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Review article

Neurotrophic factors in Parkinson's disease are regulated by exercise: Evidence-based practice☆

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ABSTRACT

We carried out a qualitative review of the literature on the influence of forced or voluntary exercise in Parkinson's Disease (PD)-induced animals, to better understand neural mechanisms and the role of neurotrophic factors (NFs) involved in the improvement of motor behavior. A few studies indicated that forced or voluntary exercise may promote neuroprotection, through upregulation of NF expression, against toxicity of drugs that simulate PD. Forced training, such as treadmill exercise and forced-limb use, adopted in most studies, in addition to voluntary exercise on a running wheel are suitable methods for NFs upregulation.

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1. Introduction

Exercise is an effective tool to slow the physical and cognitive decline resulting from aging [1]. In humans, aerobic exercise is associated with increases in blood supply and growth factors. Growth factors assist in promoting neurogenesis and synaptic plasticity through release of neurotransmitters, such as dopamine (DA), noradrenaline, serotonin

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and glutamate, which contribute to the good physical condition of exercise practitioners [1–5]. Exercise also plays an important role in reducing the risk of developing neurological disorders, such as Alzheimer's disease [6] and Parkinson's disease (PD) [7]. Recent studies have reported that physical exercise delays worsening of these conditions [8, 9].

PD is a neurodegenerative disorder characterized by cellular and molecular mechanisms leading to loss of dopaminergic neurons in the basal ganglia. This loss of dopaminergic neurons occurs in the *substantia nigra pars compacta* (SNpc). Because of dopamine depletion, patients show the following clinical features: resting tremor, akinesia and/or bradykinesia, rigidity, postural instability and gait changes [10, 11]. The etiology of PD is unknown, although several known neuroinflammatory mechanisms, including oxidative stress, nitric oxide and mitochondrial dysfunction are involved in the pathophysiology of the disease [12]. In addition, excitotoxicity (an excessive activation of neuronal amino acid receptors) also seems to mediate neuronal death in PD, especially triggered by glutamate [13, 14]. Therefore, considering that some studies have reported benefits of exercise in patients with PD, including improvement of clinical and motor aspects, it is important to understand the neurobiological mechanisms involving the practice of physical activity in PD [15].

Studies have shown that in rodents subjected to exercise after application of neurotoxins that simulate PD, loss of DA in the SNpc was reduced. The neurotoxins that are most often used for this purpose are 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [16–18], 6-hydroxydopamine (6-OHDA) [19–21], and lipopolysaccharide (LPS) [22]. These reports indicate that physical exercise acts by producing factors such as brain-derived neurotrophic factor (BDNF) [22, 23], glial cell-derived neurotrophic factor (GDNF) [24], and vascular endothelial growth factor (VEGF) [25] that stimulate neuroprotection.

How does exercise protect dopaminergic neurons against neuroinflammatory mechanisms, oxidative stress, mitochondrial dysfunction and other apoptotic processes? One hypothesis is that neurotrophic factors (NFs) are upregulated in animals induced to PD and submitted to physical exercise [26–29].

NFs are a family of proteins that function as growth factors required for the maintenance, survival, specification and maturation of neuronal populations [30–32]. The "neurotrophic hypothesis", as shown in the literature, asserts that maintenance of neuronal networks is required for the release of proteins captured by nerve terminals and transported retrogradely within neurons. When these NFs reach the nucleus, they induce gene programming to promote neuronal survival and phenotype specification [33].

Several proteins have been classified as NFs, including BDNF, GDNF, insulin-like growth factor (IGF) and VEGF. These proteins are classified as NFs due to their effects on survival, differentiation, synaptogenesis, neuronal maturation and many other physiological properties. Because of their important role in neuron survival, NFs are considered the most promising treatment for neurodegenerative diseases, including PD [31]. Despite the promising neuroprotective properties of NFs, the clinical application of these proteins into the cerebrospinal fluid in patients with PD and Alzheimer's disease has been ineffective, due to the difficulty encountered by these proteins in crossing the neurovascular unit (brain-blood barrier) [31, 34, 35].

If we consider that physical exercise is an effective alternative to promote neuroprotection of dopaminergic neurons in PD, it is necessary to investigate the relationship of NFs to physical exercise. This article is a qualitative systematic review with the objective to analyze papers based on studies using animal models of PD, in order to investigate the effect of exercise on the expression of NFs. Because of the lack of information on exercise-induced synthesis of tyrosine hydroxylase (TH) regulated by NFs in the nigrostriatal pathway in animals induced to PD, in this article we review the state of knowledge regarding TH synthesis in PD after physical training, and discuss the possible signaling pathways of different NFs.

2. Materials and methods

The literature review was conducted using the following electronic databases: NCBI PubMed, LILACS and SciELO, based on the following groups of keywords: 1) Parkinson's disease, physical activity, animal model, neurotrophic factors; 2) Parkinson's disease, exercise, animal model, neurotrophic factors; 3) Exercise, dopamine, BDNF; 4) Exercise, dopamine, GDNF; 5) Exercise, dopamine, VEGF; 6) Parkinson's disease, exercise, animal model, BDNF; 7) Parkinson's disease, exercise, animal model, GDNF; 8) Parkinson's disease, exercise, animal models, VEGF; 9) Exercise, neuroprotection, BDNF. Because we were able to find in the PubMed database the same references found in the other databases (SciELO and LILACS) as well as additional items that were not indexed in these latter, we chose to use only PubMed to locate articles. The inclusion criteria were thematic correlation, experimental studies in animal models, articles published in English, Portuguese and Spanish available in full text, with information regarding the subjects of Parkinson's disease, physical activity, animal model and neurotrophic factors, published between 2000 and 2015. Review articles and studies performed in humans were excluded. From the articles obtained, we evaluated the full texts included in this study (Fig. 1).

3. Results

Based on the descriptors, we encountered 214 articles. However, only 10 articles addressed the topic as defined in this study, confirming the scarcity of literature on the neuroprotective effect of exercise involving NFs in PD.

All the included studies suggested that physical exercise can promote neuroprotection, through upregulation of NFs expression, against the toxicity of drugs that simulate PD. Cell survival of the dopaminergic neurons is mediated by regulation of the transcription of TH encoding and synthesizing gene. TH is an enzyme involved in catecholamine biosynthesis, by acting in the conversion of tyrosine to *L*-dihydroxyphenylalanine (*L*-DOPA), which in turn is converted to dopamine by the *L*-amino acid decarboxylase aromatic enzyme [36]. Increased TH activity promotes survival of dopaminergic neurons [37]. The main features of the articles included in this review are summarized in Table 1.

4. Discussion

4.1. Overview of the effect of exercise on PD

The practice of exercise is shown in the literature as a potent therapeutic strategy available for cognitive and motor rehabilitation of patients with neurodegenerative diseases, including PD [43, 44]. However, the neurobiological mechanisms involved in the practice of physical exercise in neurodegenerative diseases are mostly unknown. The literature review revealed that the exercise methods used in most animal models are the running wheel, performed voluntarily, and forced treadmill training [45–47]. Table 1 shows that when the groups submitted to physical exercise were compared with control groups, i.e., the PD-sedentary groups, both voluntary and forced exercises had positively influenced motor behavior. The motor improvement influenced by exercise was followed by changes in the expression of NFs [48–53]. It has been speculated that the NFs may have a role in cell survival and restoration of dopaminergic cells in the nigrostriatal pathway [20, 39, 54, 55]. Despite the known ability of exercise to promote motor improvement followed by neurotrophic change in PD, it is still necessary to determine the most appropriate intensity and frequency of training to maximize the beneficial effects. Therefore, it is important to understand how exercises act on the production of NFs and how these NFs can influence on TH synthesis.

Among the methods most commonly used in studies over the last decade, treadmill training (forced exercise) was most often adopted,