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REVIEW ARTICLE

Neuroprotective Effects of Exercise Treatments After Injury: The Dual Role of Neurotrophic Factors

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Abstract: ***Background*:** Shared connections between physical activity and neuroprotection have been studied for decades, but the mechanisms underlying this effect of specific exercise were only recently brought to light. Several evidences suggest that physical activity may be a reasonable and beneficial method to improve functional recovery in both peripheral and central nerve injuries and to delay functional decay in neurodegenerative diseases. In addition to improving cardiac and immune functions, physical activity may represent a multifunctional approach not only to improve cardiocirculatory and immune functions, but potentially modulating trophic factors signaling and, in turn, neuronal function and structure at times that may be critical for neurodegeneration and regeneration.

***Methods*:** Research content related to the effects of physical activity and specific exercise programs in normal and injured nervous system have been reviewed.

***Results*:** Sustained exercise, particularly if applied at moderate intensity and early after injury, exerts anti-inflammatory and pro-regenerative effects, and may boost cognitive and motor functions in aging and neurological disorders. However, newest studies show that exercise modalities can differently affect the production and function of brain-derived neurotrophic factor and other neurotrophins involved in the generation of neuropathic conditions. These findings suggest the possibility that new exercise strategies can be directed to nerve injuries with therapeutical benefits.

***Conclusion*:** Considering the growing burden of illness worldwide, understanding of how modulation of neurotrophic factors contributes to exercise-induced neuroprotection and regeneration after peripheral nerve and spinal cord injuries is a relevant topic for research, and represents the beginning of a new non-pharmacological therapeutic approach for better rehabilitation of neural disorders.

Keywords: Exercise, inflammation, neurotrophic factors, neuropathic pain, nerve injury, nerve regeneration, survival.

1. INTRODUCTION

Exercise is able to generate endogenous neuroprotection through the activation of multiple mechanisms, such as promoting neurogenesis, improving the neurovascular unit integrity, decreasing apoptosis, and modulating inflammation. Through these mechanisms, exercise can be used as a treatment to protect from nerve damage and stroke, and to promote regeneration of injured axons and reduce neuropathic pain. In general, exercise is conceived to provide substantial neuroprotection by means of several mechanisms that induce neuronal survival. This machinery is mainly focused on the neurovascular unit, consisting of neuronal, glial and vascular cells. Neurovascular unit is clearly reinforced by exercise training but its stability is compromised by nerve lesions. Excessive excitability, chronic inflammation and microgliosis, added to maladaptive plasticity of injured nerve pathways, are major contributors of neural disorders and neuropathic pain conditions. In this scenario, neuroprotection is conveyed by exercise partly through the upregulation of neurotrophins expression, including brain derived neurotrophic factor (BDNF), nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF). These important regulatory proteins increase neurogenesis, strengthening the neuronal network and potentiating the regenerative responses to nerve insult. Exercise modalities specific to the type of injury can convey more potent neuroprotection, and animal studies have recently started to tune up training paradigms of different intensities and at critical time windows for treating injuries to the peripheral and central nervous systems. This seems also to open a strategy for setting up an endo-pharmacology of pain and regeneration,

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based on the modulation of the endogenous levels of neurotrophins by means of different exercise protocols.

This may depend on the dual role that neurotrophic factors (particularly BDNF and NGF) play after nerve injury, and the opposite effects they can exert on stimulation of neurogenesis and regeneration but also on inhibition of chronic pain and maladaptive plasticity.

2. MECHANISMS OF EXERCISE-INDUCED NEURO-PROTECTION

2.1. Effects on the Neurovascular Unit

Exercise based therapies assume that repeated neuronal activity has to be supported by the neurovascular unit, then gradual training can induce an effective adaptation and reinforcement of its integrity as a whole. The blood brain barrier (BBB) constitutes a strong filtration mechanism where endothelial cells, the basal lamina and astroglial cells work together to preserve neurovascular integrity in case of a neuronal damage. Exercise induces reduction of physical damage to the neurovascular unit, and this effect is conveyed by strengthening the BBB [1, 2]. The integrity of the BBB is foremost to maintaining appropriate filtration of supplying and toxic molecules from the vascular system and in providing an indispensable structure to the unit.

Various proteins of the extracellular matrix compose the basal lamina, including collagen type IV as a major component, proteoglycan, heparan sulphate, laminin and fibronectin, which are provided by astrocytes and endothelial cells. When this membrane is damaged, its ability to selectively permeate nutrients in the neurovascular unit is compromised, this is diagnosable with a vasogenic edema. Under ischemic conditions, the loss of selective permeability and sustained edema lead to cellular swelling. In the brain, endothelial cells and astrocytes separate from the basal lamina to promote the discharge of vascular constituents into the cerebral interstitial space [2]. Exercise training enhances the basal lamina increasing both firmness and stability to the BBB [3]. Following CNS injury, these effects are combined to decrease cerebral stroke and edema volume, and enhance neuronal recovery. Collagen type IV is found to be upregulated in exercised rats, and exercise reduced its net loss after stroke [3]. The increase of collagen type IV in exercised animals was correlated also to a reduction of behavioral deficits after stroke [3].

Integrins add stability to the basal lamina and the BBB, and provide further reinforcement to the neurovascular unit. Composed of α and β heterodimers, these proteins act as cell adhesion molecules and make adherence within extracellular matrix and basal lamina, maintaining the integrity of these structures [4, 5]. Integrins serve as receptors for several proteins and ligands within the basal lamina matrix, mainly collagen and laminin [2, 5, 6]. They also serve as signaling receptors for anchoring endothelial cells and astrocytes together, allowing dynamic changes of the BBB in response to exercise, injury and pain. In this regard, exercised rats showed significantly higher integrins expression in astroglia and endothelium following muscle [7, 8] and CNS damage [6], correlating with a decrease in the behavioral deficit [9].

Astrocytes play a key role in maintaining the neuronal framework. Since chronic exercise induces astrocytosis, often observed both in brain [10] and in spinal cord [11], part of the neuroprotective function played by astrocytes is supposed to be increased by physical activity in order to strengthen the BBB and the neurovascular unit. First, astrocytes provide a rigid framework to withstand traumas of the neurovascular unit. Their expansions cover the 90% of the brain vascular surface with a primary function in restricting permeability of the insulted BBB [2, 12-14]. Exercise-induced astocytosis is associated to better outcomes in recovery from injuries [10]. It seems then that exercise training can transform the neurovascular system and develop a vital metabolic response to CNS injury.

Angiogenesis and endothelial cell proliferation are normally scant in the adult brain. Previous studies showed that locomotion on a treadmill can increase the density of blood vessel [15-18] and cortical and striatal angiogenesis [19, 20] in the brain. In addition exercise can increase arteriogenesis, which promotes cerebral and peripheral blood flow and attenuates neuronal injury and degeneration [21, 22]. By increasing the metabolic demand, exercise may swell up the blood supply allowing the enhanced delivery of nutrients to stimulated neurons and promoting further angiogenesis [16, 23]. These changes may reduce brain damage as well [19]. Exercise improves blood flow overall in the whole body, resulting in higher levels of neurotrophic factors and activation of Schwann cells in peripheral nerves [24, 25]. Neovascularization and increased peripheral blood flow induced by physical activity are also consequences of the increased expression of angiogenesis related genes in skeletal muscles [26]. The anatomical modifications seen in angiogenesis are compelled by regulatory growth factors and proteins, namely vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1) and angiopoietins (Ang) 1 and 2. VEGF and IGF-1 expression is increased in the periphery by physical activity stimulating these factors to cross the BBB and enter the brain [27-29]. Blocking either VEGF [28] or IGF-1 [27] peripheral entry to the brain prevented the proliferation of neural precursors in the hippocampus induced by exercise, along to reduced promotion of the survival signaling that exercise induces by means of neural precursors generation [27]. VEGF mRNA expression is exponentially higher with increasing duration of exercise training, and exercise angiogenesis is shown parallel to an increase of brain VEGF mRNA and protein [28, 29]. This effect of exercise stimulates potent mitotic activity on vascular endothelial cells, affecting proliferation, survival, adhesion, migration and formation of capillary tubes [30]. BDNF seems to participate in neurogenesis or angiogenesis during exercise, since the stimulation of BDNF participates also to increase proliferation and survival of new neurons and BDNF itself can regulate baseline neurogenesis *in vivo* [31].

2.2. Effects on the Inflammatory Response

The neuroprotective action of physical activity has been linked to the ability of preventing and modulating inflammatory conditions [32]. Several studies described fewer viral and bacterial infections [33, 34], and lower incidence of

systemic low-grade inflammation [34, 35] as well as neurodegeneration and cognitive decline [36] in individuals who regularly practice physical activities. Experimental studies converge on demonstrating that sustained physical activity includes general enhancement of immune function and anti-inflammatory processes strongly enhancing neuroprotection. These effects seem to depend upon two critical parameters: intensity and duration. Through them, exercise can gradually mold and fix the inflammatory process, and lead to reduction in chronic inflammation if daily repeated and continuous. Conversely, acute exercise may promote or reduce inflammation by impacting the inflammatory cascade and increasing with intensity the release of pro-inflammatory or anti-inflammatory cytokines respectively [37]. Kohut *et al*. [38] followed older adults participating in aerobic or flexibility exercise along to 10 months, and found that physical activity induced significant reduction of interleukin 6 (IL-6), interleukin 8 (IL-8), C-reactive protein (CRP) and tumor necrosis factor α (TNFα) plasma levels, linking chronic exercise to anti-inflammatory effects. However, a meta-analysis [39] reported that a single bout of exercise enhanced the inflammatory response in patients diagnosed of type I diabetes mellitus, cystic fibrosis, and chronic obstructive pulmonary disease, whereas participation in chronic endurance training programs was associated to attenuation of the systemic inflammatory response in patients with chronic heart failure and type II diabetes mellitus. Thus, the analysis of exercise effects on particular inflammatory disorders should be conducted in relation to the mechanism by which inflammatory mediators and modulators are produced in the pathology and by the type of exercise.

2.2.1. Effects on Inflammatory Modulators

The enduring effects of chronic exercise could be attributed to the counteraction of inflammation played by acute bouts of exercise, which is partly mediated by IL-6 in addition to the neurovascular supply. IL-6 is a cytokine that may convey both pro- and anti-inflammatory effects, and is provided in peripheral tissue by T-cells, macrophages, fibroblasts, endothelial cells and osteoblasts [40]. IL-6 plays a clear role in the metabolic control of muscle cells and is released in response to eccentric muscle contraction [41]. Moderate aerobic exercise induces release of IL-6 from muscles, and its circulating levels can increase up to 100-fold during up to 1h following activity [42]. Other studies indicate that IL-6 similarly increases even after exhausting exercise, such as a marathon. Normal concentrations of IL-6 stimulate the circulation of anti-inflammatory cytokines IL-1α and IL-10, and may also inhibit the production of pro-inflammatory cytokine TNFα [42]. On the other side, IL-6 stimulates lipolysis and fat oxidation. The neuroprotective effects of exercise-induced pro-inflammatory IL-6 was first related to TNFα- insulin resistance. IL-6 mediated inhibition of TNFα production was suggested by *in vitro* [43], animal [44, 45] and human [46] studies. IL-6 easily crosses the BBB [47] and can introduce functional alterations on neurons and glial cells, with controversial effects on neuroprotection. Overexpression of IL-6 in mouse astrocytes has been linked to neurodegenerative alteration of age-dependent learning [48]. Strenuous exercise may result in IL-6 parallel brain inflammation; however a recent study demonstrated that a gradual resistance exercise combined with a protein enriched diet may reduce IL-6 expression [49], suggesting that the role of IL-6 and its dosing in exercise-induced neuro-protection requires further investigation.

Differently from IL-6, IL-8 or chemokine (CXC Motif) ligand 8 (CXCL8) is a chemokine with neuromodulatory effects. It is expressed in neurons, glia and endothelial cells. Neuroprotective effects of exercise-induced IL-8 may rely in promoting local angiogenesis in muscle [50]. IL-8 is produced in response to high [51] but not moderate intensity exercise [52, 53]. As will be discussed in paragraph 3.2, exercise intensity is a crucial parameter to modulate the expression and to determine the function of factors involved in inflammation, pain and regeneration following a nerve injury.

The link between exercise and the immune system implicates the modulation of various inflammatory processes that can be activated by factors implicated also in cognitive dysfunction and neurodegenerative diseases, that convey neuroprotection beyond the classical chemotactic reactions. For example, exercise is likely suppressing TNFα *via* pathways independent from IL-6, since TNFα decreases also in exercised IL-6 knockout mice [54]. Moreover, brief exercise can increase the expression of stromal cell-derived factor-1 (SDF-1), a pleiotropic chemokine also known as C-X-C motif chemokine ligand 12 (CXCL12). CXCL12 promotes adaptive immune responses and angiogenesis by recruiting endothelial progenitor cells from the bone marrow [55-57]. It has been shown that 3 weeks of free wheel running lead to higher CXCL12 gene and expression, along to enhanced learning and memory performances in the Tg2576 AD mouse model [58]. CXCL12 is extensively expressed in the CNS, and its presence demonstrated in cholinergic, dopaminergic and AVP-ergic brain neurons [59].

C-Reactive Protein (CRP) plays a central role in the human immune system. It is synthesized primarily in the liver, adipose tissue and vascular smooth muscle cells, and found in the blood during the acute phase of inflammation, where it is involved in activation of the complement system [60]. Hyppocampal neurons express CRP [60] as well as they show increased CRP levels in patients with neurodegenerative diseases [61]. In contrast, a number of cross-sectional studies demonstrated an inverse correlation between exercise and CRP expression [62]. However, clinical results are inconsistent since CRP levels were found significantly reduced in only half of the studies using aerobic exercise regimens in children, adult and elder subjects [63]. All these evidences confirm a direct action of physical activity on critical inflammatory players that may promote neuroprotection from nerve insults as well as from neuronal aging and degeneration.

2.2.2. Effects on Microglia and other Factors

The inhibition of microglial reaction seems to be one of the key effects of physical activity inducing neuroprotection after neural damage, as demonstrated in some recent studies [11, 65-67]. Microglial cells typically exist in a relatively

quiescent form, however when detecting damage, they proliferate and form thick clusters, turn in an amoeboid morphology and start to phagocyte cellular debris and foreign material. Microglial activity is triggered by complex signaling cascades, and after nerve injury is regulated by activity-dependent mechanisms [68, 69]. The potential role of exercise as immunomodulatory treatment within the central nervous system is particularly relevant for neuroprotection against the age related progressive decline in cognitive function. Normal aging primes microglia towards the chronic inflammatory phenotype, but as demonstrated voluntary exercise can counteract the basal shift in microglia activation of aged mice, even if the effects may be different for age, sex, and brain region [65].

Microglial activation in the central nervous system depends on the presence of purines, cytokines and chemokines that can induce their activation and stimulate protective or toxic activity after peripheral or central injuries. In this scenario, chemokines such as CCL2 and CCL21, proteases such as MMP-9 and cathepsin-S (releasing further cytokines and chemokines, such as IL-1β and fraktalkine), growth factors such as neuregulin-1 (NR1), and purines such as adenosine triphosphate (ATP) have been described [70]. All these signals stimulate the proliferation and chemotaxis of microglia in regions of the CNS in proximity to damage or to which injured afferents project, can be enhanced by increased neuronal activity, and may be modulated by physical activity. Activity-dependent increase of ATP interacting with P2 purinergic receptors has been demonstrated to be a critical event inducing activation of microglial cells and generating pathologic inflammatory and painful states [70, 71]. In turn, activated microglia and astrocytes release IL-1β, TNFα, IL-6 and other cytokines and chemokines. In primary afferents cytokines contribute to enhance the neurotransmitter release and promote consequent actions associated with neuronal damage, including amplification of central microglial activation [72], infiltration of phagocytic neutrophils [73], and damage to Schwann cells and to axons [74]. After injury, a critical role seems to be played by BDNF released from microglia. Instead of having a neurotrophic effect as under normal conditions, BDNF induces hyperexcitability of nociceptive neurons [68] and is involved in the reduced expression of the potassium-chloride cotransporter 2 (KCC2), which showed to alter the anion gradient of GABAergic interneurons into an excitatory rather than an inhibitory action [75-77]. The overall effect is an enhanced excitability of central neurons, neurotoxicity and amplification of pain stimuli.

In this pathologic environment, specific exercise training could be effective in reducing or preventing the microglia activation and associated inflammatory and neuropathic mechanisms, promoting neuroprotection and resolution of the disease. An increasing-intensity treadmill training was effective in reducing microglia [11] and its expression of BDNF [64] in the dorsal horn after sciatic injury. BDNF mRNA also decreased in dorsal root ganglia (DRG) [78], indicating that increasing-intensity or intermediate intensity exercise is able to down-regulate specific neurotrophin signaling–dependent responses to injury which may generate maladaptive excitability of sensory neurons, without significantly altering the regeneration of injured axons [64, 78]. Downregulation of KCC2 transporter is a consequence of the increased BDNF-mediated TrKB activation, which suppresses the normal Cl-dependent fast inhibition in GABAergic neurons [79]. For this reason, after peripheral injury this reaction is responsible for the inversion of the anion flux from inhibitory to excitatory on activation of GABA receptors in the dorsal horn due to primary afferent depolarization [80, 81]. Contrary to what has been often shown after exercise, the expression of BDNF is significantly reduced in spinal microglia after increasing-intensity treadmill, suggesting that increased exercise activity can rescue KCC2 by changing microglia reactivity and ceasing excitation from central BDNF. Chronic exercise may reduce central microglial reactivity and inflammation through regulation of multiple metabolic and transcriptional processes that start in the skeletal muscle. The rate of both glucose uptake and glycogen synthesis are acutely raised in skeletal muscles during exercise. Glycogen synthase kinase 3 (GSK-3) is a major regulator of the balance between the pro- and anti-inflammatory mediators in immune cells, including microglia [82]. Chronic adaptation in skeletal muscle with long-term exercise training showed an inverse relation between GSK-3 and exercise levels [83-85]. GSK-3 stimulates the release of IL-1β, IL-6 and TNFα in activated microglia, and inhibits the release of anti-inflammatory cytokines like IL-10 [86-88]. GSK3 is involved in different neuronal functions, such as neurite outgrowth, synapse formation, neurotransmission and neurogenesis, and in the brain is a sensor for deciding the cells fate. Exercise may activate some extracellular signals that are known to inhibit GSK-3, including epidermal and platelet-derived growth factors [89, 90], α1A adrenergic receptor [91] and insulin [92]. It is noteworthy that significant/prolonged inactivation of GSK-3 in microglia and astrocytes shifts balance of secreted cytokines from pro-inflammatory to anti-inflammatory [86, 93, 94].

2.3. Effects on Neurotrophins Expression

Neurotrophins are polypeptides belonging to a family of closely related proteins that induce neural proliferation, survival, migration, and differentiation [95, 96], thus fundamental for neuroprotection [97, 98]. They include NGF, BDNF, neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT4/5). Synthesized by target neurons and glial cells, their biological action is mediated by two different classes of receptors, the low-affinity P75 neurotrophin receptor (P75NTR), a member of TNF receptor superfamily, and the tropomyosin related kinase (Trk) family of receptors tyrosine kinases [99, 100]. Neurotrophins perform their action by binding to their receptors and being internalized along with the receptor and retrogradely transported to the cell nucleus, where they can play multiple survival promoting effects [99]. The unique actions played by neutrophins however do not justify a different family of target receptors from mitogenic growth factors, such as platelet-derived growth factor (PDGF) or epidermal growth factor (EGF), whose receptors are known to be tyrosine kinases. During the last years, members of other neurotrophic factor families have also been shown to activate tyrosine kinases. About a third of primary sensory afferents do not express receptors for

neurotrophins, but receptors for GDNF signaling (RET, GFRa-1, GFRa-2). GDNF is a member of the transforming growth factor-b (TGF-b) superfamily, and exerts effects similar to neurotrophins as promoting survival of brain dopaminergic, motor and sensory neurons.

Physical activity has a significant impact on neurotrophins production, as a few days of exercise increase the BDNF and NT-3 levels in muscles [101], dorsal root ganglia (DRG) [102] and spinal cord [103-105]. Following nerve injury, these effects were associated to enhanced survival and regeneration of injured axons. Other factors also participate in the exercise-dependent signaling for growth and innervation, including NGF [106, 107] and NT-4/5 [108]. In uninjured rats, chronic treadmill exercise locomotion of moderate intensity induced important changes of BDNF expression in muscle and brain, mostly in the grey matter. In parallel NT-4 expression increased in the white matter of the spinal cord, where astrocytes may be an additional source of neurotrophins. On the other side, GDNF expression in skeletal muscle seems to be directly produced by stretch, while membrane depolarization by acetylcholine (ACh) decreases its content [109]. Expression of GDNF increases in muscles and spinal cord after treadmill exercise [110, 111], and induces morphological changes at the neuromuscular junctions (NMJ) that are activity dependent [110, 112].

The most disabling problem after peripheral nerve injury is the slow growth of injured axons, impairing functional recovery, along with significant misdirection of regenerating axons, that reinnervate inappropriate targets inducing changes of the central neural circuitry [113]. Peripheral nerves are able to regenerate and there is sufficient endogenous supply of neurotrophins in the axotomized motor and sensory neurons and in Schwann cells that can guide nerve regeneration. However the trophic support diminishes with time, so that in chronic lesions a therapeutical supplement may be beneficial when target reinnervation is delayed, particularly after severe nerve injuries requiring long time for regeneration [114]. Increased BDNF and NGF induced by exercise contribute to enhance axonal regeneration after nerve injury [115-117]. However, there are also evidences that an increased neurotrophic production by physical activity may be critical in long-term neuro-rehabilitation. Indeed, BDNF and GDNF administration did not significantly increase the number of regenerated axons in freshly cut and repaired rat nerves, but can do it after chronic axotomy [114]. Nevertheless, the same neurotrophic factors may promote excitability and maladaptive plasticity, such as excessive collateral sprouting, that in turn may exacerbate symptoms of pain in peripheral neuropathies. In this scenario, setting exercise protocols for decreasing instead of increasing neurotrophins signaling may be a more efficacious strategy for treating pathologies characterized by hyperexcitability of the nervous system.

Neurotrophins are well-known mediators not only of axonal regeneration, but also of pain, particularly NGF and BDNF [118], and play several roles in the development of neuropathic pain [119, 120]. Anti-NGF and anti-TrK receptor treatments demonstrated to significantly reduce neuropathic pain in sciatic nerve injury models, and the hypoalgesic effect has been associated to the prevention of nociceptive fibers collateral sprouting into the denervated skin [120-123]. Recently, swimming training was shown to significantly reduce mechanical allodynia that was associated to a normalization of increased BDNF, NGF and GDNF levels in DRG after partial sciatic nerve ligation [124]. These results are consistent with studies in our group using an increasing-intensity treadmill training (iTR) [11, 64], that produced reduction of neuropathic pain along with decreased BDNF, NGF and GDNF up-regulation in DRG [78], BDNF expression in the dorsal horn and NGF expression in the denervated skin [64]. We found these changes accompanied by the normalization of parallel mechanisms underlying neural excitability such as microgliosis in the spinal dorsal horn [64, 124], the disregulation of cation chloride cotrans-porters expression, and the collateral sprouting of nociceptors [64]. Elevated BDNF and NGF levels in sensory pathways are generally associated with neuropathic pain and inflammatory conditions. Activated microglia release BDNF, which increases excitability of nociceptive neurons [125] leading to allodynia [126]. Mechanical hyperalgesia as induced by delayed onset muscle soreness (DOMS) after unaccustomed strenuous exercise has been associated to elevated NGF and GDNF upregulation in muscles [127].

On the other side, spinal injuries oppositely determine a loss of neurotrophic factors that has been associated to neuropathic pain conditions. Hutchinson *et al*. [128] found that resolution of allodynia after spinal cord injury was concomitant to normal BDNF mRNA levels in both lumbar spinal cord and in the soleus muscle of treadmill trained rats, but not in swimming nor in standing upright trained rats. Upregulation of BDNF in the CNS is considered a principal effect of exercise for modulating spinal and brain circuitries, and promoting neuronal repair, memory and learning. Therefore, the effects of increased physical activity on functional recovery mediated by neurotrophins may be opposed in central and peripheral neural lesions.

In the last two decades, the study of exercise-induced neurotrophins expression in the brain showed a clear relationship between exercise and BDNF-NGF impact on brain functions. There is a positive correlation between the mean distance run on a running wheel and mRNA for BDNF in the hippocampus and caudal neocortex in rats, and the elevation of neurotrophins levels in brain circuits has been related to neuroprotection and cognitive improvement in neurodegenerative disorders. Some studies have identified correlations between decreased BDNF production and disorders such as depression, schizophrenia and dementia [129, 130]. Specifically, exercise has been used to delay neurodegeneration in aged AD transgenic mice [131-133], and humans [134-136]. In these pathologies, exercise reduces the levels of detrimental factors, for example oxidative stress and inflammation [58, 131-133], and increases the expression of neurotrophic factors, such as BDNF and IGF-1 [36, 137]. One of the mechanisms proposed for changes produced by exercise in the brain is the promotion of demethylation of BDNF promoter IV in the hippocampus, enhancing brain function and plasticity [138]. BDNF produced by exercise also induced long-term

potentiation (LTP) by tetanic stimulation in the hippocampus, which showed only short-term potentiation (STP) in absence of BDNF [139]. The BDNF upregulation in the hippocampus induced by exercise was related with the improvement of cognitive function, including memory, in rodents [140], whereas downregulation of BDNF or TrkB impaired the formation of memory [141].

2.3.1. Conversion of Pro-neurotrophins into Mature Forms

Neurotrophins actions can change depending of their secretory pathway, and they can be altered not only at transcriptional mRNA level but also at protein level [142]. Neurotrophins are first synthesized as a precursor protein in the endoplasmic reticulum. These pro-neurotrophins are then transported to the Golgi apparatus for sorting into either constitutive or regulated secretory vesicles, and may be intracellularly converted into their mature form [143]. Recent studies support a "yin-yang" hypothesis that interaction of pro-neurotrophins or mature forms with p75NTR or Trk receptors, respectively, elicits different biological actions of neurotrophins, either degeneration or neuroprotection [144, 145]. For instance, proBDNF and mBDNF differently mediate apoptosis or survival by activation of p75NTR and TrkB receptors respectively [146]. Moreover, different frequency of neuronal activity may induce opposite functions of BDNF isoforms through induction of different types of receptors. Both low- (inducing long-term depression, LTD) and high- (inducing long-term potentiation, LTP) frequency of neuronal stimulation increases the extracellular proBDNF, however only high-frequency activity results in extracellular conversion of proBDNF to mBDNF [147]. Chronic voluntary exercise can increase brain BDNF concentration as a result of increasing the conversion of proBDNF into the mature form as reported by Berchtold *et al*. [148]. These results suggest that different mechanisms of plasticity may be activated by different types of neuronal stimulation, and can be induced as a result of different intensities of exercise in the intact and in the damaged neurons.

2.4. Effects on Neuronal Death and Survival Signaling Pathways Regulated by Neurotrophin Receptors

Despite the neuroprotective and pro-regenerative roles of neurotrophic factors have been extensively associated to physical activity, they also participate in apoptotic processes and may generate neurotoxic effects. The biological actions played by neurotrophins determining the fate of neurons are regulated by two different receptors: Tyrosine kinase receptors (Trk) and the p75NTR [149, 150]. NGF binds to TrkA, BDNF and NT4 to TrkB, and NT3 to TrkC. On the other hand, p75NTR can be activated by all neurotrophins, but is also able to regulate the affinity of Trk receptor for its cognate ligand. There are some evidences that Trk and p75NTR receptors may form complexes, and p75NTR increases the ligand selectivity of Trk receptors [151]. p75NTR also is component of other receptor complexes, prominently the Nogo complex [152], that participates in regulation of myelination and axonal regeneration. However, these two types of receptors are not allowed to bind each other directly. Thus by binding to p75NTR, neurotrophins can stimulate apoptosis in different cell types [153]. Proneurotrophins, as proNGF, have been demonstrated to exert this apoptotic function [154].

The biological effects of neurotrophins are determined by their proteolytic cleavage, as previously explained [144, 145]. Apoptosis by p75NTR is facilitated by binding to pro-neurotrophins and sortilin, which is a trafficking receptor. Cell death through p75NTR signaling has been observed under conditions of stress, injury or inflammation, when p75NTR has a pro-apoptotic function for developmental cell death and after nervous system injury [155]. The p75NTR activates three main signaling pathways: the NF-κB pathway, resulting in transcription of several genes involved in neuronal survival; the Jun kinase pathway, controlling other genes, some of which instead promote apoptosis; and the Rho signaling, controlling the motility of neurite growth cone. Moreover, it is known that pro-neurotrophins induce apoptosis through ligand engagement of p75NTR more effectively than mature NGF [151].

On the other side, neurotrophins boost neuronal survival and differentiation through activation of Trk receptors [150]. Each Trk controls three basic signaling pathways. After neurotrophin binding, Trks activate and recruit adaptor Src homology 2-containing proteins (Shc) and fibroblast growth factor receptor substrate 2 (FRS2), and effectors such as phosphoinositide 3-kinase (PI3K) and phospolipase C-γ (PLC-γ). Synaptic plasticity is promoted by the activation of PLC-γ1 which binds to Tyr790, and this interaction has been proposed to facilitate interactions with ion channels, such as the vanilloid receptor-1 (VR-1) channel, finally resulting in activation of Ca^{2+} and protein kinase C (PKC) regulated pathways. Moreover, Tyr490, Shc or FRS2 become tyrosine phosphorylated and provide a scaffold for other signaling proteins, then leading to activation of the Ras/MAPK (mitogen-activated protein kinase) pathway, which promotes neuronal differentiation and neurite outgrowth, or the PI3K/Akt pathway, which induces cell growth and survival [144, 145].

A number of neurotrophic factors have been associated to functions of survival and differentiation in brain and spinal neurons. Particularly, BDNF, NGF, NT-3 and IGF-1 have been involved in mediating neuroprotective effects of exercise against apoptosis [36, 156, 157]. Aerobic exercise has shown to modulate the β- Ca^{2+}/calmodulin-dependent kinase II (β-CaMKII) and the PI3K/Akt pathways *via* neurotrophic factors activation [157, 158]. Akt pathway is more sensitive to activation of IGF-1 receptor [159], whereas β-CaMKII responses are more induced by TrkB activation [160]. Different authors showed that exercise-induced BDNF production leads to activation of survival signaling through PI3K and MAPK pathways [157, 161, 162]. Moreover, blockade of TrkB in the hippocampus abolishes the plastic changes associated to exercise, such as the stimulation of MAPK and CaMKII [163, 164]. BDNF also protects against brain damage induced by hypoxia–ischemia and inhibits apoptosis by blocking caspase 3 activation. Anti-apoptotic effects of treadmill exercise have been associated to modulation of Bcl-2 family molecules, which inhibit the expression of caspases after central injuries [157, 165, 166]. GDNF is also able to inhibit caspase-3 activation and antagonize neuronal apoptosis following hypoxic–ischemic

injury [167, 168]. Neurotrophins and GDNF treatment was proposed as neuroprotective and regenerative therapy for brain neurons in neurodegenerative diseases [169-171].

2.5. Effects on Neurodegenerative Diseases

The protective impact of exercise on neurodegenerative disorders is still under evaluation, since the mechanisms underlying the potential benefits have not been determined yet. This is due to the heterogeneity of the causes and the course of degeneration in pathologies affecting mid to aged humans, such as Parkinson's disease (PD) and Alzheimer's disease (AD), to devastating younger onset diseases like Amyotrophic Lateral Sclerosis (ALS). For PD and AD, pharmacological therapies are currently inconsistent and mostly offer palliative care to patients. There is growing evidence suggesting that physical activity can generally slow down aging and prevent degenerative diseases [172, 173].

PD is a neurodegenerative disease characterized by clinical symptoms such as resting tremors, rigidity and akinesia, usually associated to a reduction of dopaminergic neurons in the nigrostriatal system [174]. A meta-analysis of the effects of exercise on PD patients showed improvement of physical functions, health-related quality of life, strength, balance and gait speed [175]. Moderate exercise training exerted neuroprotective effects in a rat model of PD, enhancing neural progenitor cell proliferation and migration associated to increased BDNF and GDNF levels, with subsequent improvement in deteriorated motor function [176]. Usually these factors are both significantly reduced in the substantia nigra of PD patients [177]. In another animal model, systemic administration of lipopolysaccharide (LPS) induced nigral cell loss associated to parkinsonism; exercise counteracted these effects in proportion to the duration of training, this parallel to elevation of BDNF levels [178]. Although it is not yet clear how much these animal models relate to PD, the experimental studies suggest that neuroprotection and plasticity are stimulated by exercise in cortical circuits to delay the onset of degeneration. This may be achieved by modulation of neurochemical status in the striatum of rats, particularly increasing neurotrophic factors and possibly by improving oxidative stress. Treadmill exercise in PD rats increased the levels of BDNF and oxidative stress markers such as superoxide dismutase (SOD), sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA II) and catalase (CAT), thus decreasing oxidative damage of lipids and protein [179]. BDNF and GDNF levels were increased in substantia nigra and striatum, respectively, after 18 weeks of treadmill, with associated restoration of mitochondrial activity, and levels of SOD and ATP, along to improvement of motor behavior [180].

The role of oxidative stress in switching from normal to pathological brain aging, and the benefits of physical activity on AD, are corroborated by studies using animal models of AD, particularly the 3xTg and the Tg2576 mice [158, 181-183]. AD is typically characterized by memory disorders associated to presence of amyloid-beta plaques (Aβ), neurofibrillary tangles, inflammation and brain neuronal loss [184]. Demonstrated effects of exercise include enhancement of mitochondrial function and reduction of oxidative stress, but also stimulation of neurogenesis and angiogenesis over secretion of neurotrophic factors, strengthening of synaptic transmission, epigenetic changes, reduction of amyloid plaques formation, and reinvigoration of cardiocirculatory and immunoendocrine functions [158, 181-183, 185, 186]. These beneficial effects are also believed to occur in humans [36, 187]. Particularly, AD symptoms has been correlated to low NGF levels and parallel higher pro-NGF levels [188]. The accumulation of Aβ-peptide restrains the conversion to mature NGF, resulting in increased concentrations of proneurotrophin. Exercise oppositely increases mature NGF levels [107, 189-191]. Noteworthy, one of these studies [191] revealed that exercise training can boost BDNF and NGF by inducing long term potentiation (LTP) and counteract the age-associated neurotrophic decay.

Circulating BDNF can be considered as a marker of age-dependent memory performance [192], since vascular low levels of BDNF have been associate to patients predisposition to AD. Exercise stimulates BDNF mRNA and protein synthesis in the hippocampus and in the cortex, and overall brain contributes to about 70-80% of the circulating BDNF [193]. Exercise induction of NGF and BDNF can in turn enhance hippocampal neurogenesis, resulting in the enhancement of cognitive function. These effects may in part counteract the pathological course of AD. GDNF plays also an important role in neuronal plasticity and survival, and particularly in the hippocampal region [194]. Although there are no sufficient studies to determine the role of GDNF under exercise stimulation, some observations suggest that GDNF is produced as well as its neuroprotective effects [176, 195].

Additional neuroprotection in AD is conveyed by exercise through modulation of inflammatory factors, such as TNFα. Increased expression of TNFα is a prominent risk for AD in elders [196]. Some studies directly link TNFα levels to aggravation of dementia in AD [197-199]. On the other side, moderate chronic exercise reduces the levels of TNFα [200], resulting in a significant decrease of TNFα gene expression in muscles of aged individuals [201].

An active lifestyle continuously providing sufficient amounts of physical activity can be considered a non-pharmacological protective approach for averting neuronal degeneration as well as to avoid the excessive use of drugs. However, the benefits of exercise appear to be inverted in the case of ALS, or at least when physical activity is intense, as in high-performance athletes. A recent recollection of data from thousands professional Italian football players established rates of morbidity significantly increased for ALS disease, notably of young onset, with at the highest risk the footballers who played for more than 5 years [202]. Other studies showed a higher risk of ALS among long-distance race runners and rugby players. The exact mechanism that triggers motoneuronal degeneration in both sporadic and familial ALS is still under evaluation. Inheritance of familial ALS is usually autosomal dominant, often linked to mutations of the copper/zinc superoxide-dismutase-1 gene (SOD-1) resulting in the typical adult-onset ALS phenotype [203]. The SOD-1 enzyme is critically involved as free radical scavenger, since it catalyzes the conversion of the superoxide anion into molecular oxygen and hydrogen peroxide. The pathophysiology of ALS is

multifactorial, since it involves complex genetic and molecular interactions, that result into damage of key target proteins and organelles within the motoneuron. Possible links between exercise and ALS comprise oxidative stress, production of free radicals and stimulation of glutamate release, all mechanisms that contribute to motoneuron death. These mechanisms may become neurotoxic as a result of excessive exercise and increased neuronal activation in susceptible individuals. On the other hand, recent studies are in favor of specific low-intensity exercise programs, particularly swimming [204] or moderate treadmill locomotion [205], that increased the lifespan and delayed the motor decline in the transgenic SOD1G93A mouse model of ALS. Recently a pilot study involved inspiratory muscle training in ALS patients and suggested a potential benefit of such exercise [206]. Moreover, flexibility, balance, strength and aerobic exercises are indicated in the management of ALS patients for postponing muscular loss, maintain aerobic responses and reduce spasticity [207-209].

3. DOSING NEUROPROTECTION BY TUNING UP EXERCISE PARAMETERS

It is still unclear to date by human studies as physical exercise can be used to make a proper device level of neuroprotection after nerve injury. Moreover, a number of training protocols have been applied for locomotion in experimental animal models of nerve injury, with conflicting evidences with regard to beneficial and deleterious effects on neuronal survival, pain and regeneration [210, 211]. Although physical activity could produce endogenous neuroprotection and cardioprotection [212, 213], the intensity, time and duration of different types of exercise have not been conclusively determined. Some studies reported that moderate or intermediate intensity and duration of exercise correlate with better outcomes as opposed to mild or exhaustive exercise [214]. Intermediate levels of exercise intensity seem to promote long-term adaptation and induce beneficial plasticity and neuroprotection. In this section we revise the evidence for several critical parameters in programming the protocol of exercise following nerve damage, focusing on the effects that each parameter may have on plasticity and recovery. The neurotrophic contribution can be modulated by tuning the parameters of training protocols in order to optimize the exercise for rehabilitation. For example, a day session of exercise is known to increase plasma and serum levels of BDNF in proportion to exercise intensity [215] in the same way of a shorter but intense bout of exercise. Longer training induces also an increase of resting BDNF levels, although ambiguity exists on the duration, type and intensity of training that are required to maintain this effect over time [216]. A better understanding of the possible neuroprotective versus neurotoxic effects of exercise on nerve injury can be traced back to the results of modulation of its main variables.

3.1. Forced Versus Voluntary Exercise

A first distinction in assessing the effects of activity treatments should compare the results of voluntary and forced exercise. Voluntary exercise can increase the expression of several molecules that stimulate with BDNF the synaptic activity and the neurite outgrowth in spinal cord and hindlimb muscles [103, 217]. On the other side, forced exercise like treadmill locomotion may produce responses of both transient and chronic stress, that after nerve injury can induce more robust neuroprotective effects, and also analgesic effects [218-222]. With regard to the effects on pain, prolonged exercise may generate chronic stress responses but nociceptive thresholds have been mostly measured after forced exercise-induced acute stress responses are resolved [218, 220]. Voluntary exercise may also elicit a stress-like response in acute phases [219] due to the increased physical activity; however, various studies showed that prolonged voluntary wheel running is anxiolytic when performed under mild to moderate stress [223-227].

Rodents models of stroke showed that forced exercise such treadmill running tends to induce better recovery than voluntary wheel running exercise [228]. Sheanan *et al*. [229] recently showed that, contrary to what demonstrated with forced exercise paradigms, voluntary short-duration running is not sufficient to induce hypoalgesia in peripheral nerve models of pain and acute inflammation. The discrepancy in the effects on neuroprotection of voluntary versus forced exercise seems to be due to the different behaviors. Even if slower, forced treadmill locomotion is more constant than voluntary running, the latter occurring in shorter spurts at faster speed, although an equal distance is covered by both the exercised groups [220]. Neuroprotection by forced exercise leads to increased neurogenesis and cerebral metabolism, decreased stroke volume and improved neurologic deficit, these also associated to the upregulation of heat shock proteins [218, 228, 230]. There seems to be sufficient evidence to support the conclusion that intermediate exercise intensities distributed over a longer time period, as provided by programming treadmill training, convey greater neuroprotection than further robust exercise over short time periods as in voluntary running.

A different response to exercise types seems to emerge in case of neurodegenerative diseases. Contrary to acute brain injury, which may require less intense but steady activity, in mouse models of AD simple voluntary exercise was sufficient to inhibit the progression of neuronal degeneration [182], and was more neuroprotective when compared to forced exercise [183]. It may be hypothetized that voluntary exercise enhances endogenous neuroprotective responses to progressive degeneration, while sustained and forced exercise can counteract more effectively the damage from acute injuries.

3.2. Intensity of Exercise

An important question for the preparation of an exercise schedule is how to establish the adequate intensity of exercise to activate neuroprotective and regenerative mechanisms, but also to prevent or inhibit maladaptive responses, such as pain and excessive excitability of motor and sensory neurons. Evidences that the neurotrophic factors expression may be dependent on the amount of activity performed during the training suggest a key role of the intensity parameter in the positive or negative modulation of neurotrophins. While some studies reported an increase [104,

105, 217, 231], others showed a decrease of neurotrophic factors following exercise [232, 233]. This discrepancy may rely on variations in the intensity of exercise applied. BDNF and NT-3 are known to increase in the lumbar spinal cord following low-to-moderate intensity exercise [101, 102, 107]. However, moderate-intensity running caused a depression of BDNF mRNA, but not of its protein, even if elevating blood lactate and corticosterone levels [234]. An increasing-intensity treadmill exercise protocol decreased BDNF, NGF and GDNF mRNA levels in the rat DRG [78], and BDNF expression in the spinal cord [64]. A similar effect was observed in the frontal cortex of mice performing high-intensity treadmill exercise, independently if continuous or intermittent [235, 236]. Thus, it seems that moderate-to-high intensities of exercise may trigger responses opposite to low intensity exercise on neurotrophins production, as a regulatory negative feedback similar to that observed under sustained neural activity and stress. Results from these studies are consistent with previous reporting decreased hyppocampal BDNF mRNA under stress and glucocorticoids stimulation, immobilization and strenuous exercise [237]. However more studies are needed to accurately understand the interplay between exercise intensity and neurotrophic factors production.

In the muscles, neurotrophic factors expression may vary depending on the type of muscle that is more stimulated by specific activities. Moreover, the amount of neurotrophin protein production across different types of skeletal muscles may depend on the intensity of exercise training [238, 239]. Low to intermediate intensity locomotion likely activates more slow-twitch than fast-twitch muscle fibers. Treadmill training increased BDNF levels in the soleus muscle (containing slow-twitch fibers), but no changes in the gastrocnemius muscle (containing fast-twitch fibers) were observed [240]. GDNF protein content also increased in the soleus and decreased in the extensor digitorum longus muscle (with high proportion of fast-twitch fibers) following low-intensity exercise [109]. Moreover, NT-4 was much more expressed in the soleus muscle slow fibers if compared with the gastrocnemius muscle fast fibers [238].

Exercise intensity may also affect the neurotrophic response to injuries depending on their severity. Acute and prolonged passive cycling treatment in spinalyzed rats increased the mRNA of BDNF, GDNF and NT-4 in motoneurons compared with small mRNA increase following the injury [241], differently to what was observed after peripheral nerve injuries [242]. In contrast, mRNA and receptors of neurotrophic factors were largely unchanged in large DRG neurons after spinal cord injury either with or without exercise [241]. These results indicate that intensity of training should be taken in consideration and adapted to different types and grades of injury in planning rehabilitative exercise protocols.

The debate is open regarding how and to what extent the exercise intensity may be adapted to the type and degree of nervous injury, in order to generate an optimal neurotrophic contribution. Possible mechanisms for neurotrophins increase following moderate intensity exercise are considered the increased conversion of pro-neurotrophins to the mature form [243], the induction of IGF-1 [244, 245] and estrogens [246, 247], as well as the reduction of leptin [245] and corticosterone concentrations [246]. It is still unclear, however, how high intensity exercise may induce the opposite effect and, therefore, trigger a downregulation of neurotrophic factors. Both high [248] or low [246] intensity exercise training enhanced BDNF concentration in the brain due to the reduction of corticosterone concentration, suggesting that mechanisms for inducing neurotrophin downregulation may be more than just activation of a cortical stress response.

Observation of rodents preferences for training to continuous forced running on a treadmill at sustained speed led us to formulate an increasing-intensity treadmill protocol (iTR) [11, 64, 78]. iTR running in rats starts at normal locomotion speed (10 cm/sec) and gradually increases (2 cm/sec every 5 minutes) until 1 hour of training session. In this way injured animals [11, 78] do not refuse the final high speed running (32 cm/sec) if slowly adapted to it without stressors or electrical shocks. Resembling this protocol, intermediate levels of exercise intensity may be applied to patients by similarly starting with normal kinesis and gradually increasing velocity until elevated but sustainable levels of activity. Such protocols may induce the patient to activate more complex responses (for example, potentiating the use of slow-twitch muscle for the control end of the movement) and their strengthening by means of gradual increase of exercise intensity.

Significant reduction of mechanical allodynia was observed after early and short-lasting iTR in the same way if after chronic constriction injury or section and suture repair of sciatic nerve [11, 249]. Normal nerve regeneration was not impaired even if reduction of hyperalgesia was parallel to the decrease of BDNF and NGF levels in DRG and spinal cord, inhibition of microgliosis and normalization of chloride cotransporters homeostasis [64, 249]. Compared to a low-intensity protocol, the iTR protocol demonstrated neuro-protective effects by counteracting the destruction of perineuronal nets (PNN) and reducing the motoneuronal synaptic stripping, partially preventing the reduction of Vglut1 synaptic buttons, after sciatic nerve lesion [250] (Fig. **1**). These findings suggest that gradually increasing the exercise intensity, such as in the iTR protocol described, may be a strategy to optimize neurotrophins actions on both sensory and motor neurons in order to reduce early neurotrophin-mediated hyper-excitability in sensory neurons but in parallel to stimulate neuroprotection of spinal motor circuitry.

3.3. Duration of Exercise

Duration of exercise bouts following an injury is also an important variable for setting activity treatments. A greater duration of exercise seems to lead to greater stimulation of the neurotrophic system. Recently serum BDNF levels were measured in adult human males after a vigorous or a moderate intensity aerobic cycle exercise bout [251]. All the exercise types caused a substantial BDNF increase, even if significantly higher BDNF elevation was found after longer duration (40 min). Other studies showed that both acute and chronic aerobic exercise lead to an increase of BDNF levels, but this is not induced in case of strength training [252-254].

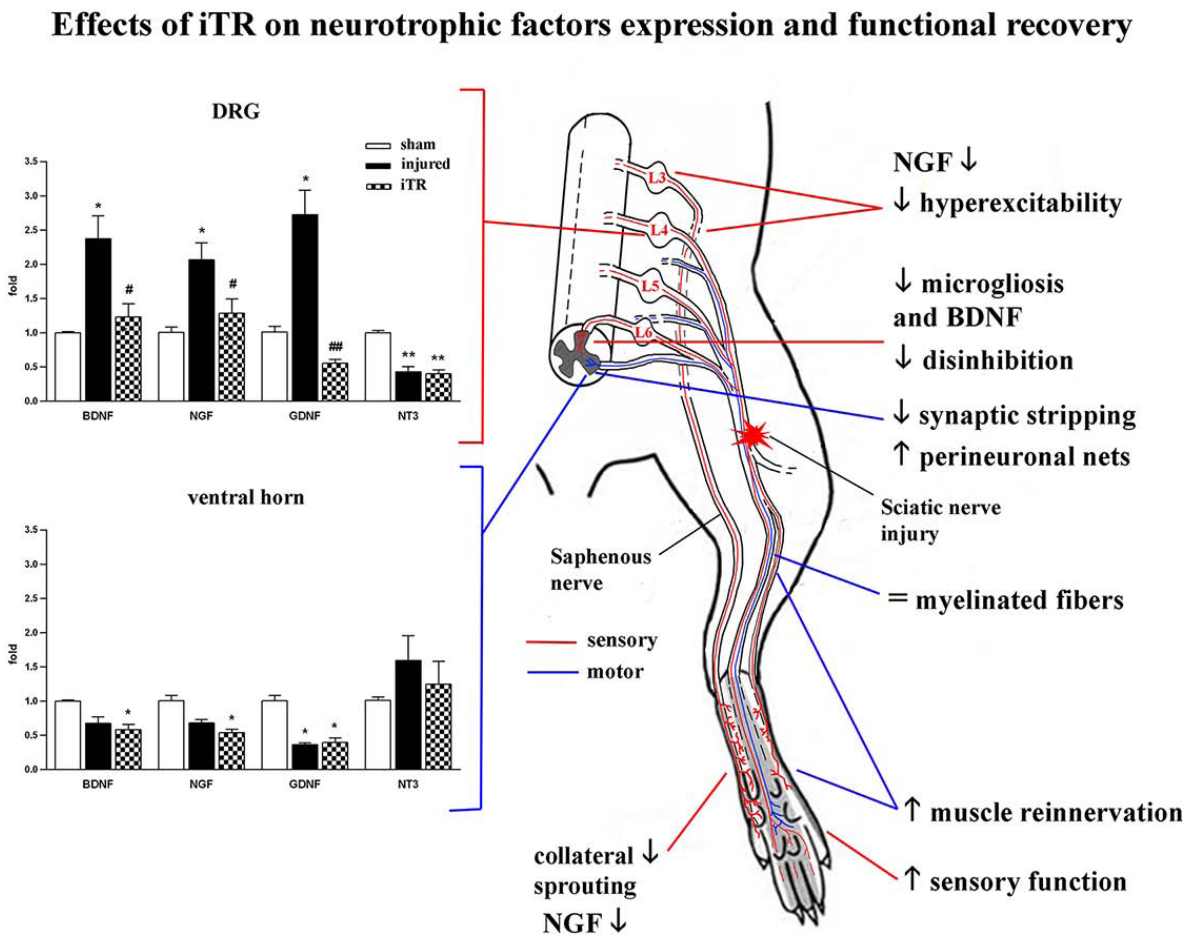

Fig. (1). Summary of the effects of the increasing-intensity treadmill (iTR) exercise protocol on the expression of neurotrophic factors and functional recovery from injury to the rat sciatic nerve. The mRNA expression of BDNF, NGF, GDNF and NT3 was assessed in sensory (dorsal root ganglia, DRG) and motor (spinal cord ventral horn) neurons of the injured paw at 8 days post-injury and after performing 5 days of training (from day 3 to day 7) (left panels). Sciatic nerve injury induced a peripheral increase of BDNF, NGF and GDNF in lumbar DRG, but their central expression tended to decrease. Conversely, NT3 expression was reduced in sensory neurons. iTR prevented the neurotrophic factors increase in DRG without significantly affecting central neurotrophin changes compared with injured untrained animals. Some effects of iTR on mechanisms of pain and regeneration are outlined (right side) and correlated to local neurotrophin reduction at the plantar paw skin, sciatic nerve, lumbar DRGs and spinal cord dorsal horn.

Based on these considerations, aerobic exercise programs for neuroprotection should take into account the volume of neurotrophin release over time.

Animal studies using chronic aerobic exercise have consistently reported the elevation of basal BDNF levels in the hippocampus, striatum and other cortical regions [19, 107, 163, 193, 255, 256]. Resistance exercise can also showed to increase hippocampal BDNF [257]. BDNF levels remained upregulated in the rat hippocampus after 28 consecutive days of exercise [148, 258], differently from other neurotrophic factors that showed tolerance to chronic exercise. Benefits of chronic exercise-induced BDNF that have been demonstrated in animal models of disease are cell survival [259], decreased depressive symptoms [260] and functional recovery after traumatic brain injury [261]. Furthermore, robust effects on cognition, learning and memory were described in healthy laboratory animals that performed either voluntary or forced exercise at disparate intensities and durations, whether assessed by Morris water maze [140, 237, 262], radial arm maze [263], Y-maze [264], object recognition tasks [265], or pain avoidance tests [191, 266].

Despite these results, there is controversy about the dependence of BDNF and GDNF expression on exercise duration. Some studies showed that short-term treadmill running (3, 7, 15 days training periods) resulted in the same BDNF levels in the hippocampus and basal forebrain of both control and exercise trained animals [267, 268]. On the other hand, a recent study showed that both high intensity interval training and continuous training increased rat brain BDNF and GDNF levels [269]. Different studies have shown that long-term exercise training at moderate intensity increased GDNF concentration in striatum, spinal cord and sciatic nerve [180, 270], while short-term exercise at low to moderate intensities did not influence the GDNF concentration as observed in the striatum and substantia nigra [178]. Therefore, production and activation of neurotrophins during exercise seem to be dependent on the duration of exercise

protocols, and the time spent in performing the activity can be tuned up to gradually increase the intensity of a specific exercise. Duration of training also affects the maintenance of neurotrophic supply. Thus, after increasing long-term training, serum BDNF expression normalizes after 8 weeks of detraining [253].

If chronic exercise provides the injured nervous system with a higher neurotrophic supply, excessive neuromuscular activity may produce opposite harmful effects for muscle reinnervation [271], reducing axonal regeneration [115, 272] and the proliferation of Schwann cells [273], and also inhibiting collateral sprouting of axons in partially denervated muscles [274-276]. Activity treatments in the form of electrical stimulation or treadmill running may result detrimental for peripheral nerve regeneration, neuropathic pain and inflammation when they are exhaustive and continuous [11, 277]. The physiological responses of adaptation to increased duration of exercise should therefore always be monitored after injury.

Another critical variable for setting the rehabilitation exercise treatment is the time of administration with respect to the nerve injury. Application of exercise prior to injury or pre-training is thought to have a neuroprotective effect, for example priming neurons for increased axonal regeneration following injury [102]. Moreover emerging evidence suggests that better recovery may be achieved when exercise is applied at early times after injury [11]. Exercise, either acute or prolonged, may affect the early expression of genes that respond for plasticity and apoptosis as well as neurotrophic factor production in a cell specific manner (differently in motor than in sensory neurons) after injury [241]. The first week after injury seems to be a crucial time window, during which starting activity at different intensities may stimulate or inhibit the neuronal regenerative response. The activation of neurotrophin signal transduction pathways peaks within 7 days for NGF, and around 7-14 days for BDNF and GDNF in injured peripheral nerves; on the contrary, other neurotrophins such NT-3 and CNTF are downregulated after injury [5, 242, 278]. Thus application of exercise during the first days from nerve injury may be critical in regulating the neurotrophic response to stimulate survival and growth of sensory [102, 279] and motor [279, 280, 281] neurons, or to inhibit excessive hyperexcitability,

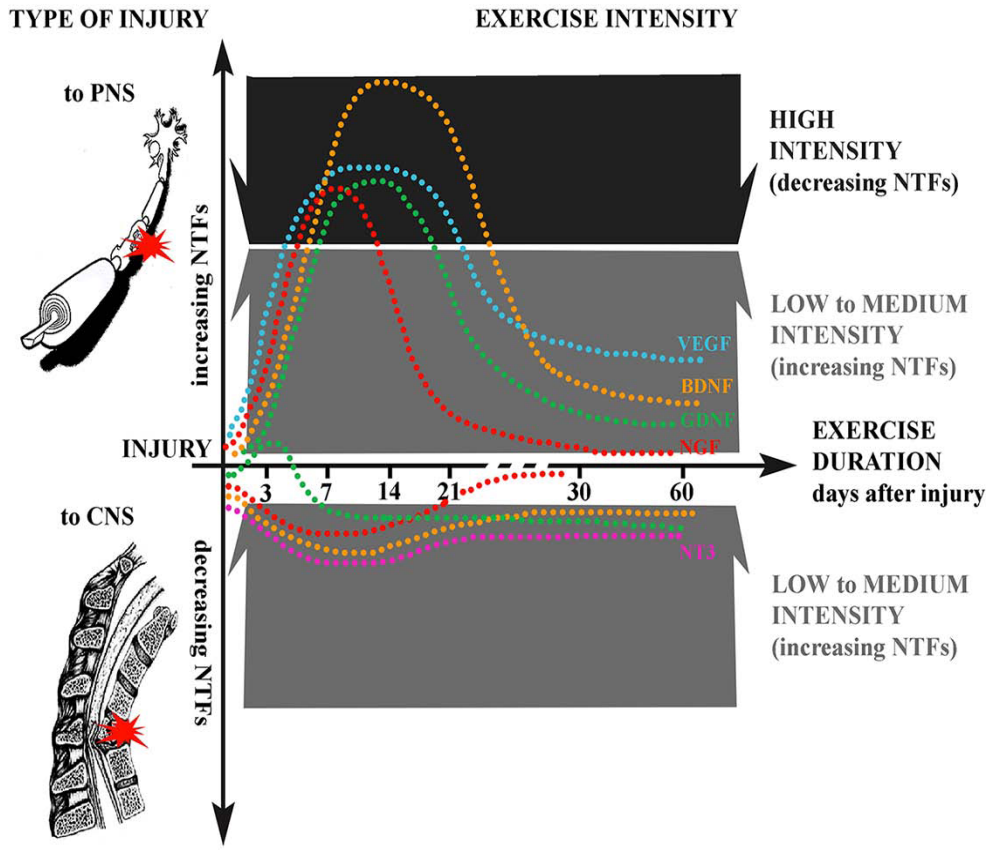

Fig. (2). Schematic of the main effects of exercise on the expression of neurotrophic factors (NTFs) after nerve injury. Depending on the type of injury, NTFs expression may increase or decrease (positive/negative dotted lines), with different effects on neuroprotection. Injury to the peripheral nervous system (PNS, top) induces the activation of NTFs signal transduction pathways peaking within 7 days for NGF, and around 7-14 days for BDNF, GDNF and VEGF in the injured nerves; on the contrary, other neurotrophins such as NT-3 are downregulated. Injuries to the central nervous system (CNS, bottom), such as spinal cord injury, reduce neurotrophic factors support. Exercise can boost or reduce NTFs levels, depending on the intensity and duration. The efficacy of exercise intensity to induce functional recovery by modulation of NTFs is also represented. Low to intermediate intensity exercise generally increase NTFs expression in both PNS and CNS, stimulating neuroprotection and regeneration, while high intensity exercise may trigger NTFs reduction and induce opposite effects, similarly to a stress response, reducing hyperexcitability.

maladaptive collateral sprouting and mechanisms of neuropathic pain [11, 64, 78, 241].

On the other side, central injuries, such as spinal cord injury, induce a loss of some neurotrophic factors support, so that early applied exercise may boost and normalize their levels. Hemisection of the spinal cord induced a decrease in BDNF and synapsin-I levels, that were restored by voluntary running exercise [282]. Of several neurotrophic factors analyzed, injury to spinal cord increased the early expression of mRNA for GDNF [283] and NT-3 and of its receptor TrkB [241]. However, cycling exercise increased the mRNA for both BDNF and GDNF, and attenuated the expression of those factors increased by spinal cord injury. Taken together, all these studies support the idea that starting exercise during the first days after injury may promote functional restoration by modulating the changes in neurotrophic factors induced by neural injuries (Fig. **2**).

4. THE DOUBLE ROLE OF NEUROTROPHIC FACTORS IN EXERCISE

In previous sections we lined out both neuroprotective and excitotoxic effects of exercise that are mediated by endogenous neurotrophins. The dichotomy of exercise effects may be explained by the dual role that neurotrophic factors play under activity-dependent increasing stimulation following nerve injury and denervation. In this context, intensity and duration of stimulation may differently convey neuroprotection by producing an enhancement or a decrease of neurotrophic factors. The expression or inhibition of neurotrophic factors, such as BDNF, can promote or inhibit pain and regeneration, depending on whether exercise activates the neurotrophin signaling and excites neurons at peripheral or central levels.

4.1. Peripheral Versus Central Neurotrophin Expression

A systematic review [284] analyzing peripheral BDNF expression after exercise suggests that basal BDNF concentrations are increased by acute aerobic but not strength exercise, although the effect is transient. Circulating BDNF originates from both central and peripheral sources. Exercise temporarily elevates basal BDNF and upregulates BDNF synthesis, release, absorption and degradation. On this line, an acute exercise bout would result in higher BDNF synthesis if compared with untrained subjects, and if exercise is repeated in subsequent training, further BDNF could be released into the bloodstream and induce more efficient absorption by both central and peripheral tissues, finally producing a cascade of neurotrophic and neuroprotective effects.

Aerobic but not strength training produces an increase of peripheral BDNF levels [252-254]. This is a consequence that muscle BDNF is not released into systemic circulation and that muscle itself is probably not a source of peripheral BDNF during chronic exercise. In fact the main source of exercise-induced BDNF appears to be the brain, and peripheral blood mononuclear cells and endothelial cells may contribute to approximately 20–30% of peripheral levels [193, 285]. Moreover, aerobic exercise may be a potent stimulator of neurotrophins in the peripheral as well as in the central nervous system, but central expression may be different from peripheral. For example, voluntary wheel running increased mRNA levels of NT-3 and its receptor TrkC in the spinal cord and in the soleus muscle, but changes in NT-3 protein were found only in the spinal cord, suggesting that the central nervous system may produce its own neurotrophins in response to exercise [217].

Brain and spinal expression of neurotrophic factors can be modulated by direct activation of noradrenergic and serotonergic pathways, with relevant effects on neuroprotection and functional recovery after injuries. Exercise-induced noradrenergic stimulation *via* β-adrenergic receptors seems to be essential for regulation of BDNF [286], since β-adrenergic blockade significantly attenuates the elevation of BDNF mRNA as induced by exercise in the cortex [287]. Moreover, some cognitive advantages of exercise, such as the reinforcement of contextual fear conditioning, are also attenuated by β-adrenoreceptors blockage [288]. Moreover, it is known that exercise mediates increased BDNF expression by stimulating the PKA pathway following the activation of β-adrenergic G-protein-coupled receptor *via* the transcription factor CREB [289]. Ubiquitously expressed, CREB is a nuclear transcription factor implicated in all cell proliferation, differentiation, adaptation and survival [290]. Through β-adrenergic receptors physical activity may not only maintain muscle metabolism after injury but also activate important pathways, such as those of MAPKs and PI3K-Akt signaling [291-294]. Motor activity directly modulates also serotonergic activity in brain and spinal cord [295], and prominent effects are observed when exercise is applied after peripheral and central nervous injuries [296, 297]. For this reason, exercise-induced BDNF alterations *via* direct serotonergic activation may be more complicated. Blockade of 5-HT2A/C receptors alters exercise-induced BDNF mRNA levels [287]. Activation of 5HT2A receptors is relevant after injury for strengthening the locomotor alternating pattern and rescuing the lost post-synaptic inhibition by restoring the spinal chloride homeostasis and counteracting central disinhibition, spasticity and neuropathic pain [297]. On the contrary, 5-HT1A receptor blockage seems to do not affect exercise-induced BDNF, although it further enhances its levels in the anterior cingulate cortex [287]. These findings indicate that exercise may activate several neural descending pathways to differently modulate neurotrophin expression in peripheral and central neurons.

4.2. Positive and Negative Feedback for Neurotrophic Factors Expression

The delicate interplay that takes place between glutamate and neurotrophic factor signaling systems represents the functional core of the activity-dependent neuroplasticity during development as well as in the adult [298]. Neurotrophic factors can directly modify the glutamate signaling by changing the expression of Ca^{2+}-regulating proteins and glutamate receptor subunits, and also indirectly by engaging the production of antioxidant enzymes, energy-regulating proteins and anti-apoptotic Bcl2 family members [299]. On the other side, glutamate can stimulate the production of

neurotrophic factors such as BDNF, promoting neurogenesis, synaptogenesis and neurite outgrowth. Mechanisms of activity-dependent survival may be triggered by exercise and intermittent fasting in prevention of neuronal death as revealed in experimental models of stroke [300]. It is usually accepted that low or intermediate intensities of exercise produce neuroprotection for brain neurons, while on the contrary high intensities may cause damage. In this case, intense and prolonged activation of glutamate receptors may provoke neuronal dysfunction and degeneration [301]. Indeed, harmful effects could appear in undue conditions of physical or psychological stress. These conditions may reverse neurotrophic factor production by providing a negative feedback regulation of the hypothalamo-pituitary-adrenocortical (HPA) axis, and trigger oxidative and stress responses [302].

Imbalance of glutamatergic neurotransmission could contribute to maladaptive serotonergic neurotransmission, and negative regulation of neurotrophic factors may be parallel also to extensive activation of noradrenergic and serotonergic pathways. However, after nerve injury, chronic exercise may affect the noradrenergic and serotonergic systems in similar ways to pharmacological interventions, increasing excitatory noradrenaline and serotonin activity in the brain [303-305]. Increased serotonergic activity after treadmill exercise [296] has shown to induce downregulation of BDNF expression in the brain [306]. We found reduced NGF, BDNF and GDNF expression in DRG and spinal cord after increasing-intensity treadmill locomotion in sciatic nerve injured rats [64, 78]. The reduction of neurotrophins expression is associated to an increased expression of β2-adrenergic and 5HT2A serotonergic receptors in lumbar spinal cord, which are reduced after sciatic nerve injury (unpublished data). These results indicate that the increased neurotrophic factor production observed after peripheral nerve injury can be modulated by exercise in order to preserve and maintain the central circuitry from maladaptive plastic changes typically associated to neuropathic conditions [64].

On the other side, sustained and excessive activation of glutamate receptors is known to be excitotoxic, particularly under conditions of reduced availability of energy and increased oxidative stress. The upregulation of NMDA receptors is a mechanism for long-term enhancement of glutamatergic activity by exercise [307]. In addition, prolonged activation of AMPA receptors can promote Ca^{2+}-mediated BDNF release for signaling through TrkB receptor [308, 309]. High intensity exercise increases BDNF levels that may lead to neuronal hyperexcitability [310]. Consequently BDNF may further induce enhancement of synaptic plasticity by strengthening the excitatory glutamatergic transmission. This positive feedback loop between BDNF and glutamatergic activities may result in increased seizure vulnerability and effects of excitotoxicity that are often seen after experimental manipulations to stimulate BDNF function, as showed in the hippocampus [311-313]. Hyperexcitability following BDNF upregulation may also account for excitotoxicity as due to increased vulnerability to kainic acid as demonstrated after injection into the hippocampus of chronically exercised rats [314].

CONCLUSION

Physical activity exerts neuroprotective effects that are conveyed by multiple mechanisms to peripheral and central neurons. The neuroprotection resulting from exercise training is an endogenous effect that may be best afforded by specific exercise protocols. Neuroprotective and pro-regenerative effects of exercise have been associated to modulation of neurotrophic factors. The enhancement of neurotrophic factors expression is connected to a number of responses, such the strengthening the neurovascular unit, the induction of astrocytosis, angiogenesis and arteriogenesis, the decrease of inflammatory response and microgliosis, and the decrease of apoptotis, that all together protect neurons from the consequences of nerve injuries and neuro-degenerative diseases. However, the effects of increasing neurotrophic factors are dichotomous, ranging from neuro-protection and nerve repair to cell death, hyperexcitability and induction of pain. Significant reduction of inflammation and neuropathic pain was recently achieved through moderate-to-high intensity exercise that was associated to a decrease of neurotrophic factors, particularly NGF, BDNF and GDNF levels in sensory neurons, after peripheral nerve injuries [64, 78, 124]. Furthermore, high intensity exercise reduces brain neurotrophins similarly to the activation of metabolic and glucocorticoid stress responses [235-237].

From a practical point of view, exercise protocols can be easily applied to induce neuroprotection in the setting of rehabilitation after nerve injuries but several critical parameters should take into account. First of all, the intensity of activity can be tuned up to reach more efficaciously the aimed outcome of training. It may be increased in order to enhance neurotrophic factor production (for example to stimulate motor and sensory nerve regeneration), or further increased till high levels to trigger the opposite effect and decrease neurotrophic factors (for example, to modulate plasticity, pain and hyperexcitability). The type of injury (peripheral versus central) is crucial to choose between different intensity exercises, since neurotrophic factor response to insult may be opposite: peripheral nerve injuries induce an increase of neurotrophic factors expression as spontaneous response to regenerate, but after spinal cord injuries a loss of neurotrophic factors has been observed and even associated to pain conditions. Moreover, exercise intensity is relevant in promoting neuroprotection at different sensory and motor modalities: for example, low-to-intermediate intensities of exercise activate slow-twitch muscle fibers to a greater extent than fast twitch muscle fibers, and stimulate sprouting and regeneration of sensory neurons, but contrarily adaptation of fast twitch muscles and reduction of sensory fiber sprouting were observed after high intensity exercise. The time window of exercise treatment after injury is another critical parameter. Since chronic and acute physical activity can have opposite effects on neuroprotection, this duality should be better assumed, particularly in individuals with underlying inflammatory conditions. The greater effects of exercise take place within

the time of higher vulnerability and plasticity of the damaged pathways. This seems to be the early time after the insult, when modulation of neurotrophic factors transcription and activation may play a stronger effect in protecting neurons from primary and secondary damage.

Physical activity may be considered an affordable and effective method to increase neuroprotection and improve functional recovery by acting on neurotrophic factors, representing an endogenous treatment. Although the application of different exercise treatments has uncovered the differences in cognitive and behavioral phenotypes in animal models of nerve injuries, more recent studies underscored the various levels by which the function of BDNF and other factors can be manipulated with activity-dependent therapies. The use of distinct intensities of activity, the preferential application at critical phases of neurotrophins expression, the regulation of pro-neurotrophins to mature neurotrophin cleavage, and the design of paradigms to differentially stimulate peripheral versus central and sensory versus motor neurons, provide a multiple repertoire of regulatory mechanisms that may be optimized for each individual pathology.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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