
Exercise training and rehabilitation of the brain in Parkinson's disease

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Abstract: Parkinson's disease (PD) is one of the most chronic progressive neurodegenerative diseases that is clinically manifested by of cardinal motor symptoms including, tremor and rigidity. The known cause of PD is the loss of dopaminergic neurons in substantia nigra in the brain. There are motor and non motor features of this disease with heterogenic complaints. The main treatment available for PD is levodopa as dopamine replacement therapy. However, after few years of treatment, PD patients experience levodopa-resistant symptoms. Other neurosurgical procedures for the treatment of PD have become a widely performed. These surgical procedures stimulate the dopaminergic neurons to produce more dopamine, but won't halt the progression of degeneration of these cells. Over the last years, many studies focused on the effect of physical therapy on PD, most of these studies have investigated the rehabilitation effects on musculoskeletal system, like gait, balance, and strength. Other studies focused on the effect of physiotherapy on non motor feature in PD, like quality of life. However, there is limited information about the beneficial impact of exercise on the brain of PD patients. In this review, we provide a brief review of the literature on exercise effects on the brain of PD. The present review was designed to gain more insight into the mechanism of improvement in PD patients with exercise and to answer in part the question of how exercise training rehabilitates the brain in PD patients.

Keywords: Exercise, Brain, Parkinson's disease

1. Introduction

Parkinson's disease (PD), one of the most common causes of disability among the elderly [1,2] is a movement disorder characterized by akinesia (the inability to initiate movement), tremors and muscular rigidity. At the physiological level, PD is caused by a deficiency of dopamine, which is a neurotransmitter that sends messages between nerve cells in the mammalian brain. First described by James Parkinson, PD has been lately defined as a collection of symptoms rather than one distinct clinical picture [3]. Thus, the diagnosis of PD can be difficult in the early stages of the disease.

PD progression is highly variable. Early PD symptoms typically include forward flexion of the neck, hips, knees, and elbows. Postural abnormalities greatly reduce the patients' ability to be ambulatory and places them at high risk for injury and falls [4,5,6]. Postural instability is a common and serious problem in PD [7]. Because of rigidity and postural changes, patients also develop a shuffling quality

to their gait and use small steps. Decreased speed and stride length are also main disturbances of gait in PD [8].

The exact benefits of exercise as a treatment for motor disability are not clear, yet as there are a small number of studies that support the concept. In one of the first reports in the literature on physical therapy for PD in 1961, Doshay compared 100 PD patients who did not receive any physical therapy with 100 PD patients who had intensive physical therapy for several years. He found, on average, less severely disabled patients in the exercising group when measuring both early and late time points over several years [9]. So, what would be the reason behind this theory considering the brain?

1.1. Mechanisms of Effects of Exercise on the Brain of PD Patients

In three large cohort studies, it was reported that moderate to vigorous exercise habits in midlife significantly reduced the risk of later-developing PD [10,11,12]. However, the mechanisms responsible for these changes are not

well investigated. Here, the possible mechanisms of action of exercise will be discussed and reviewed.

1.2. Neurotrophic Factors and Impact of Exercise in PD

Angiogenesis is the formation of new blood vessels. This process does not occur without stimulation. In PD, studies have suggested that vascular endothelial growth factor (VEGF) signaling may result in neuroprotective effects through the enhancement of dopaminergic neuron survival [11]. So an increased VEGF level in the affected areas in the brain in PD might have a potential therapeutic effect [12,13]. Beyond the neuroprotective role, Yasuhara reported that VEGF may also play a part in neurogenesis itself [14]. Using a rat model of PD they tested the neuroprotective capacity of VEGF. They found that rats receiving a continuous infusion of VEGF into the brain displayed a significant decrease in amphetamine-induced rotational behavior and a significant preservation of tyrosine hydroxylase-positive neurons and fibers compared with control animals. In our previous studies on the brain of Parkinsonian mouse, we reported increases angiogenesis on the striatum of exercised PD mice compared to sedentary PD ones [15]. These results were addressed in the way that neuroprotection role of VEGF is mediated indirectly by promoting angiogenesis in exercise.

In PD, blood flow to the brain has a functional importance not only for promoting the survival of the affected dopaminergic neurons by providing more oxygen and nutrients, but it may also help with efficient drug delivery to the affected areas. This is especially important for levodopa since a large proportion of the drug does not reach the brain, because it is rapidly converted to dopamine [16]. Increased blood flow to the affected areas of the brain would definitely help with more efficient drug delivery.

Another possible mechanism of improvement of PD with exercise is through a substance released by cells called glia derived neurotrophic factors (GDNF). GDNF is a neurotrophic factor that enhances survival and morphological differentiation of dopaminergic neurons and increases their dopamine uptake [17,18]. Despite extensive study, the mechanism of action of GDNF in cell and animal models of PD is far from fully elucidated. In dopaminergic neurons, GDNF binds to the $\alpha 1$ -subtype of GDNF family cell surface receptors, the receptors signal through receptor tyrosine kinase and can thereby phosphorylate different intracellular targets in the cell. [19].

GDNF has significant actions in promoting neuronal survival in the central nervous system, taken into consideration that GDNF can exert its neurotrophic effects at the level of cell bodies in the substantia nigra and in the axon terminals in the striatum [20, 21]. Compared to other growth factors, GDNF's ability to ensure survival of dopaminergic neurons is superior, and considered as a treatment option for PD [21,22]. When directly compared to brain-derived neurotrophic factor (BDNF), GDNF corrected behavioral deficits and protected nigrostriatal dopaminergic neurons better than BDNF. In addition, expression of both neuro-

trophic factors was no more effective than expression of GDNF alone [23].

In Gash's laboratory monkeys with PD-like symptoms showed significant functional improvements in bradykinesia, rigidity and postural instability with GDNF infusion. In the affected area, GDNF increased dopamine levels in the midbrain and globus pallidus [24]. Another study by Zheng et al. showed that GDNF significantly increased the number of neurons and the dopamine levels in the brain, with a subsequent behavioral recovery in Parkinsonian rats. These findings demonstrate that gene transfer of GDNF is efficacious even in the late stages of PD in rats [25,26]. These results were confirmed recently by Du and his colleagues who showed that GDNF gene therapy can protect the nigral DA neurons from degeneration. [27]

In human studies and based on the results of some of the animal studies, clinical trials using GDNF followed the same trend. Gill et al delivered GDNF directly into the putamen of five Parkinson's patients and their research results showed significant improvement of dopamine uptake and storage. The study also showed significant improvement with the Unified Parkinson's Disease Rating Scale (UPDRS) motor score, and ADLs of those patients [28]. Another study by Love et al provided the first neuropathological evidence that infusion of GDNF into the brain of patients with advance PD caused sprouting of dopaminergic fibers and a marked increase in the dopamine-producing nerve fibers similar to that seen in animal models [29]. Considering the long term effect of this GDNF treatment approach, a study by Patel, showed that following two years of injection of GDNF, PD patients did not show any serious side effects, and there was significant improvement in their off-medication status, QoL measures, UPDRS, and ADLs [30]. Other studies with 6 month infusion periods have shown similar results [31]. Thus, the human studies support the role of GDNF in improving neuronal function and clinical outcomes for patients with PD. Similarly, walking distances as indices of physical activity were associated with better preservation of gray matter/cortical volumes when followed up 9 years later [32]. These encouraging finding qualifies GDNF as the most interesting candidate factor to date for treating PD. As exercise training increased the level these neurotrophic factors, it could then explain in part this beneficial effect on the brain of PD patients. Moreover, treadmill exercise training was reported as potential factor for modulating neurochemical status in the striatum of rats, and promote neuroprotective role possibly by improving the oxidative stress factors [33,34], so there is also a positive role of exercise on the status of neurotransmitter in the brain of PD rats. A study by Klaissle reported that exercise regulate the generation of neural precursors in substantia nigra of rat with induced Parkinsonism (Klaissle, 2012 Oct 31;13:132). PD from another aspect is classified as brain damage related disease. In regard to those harmful factors and brain damage markers, we reported positive effect of exercise in limiting the effect of those damaging factors in the striatum

of Parkinsonian mouse and we showed improvement in the production of glial derived proteins with exercise [36]. In consistent with our findings, Dutra recently reported that exercise led to restored striatal glial fibrillary acidic protein (GFAP) expression in the striatum of Parkinsonian rat [37]. In early PD in human clinical trials, exercise also showed improvement in the motor performance and corticomotor excitability [38]. Even when patient will go to surgery for deep brain stimulation, positron emission tomography studies showed that, exercise still have recognized effect and continue to be a major part of the treatment, as it causes significant dopamine release in the ventromedial striatum and in the putamen [39].

1.3. Neuroinflammatory Components, Oxidative Damage and Exercise in PD

In regard to inflammatory processes in human body, the inflammatory component of PD is having significant attention among researchers now. Chronic inflammation is a major risk factor underlying aging and age-related diseases, like PD [40], as well as a central component to the notion of immunosenescence. On the other hand, previous studies by Ferrari and Tarelli showed how systemic inflammation may impact central inflammation and dopaminergic cell death [41]. These theories raise the possibility that peripheral inflammation could be a contributing factor in PD development. Moreover, studies in the animal models of PD by Machado supported the theory of neuroinflammation in PD [42].

The theory of neuroinflammation in PD came from the idea of microglial activation. Microglial cells can be considered as the resident macrophages of the brain and major immune cells in the CNS. The presence of microglial activation has been reported in Substantia nigra in PD in both human and animal studies [43,44]. Neurons in the SN have been shown to be particularly susceptible to microglial-mediated toxicity in vitro and in vivo [45]. Also, in another large epidemiological study conducted by Honglei in to test the relationship between inflammatory markers and diagnosis of PD in human blood samples, they found that higher level of interleukin-6 was associated with a greater risk of PD [46]. Moreover, in animal models of PD, anti-inflammatory intervention protocols were reported to be neuroprotective [47,48,49,50].

Oxidative stress is also thought to promote tissue damage in PD [51]. Generally, oxidative stress is generated by the inability to detoxify or to repair the resulting damage caused by the generation of reactive oxygen species. Mitochondrial damage as a result of oxidative stress has been reported in human PD studies [52]. Other oxidative damage ways has been reported through excitotoxicity, and nitric oxide toxicity [53]. On the other hand, the blocking of angiotensin receptor 1 on oxidative stress or/and microglial activation have recently been demonstrated in the MPTP model of PD to have a neuroprotective effects [54]. Here, the main goal of this review is not to clari-

fy deeply the Neuroinflammatory process itself in PD, or investigating the oxidative damage in PD, but rather to review the beneficial effect of exercises on those factors.

In PD, there is alteration in the neuroimmunological function [55]. Recently in Sweden, Archer reported that physical activity diminishes inflammation and elevates agents and factors involved in immunomodulatory function [55], he also found that different types of exercise attenuates or reverses the performance deficits observed in neurocognitive tasks. The effect of physical activity has been also reported by Wu et al to have a neuroprotective role on dopaminergic neurons (DA) against inflammation-induced insults, this study also showed that four weeks of running exercise before an intraperitoneal lipopolysaccharide ((LPS) injection; a drug that can induce degeneration in the SN and reduced the level of dopamine in the striatum) treatment completely prevented the LPS-induced loss of DA neurons [56]. These results came in agreement with the findings of Johnston and his colleagues who found that human interleukin-10 Gene transfer was protective in a Rat Model of PD [57]. Even when the case of PD will go to deep brain stimulation (DBS) surgery, Nozaki and his colleagues recently found significant dopamine release in the ventromedial striatum by STN-DBS during exercise, which indicates that dopaminergic activation process occurs in the motivational circuit during action [58].

Concerning the effect of physical activity and oxidative damage in PD, recent studies also showed that exercise protects the mitochondrial proteins damage in PD [38]. These results were also supported by Patki and Lau who showed the positive impact of exercise on mitochondrial function as the function of mitochondria is essential for preventing the process of neurodegeneration in PD [59]. In human studies, resistance exercise training also showed to be associated with reduced oxidative stress in subjects with PD. This reduction can be explained by increase endogenous antioxidant protection role and decrease the production of reactive oxygen and nitrogen species [60].

1.4. Exercise Effect on PD Medications

To date there is no cure for PD. Levodopa as golden standard medication for PD might results in Levodopa resistance or levodopa toxicity after 5-7 years of treatment. The dose has important role on the efficacy of the drug as we need to reduce the drug option in PD treatment by replacing this approach with safe and feasible way of treatment for PD. In this regard, studies showed that intensive rehabilitation program lead to reduction in daily medication dosage in exercised treated PD patients, while it was increased significantly in control patients [61]. Recent studies from Cleveland Clinic showed that forced exercise of lower extremities reduced the motor symptoms in PD, moreover, this study also showed that the activation of the brain region in PD using functional magnetic resonance imaging by exercise has the same pattern of activation after medication [62], so both exercise and medication might use

the same pathway to reduce the progression of PD. In our previous report, we showed increase production of dopamine in chronic Parkinsonian mice, although that increase was not significant, but it is of great clinical value as exercise wont only decrease the worsening of the disease but also able to increase the production of dopamine [63]. In agreement with our previous results, Muller and Muhlack concluded that endurance exercise induced increase in endogenous dopamine synthesis, which is indicated by beneficial effect on scored motor performance in patients with PD [64]. These excited results placed exercise therapy approach as alternative that has almost the same impact of medications in PD.

1.5. Exercise Improves Cognition and Memory in PD

Large epidemiological studies showed that physical activity is associated with decreased risk of cognitive impairment in Alzheimer's disease; these studies showed that people who exercise routinely are less prone to have Alzheimer's disease late in their life [65]. With aging, there is a physiological decline in brain function [66]. The hippocampus will shrink; often result in memory decline and impairment [67]. One of the major complications in PD as age associated diseases cognitive impairment [68]. Hippocampus is the structure of importance in memory issues. Here, there are studies which showed that aerobic exercise training is effective at reversing hippocampal volume loss in late adulthood as exercise increases the size of the anterior hippocampus. Increasing the size of hippocampus will consequently improve the memory in PD patients [69]. Other studies in this regard also showed that physical activity spares gray matter volume in late adulthood, so Physical activity is associated with reduced risk of cognitive impairment [70,71]. Another study by Laura and colleagues to examine whether exercise is beneficial for people with dementia and related cognitive impairments, they found that exercise training increases cognitive function, and positive behavior in people with dementia and related cognitive impairments [72]. There is more than one hypothesis behind the fact that physical activity reduces the risk of reduced cognition with aging and with age related diseases. One of these molecular basis hypothesis was reported by Gomeza and colleagues , who found that fibroblast growth factor messenger RNA, and astrocytes density were increased in hippocampus and cerebellum of trained rats [73]. Other researchers have reported increased synaptic plasticity with exercise training through its effect of hippocampal BDNF [74]. Here it would be important to point to the fact that BDNF influences the development of patterned connections growth and complexity of dendrites in the brain [75]. In our previous research on mouse model with chronic Parkinsonism, we reported increased expression of glial fibrillary acidic protein in the striatum [36] and increased neurogenesis [15]. In agreement with our results, Saur and colleagues recently reported that physical exercise increases GFAP expression and induces morphological changes in hippocampal astrocytes [76]. These

results raised the importance of physical activity on brain plasticity, and activation and stabilization of neuronal synapses in the brain.

In conclusion, exercise training can be considered as safe and feasible approach to rehabilitate PD. The effect of exercise is way beyond the improvement of quality of life, increased balance and muscle strength, but rather than that exercise has good ability to rehabilitate the brain in PD.

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