral striatum activity in PD patients (Sacheli et al., 2018), suggesting that exercise may participate in activation of the mesolimbic pathway, resulting in increased capacity to anticipate reward, which may contribute to mood improvement. Thus, the impacts of exercise on mood disturbance need further investigation before it is used as a routine adjunctive therapy for mood improvement.

3.2.2.4 Sensory abnormality

Pain is a kind of sensory abnormalities that interferes up to 85% of patients of PD and has been associated with hyperalgesia (Allen et al., 2015). It is one of the most annoying symptoms experienced by PD patients, whereas, recognition and management of pain is not taken seriously. The classification of PD includes central neuropathic pain, peripheral neuropathic pain, and nociceptive pain (includes musculoskeletal pain, dystonic pain, visceral pain and cutaneous pain). Statistics have shown that increased disease severity, female gender and higher medication dosage could aggravate the pain in PD (Sung, Vijiaratnam, Chan, Farrell, & Evans, 2018). Hyperalgesia may take part in the development of persistent pain in PD patients, via dopaminergic mechanisms. Dopamine and glutamate are important neurotransmitter that associated with sensitization of the CNS. It turns out that exercise could improve dopamine neurotransmission and restore dopamine D2 receptors in the dorsal striatum in PD rodent model (Allen et al., 2015). The formation of Lewy body and disease-related neuronal cell loss in the parabrachial region and the periaqueductal gray matter of the medial spinoreticulothalamic pain pathway may influence autonomic responses to pain. These findings provide relevant evidence that exercise may be able to relieve pain in PD patients. Moreover, exercise is commonly used to manage musculoskeletal pain and improve function in patients with pain

caused by spinal structure and osteoarthritis. For PD patients, symptoms such as rigidity, akinesia and dystonia could result in musculoskeletal pain and it may occur in the hips, knees, ankles, and back. And there is evidence that exercise could decrease pain by decreasing the motor cortex excitability and resulting detrimental effect on neuroplasticity (Allen et al., 2015). Most of studies focus on the motor-symptom improvement, only a few of them evaluate the effects on pain. A nonsignificant 8% reduction in pain was reported in a study of exercise for 12 weeks (Allen et al., 2015). In another study, reduction in the intensity of pain in the neck, hip, and joint has been noticed (Allen et al., 2015). Because of small number of participants and no restricted controls the existing studies have some limitation. Thus, more studies are needed to investigate if exercise could prevent the neuroplastic changes and promote pain modulation.

3.2.2.5 Autonomic dysfunction

Autonomic dysfunctions, including drooling, orthostatic hypotension, urinary dysfunction, gastrointestinal dysfunction, excessive sweating, could occur prior to the diagnosis and aggravate with the disease progression. The central and peripheral postganglionic autonomous nervous system may involve in the development of autonomic dysfunction. Evidence shows that traditional Chinese exercise, such as Baduanjin, could modulate the autonomic nervous system, balance sympathetic and parasympathetic fibers, stimulate the intestinal peristalsis, and increase the contraction of pelvic floor to improve constipation (Koh, 1982). Currently, pharmacological treatments are predominant to manage these symptoms, and there is no adequate studies investigating the relationship between exercise and autonomic dysfunction. Further work should be performed to identify if exercise also has benefits on improving autonomic dysfunctions.

3.2.3 Fatigue and decreased physical activity in Parkinson's disease

Previous study (Chen et al., 2005) has found that during the entire life cycle of men and women with PD, a significant decrease in physical activity over time was observed. Further analysis have confirmed that the physical activity of PD patients is always lower than that of individuals without PD within 12 years prior to diagnosis (Chen et al., 2005). As we all know, fatigue is very universal in PD patients (sports are more prone to fatigue), and even is one of the symptoms of the disease, it develops several years before the diagnosis of the disease. PD fatigue may be associated with decreased physical activity in PD patients, and its possible underlying mechanisms are

associated with extensive mitochondrial dysfunction. Fatigue may also reflect a potential progressive loss of dopaminergic neurons in CNS. Preclinical decline in physical activity reflects the insidious nature of the disease and unrecognized pathophysiological changes. During prodromal stage of PD without obvious motor symptoms, a combination of nonmotor symptoms with the decreased physical activity or increased fatigue might serve as an early auxiliary diagnostic indicator of PD.

3.3 Exercise improves medication efficacy and reduces side effects in Parkinson's disease

Pharmacokinetic process of drugs, including absorption, distribution, metabolism, and excretion, can be affected by anatomic and physiological status. Exercise grossly affects organ and tissue functions, therefore is associated with physiological and anatomical change and may consequently influences the pharmacokinetics of drugs (Reuter, Harder, Engelhardt, & Baas, 2000). As for PD patients, levodopa is the main pharmacological treatment for motor symptoms alleviation. However, long-term usage of levodopa will lead to motor fluctuations and involuntary movements. Statistics showed that 50% of PD patients treated with levodopa for more than 5 years will develop wearing-off and dyskinesia as complications (Baas et al., 1997). And levodopa-induced dyskinesia (LID) occurs in 40% of patients treated with levodopa for 4–6 years and truly influences their quality of life. However, the mechanism of LID is not fully understood. LID can appear as peak dose, biphasic and end-of-dose dyskinesia, and may exaggerate with the progression of disease. At present, administration of lower dose but more frequently, adding amantadine is the major solution to ameliorate LID (Speck, Schamne, Aguiar, Cunha, & Prediger, 2019). Yet, giving that the application of antidyskinetic drugs may induce other side effects in PD patients, other treatments for LID are urgently needed. Some researchers claim an increased efficacy of levodopa induced by exercise. And studies (Speck et al., 2019) of mice model have indicated that exercise can partially prevent the development of LID and attenuate the side effects of levodopa through the normalization of striatopallidal dopaminergic signaling without affecting the anti-parkinsonian effect of levodopa (Aguiar et al., 2013; Speck et al., 2019). Moreover, clinical studies (McLaughlin & Jacobs, 2017) aimed to investigate the impact of exercise on absorption and efficiency on levodopa in PD patients have reported that exercise does not modify the plasma levels of levodopa, and has no impact on the pharmacokinetics and pharmacodynamics of levodopa in PD patients. But exercise does make a significant

better motor response during the exercise condition 120–150 min after levodopa intake, suggesting that exercise may increase efficiency of levodopa and then improve the motor response to levodopa application (Muhlack, Welnic, Woitalla, & Muller, 2007). And it is found that exercise can prevent the development of the cardinal neurochemical changes in the basal ganglia which is associated with LID. All of these evidences support the hypothesis that exercise may selectively rebalance the basal ganglia function to allow levodopa to restore dopaminergic tonus partially without the development of LID.

3.4 Roles of exercise in Parkinson's disease rehabilitation

Clinically, stroke patients are encouraged to undergo early rehabilitation and various functional exercises to improve and restore the body's impaired functions. Most clinical data and experiments have proved that functional exercise has significance for the rehabilitation of stroke and improves patients' self-reliance and quality of life (Billinger et al., 2014). People with heart failure experience marked reductions in their exercise capacity which has detrimental effects on their activities of daily living, health-related quality of life, and ultimately their hospital admission rate and mortality (Ding, 2017). Numerous cardiac rehabilitation studies have demonstrated functional benefits, improvement in quality of life and clinical outcomes from exercise training in patients with heart failure (Ding, 2017). Exercise training improves oxygen utilization with increased activity of oxidative enzymes and an increase in mitochondrial content.

In the Parkinson rehabilitation study, research-based exercise interventions improve health-related quality of life (HRQL) and mobility in patients with PD (Rafferty et al., 2017). Increasing exercise by 30 min/week was associated with slower declines in HRQL (−0.16 points) and mobility (−0.04 s) and nonexercisers deteriorated 1.37 points on PDQ-39 (Rafferty et al., 2017). The benefit of exercise on HRQL was greater in advanced PD than mild PD. Additionally, exercise also improves the mood and the quality of life of PD patients who participates in activities and integrates into the community. The NPF-QII study is the largest prospective longitudinal observational study of PD patients in the natural environment. This is the first analysis of the longitudinal results of exercise habits over 2 years. Professional rehabilitation therapy, even at the beginning of the late course of PD, may slow the decline in long-term HRQL and restore the functional activity in PD patients (Rafferty et al., 2017). It is suggested that

the sustained exercise habits may be better than short-term exercise participation. Most of improvements are in the motor symptoms of PD, and even in advanced PD have the greatest benefit of HRQL with 30 min of exercise per week (Rafferty et al., 2017). Although the incremental effect of exercise is small, it still indicates that exercise has a beneficial effect on PD rehabilitation.

Some other studies have shown that Chinese traditional exercise like tai-chi, Qi-gong and the eight-section brocade exercise exhibit rehabilitative effect on PD (Ni, Liu, Lu, Shi, & Guo, 2014; Song et al., 2017). Tai-chi is a common exercise based on balance. Six months training (60 min for twice a week) of tai-chi exhibit better improvement effect on gait length increasing than resistance training, and have potential to prevent fall than stretching training (Gao et al., 2014). Other studies also showed that tai-chi could ameliorate balance and posture stability of PD patients. A study found that 3 and 6 months Qi-gong practice improves UPDRS and such effect could last for 12 months (Schmitz-Hubsch et al., 2006). Several other studies showed the similar results claiming that Qi-gong can serve as the supplementary treatment to traditional medication.

Other forms of exercise such as yoga, underwater exercise and boxing also have been reported to have positive effect on PD rehabilitation (Vivas, Arias, & Cudeiro, 2011). It is said that they can increase flexibility and balance ability and relieve anxiety and depression, leading to rehabilitative effect and improvement of life quality of PD patients.

4. Mechanisms underlying the impact of exercise on Parkinson's disease

4.1 The effect of exercise in the Parkinson's disease animal models

Although the clinical role of exercise on improving the motor symptoms of PD is quite evident, whether exercise prevents neuronal loss is not confirmed, and the cellular mechanisms underlying the benefit of exercise on PD has not been clearly investigated in human PD patients or in chronic animal disease models.

In animal experiments, studies have shown that long-term exercise diminishes neurological and motor declines in PD models (VanLeeuwen et al., 2010). Long-term exercise can not only prevent neurobehavioral and mitochondrial defects in MPTP-induced chronic PD mice (MPD), but also promote the activity of nigrostriatal neurons in chronic PD models

(LaHue et al., 2016; Lau et al., 2011). Omar Ahmad examined the effects of endurance exercise on neurological changes and behavioral performance of MPD mice, and found that after 18 weeks of exercise training, the impaired and disharmony behavior was significantly reduced together with a significant increase of glial cell line-derived neurotrophic factor (GDNF) level in the SN and striatum (Lau et al., 2011). Moreover, exercise can also significantly increase the levels of endogenous BDNF and GDNF, and improve mitochondrial dysfunction in PD model mice (Lau et al., 2011). In MPTP-induced rat model of PD, exercise can reverse the loss of dopamine in the striatum. In 6-hydroxydopamine (6-OHDA)-induced PD rat model, autonomous running and stepping rhythm movements can reverse dopamine loss in the striatum and recover behavioral deficits (LaHue et al., 2016). Therefore, lifestyle changes by increasing exercise activity might be a nonpharmacological neuroprotective method for preventing the onset of PD and improving the symptoms of PD. Therefore, it is important to explore the molecular mechanisms underlying the impact of exercise on PD. Here, we summarize the main mechanisms.

4.2 Synaptogenesis

In 1991, studies (Klockgether et al., 1991) have found that α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antagonists alleviate motor symptoms in PD, revealing that the involvement of AMPARs in PD pathologies. Previous studies have demonstrated that high-intensity exercise altered the postsynaptic glutamatergic neurotransmission, which is related to the AMPAR subunit expression and its phosphorylation status in the medium spiny striatal projection neurons of the dorsolateral striatum, a region involved in exercise control (Holschneider, Yang, Guo, & Maarek, 2007). As we know, the glutamatergic system plays an important role in motor learning.

AMPARs are a subtype of glutamate receptors and are composed of a variety of subunits, including GluR1, GluR2, GluR3, etc., which are responsible for most of the rapid excitatory neurotransmission in the CNS and mediate the process of synaptic intensity and activity. The number of AMPARs, subunit composition, and phosphorylation of subunits significantly affect the intensity of synaptic excitability and involve synaptic plasticity, including long-term potentiation and long-term depression (Jiang, Suppiramaniam, & Wooten, 2006). Previous study has found that enhanced exercise increased GluR2 transcription and their proteins

expression in MPTP mice without significant change in GluR1 protein (VanLeeuwen et al., 2010). However, in the control MPTP mice, only an increasing of GluR2 transcription was observed, without changes in protein expression. The lack of GluR1 protein expression change, as well as an increase in GluR2 expression in MPTP + exercise mice, suggested a change in AMPAR composition, with a decrease in GluR1-containing channels and an increase in GluR2-containing channels (VanLeeuwen et al., 2010). Furthermore, comparing the alterations of RI of exercise training MPTP mice with nonexercise training, the alteration of GluR2 protein in AMPARs resulted in the alteration of synaptic expression. Exercise also induced the phosphorylation of GluR2 serine 880, then the receptor internalized and retained by interact with an accessory protein, which results in a decrease in synaptic excitability (VanLeeuwen et al., 2010). Other studies found an increase in sEPSCs amplitude in cortical striatal synapses of striatal MSN of MPTP mice, while exercise can reduce the amplitude of sEPSCs in striatal neurons, suggesting a protecting role (VanLeeuwen et al., 2010). This finding confirms the previously report that the increase in spontaneous discharge of striatal neurons after dopamine depletion in PD model mice, which aggravated the neuronal damage. Also, dopamine depletion decreases the dendritic spine density, and increase the expression of AMPAR which contain GluR1 in the remaining synapses. The increased expression of AMPAR containing GluR1 and over-excitation lead to synaptic drive abnormalities in surviving synapses. Exercise can reverse this excitatory state by increasing synaptic expression of AMPAR containing GluR2. Current studies suggest that the observed decrease in sEPSC amplitude after exercise may be due to an increase in AMPAR containing GluR2 (VanLeeuwen et al., 2010). The subunit composition itself is the main determinant of the AMPAR conductivity properties. The GluR2 transcript is modified after transcription, in which the glutamine (Q) codon is converted to the arginine (R) codon, which is present in the pores of the channel, and due to the blocking of cation flow that induced by electropositive portion, AMPAR which contains GluR2 becomes a low-conductance channel, which reduces the amplitude of sEPSCs in striatal neurons and thus protects striatal neurons. Another view of the differences in sEPSC amplitude between MPTP and MPTP with exercised mice is that synaptic remodeling of the striatum glutamatergic terminal, which may lead to the changes of presynaptic glutamate release (VanLeeuwen et al., 2010). Together, these findings collectively support the role of intensive exercise in regulating synaptogenesis. That is, exercise reduces AMPAR conductance by

increasing the expression of GluR2 and its phosphorylation state, thereby to reduce cortical stria hyperactivity and ultimately, finally exercise improve the motor symptoms of PD. It is believed exercise can induce synaptogenesis to improve PD symptoms, and it may be achieved through AMPAR, which may be helpful in studying the pharmacology of AMPAR.

4.3 Neurogenesis

Neurogenesis involves the process of neural stem cells proliferation and undergoes a balanced and unbalanced division into directed progenitor cells, then, directed progenitor cells gradually migrates to functional areas, undergoes plasticity changes and establishes synaptic connections with other neurons to established neurological integrity relations. The process of enhanced hippocampal neurogenesis is one of the most reproducible effects of exercise in the brains of rodents and may be a key mechanism regulating motor-related learning and memory improvement (although the role of neurogenesis is currently controversial) (van Praag, Christie, Sejnowski, & Gage, 1999). In young animals, exercise stimulates the proliferation of neural progenitor cell populations, increasing the number of new neurons, and promotes the survival of these new cells. Interestingly, these new neurons are functionally integrated into the brain formation, but they are unique to mature granulosa cells in that they have a lower threshold of excitability (Schmidt-Hieber, Jonas, & Bischofberger, 2004; van Praag et al., 2002). This feature makes these new neurons well suited to mediate the plasticity of exercise stimulated, which enhance the role of exercise in synaptogenesis. These new neurons may replace the injured neurons.

4.4 Exercise promotes angiogenesis and enhance glucose utilization

To support exercise-induced brain function changes, such as synaptic plasticity and neurogenesis, the brain must meet increased nutritional and energy requirements. In mouse experiments, long-term exercise causes extensive growth of blood vessels in the hippocampus, striatum, cortex, and cerebellum, providing nutrient and energy (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990; Cotman et al., 2007). Long-term exercise also stimulates the expression of enzymes involved in glucose utilize and metabolism in the brain. In this process, the regulation of neurotrophic factors is involved and plays an important role (Ding, Vaynman, Souda, Whitelegge, & Gomez-Pinilla, 2006). Some studies showed that long-term

aerobic exercise lead to an adaptive alteration in the brain, induce the collateral circulation formation in the brain, which improves the brain metabolism and consequently reduce neuronal death (Duncker & Bache, 2008). Long-term exercise improves muscle cell metabolism, which prevents muscle atrophy, which also has benefits to the rehabilitation of PD patients (Chung, Thilarajah, & Tan, 2016).

4.5 Exercise inhibits oxidative stress and repairs mitochondrial damage

Long-term exercise not only promotes neurotrophic activity of nigrostriatal neurons in chronic PD models, but also prevents neurobehavioral and mitochondrial defects associated with chronic MPD (Lau et al., 2011). Neurons as extremely active cells need sustained energy supply to perform highly specialized functions, such as regulating activity of neuronal transmission, receptors, ion channels, protein transportation and synapses. Therefore, mitochondria are essential for maintaining the homeostasis and integrity of neuronal function, and mitochondrial dysfunction is considered as a contributing factor to PD-related neuronal death. In PD animal models, a large number of literatures have confirmed the oxidative stress and mitochondrial dysfunction in PD, which can be improved by long-term exercise training (Bhat et al., 2015). For example, rodent model of PD showed an elevated p53 gene expression and an increased release of cytochrome *c* from mitochondria, leading to cell death and eventually neurodegeneration, Moreover, studies also suggested that this mitochondrial disorder may be attenuated by exercise via reducing the release of cytochrome *C* (LaHue et al., 2016; Patki & Lau, 2011). Although exercise may increase reactive oxygen species dramatically, rodent models have demonstrated that exercise through the adaptive process to long-term inhibit the systemic oxidative stress, increased the level and the activity of antioxidants and oxidative damage repair enzymes (such as SOD and glutathione). Increasing the levels of serum glutathione is especially important, because in clinical studies, PD patients have a lower baseline levels of antioxidants, such as glutathione and urate, compared with people without PD (LaHue et al., 2016). Second, in animal experiments, it has been reported that exercise may reduce neurotoxin-induced oxidative stress and the level of striatal carbonylation protein, and increase the level of ATP and SOD in the striatum, thereby reducing ROS to restore mitochondrial respiration (LaHue et al., 2016).

In turn, restoration of mitochondrial function can improve nerve function and help the neuron to survival.

Another possible important mechanism underlying is that exercise can suppress inflammation, then to reduce oxidative stress and mitochondrial dysfunction. For example, exercise can inhibit the expressions of proinflammatory cytokines such as tumor necrosis factor (TNF-α) and interleukin 6 (IL-6), and promote the expression of antiinflammatory factors, which reduce the production of oxidants (LaHue et al., 2016). This is particularly important in the SN because SN is susceptible to be affected by neuroinflammatory processes and chronic mitochondrial dysfunction.

4.6 Exercise promotes neurotrophic factor production and attenuates dopaminergic neurons damage

Previous studies have found that neurotrophic factors in the brain, particularly GDNF, BDNF, IGF-1 and VEGF are the main growth factors to mediate the effects of exercise on brain health (Cotman et al., 2007; LaHue et al., 2016). These growth factors work together to produce complementary effects that can be used to support the survival of neurons, regulate the brain plasticity and brain function. In the early stage of PD, clinical studies have indicated a significant reduction in serum BDNF levels compared with healthy controls (Scalzo, Kummer, Bretas, Cardoso, & Teixeira, 2010). The expressions of BDNF and GDNF in PD brain are also significantly reduced; therefore, neuron death in PD might be caused in part by defective synaptic plasticity associated with insufficient neurotrophic input (Chauhan, Siegel, & Lee, 2001; Lau et al., 2011). In PD animal models, exercise can upregulate the growth factor production and receptors expression, reduce cellular inflammation and oxidative stress, and attenuate dopaminergic neuronal damage (Lau et al., 2011). In 6-OHDA and MPTP PD models, BDNF protects 6-OHDA and MPTP-induced dopaminergic cell from damaging, and promotes synaptic transmission widely (Ahlskog, 2011). However, in the advanced MPD animal model, the endogenous BDNF and GDNF levels in SN and striatum are unaffected compared to normal control animals (Lau et al., 2011), indicating that in the absence of neuroprotective interventions, the basic level of neurotrophic factor may not be sufficient to restore the degenerating neurons. However, long-term exercise training can upregulate the level of endogenous BDNF and GDNF, to resist the neuronal damage and degeneration. Interestingly, previous studies further found that the neurotrophic factors induced by exercise are selective and specific for the

distribution of neuronal regions (Lau et al., 2011). These results can provide new ideas for targeting treatment of neurodegenerative diseases.

In addition to promoting the production of neurotrophic factors, aerobic exercise has also been shown to trigger the release of dopamine in the human brain and increase the expression of dopamine receptors in the striatum (Fisher et al., 2013). For example, compared with sedentary subjects, PET scans (Sacheli et al., 2018) analysis before and after stationary cycling demonstrated greater dopamine release in the caudate nuclei of exercisers, which may contribute to improvement of bradykinesia, gait and cognition. Intensive treadmill training showed an increased expression of dopamine receptor DR-D2R in PD patients (Sacheli et al., 2018). Exercise reduces the ratio of dopamine transporters and vesicular monoamine transporters, which may reduce the sensitivity of dopaminergic neurons to neurotoxins and reduce the oxidation of dopamine in cells. These mechanisms may account for the beneficial effects of forced exercise in PD animal models, however, whether these animal findings can explain the pathogenesis of PD remains to be further investigated.

4.7 Exercise improves metabolism

Clinically, the onset and development of many diseases are closely related to metabolic disorders, such as diabetes and obesity, which are risk factors for cardiovascular and cerebrovascular diseases and may lead to brain dysfunction. Some studies suggest that metabolic abnormalities in some metabolic diseases may aggravate the development of neurodegenerative diseases (Cotman et al., 2007; LaHue et al., 2016). Moreover, diabetes and hypertension have been identified to be risk factors for PD (Hu, Jousilahti, Bidel, Antikainen, & Tuomilehto, 2007). Obesity can produce alpha-synucleinopathy by changing Akt phosphorylation states (LaHue et al., 2016). Furthermore, PD have similar molecular dysregulation pathway with diabetes, such as insulin receptor defects, mitochondrial dysfunction, oxidative stress and inflammation. Moreover, adipocytes could cause intracellular proinflammatory cascade reaction and induce oxidative stress and inflammation. In fact, the metabolism of PD patients changes significantly compared with healthy controls. It is well-known that exercise can improve the pathological changes of metabolic diseases (Pedersen & Saltin, 2015). Therefore, the correlation between PD and metabolic diseases indicate that exercise may have a preventative effect on PD via improving metabolism.

4.8 Exercise modulates autophagy

Accumulation of α-synuclein is significantly correlated with the presence of progressive motor deficits, which is the main symptom of PD. Growing evidence has demonstrated that exercise confers neuroprotection against PD, and exercise can reduce α-synuclein levels, but the exact molecular mechanisms responsible for exercise decreases α-synuclein remain unclear. The clearance of abnormal proteins mainly depends on the autophagic lysosomal system and the ubiquitin protease system, and autophagy is the most important mechanism for the clearance of large proteins and long-lived proteins. Studies show that exercise can increase Sirt1 expression and modulate the levels of autophagy-associated proteins, including microtubule-associated protein 1 light chain 3-II, p62, and lysosomal-associated membrane protein-2, which enhanced autophagy (Huang et al., 2019). The activation of autophagy may improve mitochondrial function and promote the clearance of α-synuclein, which contributes to restoration of impaired dopaminergic neuronal function caused by PD.

5. Conclusion and future perspective

Collective evidence has revealed that exercise could be used as an effective prevention to lower the risk of developing PD. Adequate exercise can improve motor symptoms such as bradykinesia, gait and turning performance. Simultaneously, it could alleviate nonmotor symptoms, such as cognitive deficits, sleep disorder, mood disturbance and sensory abnormality. Meanwhile, the preventative and therapeutic effects of exercise are associated with the modality as well as the duration and intensity. Exercise such as walking, cycling, dancing, treadmill training, tai-chi, yoga and some strength trainings are recommended as powerful tools for prevention and symptoms improvement of PD. Besides, moderate to vigorous intensity, along with long duration and high frequency of exercise has better benefits. Additionally, exercise also exhibits effect to enhance the medication efficiency and ameliorate the side effects of levodopa. Moreover, exercise is increasingly used as a rehabilitation treatment to enhance the life quality and ameliorate balance disability. The positive impacts of exercise on brain health might be associated with an improved mitochondrial function, enhanced production of GDNF, increased synaptic plasticity and neurogenesis, regenerated angiogenesis, balanced metabolism and enhanced glucose

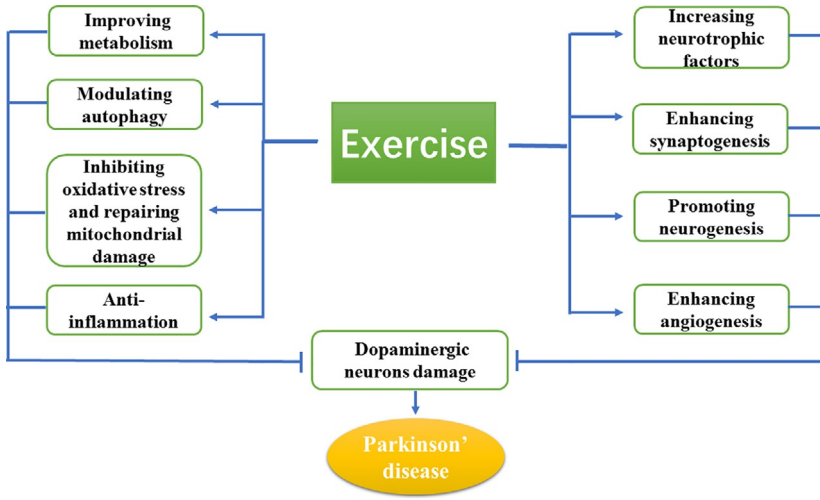

Fig. 2 The mechanism of exercise improves Parkinson's disease. Exercise can reduce dopaminergic neuron damage by reducing inflammation, inhibiting oxidative stress and repairing mitochondrial damage, modulating autophagy, and induction of neurotrophic factors, neurogenesis and angiogenesis.

utilization (Fig. 2). In this way, exercise could be applied to all patients as the complementary of pharmacological treatment. In addition, it can also benefit other diseases that occur as the comorbidity of PD.

Currently, the focus of PD treatment ought to shift from motor symptoms to nonmotor symptoms, which cause great burden to caregivers and decline the quality of life. So far, most of the PD studies related to exercise primarily focus on motor symptoms, only few of them take step into the nonmotor symptoms. Therefore, more studies need to be carried out in the future to examine the effect of exercise on nonmotor symptoms and elucidate the potential mechanisms involved in the process. Meanwhile, it is equally important to develop professional guidance of exercise for PD patients.

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