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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.

Contents

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,

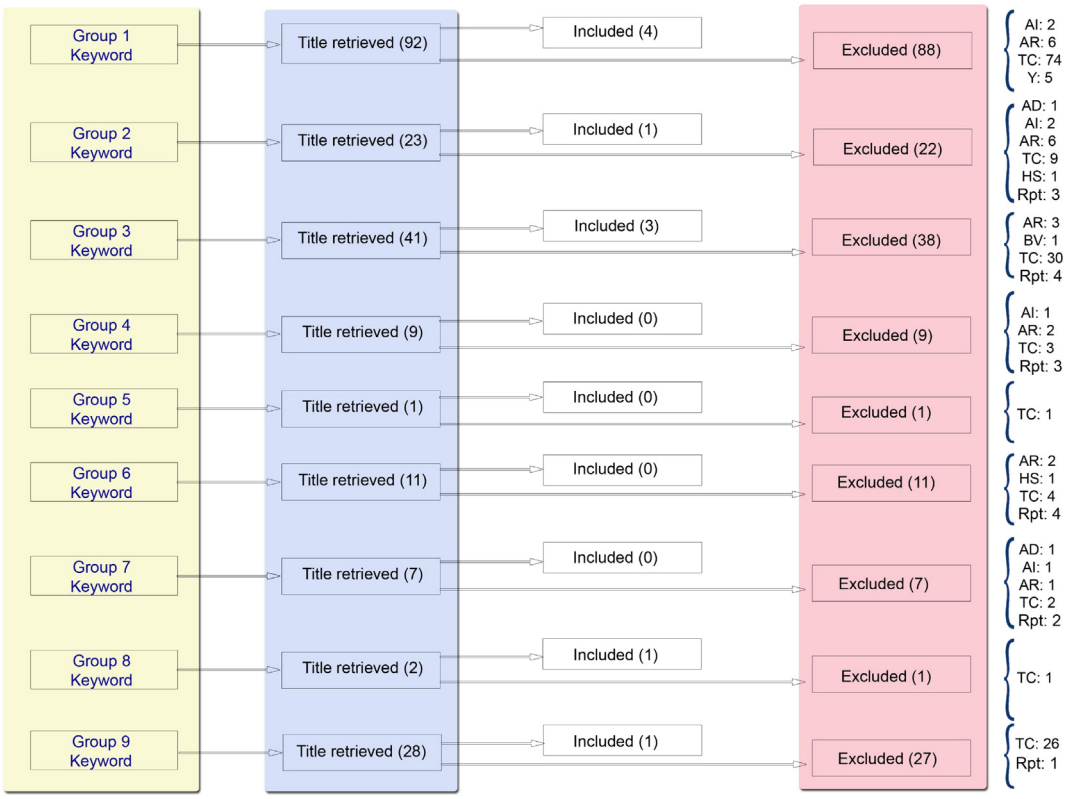

Fig. 1. Diagram showing the number of titles retrieved; articles excluded, with reasons, and final inclusion.

generally based on 5 sessions per week for 4 weeks, each session lasting from 30 to 40 min, intensity from 17 m/min to 20 m/min [18, 22, 25, 40, 55]. The six studies analyzed here that used forced training at these parameters showed motor improvement and upregulation of NF expression. The NFs associated with neuroprotection, such as BDNF [22, 23, 39–42] and GDNF [16, 22, 39, 40], were upregulated after forced physical training. The regulation of these NFs was followed by the preservation of dopaminergic cells in PD-exercise groups compared with PD-sedentary groups. In cases where sedentary animals were induced to PD by either 6-OHDA or MPTP neurotoxins, BDNF and GDNF levels, both related to enzymatic activation of TH, were very significantly reduced in the *striatum* compared to trained animals [23, 39].

In addition to the previously mentioned factors, exercise appears to change the striatal VEGF expression, suggesting that physical exercise increases the density of blood vessels and consequently assists in neuronal survival [25].

Forced exercise is considered a possible preventive strategy for the development of PD. A study of a PD-exercised group submitted to training on a treadmill during one, two or four weeks before the induction of PD by LPS, with or without a week of exercise after PD, showed that four weeks of exercise before the induction were enough to prevent a decrease in the nigrostriatal expression of BDNF and GDNF. Animals submitted to one or two weeks of physical exercise before induction of PD showed no significant protection, due to the decrease of dopaminergic cells [22].

Forced treadmill training seemed to have produced neuroprotection for dopaminergic neurons in both the SNpc and the *striatum*, even in animals induced to PD with the use of the toxins 6-OHDA and MPTP [18, 19]. Although the general consensus in the literature is that physical exercise has a neuroprotective effect, it is also suggested that the increased release of corticosterone, a suppressor factor of BNDF mRNA and protein, may jeopardize the possible beneficial effects of exercise when this is forced [57–59]. Voluntary exercise on running wheels does not significantly increase corticosterone levels [60, 61], suggesting that voluntary exercise is more suitable for the maintenance of BDNF expression [47].

4.2. Exercise and BDNF

In order to investigate whether the neuroprotection offered by exercise is BDNF-dependent, researchers studied the effectiveness of voluntary physical training with a running wheel in mice, using a 90 d program. Mice induced to an acute model of PD were divided into two groups. The first group consisted of mice with heterozygous deletion of the BDNF gene. The second group consisted of wild-type mice. Only the wild-type BDNF group exhibited neuroprotection against exposure to the toxin [18].

Researchers also analyzed voluntary training in mice that had been PD-induced by MPTP, after periods of 30, 60 or 90 d [18]. The animals that underwent 30 d of voluntary training showed no neuroprotection. The group that exercised for 60 d showed a smaller loss of dopaminergic neurons (16%) compared with the group that exercised for 30 d. The group that underwent 90 d of exercise showed a 9% loss of dopaminergic neurons compared with the group that exercised for 30 d. Thus, the study indicated that the running training for 90 d best promoted a neuroprotective effect on dopaminergic cells. Among the NFs analyzed (BDNF, GDNF, VEGF and IGF-1), BDNF appear to be primarily responsible for survival and differentiation of dopaminergic neurons [22, 23, 39, 40,56, 62–64]. The NFs studied seem to have a specific affinity to tyrosine kinase receptors, and are the first signaling molecules to reach the cell surface in order to bind to and regulate the cAMP response element binding protein (CREB). CREB is a cellular transcription factor that binds to a specific DNA sequence known as a response element to cyclic AMP (cAMP response elements, CRE), regulating gene transcription.

BDNF is an important factor in neuronal differentiation, distributed throughout the central nervous system and found in large amounts in hippocampal regions [65, 66]. This NF is also present in the *striatum* (Table 1). Thus, BDNF appears to be involved in the survival and

Table 1
Effects of exercise in PD animal models.

Author/year	Animal Model	PD induction	Aim of the study	Weekly frequency/exercise session/total length of training	Summary of issue	Conclusion
Tuon et al., 2012. [23]	Wistar Rats (male).	6-OHDA	Evaluated the effects of treadmill training on the expression of neurochemical mediators (TH and BDNF) and markers of oxidative stress (thiobarbituric acid reactive substances (TBARS) and carbonyl) in the *striatum* of rats with induced parkinsonism.	The animals underwent an exercise program of progressive running (13–17 m/min), 3 or 4 d/wk for 8 weeks. Each session lasted 50 min, with 48-h intervals.	Motion analysis: A rotational test to assess deficits in balance was used. A significant reduction in the number of asymmetrical rotations in the PD-trained group compared to the PD-sedentary group was observed. Analysis of striatal TH: The PD-trained group showed a TH level 59% higher than the PD-sedentary group. Analysis of BDNF: The PD-trained group demonstrated a 33% increase in the BDNF level compared to the PD-sedentary group.	Exercise promotes a neuroprotective effect in PD model induced by 6-OHDA.
Wu et al., 2011. [22]	C57BL/6J Mice (male).	LPS	Investigated the effects of forced treadmill training with moderate intensity to dopaminergic neuronal loss induced by an inflammatory process in the SNpc.	PD-control and PD-trained groups were familiarized with the treadmill at a speed of 9 m/min, 10 min/d for 5 days. Exercised animals underwent a 4-wk physical training. Exercised mice ran at a speed of 10 m/min for 20–60 min/d (an increase of 10 min/d), 5 d/wk in the first week, followed by 60 min at the same speed daily, 5 d/wk during the next 3 weeks.	Motion analysis: Using the RotaRod acceleration test, 4 weeks of exercise before LPS injection completely prevented motor, balance and coordination dysfunction. Analysis of PD neurons in SNpc: 4 weeks of exercise before LPS injection with or without 1 week of exercise after injection, completely blocked the loss of TH neurons induced by LPS. Two weeks of exercise before the LPS injection or 1 week of exercise after the LPS injection did not offer significant protection against loss of TH neurons induced by LPS. Four weeks of exercise before the LPS challenge completely prevented the loss of DA and 3,4-dihydroxyphenylacetic acid (DOPAC). Analysis of GDNF and BDNF in the SNpc: BDNF levels in the *striatum* and SN were unchanged after 4 weeks of exercise, as were the levels of GDNF in the SNpc and *striatum*. Four weeks of exercise before the LPS injection was enough to prevent loss of dopaminergic neurons. The exercise was also able to prevent loss of BDNF and GDNF. One week after LPS induction without preventive exercise, BDNF levels decreased in the *striatum* and SNpc. There was no alteration in the levels of GDNF in the *striatum* and SNpc after physical training or use of LPS.	Long-term physical exercise protects dopaminergic neurons in SNpc against inflammatory injury. The beneficial effect of exercise occurs after activation of the BDNF signaling pathway.
Al-Jarrah et al., 2010. [25]	C57BL/6J Mice (male).	MPTP + Probenecid.	Investigated the presence of angiogenesis in the nigrostriatal system by forced treadmill training in PD-induced mice.	Running 40 min/d, 5 d/wk at 18 m/min speed, without intervals. The protocol was individualized for each animal.	Angiogenesis analysis: 4 weeks of resistance training resulted in a significant increase in the density of blood vessels in the *striatum* of the PD-trained group compared to the PD-sedentary group. Increased density of blood vessels induced by exercise was observed when vessel identifications were performed with *anti*-cluster of differentiation 34(CD34) and VEGF. Motion analysis: Not performed in the study.	Four weeks of running exercise performed on a modified treadmill promoted angiogenesis in the mouse brain induced by chronic parkinsonism. Exercise increases blood-vessel density and can promote neuronal survival. This finding may partly explain the beneficial effect of physical exercise in patients with PD.
Gerecke et al., 2012. [38]	C57BL/6J wild-type mice and C57BL/6J mice containing heterozygous deletion of BDNF wild gene (female).	MPTP	Determined the correlation between exercise-induced neuroprotection and BDNF expression in an acute model of parkinsonism.	90 d of voluntary running for approximately 7.5 km over 24 h.	Analysis of dopaminergic neurons in the SN: Exercise promoted protection against loss of dopaminergic cells in the SN of wild-type mice with MPTP. There was no significant difference in the number of dopaminergic neurons between the sedentary wild-type group that received only saline and the exercised wild-type group that received MPTP. The exercise did not provide neuroprotection of dopaminergic neurons in exercised BDNF-deficient mice. In the exercised and BDNF-deficient mice, PD-induced by MPTP, there was a 26.49% loss of neurons in the SN compared to the exercised BDNF-deficient group that received only saline. The loss of neurons in the SN in the exercised group with PD-induced BDNF deficiency was similar to that observed in the PD-sedentary wild-type group.	Voluntary training in a running wheel for 90 days does not promote neuroprotection against toxicity of MPTP in the SN of BDNF-deficient-mice. BDNF is important in exercise-induced neuroprotection.

Tajiri et al., 2010. [39]	Sprague–Dawley Rats (female).	6-OHDA	Investigated the influence of forced treadmill training on the expression of neuroprotective factors in an acute model of parkinsonism.	Forced treadmill training was conducted at 11 m/min, 30 min/d, 5 consecutive days for 4 weeks.	Motion analysis: Not performed in the study. Motion analysis: From the second week after application of 6-OHDA, the PD-trained group showed an improvement in scores in the cylinder test compared to the PD-sedentary group. Analysis of TH: The PD-trained group showed a significant preservation of TH-positive fibers in the *striatum* and TH-positive neurons in the SNpc, compared to the PD-sedentary group. Analysis of GDNF and BDNF in the *striatum*: The levels of GDNF and BDNF increased in both sides of the *striatum* (intact and injured) of the PD-trained compared to the PD-sedentary rats. Analysis of cell migration and proliferation in the subventricular area of the *striatum*: There was a significant difference in the number of 5-bromo-2′-deoxyuridine (BrdU)/doublecortin (Dcx)-positive cells in the striatal subventricular area of the PD-trained group compared to the PD-sedentary group, demonstrating increased proliferation and migration of neural progenitor cells.	Exercise in an acute model of parkinsonism has a neuroprotective effect on the dopaminergic system and promotes neuronal migration from regulation of BDNF and GDNF in the striatal subventricular area.
Lau et al., 2011. [40]	C57BL/6J Mice (male).	MPTP hydrochloride and probenecid	Investigated motor performance of treadmill training, as well as changes in biological markers of dopaminergic neurons and the activity of neurotrophic factors in the nigrostriatal pathway.	The exercise program was performed for 1 week before, 5 weeks during treatment with MPTP/probenecid and 12 weeks after the treatment. The program consisted of 5 d/wk, 40 min/day at a speed of 15 m/min (6 m/min for 5 min, 9 m/min for 5 min, 12 m/min for 20 min, 15 m/min for 5 min and 12 m/min for 5 min).	Motion analysis: Balance and motor coordination were tested with a challenging beam. No disturbances in balance or motor performance were detected after 18 weeks of exercise in the PD group. Analysis of TH in the SNpc: After 18 weeks of exercise, the PD-trained group showed an increase in the number of TH cells. The total number of TH cells in SNpc was restored by exercise when the PD-trained group was compared to the PD-sedentary group. Analysis of biomarkers of striatal dopamine: Levels of TH, DA and dopamine active transporter (DAT) increased significantly after 18 weeks of exercise in the PD-trained group compared with the PD-sedentary group. Analysis of BDNF and GDNF: Levels of BDNF and GDNF did not change in the SN and *striatum* of the PD-sedentary group. The practice of exercise for 18 weeks significantly increased BDNF levels in the SN, but not in the *striatum*. Exercise increased GDNF levels in the *striatum*, but not in the SN. The amount of GDNF in the SN of the PD-trained group was still significantly higher than in the PD-sedentary group.	Exercise for 18 weeks prevents motor deficits through a neuroprotective effect and promotes neurotrophic activity of dopaminergic neurons.
Fredriksson et al., 2011. [41]	C57BL/6J Mice (male).	MPTP	Investigated BDNF expression, dopamine level and motor performance in exercise-trained animals with short (3 weeks) and long-term (14 weeks) exercise performed in running wheel.	Short-term training protocol: 30 min/d, 5 consecutive days/wk for 3 weeks. Long-term training protocol: 30 min/d, 4 consecutive days for 14 weeks	Motion analysis: 3 weeks of exercise partially restored motor activity in the acute model. Striatal dopamine: The 14-week exercise routine, maintained for 9 weeks after the final MPTP administration, attenuated the loss of DA. The PD-trained group showed a higher dopamine level than the PD-sedentary group. Parietal BDNF: Training for 14 weeks, raised concentrations of BDNF in the PD-trained group compared with the PD-sedentary group.	Running exercise attenuates the MPTP-induced dopamine loss and promotes an increase in BDNF expression. These factors are related to motor improvement promoted by exercise.
Faherty et al., 2005. [16]	C57BL/6J Mice (female).	MPTP	Investigated the effects of enriched environment with physical activity in modulation of nigral dopaminergic death in PD-induced animals.	The groups were pre-conditioned in 3 different environments: Enriched environment (2 running wheels and tunnel systems), Exercise (1 running wheel), and Standard Environment (without equipment). The running wheels were freely available, where the animals ran voluntarily for 3 months. The activity of each animal was not monitored individually.	Analysis of the number of dopaminergic neurons in the SNpc of the enriched-environment MPTP-group: The difference in environments did not affect the number of dopaminergic neurons in the enriched-environment MPTP-group or the standard-environment MPTP-group. Analysis of GDNF, BDNF and IGF-1 mRNA in SN of the enriched-environment MPTP-group: Animals placed in an enriched environment demonstrated a 180% increase in GDNF expression, and reductions of 50% of IGF1 and 32% of BDNF when compared to animals in the standard environment.	The study suggests that exposure to an enriched environment (combination of exercise, social interaction and learning) or exercise alone for 3 months protects against the toxicity of MPTP. Moreover, changes in mRNA expression of GDNF contribute to dopaminergic nigrostriatal neuroprotection. The results suggest the use of exercise as a prevention/support tool in the treatment of PD.

(continued on next page)

Table 1 (*continued*)

Author/year	Animal Model	PD induction	Aim of the study	Weekly frequency/exercise session/total length of training	Summary of issue	Conclusion
					Analysis of the number of dopaminergic neurons in the SNpc of the exercise-environment MPTP-group: The exercise of voluntary running for 3 months without other environmental interventions, protected the exercise-environment group against MPTP toxicity compared to the standard-environment MPTP group. However, this protection (16% loss) was lower than that found in the enriched-environment MPTP group (0% loss). Analysis of GDNF, BDNF and IGF-1 mRNA in the SN and *striatum* of the exercise MPTP-group: Running promoted a 35% decrease in IGF1 and a 250% increase in the expression of GDNF (not significant) compared to the standard environment -MPTP. In the *striatum*, there was a 37% reduction in the IGF1 receptor and a 50% increase in BDNF expression.	
Cohen et al., 2003 [24]	Long-Evans Rats (male)	6-OHDA	Examined GDNF expression level after a forelimb constraining.	Animals received a cast on a forelimb for 7 days prior to being given an ipsilateral infusion of 6-OHDA into medial forebrain bundle.	Motion analysis: Forced forelimb-use for 7 days prior to an ipsilateral infusion of 6-OHDA attenuated the apomorphine-induced rotational behavior as well as decreased asymmetry when both right and left sides were compared. Analysis of GDNF: GDNF levels increased in *striatum*, corresponding to the overworked forelimb. GDNF levels in the opposite side were unchanged. Analysis of DA and DOPAC: Loss of striatal DA and DOPAC contents were attenuated in animals casted compared to PD-sedentary group.	The study suggests that forced limb-use could be neuroprotective against injury to nigrostriatal pathway. This protection involves increasing GDNF expression level.
Real et al., 2013 [42]	Wistar Rats (male)	6-OHDA	Investigated the role of BDNF in intermittent treadmill exercise-induced animals, evaluating histological/neurochemical changes in unilateral PD.	Intermittent treadmill training was performed for 40 min/d, 3 d/wk at a speed of 10 m/min before and/or after four weeks after the induction of PD.	Analysis of BDNF, TH: BDNF protein levels decreased in SNpc of the PD-sedentary group when compared to the control group and exercised groups. Analysis of TH: No differences of TH levels by immunoblotting and immunostaining in exercised, non-parkinsonian rats in relation to PD-sedentary and non-parkinsonian rats were observed. TH staining decreased in PD-sedentary and PD-sedentary + BDNF receptor blockade blocker groups when compared to control group. Immunoblotting revealed that TH levels in SNc decreased only in the PD-sedentary group when compared to other groups.	Intermittent treadmill training increased BDNF and TH levels in unilateral PD.

maintenance of dopaminergic neurons, and therefore improves motor performance [24]. BDNF has been shown to be a crucial NF in exercise-dependent neuroplasticity, neuron preservation in cases of brain injury, and other functions throughout life, such as learning and memory [67–69]. These functions have been demonstrated in studies using adult rodents in cell-culture experiments, where upregulation of BDNF promoted the survival of nigrostriatal neurons and other cortical regions [70–72].

It is known that there is a close relationship between BDNF and the TrkB receptor (a receptor of the tyrosine kinase family, which shows a high affinity to BDNF). Activation of this receptor by BDNF is one of the regulators of TH gene transcription [73].

4.3. Exercise and CREB

Among the mechanisms related to exercise-dependent neuroplasticity, CREB is directly involved in regulating TH expression in PD [73, 74]. Activation of the tyrosine kinase receptor is responsible for CREB activation, which, in turn, regulates the TH gene transcription, playing a crucial role in exercise-dependent neuroplasticity. With exercise, CREB is activated by different signal transducers, such as mitogen-activated protein kinase (MAPK), calcium calmodulin kinase II (CaMKII) and *N*-methyl-D-aspartate receptor (NMDA-R) in both the hippocampus and *striatum* plasticity [75].

Physical exercise induces neuroplasticity not only under normal physiological conditions, but also in cases of brain injury. Exercise-induced neuroplasticity under physiological conditions, and in cases of brain injury, occurs by increasing enzymatic activity of TH, acting on the survival and synthesis of dopamine neurons [49].

4.4. Exercise and GDNF

In recent years, the GDNF and GDNF family ligands (GFL) have been studied because of their involvement in the survival of dopaminergic and noradrenergic neurons. The GFL family is composed of four neurotrophic factors, GDNF, neurturin (NRTN), artemin (ARTN) and persephin (PSPN). These four factors belong to the transforming growth factor β (TGF-β) superfamily, which are proteins composed of a number of cytokines and neurotrophins, responsible for controlling cell proliferation and differentiation in most cells [76].

GDNF is expressed in several brain areas, and is most prominent in areas that receive catecholaminergic afferents [77], such as the *striatum* and *thalamus* [78, 79]. The reports listed in Table 1 indicate that GDNF has a dual trophic function: neuroprotection and neuroregeneration. These trophic effects of GDNF are described as TGF-β-dependent. TGF-β acts as a modulator of GDNF signaling and participates in GFRα co-receptor translocation (1-4) in the cell membrane, where they associate with their respective co-receptors GDNF, NRTN, ARTN and PSPN. The association between ligands and co-receptors forms the GFL-GFRα complex, which is responsible for recruiting a dimer of transmembrane tyrosine kinase (RET). GDNF has a strong affinity to GFRα1 and is more susceptible to the formation of the GFL-GFRα complex, but it can also be formed through binding to receptors (GFRα2-4) with lower affinity. The aggregation of RET, in turn, triggers the transphosphorylation of tyrosine residues of the RET kinase molecule, initiating the process of intracellular signaling. Then, a series of cascades occurs, including MAPK and phosphoinositide 3-kinase (PI3K) [80]. These cascades play a role in neuronal growth and survival through activation of CREB and protein kinase B (Akt), acting in cell proliferation and transcription [80, 81]. Moreover, extracellular signal-regulated kinase (ERK), a downstream effector of GDNF, seems to be activated after exercise continues at an increased level for up to 1 month [24]. GDNF also seems to be able to modulate microglial activation through GFRα1. Thus, GDNF triggers signaling cascades, which are responsible for the inhibition of microglial activation [82].

4.5. Exercise and VEGF

The brain plasticity promoted by exercise is not limited to neurons, but also involves astrocytes and microvascular cells. Microvascular changes are regulated by angiogenesis, responsible for the formation of new blood vessels from pre-existing vessels. Survival and homeostasis depend on appropriate sources of oxygen and nutrients, which in turn depend on blood vessels and capillaries. A series of growth factors contributes to angiogenesis, but VEGF seems to be the main factor responsible for this process and is also associated with vasculogenesis in embryonic stages [83].

Among the strategies used to treat vascular lesions, exercise is an important factor responsible for VEGF regulation [84, 85]. VEGF is a signaling protein composed of five main members: VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor (PlGF) [86]. Its function is associated with promotion of vasculogenesis and angiogenesis, restoring oxygen support in regions where blood flow is inadequate [87–89]. Two members of the VEGF family, VEGF-A and VEGF-B, have therapeutic roles in neurodegenerative diseases [90, 91]. According to the literature, VEGF-A is involved in both pathogenesis and treatment of PD [90, 92]. Studies that implanted VEGF-A secreting cells unilaterally in the *striatum* of adult rats with PD induced by 6-OHDA suggest that the neuroprotective effect is dose-dependent [92]. A low dose of one VEGF-A had a protective effect, while a high dose led to non-protective effects, such as a deregulated increase in the density of blood vessels and consequently, cerebral edema. It is believed that the angiogenesis promotion and increased glial proliferation attributed to VEGF-A occur through binding competitively to semaphorin 3A, a protein known to induce neuronal apoptosis, by specific receptors [93, 94]. VEGF-B has also shown an indirect role in neuronal survival in vivo and in vitro, without altering the angiogenic effect [95, 96]. VEGF-B acts by reducing the regulation of pro-apoptotic proteins such as BH3 proteins. Additionally, VEGF-B shows a safer profile as a neuroprotective molecule, since it apparently does not have undesirable effects such as those shown by VEGF-A [95]. The unregulated expression of this neurotrophin and its malfunctions are related to the pathogenesis of diseases that act by an inflammatory process, such as PD [97]. As described in the literature, VEGF-A, VEGF-B and their respective receptors, VEGFR1 and VEGFR2, are expressed in neurons and astrocytes under inflammatory conditions. The mesencephalon of rats with PD induced by rotenone showed exaggerated expression of VEGF-A and VEGF-B in nigral dopaminergic neurons. In contrast, VEGF-A and VEGF-B are also described as agents for a therapeutic effect involved in dopaminergic neuron survival and glial proliferation [96].

The members of the VEGF family bind to three different tyrosine kinase receptors. As usually happens in the activation of tyrosine kinase receptors, a dimer is formed. This dimer is constituted by binding of VEGF, which are dimeric glycoproteins, to tyrosine kinase receptors. Therefore, the autophosphorylation of the cytoplasmic tyrosine kinase receptor occurs, triggering a series of signaling cascades, such as MAP kinase, AKT and phospholipase C (PLC), which in turn activate the regulation of transcription factors, promoting the regulation of angiogenesis and neuroprotective effects [98]. VEGF-A binds to two similar receptors, VEGFR1 and VEGFR2, with high affinity. VEGF-B binds to VEGFR1, whereas other isoforms of VEGF bind to VEGFR2 and VEGFR3 [99].

4.6. Exercise and IGF-1

Another NF active in neuroprotection that is promoted by exercise is the insulin-like growth factor 1 (IGF-1) [100]. IGF-1 acts in several ways, including maintenance of the body's metabolism, regulation of plasma lipid concentrations and regulation of insulin activity [101]. In addition to its central role in the regulation of somatic functions, IGF-1 is also important in neuronal functions [102, 103]. During the development of the nervous system, IGF-1 plays a

mostly neurotrophic role in stimulating differentiation and survival of neuronal populations. In the adult nervous system, IGF-1 acts as a neuromodulator and is involved in synaptic plasticity, especially in regions where the IGF-1 receptor (IGF-1R) is expressed [104]. The tyrosine kinase receptor (IGF-1R) is largely expressed in nigral dopaminergic neurons and in different regions of the hippocampus [105]. Several biological functions of IGF-1 are mediated by IGF-1R, which triggers intracellular signal transduction [106].

The decrease of IGF-1 levels is associated with the decline in brain function resulting from aging, and the appearance of neurodegenerative diseases such as PD. Similarly to BDNF, IGF-1 possibly activates CaMKII and MAPK cascades, regulating vesicular release through modulation of synapsin I [107]. Cascades such as PI3K/Akt-CREB are also activated by IGF-1 and regulate the transcription of pro-apoptotic genes [108, 109]. The importance of IGF-1 in neuronal survival is highlighted in a study in which receptors of IGF-1 were blocked and death of dopaminergic neurons was induced [110].

4.7. How do neurotrophic factors modulate TH synthesis?

According to the reports listed in Table 1, there is scientific evidence for a relationship between physical activity and regulation of NF expression in PD. This relationship is expressed through a complex mechanism. Furthermore, this subject is little discussed, considering the direct or indirect influence of exercise-induced NF expression on TH synthesis (see Fig. 2). BDNF and GDNF act directly in CREB activation, thereby regulating transcription of the TH gene and increasing enzyme activity. In addition to activating CREB, BDNF also participates indirectly through synapsin I, which regulates synaptic activity. VEGF acts indirectly on dopaminergic survival, by regulating angiogenesis and the blood supply and reducing the activation of pro-apoptotic proteins. It is still a matter for discussion as to whether IGF-1 has a critical role in participation in the trophic effects of exercise in PD. It is possible that, similarly to VEGF, IGF-1 participates indirectly, regulating the transcription of *anti*-apoptotic genes and modulating the activity of synapsin I.

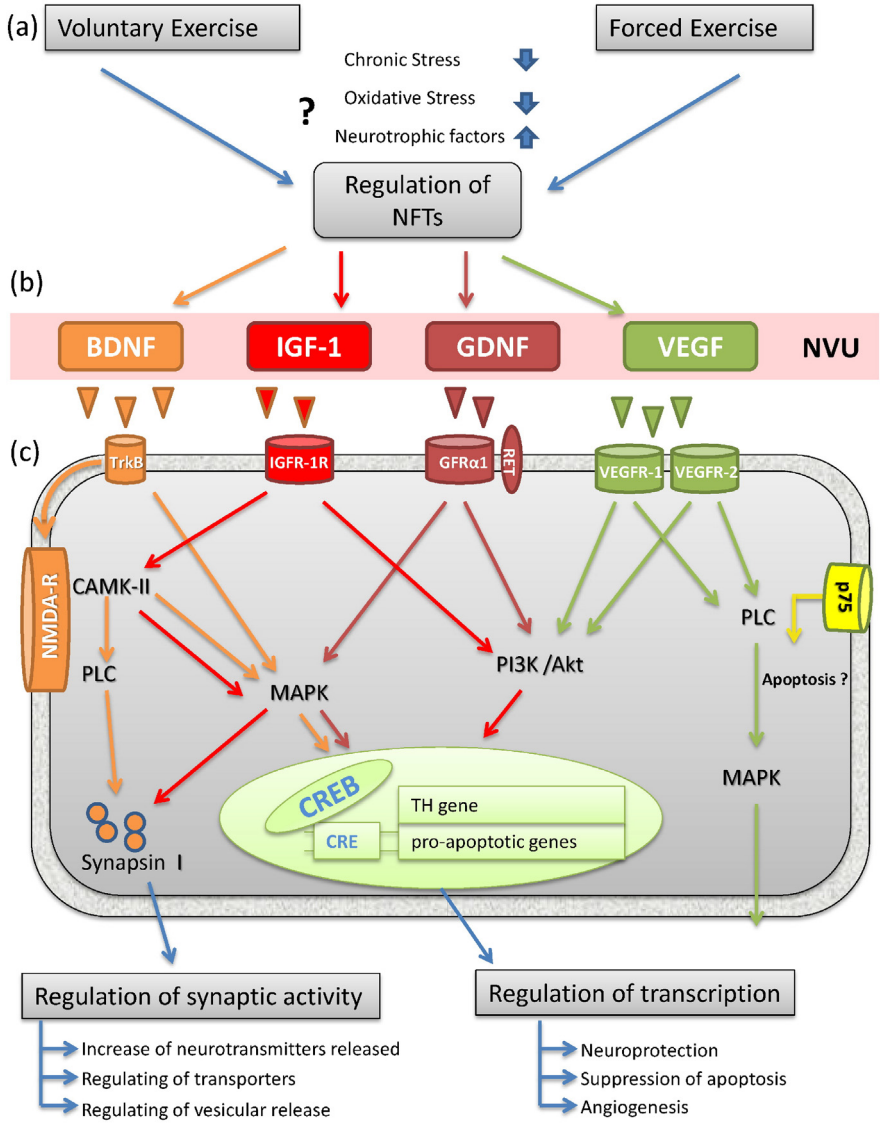

Fig. 2. Mechanism of physical activity-dependent neuroprotection: (a) Both types of physical activity promote increased release of NTFs. Apparently, forced exercise increases the amount of NTFs released. The exact mechanism related to voluntary exercise is unknown. (b) BDNF, IGF-1, GDNF and VEGF derivatives of the central and/or peripheral nervous system modulated by exercise cross the neurovascular unit (NVU). (c) BDNF activates MAPK, and GDNF activates the MAPK and PI3K/Akt signaling cascades responsible for activating CREB and synapsin I, regulating the transcription of TH and maximizing the synaptic activity. CaMKII modulates the capacity of BDNF to regulate CREB and synapsin I during exercise. VEGF-A and VEGF-B bind to receptors 1 and 2, activating signaling cascades (Akt, MAPK and PLC). VEGF regulates angiogenesis and the reduction of pro-apoptotic proteins. IGF-1 acts by promoting the regulation of synaptic activity via modulating synapsin I by CaMKII and MAPK. PI3K/Akt-CREB is also activated by IGF, regulating the transcription of pro-apoptotic genes.

5. Perspectives

Experimental studies that consider other forms of exercise in PD, for example, muscle strengthening, are few. It is also important to focus on studies that include other neuroanatomical structures in addition to the nigrostriatal pathway, such as the spinal cord, cerebellum and nerves, in order to better understand the neuroprotective effect of exercise on the central nervous system and muscles.

Although dopaminergic neurons are the main structures affected in early PD, astrocytes and glial cells are also involved in this neurodegenerative process. However, the responses of glial cells mediated by exercise in PD are still poorly explored.

The literature does not report possible harmful effects of NFs related to physical exercise in PD. It is known, for example, that the interaction of neurotrophic factors with p75 might lead to apoptosis through caspase activation by p53 [111]. Thus, the possible harmful effects of NFs in the PD-exercise group are an important aspect requiring study.

6. Conclusion

Studies on animal models with induced PD have been important to elucidate neurobiological mechanisms related both with exercise and PD. The literature suggests that NFs participate, and BDNF and GDNF are the most studied members of this family. These NFs have been primarily responsible for dopaminergic survival in PD. Changes in the expression of these proteins are associated with the possible cause of PD and survival of the remaining dopaminergic cells.

GDNF and BDNF appear to be closely linked to the TH enzyme transcription required for DA synthesis. These NFs regulate the activity of signaling cascades responsible for TH gene transcription. NFs such as VEGF and IGF-1 appear to indirectly participate in neuroprotection, as regulators of blood supply and synaptic activity, respectively. VEGF and IGF-1 also act in reducing pro-apoptotic proteins.

It remains unclear which physical exercises and intensities can enhance the exercise-dependent neuroprotection.

Forced exercise performed on a treadmill has been the most widely adopted in studies. Voluntary exercise on a running wheel also seems to upregulate the expression of NFs. However, it is unclear which exercise (forced versus voluntary) is the most appropriate to stimulate the production of NFs inducing possible benefits in the neural circuitry related to motricity in PD.

References

[1] S.J. Colcombe, A.F. Kramer, K.I. Erickson, P. Scalf, E. Mcauley, N.J. Cohen, et al., Cardiovascular fitness, cortical plasticity, and aging, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 3316–3321.

[2] K.B. Blomquist, F. Danner, Effects of physical conditioning on information-processing efficiency, Percept. Mot. Skills 65 (1987) 175–186.

[3] R.L. Rogers, J.S. Meyer, K.F. Mortel, After reaching retirement age physical activity sustains cerebral perfusion and cognition, J. Am. Geriatr. Soc. 38 (1990) 123–128.

[4] L.F. Berkman, T.E. Seeman, M. Albert, D. Blazer, R. Kahn, R. Mohs, et al., High, usual and impaired functioning in community-dwelling older men and women: findings from the MacArthur Foundation Research Network on Successful Aging, J. Clin. Epidemiol. 46 (1993) 1129–1140.

[5] D.A. Evans, L.A. Beckett, M.S. Albert, L.E. Hebert, P.A. Scherr, H.H. Funkenstein, et al., Level of education and change in cognitive function in a community population of older persons, Ann. Epidemiol. 3 (1993) 71–77.

[6] R.P. Friedland, T. Fritsch, K.A. Smyth, E. Koss, A.J. Lerner, C.H. Chen, et al., Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 3440–3445.

[7] H. Chen, S.M. Zhang, M.A. Schwarzschild, M.A. Hernan, A. Ascherio, Physical activity and the risk of Parkinson disease, Neurology 64 (2005) 664–669.

[8] A.D. Speelman, B.P. van de Warrenburg, M. van Nimwegen, G.M. Petzinger, M. Munneke, B.R. Bloem, How might physical activity benefit patients with Parkinson disease? Nature Reviews Neurology 7 (2011) 528–534.

[9] M.J. Zigmond, J.L. Cameron, B.J. Hooffer, R.J. Smeyne, Neurorestoration by physical exercise: moving forward, Parkinsonism Relat. Disord. 18 (2012) 147–150.

[10] A.E. Lang, A.M. Lozano, Parkinson's disease. Second of two parts, N. Engl. J. Med. 339 (1998) 1130–1143.

[11] S. Fahn, Description of Parkinson's disease as a clinical syndrome, Ann. N. Y. Acad. Sci. 991 (2003) 1–14.

[12] W. Dauer, S. Przedborski, Parkinson's disease: mechanisms and models, Neuron 39 (2003) 889–909.

[13] M.F. Beal, Excitotoxicity and nitric oxide in Parkinson's disease pathogenesis, Ann. Neurol. 44 (1998) 110–114.

[14] M.C. Rodriguez, J.A. Obeso, C.W. Olanow, Subthalamic nucleus-mediated excitotoxicity in Parkinson's disease: target for neuroprotection, Ann. Neurol. 44 (1998) 175–188.

[15] L.L. Takano, H.R. Leite, A.L. Rosso, M. Vincent, C.L. Corrêa, Effect of the body weight support associated to treadmill approach in Parkinson disease, Top. Geriatr. Rehabil. 30 (2014) 290–295.

[16] C.J. Faherty, K. Raviie Shepherd, A. Herasimtschuk, R.J. Smeyne, Environmental enrichment in adulthood eliminates neuronal death in experimental parkinsonism, Mol. Brain Res. 134 (2005) 170–179.

[17] M.J. Zigmond, R.K. Leak, K. Mirnics, V.A. Russell, Triggering endogenous neuroprotective processes through exercise in models of dopamine deficiency, Parkinsonism Relat. Disord. 15 (2009) 42–45.

[18] K.M. Gerecke, Y. Jiao, A. Pani, V. Pagala, R.J. Smeyne, Exercise protects against MPTP-induced neurotoxicity in mice, Brain Res. 134 (2010) 72–83.

[19] J.L. Tillerson, A.D. Cohen, J. Philhower, G.W. Miller, M.J. Zigmond, T. Schallert, Forced limb-use effects on the behavioral and neurochemical effects of 6-hydroxydopamine, J. Neurosci. 21 (2001) 4427–4435.

[20] J.L. Tillerson, W.M. Caudle, M.E. Reveron, G.W. Miller, Exercise induces behavioral recovery and attenuates neurochemical deficits in rodent models of Parkinson's disease, Neuroscience 119 (2003) 899–911.

[21] M.V. Mabandla, V.A. Russell, Voluntary exercise reduces the neurotoxic effects of 6-hydroxydopamine in maternally separated rats, Behav. Brain Res. 211 (2010) 16–22.

[22] S.Y. Wu, T.F. Wang, L. Yu, C.J. Jen, J.I. Chuang, F.S. Wu, et al., Running exercise protects the substantia nigra dopaminergic neurons against inflammation-induced degeneration via the activation of BDNF signaling pathway, Brain Behav. Immun. 25 (2011) 135–146.

[23] T. Tuon, S.S. Valvassori, J. Lopes-Borges, T. Luciano, C.B. Trom, L.A. Silva, et al., Physical training exerts neuroprotective effects in the regulation of neurochemical factors in an animal model of Parkinson's disease, Neuroscience 227 (2012) 305–312.

[24] A.D. Cohen, J.L. Tillerson, A.D. Smith, T. Schallert, M.J. Zigmond, Neuroprotective effects of prior limb use in 6-hydroxydopamine-treated rats: possible role of GDNF, J. Neurochem. 85 (2003) 299–305.

[25] M. Al-Jarrah, M. Jamous, K. Al Zailaey, S.O. Bweir, Endurance exercise training promotes angiogenesis in the brain of chronic/progressive mouse model of Parkinson's Disease, NeuroRehabilitation 26 (2010) 369–373.

[26] S.A. Neeper, F. Gómez-Pinilla, J. Choi, C. Cotman, Exercise and brain neurotrophins, Nature 373 (1995) 109.

[27] S.A. Neeper, F. Gómez-Pinilla, J. Choi, C.W. Cotman, Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain, Brain Res. 726 (1996) 49–56.

[28] J.P. Kesslak, V. So, J. Choi, C.W. Cotman, F. Gómez-Pinilla, Learning upregulates brain-derived neurotrophic factor messenger ribonucleic acid: a mechanism to facilitate encoding and circuit maintenance? Behav. Neurosci. 112 (1998) 1012–1019.

[29] A.A. Garza, T.G. Ha, C. Garcia, M.J. Chen, A.A. Russo-Neustadt, Exercise, antidepressant treatment, and BDNF mRNA expression in the aging brain, Pharmacol. Biochem. Behav. 77 (2004) 209–220.

[30] G.K. Siegel, N.B. Chauhan, Neurotrophic factors in Alzheimer's and Parkinson's disease brain, Brain Res. Rev. 33 (2000) 199–227.

[31] D. Kirik, B. Georgievska, A. Bjorklund, Localized striatal delivery of GDNF as a treatment for Parkinson disease, Nat. Neurosci. 7 (2004) 105–110.

[32] A.M. Sullivan, A. Toulouse, Neurotrophic factors for the treatment of Parkinson's disease, Cytokine Growth Factor Rev. 22 (2011) 157–165.

[33] C.B. Ibáñez, Message in a bottle: long-range retrograde signaling in the nervous system, Trends Cell Biol. 17 (2007) 519–528.

[34] P. Aebischer, J. Ridet, Recombinant proteins for neurodegenerative diseases: the delivery issue, Trends Neurosci. 24 (2001) 533–540.

[35] M.H. Tuszynski, Growth-factor gene therapy for neurodegenerative disorders, Lancet Neurol. 1 (2002) 1–7.

[36] Nagatsu T, Levitt M, Udenfriend S. Tyrosine hydroxylase. The initial step in norepinephrine biosynthesis. J. Biol. Chem. 239, 1964,2910–17.

[37] Z. Qi, G.W. Miller, E.O. Voit, Computational systems analysis of dopamine metabolism, PLoS One 3 (2008), e2444.

[38] K.M. Gerecke, Y. Jiao, V. Pagala, R.J. Smeyne, Exercise does not protect against MPTP-induced neurotoxicity in BDNF haploinsufficient mice, PLoS One 7 (2012), e43250.

[39] N. Tajiri, T. Yasuhara, T. Shingo, A. Kondo, W. Yuan, T. Kadota, Exercise exerts neuroprotective effects on Parkinson's disease model of rats, Brain Res. 1310 (2010) 200–207.

[40] Y.S. Lau, G. Patki, K. Das-Panja, W.D. Le, S.O. Ahmad, Neuroprotective effects and mechanisms of exercise in a chronic mouse model of Parkinson's disease with moderate neurodegeneration, Eur. J. Neurosci. 33 (2011) 1264–1274.

[41] A. Fredriksson, I.M. Stigsdotter, A. Hurtig, B. Ewalds-Kvist, T. Archer, Running wheel activity restores MPTP-induced functional deficits, J. Neural Transm. 118 (2011) 407–420.

[42] C.C. Real, A.B.F. Ferreira, G.P. Chaves-Kirsten, A.S. Torrão, R.S. Pires, L.R.G. Britto, BDNF receptor blockade hinders the beneficial effects of exercise in a rat model of Parkinson's disease, Neuroscience 237 (2013) 118–129.

[43] L. Teri, L.E. Gibbons, S.M. McCurry, R.G. Logsdon, D.M. Buchner, W.E. Barlow, et al., Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial, JAMA 290 (2003) 2015–2022.

[44] V.A. Goodwin, S.H. Richards, R.S. Taylor, A.H. Taylor, J.L. Campbell, The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis, Mov. Disord. 23 (2008) 631–640.

[45] R. Marin, A. Williams, S. Hale, B. Burge, M. Mense, R. Bauman, et al., The effect of voluntary exercise exposure on histological and neurobehavioral outcomes after ischemic brain injury in the rat, Physiol. Behav. 80 (2003) 167–175.
[46] Y.R. Yang, R.Y. Wang, P.S. Wang, S.M. Yu, Treadmill training effects on neurological outcome after middle cerebral artery occlusion in rats, Can. J. Neurol. Sci. 30 (2003) 252–258.
[47] Z. Ke, S.P. Yip, L. Li, X.X. Zheng, K.Y. Tong, The effects of voluntary, involuntary, and forced exercises on brain-derived neurotrophic factor and motor function recovery: a rat brain ischemia model, PLoS One 6 (2011), e16643.
[48] E. Carro, J.L. Trejo, S. Busiguina, I. Torres-Aleman, Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy, J. Neurosci. 21 (2001) 5678–5684.
[49] C.W. Cotman, N.C. Berchtold, Exercise: a behavioral intervention to enhance brain health and plasticity, Trends Neurosci. 25 (2002) 295–301.
[50] F. Gomez-Pinilla, Z. Ying, R.R. Roy, R. Molteni, V.R. Edgerton, Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity, J. Neurophysiol. 88 (2002) 2187–2195.
[51] M.P. Mattson, S. Maudsley, B. Martin, A neural signaling triumvirate that influences ageing and age-related disease: insulin/IGF-1, BDNF and serotonin, Ageing Res. Rev. 3 (2004) 445–464.
[52] C.W. Wu, Y.C. Chen, L. Yu, H.I. Chen, C.J. Jen, A.M. Huang, et al., Treadmill exercise counteracts the suppressive effects of peripheral lipopolysaccharide on hippocampal neurogenesis and learning and memory, J. Neurochem. 103 (2007) 2471–2481.
[53] G.S. Griesbach, D.A. Hovda, F. Gomez-Pinilla, Exercise-induced improvement in cognitive performance after traumatic brain injury in rats is dependent on BDNF activation, Brain Res. 1288 (2009) 105–115.
[54] G.M. Petzinger, J.P. Walsh, G. Akopian, E. Hogg, A. Abernathy, P. Arevalo, et al., Effects of treadmill exercise on dopaminergic transmission in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury, J. Neurosci. 27 (2007) 5291–5300.
[55] M.C. Yoon, M.S. Shin, T.S. Kim, B.K. Kim, I.G. Ko, Y.H. Sung, et al., Treadmill exercise suppresses nigrostriatal dopaminergic neuronal loss in 6-hydroxydopamine-induced Parkinson's rats, Neurosci. Lett. 423 (2007) 12–17.
[56] J.H. Son, H.S. Chun, T.H. Joh, S. Cho, B. Conti, J.W. Lee, Neuroprotection and neuronal differentiation studies using substantia nigra dopaminergic cells derived from transgenic mouse embryos, J. Neurosci. 19 (1999) 10–20.
[57] M.J. Schaaf, R.W. Hoetelmans, E.R. De Kloet, E. Vreugdenhil, Corticosterone regulates expression of BDNF and trkB but not NT-3 and trkC mRNA in the rat hippocampus, J. Neurosci. Res. 48 (1997) 334–341.
[58] M.J. Schaaf, J. De Jong, E.R. De Kloet, E. Vreugdenhil, Downregulation of BDNF mRNA and protein in the rat hippocampus by corticosterone, Brain Res. 813 (1) (1998) 112–120.
[59] M.J. Schaaf, E.R. De Kloet, E. Vreugdenhil, Corticosterone effects on BDNF expression in the hippocampus. Implications for memory formation, Stress 3 (2000) 201–208.
[60] H. Van Praag, B.R. Christie, T.J. Sejnowski, F.G. Gage, Running enhances neurogenesis, learning, and long-term potentiation in mice, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 13427–13431.
[61] S. Yanagita, S. Amemiya, S. Suzuki, I. Kita, Effects of spontaneous and forced running on activation of hypothalamic corticotropin-releasing hormone neurons in rats, Life Sci. 80 (2007) 356–363.
[62] J. Zhou, H.F. Bradford, G.M. Stern, The stimulatory effect of brain-derived neurotrophic factor on dopaminergic phenotype expression of embryonic rat cortical neurons in vitro, Dev. Brain Res. 81 (1994) 318–324.
[63] S. Theofilopoulos, J. Goggi, S.S. Riaz, E. Jauniaux, G.M. Stern, H.F. Bradford, Parallel induction of the formation of dopamine and its metabolites with induction of tyrosine hydroxylase expression in foetal rat and human cerebral cortical cells by brain-derived neurotrophic factor and glial-cell derived neurotrophic factor, Dev. Brain Res. 127 (2001) 111–122.
[64] O. Guillin, C. Demily, F. Thibaut, Brain-derived neurotrophic factor in schizophrenia and its relation with dopamine, Int. Rev. Neurobiol. 78 (2007) 377–395.
[65] M. Hofer, S.R. Pagliusi, A. Hohn, J. Leibrock, Y.A. Barde, Regional distribution of brain-derived neurotrophic factor mRNA in the adult mouse brain, EMBO J. 9 (1990) 2459–2464.
[66] D.K. Binder, H.E. Scharfman, Brain-derived neurotrophic factor, Growth Factors 22 (2004) 123–131.
[67] S.L. Patterson, L.M. Grover, P.A. Schwartzkroin, M. Bothwell, Neurotrophin expression in rat hippocampal slices: a stimulus paradigm inducing LTP in CA1 evokes increases in BDNF and NT-3 mRNAs, Neuron 9 (1992) 1081–1088.
[68] S.L. Patterson, C. Pittenger, A. Morozov, K.C. Martin, H. Scanlin, C. Drake, et al., Some forms of cAMP-mediated long-lasting potentiation are associated with release of BDNF and nuclear translocation of phospho-MAP kinase, Neuron 32 (2001) 123–140.
[69] S. Linnarsson, A. Bjorklund, P. Ernfors, Learning deficit in BDNF mutant mice, Eur. J. Neurosci. 9 (1997) 2581–2587.
[70] D.M. Holtzman, D.H. Lowenstein, Selective inhibition of axon outgrowth by antibodies to NGF in a model of temporal lobe epilepsy, J. Neurosci. 15 (1995) 7062–7070.
[71] M.N. Patel, J.O. McNamara, Selective enhancement of axonal branching of cultured dentate gyrus neurons by neurotrophic factors, Neuroscience 69 (1995) 763–770.
[72] M.A. Pelleymounter, M.J. Cullen, M.B. Baker, M. Gollub, C. Wellman, The effects of intrahippocampal BDNF and NGF on spatial learning in aged Long Evans rats, Mol. Chem. Neuropathol. 29 (1996) 211–226.
[73] M. Fukuchi, H. Fujii, H. Takachi, H. Ichinose, Y. Kuwana, A. Tabuchi, et al., Activation of tyrosine hydroxylase (TH) gene transcription induced by brain-derived neurotrophic factor (BDNF) and its selective inhibition through Ca(2+) signals evoked via the N-methyl-D-aspartate (NMDA) receptor, Brain Res. 1366 (2010) 18–26.
[74] S. Finkbeiner, S.F. Tavazoie, A. Maloratsky, K.M. Jacobs, K.M. Harris, M.E. Greenberg, CREB: a major mediator of neuronal neurotrophin responses, Neuron 19 (1997) 1031–1047.
[75] S. Vaynman, Z. Ying, F. Gomez-Pinilla, Interplay between brain-derived neurotrophic factor and signal transduction modulators in the regulation of the effects of exercise on synaptic-plasticity, Neuroscience 122 (2003) 647–657.
[76] M.S. Airaksinen, M. Saarma, The GDNF family: signalling, biological functions and therapeutic value, Nat. Rev. Neurosci. 3 (2002) 383–394.
[77] O. Lindvall, U. Stenevi, Dopamine and noradrenaline neurons projecting to the septal area in the rat, Cell Tissue Res. 190 (1978) 383–407.
[78] M. Trupp, N. Belluardo, H. Funakoshi, C.F. Ibáñez, Complementary and overlapping expression of glial cell line-derived neurotrophic factor (GDNF), c-ret proto-oncogene, and GDNF receptor-alpha indicates multiple mechanisms of trophic actions in the adult rat CNS, J. Neurosci. 17 (1997) 3554–3567.
[79] A. Pascual, M. Hidalgo-Figueroa, J.I. Piruat, C.O. Pintado, R. Gómez-Díaz, J. López-Barneo, Absolute requirement of GDNF for adult catecholaminergic neuron survival, Nat. Neurosci. 11 (2008) 755–761.
[80] Z. Chen, Y. Chai, L. Cao, A. Huang, R. Cui, C. Lu, et al., Glial cell line-derived neurotrophic factor promotes survival and induces differentiation through the phosphatidylinositol 3-kinase and mitogen-activated protein kinase pathway respectively in PC12 cells, Neuroscience 104 (2001) 593–598.
[81] B. Chen, D. Dowlatshahi, G.M. MacQueen, J.F. Wang, L.T. Young, Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication, Biol. Psychiatry 50 (2001) 260–265.
[82] S.M. Rocha, A.C. Cristovão, F.L. Campos, C.P. Fonseca, G. Baltazar, Astrocyte-derived GDNF is a potent inhibitor of microglial activation, Neurobiol. Dis. 47 (2012) 407–415.
[83] D.P. Berger, L. Herbstritt, W.A. Dengler, D. Marme, R. Mertelsmann, H.H. Fiebig, Vascular endothelial growth factor (VEGF) mRNA expression in human tumor models of different histologies, Ann. Oncol. 6 (1995) 817–825.
[84] R.A. Swain, A.B. Harris, E.C. Wiener, M.V. Dutka, H.D. Morris, B.E. Theien, et al., Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat, Neuroscience 117 (2003) 1037–1046.
[85] Y.H. Ding, J. Li, Y. Zhou, J.A. Rafols, J.C. Clark, Y. Ding, Cerebral angiogenesis and expression of angiogenic factors in aging rats after exercise, Curr. Neurovasc. Res. 3 (2006) 15–23.
[86] N. Ferrara, W.J. Henzel, Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells, Biochem. Biophys. Res. Commun. 161 (1989) 851–858.
[87] H.P. Gerber, A.K. Malik, G.P. Solar, D. Sherman, X.H. Liang, G. Meng, K. Hong, J.C. Marsters, N. Ferrara, VEGF regulates haematopoietic stem cell survival by an internal autocrine loop mechanism, Nature 417 (2002) 954–958.
[88] N. Ferrara, H.P. Gerber, J. Lecouter, The biology of VEGF and its receptors, J. Nat. Med. 9 (2003) 669–676.
[89] E. Zelzer, R. Mamluk, N. Ferrara, R.S. Johnson, E. Schipani, B.R. Olsen, VEGFA is necessary for chondrocyte survival during bone development, Development 9 (2004) 2161–2171.
[90] K. Jin, Y. Zhu, Y. Sun, X.O. Mao, L. Xie, D.A. Greenberg, Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 11946–11950.
[91] Y. Sun, K. Jin, J.T. Childs, L. Xie, X.O. Mao, D.A. Greenberg, Vascular endothelial growth factor-B (VEGFB) stimulates neurogenesis: evidence from knockout mice and growth factor administration, Dev. Biol. 289 (2006) 329–333.
[92] H.F. Dvorak, L.F. Brown, M. Detmar, A.M. Dvorak, Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis, Am. J. Pathol. 146 (1995) 1029–1039.
[93] T. Yasuhara, T. Shingo, K. Muraoka, Y. Wen Ji, M. Kameda, A. Takeuchi, et al., The differences between high and low-dose administration of VEGF to dopaminergic neurons of in vitro and in vivo Parkinson's disease model, Brain Res. 1038 (2005) 1–10.
[94] T. Yasuhara, T. Shingo, K. Kobayashi, A. Takeuchi, A. Yano, K. Muraoka, et al., Neuroprotective effects of vascular endothelial growth factor (VEGF) upon dopaminergic neurons in a rat model of Parkinson's disease, Eur. J. Neurol. 19 (2004) 1494–1504.
[95] Y. Li, F. Zhang, N. Nagai, Z. Tang, S. Zhang, P. Scotney, et al., VEGF-B inhibits apoptosis via VEGFR-1-mediated suppression of the expression of BH3-only protein genes in mice and rats, J. Clin. Invest. 118 (2008) 913–923.
[96] T. Falk, S. Zhang, S.J. Sherman, Vascular endothelial growth factor B (VEGF-B) is up-regulated and exogenous VEGF-B is neuroprotective in a culture model of Parkinson's disease, Mol. Neurodegener. 4 (2009) 49.
[97] T. Yasuda, M. Fukuda-Tani, T. Nihira, K. Wada, N. Hattori, Y. Mizuno, H. Mochizuki, Correlation between levels of pigment epithelium-derived factor and vascular endothelial growth factor in the striatum of patients with Parkinson's disease, Exp. Neurol. 206 (2007) 308–317.
[98] S. Soker, H. Fidder, G. Neufeld, M. Klagsbrun, Characterization of novel vascular endothelial growth factor (VEGF) receptors on tumor cells that bind VEGF165 via its exon 7-encoded domain, J. Biol. Chem. 271 (1996) 5761–5767.
[99] P. Carmeliet, C. Ruiz De Almodovar, VEGF ligands and receptors: implications in neurodevelopment and neurodegeneration, Cell. Mol. Life Sci. 70 (2013) 1763–1778.
[100] C. Lopez-Lopez, D. LeRoith, I. Torres-Aleman, Insulin-like growth factor I is required for vessel remodeling in the adult brain, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 9833–9838.
[101] D.R. Clemmons, The relative roles of growth hormones and IGF-1 in controlling insulin sensitivity, J. Clin. Invest. 113 (2004) 25–27.
[102] A. Wilkins, S. Chandran, A. Compston, A role for oligodendrocyte-derived IGF-1 in trophic support of cortical neurons, Glia 36 (2001) 48–57.
[103] C. Vicario-Abejon, M.J. Yusta-Boyo, C. Fernandez-Moreno, F. De Pablo, Locally born olfactory bulb stem cells proliferate in response to insulin-related factors and

require endogenous insulin-like growth factor-I for differentiation into neurons and glia, J. Neurosci. 23 (2003) 895–906.
[104] I. Torres-Aleman, Insulin-like growth factors as mediators of functional plasticity in the adult brain, Horm. Metab. Res. 31 (1999) 114–119.
[105] A. Quesada, H.E. Romeo, P. Micevych, Distribution and localization patterns of estrogen receptor-beta and insulin-like growth factor-1 receptors in neurons and glial cells of the female rat substantia nigra: localization of ERbeta and IGF-1R in substantia nigra, J. Comp. Neurol. 503 (2007) 198–208.
[106] D. Leroith, H. Werner, D. Beitner-Johnson, C.T. Roberts Jr., Molecular and cellular aspects of the insulin-like growth factor I receptor, Endocr. Rev. 16 (1995) 143–163.
[107] F.L. Roudabush, K.L. Pierce, S. Maudsley, K.D. Khan, L.M. Luttrell, Transactivation of the EGF receptor mediates IGF-1-stimulated shc phosphorylation and ERK1/2 activation in COS-7 cells, J. Biol. Chem. 275 (2000) 22583–22589.
[108] A.J. Barber, M. Nakamura, E.B. Wolpert, C.E. Reiter, G.M. Seigel, D.A. Antonetti, et al., Insulin rescues retinal neurons from apoptosis by a phosphatidylinositol 3-kinase/Akt-mediated mechanism that reduces the activation of caspase-3, J. Biol. Chem. 276 (2001) 32814–32821.
[109] M. Nakamura, A.J. Barber, D.A. Antonetti, K.F. Lanoue, K.A. Robinson, M.G. Buse, Excessive hexosamines block the neuroprotective effect of insulin and induce apoptosis in retinal neurons, J. Biol. Chem. 276 (2001) 43748–43755.
[110] A. Quesada, P.E. Micevych, Estrogen interacts with the IGF-1 system to protect nigrostriatal dopamine and maintain motoric behavior after 6-hydroxdopamine lesions, J. Neurosci. Res. 75 (2004) 107–116.
[111] S.J. Allen, D. Dawbarn, Clinical relevance of the neurotrophins and their receptors, Clin. Sci. (Lond.) 110 (2006) 175–191.