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Review article

The role of exercise on peripheral nerve regeneration: from animal model to clinical application

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ABSTRACT

Peripheral nerve injury is a complex condition with a variety of signs and symptoms depending on the severity and nerves involved. Peripheral nerve damage may lead to sensory and motor functions deficits and even lifelong disability, causing important socioeconomic costs worldwide. Despite the increase in knowledge of the mechanisms of injury and regeneration, a full functional recovery is still unsatisfying in the majority of patients. It is well known that exercise promotes physical and psychological well-being, by ameliorating general health. In the last years, there has been a growing interest in evaluating the effects of exercise on the peripheral nervous system. Experimental works with rodent models showed the potential utility of exercise following peripheral nerve injuries, as evinced by increasing axon regeneration, muscle reinnervation, better recovery of strength, muscle mass and higher expression of neurotrophic factors. Moreover, clinical evidence showed positive trends in favour of physical therapy following peripheral nerve damage based on the improvement of range of motion (ROM), muscle power grade and pain. After a brief overview of peripheral nerve anatomy and the different types of nerve injury, the present review aims to summarize the impact of exercise on peripheral nerve regeneration. Some clinical evidence regarding the effect of exercise after peripheral nerve injury will also be discussed.

1. Introduction

Peripheral nerve injuries arising from trauma or disease can lead to sensory, motor deficits and neuropathic pain which may be the cause of life-long disabilities. The peripheral axons after severe nerve injury are able to regenerate, even if a full functional recovery is generally very poor [1]. Since slow axon regeneration represents one of the main cause for poor recovery, it has emerged as a target to treat peripheral nerve injuries [2].

An extensive literature provides incontrovertible evidence that physical exercise plays a neuroprotective role both in the central and peripheral nervous system through the activation of different processes. Exercise promotes neurogenesis and neurotrophins expression, improving the neurovascular unit integrity, decreasing apoptosis and modulating inflammation. Evidence for the potential utility of exercise following peripheral nerve injuries comes from distinct lines of research: experimental evidence, primarily in rodents, demonstrating the impact of exercise on synaptogenesis, myelination, neural functioning, growth, development and muscle reinnervation; preliminary clinical evidence suggesting that exercise could improve range of motion (ROM), muscle power grade and pain.

Rodent models of nerve injury allowed us to better comprise the regeneration mechanisms promoted by exercise after peripheral nerve damage. However, clinical applications remain poor, partly because such

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models are too far from the situation in humans. In fact, in human injuries, axons are generally required to extend over much longer distances than in rodents, and target tissues remain without axonal contact for extended amounts of time. Moreover, postsurgical treatment normally does not allow movement of the surgically repaired nerves, so the application of exercise protocol as a tool to promote nerve regeneration remains unclear.

The purpose of this review is to identify and examine the literature specifically relating to exercise following peripheral nerve injury. This review aims to (1) provide an overview on peripheral nerve anatomy and the types of nerve damage, (2) review some of the work done recently regarding the impact of exercise in promoting nerve regeneration.

2. The anatomy of peripheral nerve

The peripheral nervous system (PNS) comprises all the parts of the nervous system that are outside the brain and spinal cord. The PNS includes motor, sensory and autonomic neurons of spinal and cranial nerves, as well as roots, trunks, ganglia and plexus [3]. This system represents the way for the relay of sensory and motor impulses between the central nervous system (CNS) and the body surface, internal organs, smooth and skeletal muscles.

The peripheral nerves extend from the spinal cord and brainstem and may comprise both motor and sensory nerve fibers. The motor (efferent) portion of PNS comprises somatic motor division and the autonomic motor division. The cell bodies of somatic motor neurons are localized in the ventral horn of the spinal cord. Their axons leave the spinal cord via the ventral root and innervate skeletal muscle fibers responsible for movements. Somatic motor neurons are classified in alpha MNs (α-MNs), beta MNs (β-MNs) and gamma MNs (γ-MNs). The first one highly myelinated, exclusively innervates extrafusal muscle fibers [4]. The β-MNs, representing the least expressed MNs subtype, are involved in the innervation of both intrafusal and extrafusal muscle fibers [5]. The γ-MNs innervate intrafusal muscle spindle fibers. They maintain the fibers at a functional length, contributing to the regulation of muscle contraction.

The visceral MNs belonging to the autonomic nervous system, innervate smooth muscles (i.e., heart, blood vessel) and glands. The visceral MNs of the sympathetic nervous system have their cell bodies in the intermedio-lateral cell column from thoracic segment 1 (T1) to the lumbar segment 2 (L2) of the spinal cord. The cell bodies of autonomic MNs of the parasympathetic nervous system are located in the brainstem nuclei for oculomotor nerve (III), facial nerve (VII), glossopharyngeal nerve (IX), and vagus nerve (X), and in the intermediolateral cell column from sacral segments 2 to 4 (S2–S4) of the spinal cord.

The sensory (afferent) division of the PNS comprises two major categories of fibers, somatic and visceral sensory fibers, organized into cranial and spinal ganglia located along the brainstem and in the dorsal root of the spinal cord. The somatic afferent axons transduce sensory impulses, such as joint position, muscle stretch, touch, pressure, temperature, itch, and pain, from the surface or inside of the body to the CNS [6]. The visceral sensory fibers carry conscious sensations (e.g., gut distention and cardiac ischemia) and unconscious visceral sensations (e.g., blood pressure and chemical composition of the blood). They are also involved in transmitting gustatory information from the taste buds [7]. Each peripheral nerve is made of nerve bundles characterized by nerve fibers and supportive connective tissue that consists of three distinct components called endoneurium, perineurium, and epineurium (Figure 1). Endoneurium represents the innermost connective tissue needed to wrap the nerve and isolate it from the external environment. Endoneurium is formed by two different laminae: one external characterized by collagen type I and II longitudinally oriented, and one internal, with a network of fine collagen fibers tightly connected to the basal laminae which are constituted by collagen type IV, laminin, fibronectin, and heparan sulfate [8]. Myelinating Schwann cells rest on the basal lamina and are separated from the axonal membrane through the periaxonal space [9]. Fibroblasts, macrophages, and mast cells are also present in the endoneurium.

Perineurium isolates groups of axons to form nerve fascicles and represents the main diffusion barrier between the endoneurium and the extrafascicular tissues [10]. The thickness of the perineurium is variable between 1 and 100 μm and it forms a tubular wrapping that allows some axonal movement inside the fascicles. The perineurium is formed by connective tissue and perineurial cells. These flattened cells, connected by tight junctions, are arranged to form concentric layers separated by collagen. The number of perineurial cell layers is related to the size of the fascicle. Large nerve fascicles consist of many concentric layers, whereas a single layer of perineurial cells surrounds small distal fascicles.

The epineurium represents the outermost layer of nerve connective tissues which encloses the whole nerve, providing protection from the mechanical force. It is constituted by a dense connective tissue, characterized by bundles of types I and III collagen fibrils and elastic fibers arranged in an undulated orientation, and by adipose tissue. Moreover,

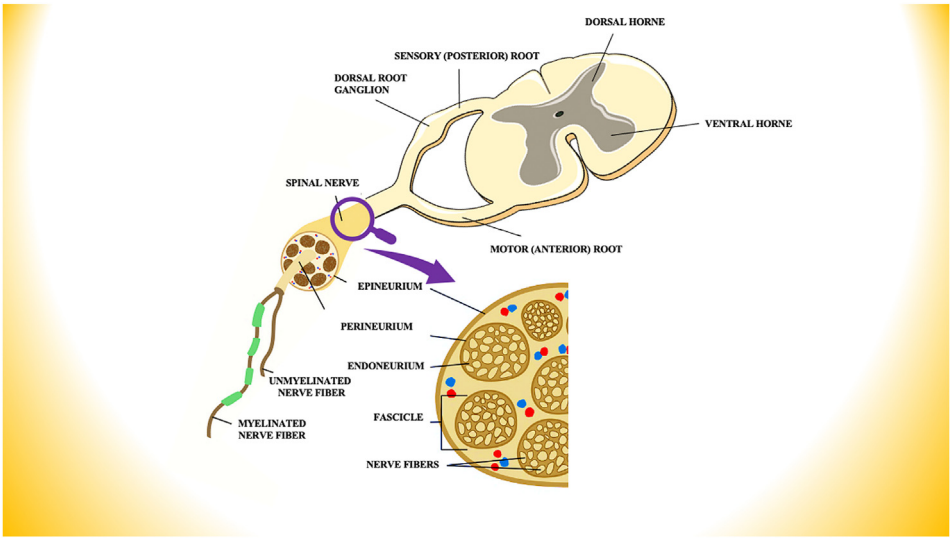

Figure 1. Schematic representation of anatomical structures of peripheral nerves. Each nerve fiber is surrounded by the endoneurium consisting of loose connective tissue. The individual neurons are grouped into bundles, known as fascicles, and each of these is surrounded by the perineurium, formed by connective tissue. The epineurium, consisting of dense connective tissue, represents the outermost layer that encloses the whole nerve.

the surface of the epineurium is nourished by a thin vascular plexus known as the vasa nervorum [11]. Within a peripheral nerve, there are both myelinated and nonmyelinated nerve fibers. Both types of fibers are supported by Schwann cells, representing the most abundant glial cells of the PNS [12]. Schwann cells exist in two different cell types: Remak cells, or non-myelin Schwann cells, and myelin Schwann cells. Remak cells envelop all the small-diameter axons, including axons of the autonomic nervous system. These cells promote the correct development of the PNS and exert regeneration activity after an injury by promoting axonal plasticity, growth, and sprouting [13]. Myelinating Schwann cells are 2–3 times longer than Remak cells and much bulkier. They are radially and longitudinally polarized cells wrapping several times around the axon to form a compact myelin cuff around it, by delimiting nodal, paranodal, juxtaparanodal, and internodal compartments [9]. Although both Remak cells and myelin Schwann cells ensure axons with metabolic and trophic support, only myelin Schwann cells play a central role to accelerate nerve impulse conduction. In a demyelinated nerve fiber, the electrical impulse moves continuously in wave motions, whereas, in the myelinated fibers, the conduction is done through a saltatory propagation. The myelin avoids the electric current from leaving the axon, by depleting the capacitance and increasing the electric resistance along the cell membrane. In this way, the action potential travels rapidly along the myelinated axon, jumping between the nodes of Ranvier.

The conduction velocity is related not only to myelin sheath thickness but also to axonal diameter. In fact, non-myelinated axons less than 1 μm in diameter shows conducting action potential less than 1 m/s, whereas large-diameter heavily myelinated axons conduct at a rate of approximately 100 m/s [12].

3. Peripheral nerve injuries

Unlike the CNS which is protected by bone and layers of meninges, peripheral nerves have poor physical protection and are localized superficial throughout the human body. Therefore, peripheral nerve injuries due to trauma, metabolic or hereditary poly-neuropathies, or nerve sheath tumours, represent a common condition. Results from a retrospective study [14], conducted from 1989 to 2014 showed that the most frequent cause of peripheral nerve injuries is vehicular accidents (46.4%) followed by penetrating trauma (23.9%), falls (10.9%), gunshot wounds (6.6%), car accidents involving pedestrians (2.7%), sports (2.4%) and miscellaneous (7.2%). Traumatic nerve injuries interest more often young adults aged between 20 to 39 years, with a total incidence of approximately 350,000/year. Moreover, males resulted in more affected with 74% of traumatic injuries [15].

Peripheral nerve injuries can be defined using Seddon's or Sunderland's classification (Table 1). The first classification system was created in 1943 by Seddon, who described three types of injury, i.e., neurapraxia, axonotmesis and neurotmesis, whose gravity dependent on the extent of damage to axons and coating tissues [16] (Figure 2). The classification of Sunderland identifies five degrees of injury adding two more types of axonotmesis [17]. Neurapraxia is the first degree and mildest type of peripheral nerve injury, occurring when the myelin sheath of the nerve is damaged. In fact, it is elicited by focal demyelination or ischemia. In this type of injury, the axons maintain their integrity and the endoneurium, perineurium, and epineurium remains intact. Although no Wallerian degeneration phenomena were observed, the conduction of nerve impulses in the injured area is blocked and motor and sensory connection result compromised [18]. Generally, motor fibers are more affected as compared to sensory, but muscles do not show denervation or atrophy on electromyography (EMG) [19]. The focal conduction block is temporary and resolves fully within 12 weeks once myelination is recovered, without the need for surgical intervention [20]. The second level of peripheral nerve injury is the axonotmesis, generally caused by crush, stretch or percussion [21]. In Sunderland's second-degree injuries, the axon and its myelin coating are disrupted, whereas, the integrity of the outer connective tissue covers are maintained. The third-degree injuries verify when the axon, myelin, endoneurial tubes, and connective tissue components are damaged and/or transected, despite the perineurium is preserved. The fourth-degree injuries occur when the axon, endoneurium and perineurium are damaged and only the epineurium remains intact. In axonotmesis, Wallerian degeneration occurs in the nerve segment distal to the injury and recovery may occur if the axonal sprout from the proximal stump reaches the proper endoneurial tubes in the distal stump, to reinnervate the target organ [22]. In the reparative process, the Schwann cells exert a key role to guide axonal growth from the proximal stump across the injury site towards the distal stump [23].

Neurotmesis represents the severest type of injury, characterized by a complete disconnection between the two segments of the injured nerve, affecting the axons, disrupting and distorting all coating layers, including the epineurium. This type of injury occurring after a cut lesion causes a complete sensory and motor deficit to the skin and muscles innervated by the nerve. The loss of the collagen coatings and their guiding function in the axonal regrowth interferes with the normal regenerative process, and surgical intervention is necessary to ensure the recovery of the injured nerve [24, 25].

The phenomena of nerve repair trigger a cascade of events involving Schwann cells, fibroblasts, macrophages and other blood cells (Figure 3). In brief, when axons start to collapse, the Schwann cells discard their ensheathing myelin and differentiating into a cell phenotype promoting regeneration. In particular, these cells align together to realize the bands of Bungner, which are responsible for guiding the axon from the proximal to the distal site, across the gap. Moreover, Schwann cells respond adaptively to damage by releasing different neurotrophic factors such as brain-derived neurotrophic factor (BDNF), glial cell line-derived

Table 1. Seddon and Sunderland classification of nerve injury.

Seddon's classification	Sunderland's classification	Injured Tissue	*Spontaneous recovery*	Electromyography
Neurapraxia	Grade I	Myelin	Yes	Normal morphology and poor motor unit action potential recruitment
Axonotmesis	Grade II	Myelin, axon	Yes, slower than neurapraxia	Abnormal activity
Axonotmesis	Grade III	Myelin, axon, endoneurium	Not very likely, surgical intervention may be needed	
Axonotmesis	Grade IV	Myelin, axon, endoneurium, perineurium	Highly unlikely, surgical intervention is necessary	
Neurotmesis	Grade V	Myelin, axon, endoneurium, perineurium, epineurium	No, surgical intervention is necessary	Abnormal activity

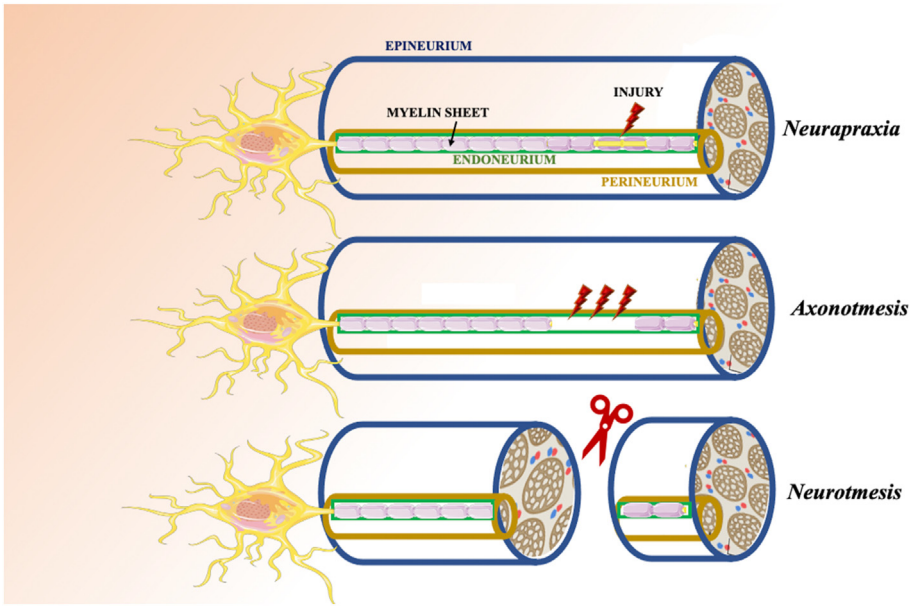

Figure 2. Seddon's classification of peripheral nerve injuries. Neurapraxia represents the mildest type of injury which does not imply loss of nerve continuity. It occurs after a minor contusion or compression of a peripheral nerve. Axonotmesis consists of the breakdown of the axon and subsequent Wallerian degeneration by nerve crush. However, endoneurial tube structures are well preserved. Neurotmesis represents the severest injury secondary to an avulsion or crush or cut with complete axonal transection. The axon, endoneurium, perineurium and epineurium are disrupted.

neurotrophic factor (GDNF), nerve growth factor (NGF), vascular endothelial growth factor (VEGF) and pituitary adenylyl cyclase-activating peptide (PACAP) [26, 27]. Beside Schwan cells, also macrophages are recruited to remove degenerated axons and myelin debris [28]. In the early phase of peripheral nerve injury, the activation of macrophages promotes the release of pro-inflammatory cytokines, whereas, in the later stages, they downregulate the pro-inflammatory cytokine expression and upregulate anti-inflammatory cytokine production in the distal nerve stump [29].

4. The influence of exercise on peripheral nerve regeneration

The physical activity represents a useful means to improve health and general well-being [30]. Its beneficial effects were observed in different pathologies, including cardiovascular and pulmonary diseases, metabolic disorders, muscle, bone, and joint pathologies as well as neurodegenerative diseases [31, 32, 33, 34, 35, 36]. The positive role of exercise on the nervous system was observed at multiple levels including axonal growth, phenotypic changes in peripheral structures and neurotrophins levels [37]. Several studies, displayed in Table 2, have investigated the impact of physical exercise on peripheral nerve regeneration and functional recovery. The effects of exercise can be influenced by different parameters such as intensity and volume of training as well as the different type of nerve injury [38]. Marqueste et al. [39], demonstrated that in rats with peroneal nerve injuries, after 10 weeks of treadmill running at 10 m/min for 1.5 h, twice a day per 5 days/week, fast nerve fibers improved both in proportion and conduction velocity. Moreover, the voluntary running-wheel exercise reduced the levels of the myelin-associated glycoprotein (MAG), an axonal growth inhibitor, suggesting one of the mechanisms played by exercise to promote axonal growth [40]. Molteni et al. [41], investigated the effect of exercise on nerve regeneration in rodents following unilateral sciatic nerve crush. They showed the increased neurite outgrowth of dorsal root ganglia neurons in trained rats performing 3–7 days of voluntary wheel exercise. Interestingly, the neurite length was closely related to the distance performed by the mice. Moreover, neurons of trained animals showed high levels of BDNF, which exerts a key role to promote neuronal plasticity and axonal regeneration [42]. In accord, another study showed increased levels of BDNF in dorsal root ganglion neurons of rats exposed to voluntary wheel running for 3 or 7 days with an increasing load of 100gr every day, as compared to the

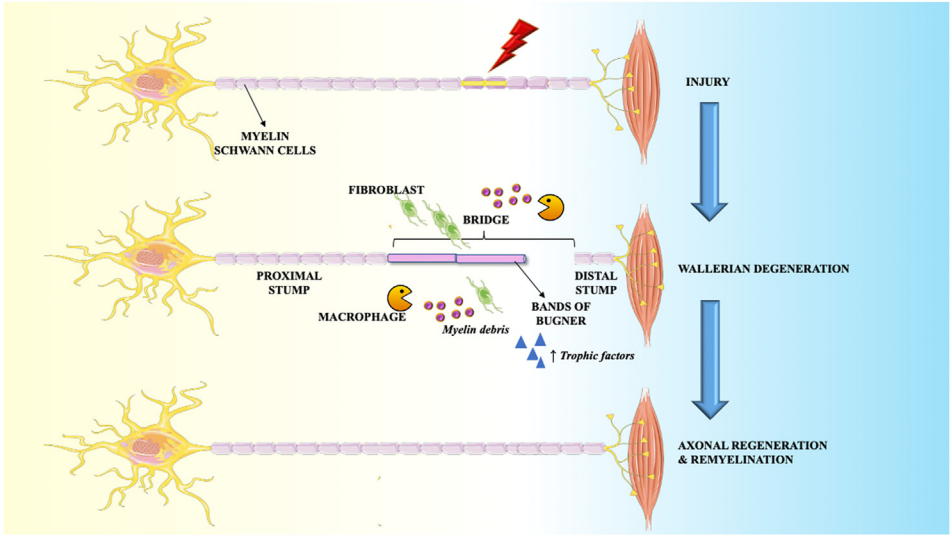

Figure 3. Schematic representation of the process of degeneration and regeneration after peripheral nerve injury. Following peripheral nerve injury, the proximal and distal stumps of the injured nerve undergo structural and molecular changes to allow the process of axonal regeneration. Schwann cells recruit macrophages to clear the cellular and myelin debris and secrete different neurotrophic factors. Then, Schwann cells undergo a striking elongation to form the Bungner bands, representing regeneration tracks. Signals from fibroblasts and macrophages drive Schwann cells migration through the bridge, to ensure a proper axonal regeneration.

Table 2. Benefits of exercise in rodent models of peripheral nerve injury.

Species	Mode of exercise	Pain model	Benefit	References
Rat	Treadmill running	Left peroneal nerve was sectioned then immediately self-anastomosed.	Better functional recovery of muscle sensory axons	[39]
	Treadmill running	Sciatic nerve transection and repair	Enhancement of muscle reinnervation	[54]
	Treadmill running	Sciatic nerve transection and repair	Improvement of muscle reinnervation and increase of regenerated axons number	[53]
	Treadmill running	Sciatic nerve transection and repair	Enhancement of functional muscle reinnervation.	[46]
	Treadmill running	Sciatic nerve transection and repair	Better motor axon regeneration and muscle fiber reinnervation	[56]
	Treadmill running	Sciatic nerve transection and repair	Enhancement of motor axon regeneration	[57]
Mouse	Treadmill running	Sciatic nerve transection and repair	Enhancement of motor axon regeneration	[45]
	Treadmill running	Common fibular nerve transection and repair	Enhancement of axon regeneration	[47]
	Treadmill running	Common fibular and tibial nerves were cut and repaired using a graft of the same nerve from BDNF−/− in Schwann cells or WT mice	Enhanced axon elongation	[44]
	Treadmill running	Median nerve transection and repair	Better recovery of strength, muscle mass and higher expression of neurotrophic factors	[52]
Rat	Wheel running	Unilateral sciatic nerve crush	Increased nerve regeneration and high levels of BDNF	[41]
Mouse	Wheel running	Long-gap sciatic nerve injury	Higher innervation ratio of muscle spindles and higher number of axons/myelin in the tube.	[58]

sedentary group [43]. The effect of exercise on BDNF expression to facilitate axon regeneration was also investigated by Wilhelm et al., [44]. In this study, mice common fibular and tibial nerves were cut and repaired with a graft of the same nerve from transgenic mice lacking BDNF in Schwann cells (BDNF−/−) or wild-type mice (WT). Mice subjected to the treadmill for 5 days/week for 2 weeks showed an increase in axons growth, despite the lack of Schwann cells-derived BDNF from the graft compared to the untrained group. These results suggested that two weeks of daily treadmill training after nerve transection results in enhanced axon elongation, likely due to an increased expression of BDNF mRNA in MN cells bodies. These findings are in accord with other studies performed in mice and rats treated with moderate daily exercise for 2 weeks following sciatic nerve transection and repair, which showed an enhancement of axon regeneration [45] and a modest improvement in functional recovery [46]. The enhancement of axon regeneration produced by treadmill training had been previously demonstrated by Sabatier et al., [47], who studied the effect of different protocols of treadmill training on mice after common fibular nerve injury. In particular, mice were divided into groups of low-intensity continuous training (60 min of running at 10 m/min 5 days/week for 2 weeks), low-intensity interval training (10 reps, 20 min total), and high-intensity interval training (2 min of running at a higher speed of 20 m/min followed by 5 min of rest repeated for 2, 4 or 10 times). The authors showed a significant enhancement of axon regeneration in mice that perform continuous training or high-intensity interval training except for the 10-rep interval training group that trained at 10 m/min. Interestingly, male and female mice responded differently to exercise.

Sex differences in the response to treadmill training were found by Wood et al., [48], whose showed that interval training regimen was effective in improving regeneration only in females, whereas continuous treadmill running for an hour at slow speed promotes axon regeneration only in males, due to the increase of serum testosterone levels. Moreover, castration via surgical removal of the testes prevents treadmill training effects on axon regeneration [48]. The systemic blockade of androgen and estrogen receptor, blocks exercise enhancement of axon regeneration in both sexes [49, 50, 51], suggesting that the effect of exercise is strictly related to androgen and estrogen receptors action. Another study showed that Sabatier's low-intensity protocol performed for 6 weeks, not only promoted axons regeneration but also improved grip strength in male mice after median nerve injury, suggesting a possible enhancement of functional recovery due to training [52]. Udina et al., [53], explored the effect of passive bicycle and active moderate treadmill training in rats following sciatic nerve injury. In particular, the passive group was submitted to one month of daily sessions of 30 min of passive cycling at 45 rpm 2 times with 10 min of rest (under isoflurane anaesthesia), whereas the active group performed a month of treadmill daily sessions of 30 min of walking at a 4.6 m/min with 10 min rest. The results showed that both active and passive training enhanced muscle reinnervation and axon regeneration, by reducing the altered excitability of spinal reflex after nerve lesion. Furthermore, the electrical stimulation combined with moderate treadmill training improved nerve regeneration of adult rats following right sciatic nerve injury, giving higher levels of muscle reinnervation compared to untrained mice [54]. Another study analyzed the effect of swimming training in rats after sciatic nerve injury applied during acute (24 h) and late (14 days). The swimming protocol consisted of 30 min each weekday for 2 weeks. The results showed that swimming exercise performed during both the acute and late phases after axonotmesis, accelerated nerve fiber regeneration, by increasing the diameter of axon and nerve fibers and promoting synaptic elimination [55]. In order to identify the most appropriate time to begin training after sciatic nerve injury, Brandt et al. [56], compared the effects of treadmill exercise begun at the first signs of muscle reinnervation (~3 weeks) to the effects of training begun immediately after peripheral nerve injury. The authors found that delayed exercise was valid to promote axon regeneration and muscle fibers reinnervation, however, it was less effective than immediate exercise in restoring Hoffmann's reflex.

Interestingly, Cannoy et al. [57], showed that rats following sciatic nerve injury subjected to the more strenuous exercise of walking an upwardly sloped treadmill showed enhanced regeneration of motor axons and muscle reinnervation, but poor functional recovery as compared to animals performing exercise on a level treadmill or no exercise at all. This result could be due to the minor effect of upslope treadmill training on proprioceptive sensory feedback from the reinnervated muscles [57]. A recent study evaluated the effects of voluntary wheel training on mice after one week from surgery on sciatic nerve treated with an acellular conduit associated with human Sk-34 cell transplantation [58]. The results showed increased numbers of axons/myelin in the tube and the contractile function in the exercise group.

Instead, no significant difference was found between the amount of exercise executed and the recovery of muscle mass, confirming the importance of the exercise quality and intensity for nerve regeneration rather than exercise volume [57].

5. Clinical studies of exercise and peripheral nerve injury

Conversely to results obtained in the animal models, the effectiveness of physical therapy following nerve injury in human patients showed unclear data.

A recent review [59] evaluated the physical exercise interventions for individuals with spinal cord injury. Of the 25 selected studies, 5 used aerobic exercise training; 2 studies presented resistance training interventions, 2 presented balance training interventions, 11 studies used gait training intervention, 5 studies used a combination of interventions in their methodology. The results showed that there is more evidence available for gait training, with more methodological rigor comparing to other types of physical therapy, probably because it represents the primary priority of spinal lesion affected patients. Another study [60] reported the effect of continuous and personalized intensive motor rehabilitation (R.I.C.) method, consisting in stretching, joint mobilization, active exercises, electro-stimulation, and strong psychological motivation, in two patients affected by medullary lesion. The results showed improvement in muscle strengthening and motor performances.

However, variations in the type and severity of nerve injury, type of exercise protocol applied, time and intensity of training as well as the coexistence of other pathologies seem to be the primary factors explaining the controversial results reported.

Several studies suggested exercise as a non-pharmacological approach to positively affect various aspects of non-traumatic nerve disease such as chemotherapy-induced peripheral neuropathy (CIPN) [61, 62, 63, 64, 65, 66]. The positive effects of exercise are related to decreasing pain and improving physical function [67] as well as improvement of deep sensitivity [68], perception of hot and coldness [69], and static balance performance [70]. Considering that exercise and peripheral muscle stimulation may decrease axonal degeneration and sustain peripheral neuronal function, physical activity, and limb/region-specific rehabilitation could improve balance, strength, and the quality of life of CIPN affected patients [67]. However, other studies were not able to find a beneficial role of exercise on CIPN signs/symptoms probably due to small sample sizes and rudimentary CIPN assessment [71, 72]. Different studies also showed patients with diabetic neuropathy benefit from exercising like endurance [73, 74], balance [75, 76] and multimodal training [77, 78]. However, since tendinosis is one of the musculoskeletal manifestations of diabetic neuropathy [79], due to multifactorial process characterized by excessive accumulation of advanced glycation end products, inflammatory response dysfunction, neuro-vascularization, peripheral neuropathy, and vasculopathy [80], the exercise it is not always practicable or it doesn't give the expected results.

In cases of patients with carpal tunnel syndrome, the result of an irritation, compression, or stretching of the median nerve, exercise and mobilization centred on nerve gliding and soft tissue mobilization, showed poor efficacy to improve symptoms and functional ability [81]. In contrast, Ballestero-Pérez et al. [82], showed that, although the standard conservative approach represents the best option for the management of carpal tunnel syndrome, the addition of nerve gliding exercises may improve the patient recovery by accelerating the rehabilitation process and avoiding the surgical intervention. In Bell's palsy, an acute disorder of the facial nerve, different physical rehabilitation protocols, based on active therapy, passive therapy or a combination of passive and active methods (e.g., massage/manipulation with active exercise regime), induced an improvement of facial movement and/or function [83]. Instead, other studies showed that the facial exercises, including strengthening and stretching, endurance, therapeutic and facial mimic exercises, seem to not produce significantly more improvement than the control treatment or no treatment [84, 85]. Another study [86] evaluated the effects of the rehabilitation process, starting three weeks after brachial plexus injury. The protocol included electrostimulation, kinesiotherapy, comprising passive range of motion (ROM) exercise to promote joint suppleness, and hydrotherapy, through exercises in a pool to remove gravity. Interestingly, the patient who achieved the best overall recovery, in term of sensitivity, muscular strength and pain, was also the most motivated and had a high degree of the initiative for the rehabilitation program. In accord, a case report, involving a 58-year-old woman affected by brachial plexus injury, showed that a twice-weekly rehabilitation program based on supervised passive ROM exercises, stretching exercises as well as a home exercise program, significantly improved ROM, muscle power grade and pain [66]. Recently, a new protocol was developed on patients 12 months post-surgery after traumatic upper brachial plexus injury. The physical therapy treatment was based on passive and active-assisted exercises to range of motion (ROM) for flexion, abduction and external rotation of the shoulder, and elbow flexion; muscle strengthening with progressive resistance exercises; motor reeducation training for muscle activation and stretching of shortened muscles. Although the reported studies showed positive trends in favour of physical therapy following peripheral nerve damage, the heterogeneity of type of injury as well as protocol used, influence the strength of the results and prevent reliable comparison between the different approach exercise-based.

6. Conclusion

A number of studies over the past several decades have shown the positive role of exercise on nerve regeneration and functional recovery in animal models after peripheral nerve injury. On the other hand, the efficacy of physical therapy to improve nerve regeneration in human after nerve damage, remains uncertain, since, in the case of extensive injuries, exercise may not be an option for a recovering patient. However, knowledge of many of the beneficial effects of exercise, such as the increase of neurite outgrowth, local neurotrophic factor levels and grip strength, as well as synaptic conduction velocity, makes it reasonable to translate such knowledge to clinical practice.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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