Basic mechanisms of peripheral nerve injury and treatment via electrical stimulation

https://doi.org/10.4103/1673-5374.335823

Abstract

Previous studies on the mechanisms of peripheral nerve injury (PNI) have mainly focused on the pathophysiological changes within a single injury site. However, recent studies have indicated that within the central nervous system, PNI can lead to changes in both injury sites and target organs at the cellular and molecular levels. Therefore, the basic mechanisms of PNI have not been comprehensively understood. Although electrical stimulation was found to promote axonal regeneration and functional rehabilitation after PNI, as well as to alleviate neuropathic pain, the specific mechanisms of successful PNI treatment are unclear. We summarize and discuss the basic mechanisms of PNI and of treatment via electrical stimulation. After PNI, activity in the central nervous system (spinal cord) is altered, which can limit regeneration of the damaged nerve. For example, cell apoptosis and synaptic stripping in the anterior horn of the spinal cord can reduce the speed of nerve regeneration. The pathological changes in the posterior horn of the spinal cord can modulate sensory abnormalities after PNI. This can be observed in cases of ectopic discharge of the dorsal root ganglion leading to increased pain signal transmission. The injured site of the peripheral nerve is also an important factor affecting post-PNI repair. After PNI, the proximal end of the injured site sends out axonal buds to innervate both the skin and muscle at the injury site. A slow speed of axon regeneration leads to low nerve regeneration. Therefore, it can take a long time for the proximal nerve to reinnervate the skin and muscle at the injured site. From the perspective of target organs, long-term denervation can cause atrophy of the corresponding skeletal muscle, which leads to abnormal sensory perception and hyperalgesia, and finally, the loss of target organ function. The mechanisms underlying the use of electrical stimulation to treat PNI include the inhibition of synaptic stripping, addressing the excessive excitability of the dorsal root ganglion, alleviating neuropathic pain, improving neurological function, and accelerating nerve regeneration. Electrical stimulation of target organs can reduce the atrophy of denervated skeletal muscle and promote the recovery of sensory function. Findings from the included studies confirm that after PNI, a series of physiological and pathological changes occur in the spinal cord, injury site, and target organs, leading to dysfunction. Electrical stimulation may address the pathophysiological changes mentioned above, thus promoting nerve regeneration and ameliorating dysfunction.

Key Words: axonal transport; brain-derived neurotrophic factor; dorsal horn stimulation; dorsal root ganglion stimulation; electrical stimulation; nerve regeneration; neuropathic pain; peripheral nerve injury; spinal cord dorsal stimulation

Introduction

Peripheral nerve injury (PNI) can lead to severe sensorimotor impairment and chronic neurogenic pain (Li et al., 2021; Xing et al., 2021), and is a prevalent cause of disability worldwide (Martinez-Marcos and Sañudo, 2019). Sunderland (1951) classified PNI into five grades according to the extent of injury and loss of function. The first grade describes a conduction block, which is the physiological interruption of nerve conduction along the axon at the site of injury, with an intact nerve structure and no Wallerian degeneration. Self-repair is expected in these cases. The second grade is characterized by axonal interruption, an intact endoneurium, and Wallerian degeneration. In these cases, nerve self-repair is observed with a speed of 1 mm/d. The third, fourth, and fifth grades involve injury to the endoneurial tubes, perineurium, and epineurium, respectively. Although self-repair is expected in the third grade, this is usually slow and incomplete. Thus, surgical intervention may eventually be required. Patients with grades four and five PNI are not expected to exhibit self-repair capacity, and surgical intervention is often necessary (Davis, 2020). The last decade has brought many surgical innovations in the treatment of PNI. However, there have been no significant improvements in the success of rehabilitation, as patients continue to experience somatosensory disorders. Moreover, 57% of patients with PNI are between 16 and 35 years of age, and 25% of patients with upper limb PNI are unable to return to work within 1.5 years post-operation (Kouyoumdjian et al., 2017). Therefore, PNI is associated with long-term disability and financial difficulties.

Treatments for PNI range from conservative approaches to surgical interventions. Conservative approaches include pharmacological treatments, cell-based therapies, and physical therapy. Pharmacological treatments have been found to improve axonal regeneration. Commonly used neurotrophic drugs include B vitamins, methylcobalamin, and exogenous neurotrophic factors (Ehmedah et al., 2019; Karagyaar et al., 2020; Sawangjit et al., 2020). However, because local drug concentrations in the peripheral blood tend to be low, pharmacological treatments often fail to achieve sustained clinical benefits. Recent years have seen tremendous progress in cell-based therapies such as those employing Schwann cells (SCs), mesenchymal stem cells (MSCs), bone marrow stromal stem cells, and skin precursor cells (Kubiak et al., 2020). Among these, MSCs can secrete various growth factors and support both nerve cells and SCs. A recent study indicated that exosomes from MSCs may be useful in a novel therapeutic strategy for PNI, as they can promote neurite outgrowth in dorsal root ganglion (DRG) and cortical neurons (Dong et al., 2020). However, difficulties associated with obtaining and sustaining such materials severely limit the clinical applications of cell therapy. Common physical therapies include phototherapy, magnetic therapy, acupuncture, and functional training. Despite the large variety of options, the treatment effects are not satisfactory. When spontaneous recovery is not observed in clinical practice, surgical interventions are often necessary. However, it is difficult to...
determine the optimal time for surgical intervention (Midha and Grochmal, 2019).

Compared with conservative approaches and surgical treatment, electrical stimulation (ES) is a safe and effective treatment option that can be applied in the vast majority of patients. Generally, patients without malignant tumors, high fever, coma, active bleeding, skin damage, or acute suppurative inflammation are eligible to receive ES. A previous study showed that ES can cause twisting of the axons and cytoarchitecture, leading to edema (Martellucci, 2015). However, recent studies reported that ES is efficacious in promoting axonal regeneration and functional rehabilitation in PNI patients (Gordon, 2016; Barber et al., 2018; Power et al., 2020). In addition, ES can be used to treat neuropathic pain after PNI. However, the physiological changes underlying PNI and the therapeutic effects of ES are complex. In this review, we summarize the physiological changes associated with PNI and the specific mechanisms of ES treatment at three levels: the cell body, the site of injury, and the target organ, to reflect a holistic view. Our goal was to generate theoretical guidance for further clinical ES applications.

Search Strategy and Selection Criteria

We used PubMed (https://www.ncbi.nlm.nih.gov/pubmed) to collect relevant papers published from inception to 2021 for inclusion in this narrative review. Our search keywords were: “peripheral nerve injury”, “electrical stimulation”, “peripheral nerve regeneration”, “spinal cord dorsal stimulation”, “dorsal horn stimulation”, “dorsal root ganglion stimulation”, “neuropathic pain”, “brain-derived neurotrophic factor”, “axonal transport”, “transcutaneous electronic nerve stimulation”, and “skeletal muscle stimulation”. After eliminating duplicates from the retrieved studies, we read the titles and abstracts of each article as a preliminary screening process, and then read the full texts to eliminate studies that did not cover the mechanisms of peripheral nerve injury and stimulation. The literature search process was primarily completed by author XLC.

The Mechanisms of Peripheral Nerve Injury

PNI is a common neurological condition that may cause motor and sensory disturbances as well as neuropathic pain. Pathological changes occur not only at the site of direct injury, but also throughout the affected regions of the central nervous system. In addition, target organs can be affected due to prolonged denervation. Therefore, the pathological mechanisms are complex, necessitating a holistic view. Changes at different levels are discussed in the following sections (Table 1).

| The first to study this field | The greatest contributions to this field | The affected site | Main mechanism |
|-------------------------------|----------------------------------------|------------------|---------------|
| Adams et al., 1966            | Shen et al., 2019                      | Skeletal muscle  | Oxidative stress and inflammatory responses result in skeletal muscle atrophy |
| Bray and Aguayo, 1978         | Mackinnon et al., 2007                 | Peripheral nerve axons | Wallerian degeneration and axonal staggered regeneration |
| Schmalbruch, 1988             | Navarro et al., 2007                   | Spinal cord      | Motor neuron apoptosis and synaptic stripping |
| Sato and Perl, 1991           | Durakul et al., 2012                   | Sensory receptors | The thresholds of thermoreceptors and nociceptors are decreased |
| Kajander et al., 1992         | Hussain et al., 2020                   | Spinal cord      | Excessive discharge of dorsal root ganglion neurons caused by inflammatory response; the numbers of microglia and morphological change |
| Rabinovsky et al., 1992       | McGregor and English, 2018             | The inner tube of nerve fibers and growth factors | The inner tube of nerve fibers narrows gradually and the ability of express growth factor decreases gradually |

Neurophysiological changes associated with PNI-induced spinal cord injury

Motor neuron apoptosis and synaptic stripping in the ventral horn of the spinal cord

After PNI, motor neurons in the anterior horn of the spinal cord often undergo apoptosis. Current research suggests that there are two explanations for motor neuron apoptosis after PNI (Hart et al., 2008). The first is oxidative stress, and the second is significant upregulation of the expression of apoptosis-related genes Caspase-3, Caspase-8, tumor necrosis factor-related apoptosis-inducing ligand receptor, tumor necrosis factor receptor, and Fas after PNI. Consistent with the abovementioned mechanism, injection of a Bcl-12-expressing vector 1 week prior to root avulsion was found to increase the survival of lesioned motor neurons by 50% (Natsune et al., 2002).

Synaptic stripping is another cause of functional loss after PNI. PNI usually causes activation and proliferation of microglia in the spinal cord. Upon activation, microglia migrate and penetrate toward the axotomized ventral horn, interposing themselves between ventral horn cell bodies and synapses undergoing detachment. The phenomenon in which microglia ‘lift’ these synapses has been termed “synaptic stripping” (Salvany et al., 2021). Synaptic stripping can induce la axons and synapses to rewire to Ia fibers. Although motor and la axons can reinnervate muscles, la axons cannot return to the ventral horn. Consequently, individuals with this type of PNI show deficits during high force-related motor tasks due to the absence of la axons (Yule et al., 2017).

Given this information, we hypothesized that motor neuron apoptosis can cause double failure in the PNI axon and synapse, thereby creating a need for reactive microglia to scavenge debris. After neuronal apoptosis, microglia aggregate around neuronal debris. Thus, immune surveillance appears to play an important role in the injured nervous system during neuronal cell death.

Ectopic DRG activity in the dorsal horn of the spinal cord

The DRG, also called the sensory ganglia, is a gathering place for the synaptization of motor sensory neurons. Neuronal DRG neurons are pseudounipolar, and are located in the intervertebral foramen between the vertebral column. Each cell body has two axons: one peripheral axon and one central axon that transmits electrical signals from the peripheral to the dorsal horn of the spinal cord (Esposito et al., 2019). There are three types: large, medium, and small, according to diameter size. Large DRG neurons are associated with proprioceptive sensation, and play an important role in transmitting non-nociceptive sensation and inhibiting nociceptive sensation. Medium neurons relay tactile information, while small neurons are implicated in sensations of pain and touch, and often form unmyelinated C-fiber sensory nerves. Therefore, the DRG is closely associated with sensory abnormalities and pain (Esposito et al., 2019). Excessive neuronal firing is believed to be a critical factor resulting in nerve pain (Mouton et al., 2018), and the inflammatory response induced by PNI commonly causes DRG neurons to fire excessively. A large number of inflammatory cells, including leukocytes, astrocytes, T lymphocytes, SCs, and neutrophils in the dorsal horn. If the original peripheral nerve is restored, these inflammatory cells continue to deliver excitatory cytokines, and thus contribute to extended pain.

The relationship between microglia and pain has received widespread attention. Animal studies have shown a number of spinal dorsal horn microglia and morphological changes following PNI, and these are considered to underlie the pathogenesis of neuropathic pain (Inoue and Tsuda, 2018). PNI rapidly activates NK-κB in the DRG, and colony stimulating factor 1 (CSF1) is transported anterogradely along axons to the spinal dorsal horn. A DAP12-dependent pathway via CSF1R contributes to the local expansion of microglia via proliferation in the spinal dorsal horn. These microglia convert from having normal morphology to over-reactive morphology in response to inflammatory factors. Cell morphological analyses have revealed that PNI induces microglia to change their phenotype to a reactive hypertrophic shape, for instance, that with a reduced process length and complexity, and an increased volume (Batti et al., 2016). Several studies have reported that activated microglia produce and release a variety of bioactive diffusible factors in response to extracellular ligands via their cognate receptors, and that these factors can influence spinal dorsal horn neuronal function. Furthermore, reciprocal microglia appear to play a causal role in spinal dorsal horn neuronal injury related to PNI (Inoue and Tsuda, 2018). Such signaling can lead to the secretion of brain-derived neurotrophic factor (BDNF) by activated microglial cells, which can enhance excitatory synaptic transmission to excitatory neurons.

A study conducted using a neuropathic pain model indicated that greater neuropathological damage may be correlated with changes in nerve growth factor (NGF), neurotrophin 3, and insulin-like growth factor, while vascular endothelial growth factor may attenuate pain behavior and prevent neuropathic stress by influencing transient receptor potential ankyrin 1 activity (Hulse et al., 2015). These changes can increase the excitability of the DRG (Hilt et al., 2000; Simmons and Feldman, 2002; Generaal et al., 2016). The T-junction, which is located between the axon and cell soma, is also regarded as a key region in aberrant neuronal activity. The T-junction acts as a low-pass filter that limits the rate at which peripheral signals can be transmitted. Previous studies have shown that the T-junction in DRG neurons permits an increased amount of high-frequency burst firing after PNI. This alteration in the filtering action of the T-junction may also cause hyperexcitability following PNI (Riedel et al., 2016).

The injury site

After PNI, axons sprout from the broken ends of proximal axons. The speed of axonal regeneration is affected by axonal transportation and proximal growth factors, which are secreted by SCs in the reconstructed basement membrane tube.

Staggered axonal regeneration

Wallerian degeneration is initiated immediately after PNI in the distal nerve stump, suggesting that these axons denature and disintegrate. Thus, one aim of this treatment is to use microenvironmental factors that are specific to the microenvironment. In the early stage of injury, these signals appear to mainly recruit M1 macrophages, which secrete pro-inflammatory cytokines. This can thereby
enhance inflammatory reactions and tissue necrosis (Zigmund and Echevarria, 2019). SCs are activated and involved in the entire process of injury and regeneration. After Wallerian degeneration, the proximal section begins axonal regeneration by forming a growth cone. The proliferating SCs form Bungner bands, which guide the growth of newly sprouting axons. If a growth cone reaches the endoneurial tube, it has a better chance of reaching the target organ (Gordon, 2016). NGF is upregulated in SCs during injury, which promotes the growth and proliferation of SCs and provides trophism to the outgrowing axon. In those without normal regeneration, this outgrowth can be seen as low-affine nerve growth factor receptor (p75), a member of the tumor necrosis factor receptor family.

These changes had an overall effect on nerve regeneration. Furthermore, endothelial cells form a physical barrier called the blood-nerve barrier. The interruption by reinnervation initiated by PNI can also increase the chance of a stable and functional microenvironment, which can also contribute to slow axonal regeneration (Yi et al., 2017).

Growth factors and the inner tube of nerve fibers
Progressive decreases in the levels of growth factors are another reason for postinjury neuronal regeneration after PNI. The secretion and expression of growth factors begins almost immediately after nerve injury, and return to normal levels 35 days later (McGregor and English, 2018). In cases of prolonged nerve injury, the ability of SCs to express growth factors in the distal region of injured axons gradually decreases. As it is difficult to maintain the proliferation of supporting axons for a long duration, the rate of axonal growth may gradually decrease.

The state of the nerve fiber tube is an important factor affecting the recovery of peripheral nerve function. As macrophages engulf and clear away the fragments of the degenerated axon and myelin sheath, it may be a long time before new axon buds enter the inner tube of nerve fibers (Cattin and Linker, 2018). The absence of tube components can decrease extracellular fluid pressure, which can lead to collapse or a progressive decrease in the diameter of the endoneurial tube. In addition, the absence of tube components may enable the number of collagen fibers in the endoneurium to slowly increase, which can lead to thickening of the endoneurial tube and decreased ease of growth for new axial buds (Krupat et al., 2017).

In summary, after axonal injury, axons near the injury site begin to produce new axon buds. However, staggered axonal growth may lead to a progressive prolongation of the amount of time required for the axons to pass through the endoneurial tube. In this instance, in time can weaken the proliferation-promoting ability of SCs at the far end of the injury. Cumulative narrowing of the inner neural membrane tube and nonspecific reinnervation can also exacerbate the passage of injured axons.

Target organs
Atrophy of skeletal muscles
PNI often leads to impaired sensory motor function. Skeletal muscles, which control human movement, are innervated by the nervous system. All voluntary movements in daily life are made possible by muscle contractions. Compared with the atrophy of skeletal muscles, that of denervated muscle has more attraction from researchers. Once a nerve is transected, target muscles lose their ability to “pump” muscles due to the loss of nerve innervation. This leads to relatively reduced perfusion of the target muscle, which can result in skeletal muscle atrophy. A previous study indicated that PNI-induced changes in the cross-sectional width of skeletal muscles to decrease by 70% within 2 months (Willand et al., 2015).

During skeletal muscle atrophy, a series of biochemical and physiological alterations occur in atrophic muscle, which trigger changes in gene expression. Shen et al. (2019) identified thousands of genes that were differentially expressed in the anterior tibial muscle at different times after sciatic nerve transection via cdNA microarray. They divided the period encompassing the 28 days after nerve injury into four transcriptional phases, and examined the activation of different functional genes and signaling pathways within each phase. In the first phase, they explored the genes that induced the atrophy that occurred following the strain of stress stage (0–12 hours), “inflammation stage” (12 hours–3 days), “atrophy stage” (3–14 days), and “atrophy fibrosis stage” (14–28 days) (Mancinelli et al., 2019). The oxidative stress stage is characterized by an increase in cytokine and pancreatic enzymes, which are responsible for the production of reactive oxygen species (ROS). This can be interpreted to mean that a large number of ROS are produced due to oxidative stress in transcription phase 1 (He et al., 2017). Hypoxia-inducible factor 1 (HIF-1) signaling pathways are activated to eliminate ROS, and thus avoid cellular damage (Eyrich et al., 2019). Then, in the inflammation stage, inflammation-related genes, such as tumor necrosis factor (TNF) and transforming growth factor-beta, are triggered by ROS.

Inflammatory proteins are activated by upstream signals and increases in the expression of cachexia-related genes. ROS and inflammatory proteins persistently damage skeletal muscles, causing the activation of proteasome signaling pathways. The process causes proteasomal degradation, leading to muscle atrophy. Inactivation of insulin can also activate the ubiquitin proteolytic system, causing skeletal muscle hypertrophy (O’Neill et al., 2016). Furthermore, the metabolic shift from glycolytic to oxidative processes can lead to the atrophy of skeletal muscles. For example, a study by Ma et al. (2019) confirmed that the ratio of MyHC II-positive fibers in the soleus rose significantly after denervation, suggesting that denervation leads to the slow transformation of skeletal muscle fibers into the fast glycolytic fibers. The soleus muscle has a greater cross-sectional area and inflammatory reactions are both associated with denervated skeletal muscle atrophy. Accordingly, antioxidant and anti-inflammatory therapy may be an important strategy for preventing the initial atrophy of denervated skeletal muscle.

Sensory perception degeneration and nociception overactivity
Initially, changes in skeletal muscle strength are a primary concern for patients. However, their pain sensitivity shift significantly as motor function is gradually regained. Sensory receptors can be divided into mechanoreceptors, thermoreceptors, and nociceptors. A mechanoreceptor is a sensory neuron that responds to mechanical pressure or distortion. PNI results in the loss of mechanical pressure because of the absence of mechanoreceptors. In clinical settings, neuropathic pain is measured in terms of cold intolerance. Aδ and C fibers transmit the sensation of temperature, and PNI results in the nerve ending being terminated. The absence of the endoneurium tubes can lead to Aβ fibers that are myelinated while the C fibers are not myelinated. Aβ fibers mainly convey sensitivity to cold and pain (rapid pain, “pinprick” sensations), and carry this information from the peripheral to the central nervous system. Aδ fibers are unmyelinated and are primarily related to heat and pain (slow pain, “burning” sensations) (Sène, 2018). Both fibers contain neurotransmitter receptors in the skin that are known as transient receptor potential (TRP) channels. TRP channels are important mediators of sensory signals, and have a strong impact on cellular function and signaling pathways. As “cellular sensors”, they respond to changes in temperature, pH, pressure, and chemicals in the cellular environment (Sakaguchi and Morii, 2020). Kambir et al. (2014) found that the thermosensitive TRP channels in the skin contribute to thermal intolerance via three mechanisms. Specifically, thermal intolerance can result from 1) an increase in the expression of TRP channels on nerve fibers and keratinocytes, 2) a prolongation in the threshold of TRP channels, leading the receptors to be activated by lower intensity stimuli, or 3) sprouting from non-injured nerve fibers. For example, Duraku et al. (2012) observed reinnervation that occurred in transected rat tibial and peroneal nerves due to sprouting of non-injured nerve fibers. Upregulated and activated TRP channels increased nociceptive nerve fiber excitation by activating TRP channels directly. This manifested as mechanical and cold hypersensitivity. This viewpoint was further confirmed by Mickle et al. (2016), who blocked TRP channels individually and found that different TRP fibers excite different aspects of initial pain.

The nociceptive system modulates peripheral pain signal transduction. Peripheral nociceptive neurons are initially excited when free nerve endings (Aδ and C fibers) receive noxious stimuli or undergo injury. Over time, primary afferent Aδ- and C-nociceptors in the injured nerve area start to respond to non-noxious stimuli in an amplified way, leading to the development of hyperexcitability and spontaneous activity. This can be explained by the dramatically reduced firing thresholds of the Aδ fibers. Previous studies have explored the underlying mechanisms by which primary nociceptors are activated by the organ of sensory receptors that infiltrate the injured site. Generally speaking, primary nociceptors are more likely to fire following an injury. Inflammatory factors can cause changes in the genetic and molecular composition of nociceptors, leading to an increase in primary nociceptor excitability (Bjorgen et al., 2018).

The peripheral nerve contains sensory and motor fibers. Previous studies have suggested that injured sensory fibers are responsible for neuropathic pain. However, recent evidence has indicated that motor fiber injury is essential to neuropathic pain. The expression of voltage-gated sodium channels is altered in DRGs after PNI. This change forms the basis of ectopic discharges, and eventually leads to neuropathic pain. Chen et al. (2011) reported that the selective injury of motor fibers can lead to the upregulation of voltage-gated sodium channels in DRGs, and that this process might be mediated by the co-expression of TNF-α and in bilateral DRGs. In their follow-up study, they showed that the overexpression of TNF-α induced hyperalgesia via calcipain-2, which activated satellite glia to produce extra NGF. This, in turn, enhanced nociceptor excitability, resulting in apparent mirror-image pain. In addition, Liu et al. (2016) reported that to motor fibers via TRPV1 and TRPA1 expression and potentiation at spinal C-fiber synapses, indicating that nocous inputs from muscle afferents induce long-lasting central sensitization. Hence, in contrast to sensations at the skin level, changes in muscle innervation should be investigated to fully understand neuropathic pain.

Summary of the basic mechanisms of PNI
The above-mentioned data indicate that regenerated axons cannot effectively continue their target-end organ connections. Therefore, a large number of patients with PNI fail to completely recover normal function. The reasons are listed as follows:...
Sensory changes affect the peripheral nerves, spinal cord organization, and plasticity of the brain, and all three can affect early regeneration and later neuropathic pain. The slow speed of regeneration delays the rate at which the proximal end crosses the surgical gap. Furthermore, non-specific reinnervation reduces the chance of regeneration. Generally, SCS supports axonal regeneration after injury in the peripheral nervous system. However, SCS gradually lose regeneration-supporting features and eventually die. The denervation of skeletal muscle cells and sensory abnormalities can lead to early loss of function. Furthermore, decreases in the activation threshold of thermoreceptors and nociceptors can gradually lead to neuropathic pain. The slow rate of nerve regeneration may account for negative sensory symptoms. However, the negative sensory symptoms that can recover the remaining positive sensory symptoms associated with PNI are difficult to treat. Nociceptor excitability can increase as the rate of decreased firing thresholds. Furthermore, common noxious stimuli are still likely to cause hyperexcitability in nociceptors. Hence, treatments are needed for the positive symptoms of PNI.

### The Mechanisms of Electrical Stimulation for the Treatment of Peripheral Nerve Injury

As stated above, PNI can trigger a series of pathophysiological changes at the level of the cell body, at the site of injury, and in the target organ, thus reflecting the overall structure of the nervous system. ES has received much attention from PNI researchers as an effective treatment for nerve regeneration. Several studies have examined the effects of ES on the cell body and target organ in models of PNI, including the stimulation of sites aside from the site of injury, and most have reported a good outcome. In the sections that follow, we discuss the mechanisms of ES for the treatment of PNI in terms of changes in the cell body, local sites, and end organs (Table 2).

| The first study to examine this field | The greatest contributions to this field | The stimulation site | The main mechanism of stimulation |
|-------------------------------------|----------------------------------------|---------------------|----------------------------------|
| Kosman et al., 1948                 | Salmons, 2009                          | Skeletal muscle electrical stimulation | Promote skeletal muscle regeneration and prevent muscular atrophy |
| Taub et al., 1974                   | Linderoth and Foreman, 1999            | Spinal cord stimulation | Inhibit apoptosis and synaptic stripping |
| Burton, 1976                        | Johnson and Tabasam, 2003               | Transcutaneous electrical nerve stimulation | Mediate decreased local inflammatory mediators and elevated pain thresholds |
| Kadekaro et al., 1985               | Schmidt, 2019                          | Dorsal root ganglion stimulation | Supress the excitablity of the dorsal root ganglion |
| Gybels and Vancalenbergh, 1990      | Gordon, 2016                           | Peripheral nerve electrical stimulation | Promote axon regeneration and the exactness of axon growth; activated Schwann cells secrete glutamate and glutamate to enhance the ability of regeneration and inhibit apoptosis |
| Leem et al., 1995                   | Wang et al., 2019                      | Subcutaneous electrical stimulation | Reduce inflammatory response and neuronal apoptosis and activate Aβ and Aδ fibers to relieve pain |

| The greatest contributions to this field | The stimulation site | The main mechanism of stimulation |
|----------------------------------------|---------------------|----------------------------------|

**Table 2** | Summary of the studies regarding neuron electrostimulation in PNI

*Cell body arrangement in the dorsal horn of the spinal cord*

Most previous studies have prioritized ES of the site of injury for treating PNI. However, we anticipate that proximal neuronal cell bodies will be important PNI therapeutic targets in the future. Previous studies have confirmed that activity of the wide-dynamic range neurons of the dorsal horn is decreased by spinal cord stimulation (SCS). However, even after SCS is switched off, the alleviating effects last for a long time (Jensen and Brownstone, 2019). A clinical trial indicated that SCS can produce coordinated spinal motor output and facilitate the restoration of the sensorimotor network of the spinal cord (Formento et al., 2018). Apoptosis and synaptic stripping are the reasons for the functional loss following PNI. Accordingly, a previous study investigated whether SCS can promote functional recovery by inhibiting apoptosis and synaptic stripping (Pei et al., 2019a). These researchers found that SCS could reduce the Ca²⁺ influx and stabilize the intracellular environment, which led to reduced motor neuron apoptosis in the ventral horn of the spinal cord (Pei et al., 2015).

La et al. (2019) showed that an electric field targeting the spinal cord also increased the expression of anti-apoptotic Bcl-2 and decreased the expression of the apoptosis-related Bax gene after sciatric nerve transection. Glial cells are also involved in the effects of ES. Some studies have indicated that, if directly applied to the spinal cord, ES will have a robust effect on gene expression (Sun et al., 2017; Stephens et al., 2018). For instance, levels of glial cell-related proteins glial fibrillary acidic protein and cFas osteosroma oncogene increased after ES in a PNI mouse model (Tilley et al., 2017; Shinoada et al., 2020). This suggests that glial cells may directly respond to ES and therefore contribute to motor recovery. As we discussed above, neuroglia can play an important role in PNI.

Accordingly, we speculate that ES can accelerate the speed of functional recovery and reduce neuropathic pain in cases of PNI. However, complications from ES have been reported to occur in 30% to 40% of patients, such as electrode migration, infection, and wound breakdown (Sakaguchi and Mori, 2020). For uninsured patients, typical out-of-pocket costs for SCS are $15,000–$50,000 or more. Thus, the potential complications and cost of SCS limit its use in PNI. Many studies have examined physiological and safe techniques for stimulating the spinal cord. For example, electrical acupuncture and interference electrotherapy may be alternatives to promoting functional recovery after PNI.

**Suppressing DRG excitability**

SCS relieves pain by retraining primary sensory neurons. However, DRG stimulation has a similar effect to ES by directly suppressing excitability of the DRG, which is also a site of pain pathogenesis, and can bring about changes in DRG neuronal activity by altering activity in the T-junction. DRG stimulation blocks nociceptive signals from the periphery and enhances the filtering properties of the T-junction (Schmidt, 2019).

Koopmeiners et al. (2013) used neurophysiological techniques to measure the excitability parameters of uninjured cultured DRG cells after the application of ES. After ES, they found that fewer neurons could produce bursts of multiple action potentials, and that the conduction velocity was greatly reduced. This suggests that ES can lead to reduced neuronal excitability.

Computational modeling analyses have revealed stimulation-induced reduced action potentials traveling from the periphery in nociceptive neurons after PNI. Low-frequency filtering ofafferent activity is proposed to greatly reduce the excitation that takes place via hyperpolarization of the soma and the mismatch in impedance between the peripheral stem and central axons. When the filter is attenuated, pain signals can pass through the T-junction at a faster frequency. Elevated T-junction filtering can be mediated by the suppression of Ca²⁺–dependent K conductance. The activated K channels produce a sustained somatic hyperpolarization offset in the stem axon and T-junction. Hyperpolarization of the T-junction increases the degree of change in the transmembrane potential, which is essential to the propagation of action potentials. When the pain signals are generated from the periphery, T-junction filtering is not amplified due to the absence of Ca²⁺ and K channels.

One study compared over 500 DRG stimulator and 2000 spinal cord stimulator implants over a 1-year period. The researchers reported that DRG stimulation had a favorable safety profile, with fewer adverse events compared with SCS. A pooled analysis further verified the effectiveness and safety of DRG stimulators (Huysen et al., 2020).

**Local sites**

**Staggered axonal regeneration**

Recent studies indicating that ES can enhance reinnervation after PNI have focused consistently on ES of a proximal nerve at the injury site. However, the exact cellular mechanisms by which ES accelerates nerve regeneration are still unclear. The intracellular Ca²⁺ wave, which is initiated at the site of axotomy induced by ES, plays a key role in nerve regeneration. The intracellular Ca²⁺ wave is generated along the axonal and neuronal cell body. In the neuronal soma, increased Ca²⁺ induces upregulation of BDNF and its receptor tropomyosin receptor kinase B (TrkB). The overexpression of BDNF can inhibit the phosphodiesterases that degrade cyclic adenosine monophosphate (cAMP), leading to sustained elevated levels of cAMP (Al-Majed et al., 2000a).

Raised cAMP levels can increase the expression of regeneration-associated genes such as Td1 tubulin and growth-associated protein-43. Cytoskeletal assembly is enhanced through activation of the cAMP response element binding (CREB) protein, regulation of Td1 tubulin, and the inhibition of Rho, which is a protein in the p75 NgR receptor (p75-NgR) pathway (McGregor and English, 2018). CREB activation is induced by the mitogen-activated protein kinase (MAPK) pathway. When a specific p38 MAPK inhibitor is implemented, CREB activation and neurite outgrowth are also suppressed. Hence, local activation of the p38 MAPK pathway may play an important role in promoting neurite outgrowth (Kawamura and Kano, 2019). To further confirm that the potential effect of ES is produced by the neuron cell body, Al-Majed et al. (2000b) inhibited propagation from the injury site to the axon, and found no therapeutic effects on PNI. However, in addition to BDNF and TrkB, reports have examined other possible pathways. In PC12 mutant cells with injured NGF-induced neurite outgrowth, ES can also enhance neurite outgrowth through p38 mitogen activation (Huang et al., 2016). Further studies are needed to examine if the ES can produce substantial therapeutic effects via the cell body (Figure 1).

In recent years, ES at the injury site has gradually attracted increased attention. The long and variable delays in the regeneration process can inhibit regenerating axons from successfully crossing the surgical gap and entering the distal nerve stumps. Axonal regeneration can be accelerated by 1 hour of ES (Gordon, 2000). Brashart et al. (2002) also found that 1 hour of 20-Hz stimulation could temporally compress staggered regeneration. Furthermore, they found that ES could synchronize distal sump reinnervation. The number of regenerating axons that cross the surgical gap is increased. ES is because this facilitates the onset of motor axon regeneration without accelerating its speed. Moreover, continuous 20-Hz ES of the axons proximal
SC activity
SCs are also believed to be involved in peripheral nerve therapy. ES can stimulate SCs to secrete glutamate, which can increase SC-derived exosomes and intracellular Ca\(^{2+}\) concentrations (Lopez-Leal and Court, 2016). Since cAMP and BDNF are Ca\(^{2+}\)-dependent, increases in Ca\(^{2+}\)-dependent protein may result from ES-induced glutamate secretion.

The role of SCs in vesicular transfer has recently received increased attention. In vivo, crucial regenerative molecules delivered by SCs might contribute to axonal extension. As mRNAs are deposited on the distal axon in a dormant state, the transfer of mRNA from SCs to axons may supply transcripts for translation induced by electrical stimulation (Rigon and Negro, 2020). SC-derived exosomes include mRNA, miRNA, and protein cargoes, which can promote damaged axonal regeneration, as verified in vitro and in vivo studies. P75\(^{++}\) is present in SC-derived exosomes, and is also found in abundance in the injury site. This protein can modulate growth from filopodia to the axon of RHoA. It has also been previously been shown that SC-derived exosomes can be selectively internalized by axons in vitro and in vivo. Furthermore, SC-secreted exosomes, but not fibroblast-derived exosomes, markedly increase axonal regeneration by acting locally on axons (Ribotta et al., 2012). SC-derived exosomes can promote axonal regeneration. Wang et al. (2020) demonstrated in vivo that the regenerative capabilities of injured sciatic nerves can be greatly enhanced by delivering SC-derived exosomes to axons. In addition, Zhou et al. (2018) verified that while cyclic mechanical stimulation promotes SC proliferation, SC-secreted exosomes could enhance the proliferation of injured DRG cells, and SC-secreted exosomes could increase the transport of glucose transporter type 4 (GLUT-4) to the plasma membrane.

A recent study reported that ES could shift the macrophage phenotype from a proinflammatory to a pro-repair phenotype (McLean and Verge, 2016). In this way, ES could rapidly remove myelin debris. As SCs restore the nonreactive myelinating state, they may be useful in remyelinating nerves and increasing clinical outcomes by increasing axonal regeneration (Schiller et al., 2020). However, Wang et al. (2020) demonstrated in vivo that the regenerative capabilities of injured sciatic nerves can be greatly enhanced by delivering SC-derived exosomes to axons. In addition, Zhou et al. (2018) verified that while cyclic mechanical stimulation promotes SC proliferation, SC-secreted exosomes could increase the transport of glucose transporter type 4 (GLUT-4) to the plasma membrane.

The major drawbacks of ES include the need for surgery and the risk of potential complications at the electrode implantation site, such as infection and wire movement. Most ES of the injury site for the treatment of PNI is based on animal experiments. However, there is a significant difference in nerve length and width between humans and animals. Power et al. (2020) also reported that axonal regeneration in humans is different from that of the injured nerve. They observed that ES enhanced muscle reinnervation and promoted functional recovery after PNI. ES briefly decreases inflammatory reactions and increases neuronal activity, favorably altering the immune microenvironment in demyelinated nerves. Thus, ES may have beneficial therapeutic effects when applied to other pathologies.

In conclusion, the major therapeutic effects of ES are mediated by the cell body. Thus, SCs and DRG, which have direct effects on the cell body, may be more effective than ES at promoting axonal regeneration. However, a major obstacle to ES is the promotion of local SCs or correct regeneration across the gap. Hence, combined stimulation of the spinal cord and injury site may be the best treatment option. Given the complicated causes of PNI, it is difficult to determine whether implanted electrodes are ideal in terms of costs and outcomes. Conversely, implanted electrical stimulation (ES) can promote damaged axonal regeneration, as verified via in vitro and in vivo studies. P75\(^{++}\) is present in SC-derived exosomes, and is also found in abundance in the injury site. This protein can modulate growth from filopodia to the axon of RHoA. It has also been previously been shown that SC-derived exosomes can be selectively internalized by axons in vitro and in vivo. Furthermore, SC-secreted exosomes, but not fibroblast-derived exosomes, markedly increase axonal regeneration by acting locally on axons (Ribotta et al., 2012). SC-derived exosomes can promote axonal regeneration. Wang et al. (2020) demonstrated in vivo that the regenerative capabilities of injured sciatic nerves can be greatly enhanced by delivering SC-derived exosomes to axons. In addition, Zhou et al. (2018) verified that while cyclic mechanical stimulation promotes SC proliferation, SC-secreted exosomes could increase the transport of glucose transporter type 4 (GLUT-4) to the plasma membrane.
after PNI, especially those in the injury site. Recently, an increasing number of studies have observed cellular and molecular changes at the level of the central nervous system, including at the site of injury and in the target organs following PNI. To the best of our knowledge, this is the first review of the existing literature to summarize and discuss changes after PNI and the mechanisms of ES from three different levels. As discussed, changes after PNI have been discovered at the level of the cell body (dorsal and ventral root), the site of injury, and in the target organs (Figure 2).

**Figure 2** | Following PNI, several molecular and cellular changes are observed at the local site of injury and the target organs. The effects of ES therapy on peripheral neurogenesis vary according to the position of stimulation. See the text for a detailed description. DRG: Dorsal root ganglion; ES: electrical stimulation; PNI: peripheral nerve injury; SCs: Schwann cells; SDH: spinal cord dorsal horn; SQS: subcutaneous electrical stimulation; SVH: spinal cord ventral horn.

PNI mainly involves the skin, skeletal muscles, spinal cord, and brain. It implices a nervous system injury axis that includes the peripheral nerves, corticospinal tract, and spinohalamic tract. The effects of ES therapy on peripheral neurogenesis vary according to the position of stimulation (Table 3).

Although ES therapies are useful for treating PNI, they also have side effects. ES can lead to twisting of the axon and cytoarchitecture, leading to edema and secondary demyelination of the axons post-injury. The main side effects of ES therapy include peripheral neurogenesis, which is a nervous system injury axis that includes the peripheral nerves, corticospinal tract, and spinohalamic tract. The effects of ES therapy on peripheral neurogenesis vary according to the position of stimulation (Table 3).

**Limitations**

There are several limitations to this review. First, we did not consider PNI-induced changes in activity in the brain, which is the highest level of the nervous system. Moreover, although there are multiple causes of PNI and different degrees of nerve injury, we did not consider these variables. The parameters of electrical stimulation are an important consideration in the effects of electrical stimulation for PNI. Although most studies used a treatment strategy including 20 Hz of ES for 1 hour, identification of the optimal parameters will require further exploration. Finally, due to limited space, time, and energy, some relevant studies may have been excluded.

**Future Prospects and Conclusions**

Many researchers have examined the basic mechanisms of PNI, as well as potential treatment via electrical stimulation. However, previous studies have focused primarily on cellular and molecular changes in single sites...
15 Hz/NM*/NM*/30 min/6.5 mA
Sciatic nerve transaction injury and its proximal and distal ends were inverted and sutured
Protects sensory neurons and anterior horn
Placed in the epidural space of spinal cord (T10 and L3)
Animal experiments
ES of the neuronal cell bodies can protect motor and sensory neurons in spinal cord after PNI. In addition, it promotes the regeneration of myelinated nerve fibers to repair injured peripheral nerve.

50 Hz/NM*/charge-balanced square pulse/72/70% motor threshold, 0.3–10 mA. 100 Hz/200-400 μs/charge balanced/1 h/visible muscle contraction, 2–3 mA
Tibial nerve transaction injury; immediate repair
cFOS and SHT3α and GABAb1/ attenuate the neuroinflammatory response to relieve pain Elevated muscle-driven GDNF Implanted in the gastrocnemius muscle
Animal experiments
SCS could relieve pain after PNI by regulation of relevant ion channels and gene expression.

20 Hz/0.1 ms/ NM*/1 h, 0.3 mA, subthreshold
Ensory and motor branches of the pudendal nerve bilaterally; crush injury
Neuro regeneration through upregulating BDNF and β3-tubulin
Pudendal nerve
Animal experiments
The levels of nutrient factor mRNA were increased and peripheral nerve regeneration was promoted by targeting ES of skeletal muscle.

20 Hz/100 μs/NM*/1 h, 1.5 mA, right ear flutter
Facial nerve crush injury
Improved facial nerve specific pathway regeneration
Facial nerve
Animal experiments
This is the first study to apply an implantable device to ES for facial nerve injury, accelerating functional recovery and induction of motor neuronal path-specific regeneration.

60 Hz/250 μs/NM*/15 min/3 V
Sciatic nerve transaction injury; implementation of microsurgical epineural sutures
Nerve regeneration and muscle reinnervation
Epipidal space of motor cortex in the brain
Animal experiments
ES of the motor cortex induces a higher rate of nerve re-innervation and a faster functional recovery than electrical stimulation of peripheral nerves after PNI.

20 Hz/0.1 ms/balanced biphasic pulses/1 h
Common peroneal nerve transaction injury; sutured with a two-layer closure
RAG/increased the length of nerve regeneration and regenerating axons
Common peroneal nerve
Animal experiments
It is the first time to apply conditioning ES to an in vivo model of peripheral nerve regeneration. Findings from this study demonstrate that this treatment strategy accelerates nerve regeneration.

20 Hz/0.1 ms/balanced biphasic pulses/1 h/visible twitch in the lower limb flexors
Tibial nerve transaction injury; immediate microsurgical repair surgery
Neuro regeneration and functional recovery
Tibial nerve
Animal experiments
Conditioning ES can promote the regeneration of target nerves and the recovery of functional activity, which can be given preoperatively.

200 Hz/200 μs/on: off = 1:2/30 min/visible toe and foot movement
Sciatic nerve transaction injury; implementation of repair surgery
Axon regeneration through promoting autophagy flux in the distal nerve segments
Skin
Animal experiments
ES of denervated muscle can increase cell autophagy flux level in the nerve distal to injury, which is conducive to nerve regeneration.

References

Adams JP, Fee N, Kenmore PI (1966) Tear-gas injuries. A clinical study of hand injuries and an experimental study of its effects on peripheral nerves and skeletal muscles in rabbits. J Bone Joint Surg Am 48:436-442.

Al-Majed AA, Brushart TM, Gordon T (2000a) Electrical stimulation accelerates repair surgery in peripheral nerve regeneration. J Neurosci 20:608-615.

Barber B, Seikaly H, Ming-Chan K, Beaudry R, Rychlik S, Olson J, Curran M, Dziegielewski P, Biron V, Harris J, McNeely M, O’Connell D (2018) Intraoperative Brief Electrical Stimulation of the Spinal Accessory Nerve (BEST SPIN) for prevention of shoulder dysfunction after oncostatic neck dissection: a double-blind, randomized controlled trial. J Otalaryngol Head Neck Surg 47:7.

Batti L, Sundukova M, Murana E, Pimpinella S, De Castro Reis F, Pagani F, Wang H, Al-Majed AA, Brushart TM, Gordon T (2000a) Electrical stimulation accelerates repair surgery in peripheral nerve regeneration. J Neurosci 20:608-615.

Burton C (1976) Transcutaneous electrical nerve stimulation to relieve pain. Postgrad Med 59:105-108.
Esposito MF, Malaryi R, Hanes M, Deer T (2019) Unique characteristics of the dorsal root ganglion as a target for neuromodulation. Pain Med 20:523-530.

Eyrich NW, Potts CR, Robinson MH, Maximić V, Kenney AM (2019) Reactive oxygen species signaling promotes hypoxia-inducible factor 1α stabilization in sonic hedgehog-driven cerebellar progenitor cell proliferation. Mol Cell Biol 39:e00268-00218.

Fei J, Gao L, Li HH, Yuan QL, Li Li (2019) Electrocorticupump promotes peripheral nerve regeneration after facial nerve crush injury and upregulates the expression of glial cell-derived neurotrophic factor. Neural Regen Res 14:673-682.

Fornento E, Minassian K, Wagner F, Mignardot JB, Le Goff-Mignardot CG, Rowald A, Bloch J, Micera S, Capogrosso M, Coutelle G (2018) Electrical spinal cord stimulation must preserve proprioception to enable locomotion in humans with spinal-cord injury. Nat Neurosci 21:1728-1741.

Franz CK, Ruthshauer U, Rufase VF (2008) Intrinsic neuronal properties control selective targeting of regenerating motorneurons. Brain 131:1492-1505.

Fu T, Jiang L, Peng Y, Li Z, Liu S, Lu J, Zhang F, Zhang J (2020) Electrical muscle stimulation accelerates functional recovery after nerve injury. Neuroscience 426:179-188.

General E, Milaneschi Y, Jansen R, Eliziga BM, Dekker J, Pennix BW (2016) The brain-derived neurotrophic factor pathway, life stress, and chronic multi-site musculoskeletal pain. Mol Pain 12:1-9.

Gordon T (2016) Electrical stimulation to enhance axon regeneration after peripheral nerve injuries in animal models and humans. Neurotherapeutics 13:295-310.

Gordon T (2020) Peripheral nerve regeneration and muscle reinnervation. Int J Mol Sci 21:8652-8676.

Gu N, Eyp UB, Murugan M, Peng J, Matta S, Dong H, Wu Li (2016) Microglial P2Y12 receptors regulate microglial activation and surveillance during neuropathic pain. Brain Behav Immun 55:82-92.

Gyebels J, Vancalenbergh F (1990) The treatment of pain due to peripheral-nerve injury by electrical-stimulation of the injured nerve. Adv Pain Res Ther 13:217-222.

Hart AM, Terenghi G, Wiberg M (2008) Neuronal death after peripheral nerve injury and experimental strategies for neuroprotection. Neuroreport 30:999-1011.

He L, He T, Farrar S, Ji L, Liu T, Ma X (2017) Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. Cell Physiol Biochem 44:532-553.

Hilz MJ, Matthol H, Neunödler B (2000) Diabetic somatic polyneuropathy. Pathogenesis, clinical manifestations and therapeutic concepts. Fortschr Neurol Psychiatr 68:278-288.

Huang J, Ye Z, Xu K, Lu L, Lu Z (2010) Electrical stimulation induces calcium-dependent release of NGF from cultured Schwann cells. Glia 58:622-631.

Hulse RP, Beazley-Long N, Ved N, Bestall SM, Riaz H, Singhal P, Ballmer Hofer K, Harper SJ, Bates DO, Donaldson LF (2015) Vascular endothelial growth factor-A165b prevents diabetic neuropathic pain and sensory neuronal degeneration. Clin Sci (Lond) 129:741-756.

Huo R, Han SP, Liu FY, Shou XJ, Liu LV, Song TJ, Zhai F, Zhang R, Xing GG, Han JS (2020) Responses of primary afferent fibers to acupuncture-like peripheral stimulation at different frequencies: characterization by single-unit recording in rats. Neurosci Bull 36:907-918.

Hussain G, Wang J, Rasul A, Anwar H, Qasim M, Hussain R, de Klerk J, Micera S, Capogrosso M, Coutelle G (2018) Electrical spinal cord stimulation must preserve proprioception to enable locomotion in humans with spinal-cord injury. Nat Neurosci 21:1728-1741.

Inoue K, Tsuda M (2018) Microglia in neuropathic pain: cellular and molecular mechanisms. Int J Biol Sci 16:116-134.

Kajander KC, Walskala S, Bennett GJ (1992) Spontaneous discharge originates in the dorsal root ganglion at the onset of a painful peripheral neuropathy in the rat. Neurosci Lett 138:F1555-1564.

Kambiz S, Duraku LS, Holstege JC, Hovius TE, Ruigrok TJ, Walbeehm ET (2014) Thermostimulate sensory axons. Neuroscience 46:595-603.

Karagüür M, Rostovtseva A, Semina E, Klimovich P, Balabanov Y, Makaveych P, Popov V, Stampolsky D, Tkachuk V (2020) A bicostinoid plasma encoding brain-derived neurotrophic factor and urinoenzyme plasminogen activator stimulates peripheral nerve regeneration after injury. J Pharmacol Exp Ther 372:248-255.

Karawmsoo K, Kano Y (2019) Electrical stimulation induces neurite outgrowth in PC12m3 cells via the p38 mitogen-activated protein kinase pathway. Neurosci Lett 698:81-84.

Khodabakh A, Maddal N, Prabh K, Koves TR, Jackman CP, Muoio DM, Bursac N (2019) Electrical stimulation increases hypertrophy and metabolic flux in tissue-engineered human skeletal muscle. Biomaterials 198:259-269.

Koetsier E, Franken G, Dejts J, Heijmans L, van Kuijk SM, Linderoth B, Joosten EA, Maino P (2020) Mechanism of dorsal root ganglion stimulation for pain relief in painful diabetic polyneuropathy is not dependent on GABA release in the dorsal horn of the spinal cord. CNS Neurosci Ther 26:136-143.

Koopmansens AS, Mueller S, Kramer J, Hogan Qi (2013) Effect of electrical field stimulation on dorsal root ganglion neuronal function. Neuroendocrinology 16:304-311.

Kosman AJ, Wood EC, Osborne SI (1948) Effect of electrical stimulation upon atrophy of partially denervated skeletal muscle of the rat. Am J Physiol 154:451-454.

Kouyoumdjian JA, Graca CR, Ferreira VFM (2017) Peripheral nerve injuries: a retrospective survey of 1124 cases. Neurol India 65:551-555.

Krupc C, Rosén B, Boreckstyns M, Isen Sørensen A, Lundborg G, Moldovan M, Archibald SJ (2017) Sensation, mechanoreceptor, and nerve fiber function after nerve regeneration. Ann Neurol 82:940-950.

Kubiak CA, Grochmal J, Kung TA, Cederrows S, Viskas R, Kemp SW (2020) Stem-cell-based therapies to enhance peripheral nerve regeneration. Muscle Nerve 61:449-459.

La Z, Zhou M, Lim LT, Oh S, Xing H, Liu N, Yang Y, Liu X, Zhong L (2019) Proteomics and transcriptomics analysis reveals clues into the mechanism of the beneficial effect of electrical stimulation on rat denervated gastrocnemius muscle. Cell Physiol Biochem 52:769-786.

Lamberts S, Taube A, Schober A, Platzbecker B, Gorgens SW, Schlich R, Jeruschke K, Weiss J, Eckardt K, Eckel J (2012) Contractile activity of human skeletal muscle cells prevents insulin resistance by inhibiting pro-inflammatory signalling pathways. Diabetologia 55:1128-1139.

Leem JW, Park ES, Paik KS (1995) Electrophysiological study for the antinoceptive effect of transcutaneous electrical stimulation on mechanically evoked responsiveness of dorsal horn neurons in neuropathic rats. Neurosci Lett 192:197-200.

Li C, Liu SY, Wu P, Zhang PX (2021) Cortical plasticity and nerve regeneration after peripheral nerve injury. Neural Regen Res 30:999-1011.

Liml T, van Dongen E, Huqy J, Staats P, Kramer J (2016) The dorsal root ganglion as a therapeutic target for chronic pain. Reg Anesth Pain Med 41:511-519.

Londero B, Foreman RD (1988) Physiology of spinal cord spinal stimulation: review and update. Neuromodulation 2:150-164.

Liu Q, Wang X, Yu S (2018) Pathophysiologcal changes of physical barriers of peripheral nerves after injury. Front Neurosci 12:597.

Liu XG, Pang RR, Zhou Li, Wei KH, Zang Y (2016) Neuropathic pain: sensory nerve injury or motor nerve injury? Adv Exp Med Biol 904:59-75.

Lopez-Leal R, Court FA (2016) Schwann cell exosomes mediate neuron-glia communication and enhance axonal regeneration. Cell Mol Neurobiol 36:429-436.

Lyme MA, Nichols TR, Kajetaz E, Maas H (2017) Musculotendon adaptations and preservation of spinal reflex pathways following agonist-to-antagonist tendon transfer. Physiol Rep 5:e13201.

Ma W, Zhang R, Huang J, Xie X, Yang X, Wang J, Liu H, Ding F, Zhu J, Sun H (2019) POQ accelerates skeletal muscle atrophy, mitophagy and fibril type transition induced by denervation via inhibition of the inflammatory signaling pathways. Ann Transl Med 7:440.

Mackinnon SE, Dellon AL (1992) Reinnervation of distal sensory nerve environments by denervation via inhibition of the inflammatory signaling pathways. Ann Transl Med 7:440.

Macknik SE, Dellon AL (1992) Reinnervation of distal sensory nerve environments by denervation via inhibition of the inflammatory signaling pathways. Ann Transl Med 7:440.
