



The Use of Shock Waves in Peripheral Nerve Regeneration: New Perspectives?

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Abstract

Low-energy extracorporeal shock wave treatment (ESWT) is a relatively new therapeutic tool that is widely used for the treatment of epicondylitis and plantar fasciitis and to foster bone and wound healing. Shock waves, sonic pulses with high energy impact, are thought to induce biochemical changes within the targeted tissues through mechanotransduction. The biological effects of ESWT are manifested in improved vascularization, the local release of growth factors, and local anti-inflammatory effects, but the target cells too are influenced.

ESWT appears to have differential effects on peripheral nerves and has been proved to promote axonal regeneration after axotomy. This review discusses the effects of ESWT on intact and injured peripheral nerves and suggests a multiple mechanism of action.



1. INTRODUCTION

Shock waves are transient short-term sonic pulses with a high-peak pressure up to 100 Mpa, followed by a negative pressure of about 5–10 MPa. They have rapid rise times of the order of nanoseconds and short pulse durations ranging up to 5 μ s. Shock waves are induced electrohydraulically and then reflected by a focusing device with either parabolic or ellipsoid geometry. The spatial shape of the pressure field depends on the form of this reflector, and shock waves may therefore be applied in a focused or a defocused manner. Moreover, shock waves can be applied extra- or intracorporeally and either low- or high energy levels may be used.

Focused shock waves are used to disintegrate solid aggregations such as kidney stones or solid deposits in tissues (calcified tendons) that usually contain minerals. For these applications, a high energy level is necessary in order to destroy the kidney stones or calcifications. The high energy transmission in cases of focused shock wave treatment necessitates intravenous sedation or even general anesthesia as this procedure is often very painful. Defocused shock waves are administered in soft tissue diseases such as chronic wounds or ulcerations, and recent applications include ischemic heart disease too (Zimpfer et al., 2009). Defocused shock waves display a different shape of acoustic pressure distribution and hence a larger tissue area is affected. Accordingly, defocused low-energy shock wave treatment does not induce pain in most cases.

Although most shock wave treatments are applied extracorporeally (extracorporeal shock wave treatment, ESWT), this treatment does not produce satisfactory results in all cases. In this situation, the use of intracorporeal shock waves may be suggested, for example, endoscopic intracorporeal shock wave lithotripsy for the treatment of bile stones refractive to traditional endoscopic methods (Attila, May, & Kortan, 2008).

Shock wave treatment may also be divided into high- and low-transfer-energy categories. While both treatment modalities are of therapeutic value, high-energy shock wave treatments are typically used for the destruction of solid aggregations inside or outside tissues, whereas low-energy treatment is administered for tissue repair and regeneration (Mittermayer et al., 2012).

The use of shock waves as a therapeutic approach has a relatively short history. Shock wave treatment was first used for the destruction of urinary stones, including those in the kidney, in the 1980s (Chaussy et al., 1982). A decade later, two groups reported successful treatment of calcifying

tendinopathies of the shoulder by the disintegration of calcified deposits, and shortly afterward shock wave treatment was introduced into other fields of medicine. ESWT has become a widely utilized therapeutic tool in regenerative medicine in recent years. It is frequently and successfully administered in painful conditions such as humero-radial epicondylitis (tennis elbow), plantar fasciitis, and other pathological conditions affecting bone-related structures. Chronic wounds, ulcerations, and ischemic heart failure have also been successfully targeted by ESWT (Mittermayer et al., 2012; Nishida et al., 2004; Zimpfer et al., 2009).

In this review, we focus on the use and effects of defocused low-energy ESWT in the peripheral nervous system.



2. FEATURES OF PERIPHERAL NERVE REGENERATION IN RODENTS AND HUMANS: HOW TO SPEED UP SLOW REGENERATION?

Injuries to peripheral nerves are followed by a rapid process of degenerative events called Wallerian degeneration. These events include changes that are effective in the anterograde direction from the injury site, that is, the disconnection of axons from the target organ, for example, the motor endplate, the breakdown of axon and myelin in the distal stump of the injured nerve, and changes that affect the proximal nerve stump (degeneration up to the first Ranvier node) and mainly the cell body retrograde from the injury: chromatolysis (the classical term for the disintegration of the rough endoplasmatic reticulum), dislocation of the nucleus, and shrinkage of the dendritic tree. The degenerative processes are followed by regenerative events, provided that the injured nerve stumps are in close vicinity and the regenerating axons from the proximal stump are able to enter the vacated endoneural sheaths in the distal stump. The regrowth of axons is supported by the rapid proliferation of Schwann cells in the distal stump providing a contact guide for them. The proliferating Schwann cells align to form the bands of Büngner and restructure the extracellular matrix that contains growth-promoting molecules such as laminin and fibronectin. The growth cone of the regenerating axons actively synthesizes transmembrane integrin molecules, for example, integrin-type alpha5-beta1, which interacts with fibronectin, thereby ensuring the axonal growth. In this way, all the conditions required for the successful regeneration and reinnervation of the targets are provided.

While axons in the rodent peripheral nervous system regenerate at a speed of 2–3 mm/day, so that relatively short distances are rapidly bridged by growing axons, human peripheral nerve injuries are followed by a slower rate of regeneration (1 mm/day). Given the fact that some motor and sensory axons projecting into the lower limb may reach or exceed a length of 1 m, the regeneration and reinnervation of peripheral targets may clearly be an extremely slow process. The slow regeneration in human peripheral nerves is further hampered by the predegenerative process occurring in the distal parts of the nerve to be occupied by regenerating fibers (Gordon, 2010; Gordon et al., 2009).

In view of the long recovery and rehabilitation process after injuries to peripheral nerves, there is a great need for the development of procedures that promote peripheral nerve regeneration in humans and thereby decrease the related social and health-care costs. While the effects of shock waves on wound healing, (Schaden et al., 2007), bone regeneration (Ogden, Alvarez, Levitt, Cross, & Marlow, 2001), and the integration of skin grafts (Kuo et al., 2009; Stojadinovic et al., 2008) have been extensively studied, very little is known as concerns its effects on peripheral nerve regeneration (Hausner et al., 2012; Wu, Lun, Chen, & Chong, 2007).



3. PRESUMED BIOLOGICAL EFFECTS OF ESWT

Shock waves are mechanical events that can stimulate tissues and especially cells. The conversion of physical forces into biochemical signals is a fundamental process required for the development and the physiology of organisms. This process is referred to as mechanotransduction. Physical forces exert a direct influence on protein folding, and force-induced effects on the three-dimensional structures of proteins are therefore involved in a general mechanism through which the activities of enzymes or the interactions between proteins may lead to signal modification (Orr, Helmke, Blackmann, & Schwartz, 2006). The manner in which ESWT-induced mechanotransduction is manifested in target cells and tissues is still not clear. There are a number of proved facts or theories concerning the cascade of actions stemming from shock wave treatment and resulting in angiogenesis or neovascularization (Sadoun and Reed, 2003; Stojadinovic et al., 2008; Wang et al., 2004), anti-inflammatory effects (Davis et al., 2009), the release of growth factors (Hausdorf et al., 2011), and the activation of progenitor cells and stem cells (Mittermayer et al., 2012; Sadoun and Reed, 2003).

There are various mechanisms behind the effects in tissues treated with shock waves. It has been reported that angiogenesis is induced by increased levels of vascular endothelial growth factor-A, which in turn is triggered by upregulated activities of nitric oxide synthase (NOS), and extracellular signal-regulated kinase. On the other hand, enhanced NOS activity also appears to be responsible for the activation of hypoxia-inducible factor-1 in a variety of cells, depending on the target of ESWT. Low-energy shock wave treatment has likewise proved to be effective in downregulating immune responses in acute wounds. ESWT has been reported to reduce the invasion of macrophages and polymorphonuclear leucocytes into the wound area, together with the suppressed production of proinflammatory cytokines and chemokines at the wound matrix (Davis et al., 2009; Kuo et al., 2009). Similar to its role in inducing angiogenesis in shock wave-treated tissues, the regulatory function of NOS has been suggested in the downregulation of inflammatory events in these conditions (Fig. 3.1; Mariotto et al., 2009). Others have described the increased release of fibroblast growth factor-2, acting on osteoblasts (Hausdorf et al., 2011), while osteocalcin, a major bone protein playing an important role in bone mineralization, is reportedly upregulated in regenerating the bone after ESWT (Martini et al., 2003). In contrast with these molecules, the role of transforming growth factor-beta remains controversial (Hausdorf et al., 2011; Martini et al., 2003).

It has been suggested that mesenchymal stem cells may differentiate toward tissue-specific progenitor cells such as osteoblasts in response to ESWT (Chen et al., 2004), and the moderate recruitment of endothelial progenitor cells has been described (Tinazzi et al., 2011). However, the extent to which these mechanisms are able to contribute to the tissue repair following ESWT is not clear at present.



4. EFFECTS OF ESWT ON PERIPHERAL NERVES

4.1. Effects of ESWT on sensory nerves

Shock waves have been used extensively to study their effects on sensory nerves and nerve endings. Application of 1000 impulses of shock waves (0.08 mJ/mm, 2.4 Hz) resulted in the degeneration of sensory nerve fibers and endings followed by reinnervation of the affected skin areas (Ohtori et al., 2001). These changes were accompanied by the reversible and rapid loss of the immunohistochemical markers protein gene product 9.5 and

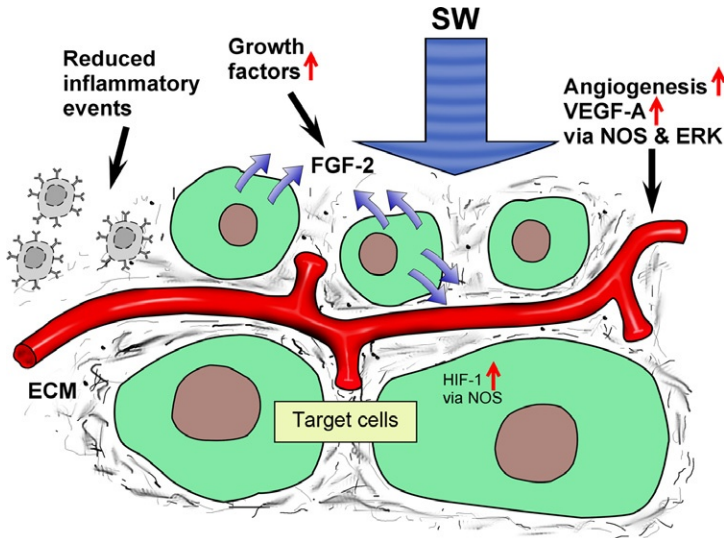


Figure 3.1 Schematic drawing depicting the sites of action by shock waves in various tissues (with the exception of peripheral nerves). The target cells of shock wave treatment are embedded in the extracellular matrix, surrounded by various other cell types, including resident and invading mononuclear and polymorphonuclear immune cells. ESWT has been proved to induce the release of growth factors (e.g., FGF-2) from the cells surrounding the target cells, to improve angiogenesis within the tissues, and to reduce the secretion of inflammatory cytokines and the invasion of immune cells. On the other hand, tissue-specific target cells are known to secrete factors such as hypoxia-inducible factor-1 (HIF-1). Several of these processes are regulated via the activation of nitric oxide synthase (NOS); it should be noted that the extent to which these processes are induced varies with the type of tissue (ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; FGF-2, fibroblast growth factor-2; VEGF-A, vascular endothelial growth factor-A; SW, shock waves).

calcitonin gene-related peptide. However, a second application of the same dose of shock waves had a cumulative effect on the treated nerves, leading to delayed reinnervation (Takahashi, Ohtori, Saisu, Moriya, & Wada, 2006). It appears, therefore, that shock wave-treated nerves develop a “memory effect” after the first treatment, and ESWT repeated shortly after the first treatment is not beneficial. It is expected that ESWT induces subtle changes in the affected neurones whose axons have been treated. Murata et al. (2006) detected an increased expression of activating transcription factor 3 (ATF-3) and growth-associated phosphoprotein 43 (GAP-43) in dorsal root ganglion neurones of shock wave-treated rats, indicating that the molecular changes after ESWT are not restricted to the treated axons: their cell bodies are also

activated in a retrograde manner. The question remains open as to whether doses of ESWT in the therapeutic range would induce similar changes as the 2000 impulses applied in this study. ATF-3 and GAP-43 are markers thought to be associated with the activation of neurones and glial cells (Schwann cells) after peripheral nerve injuries (Hunt et al., 2004; Saito and Dahlin, 2008).

As regards the dose–effect relationship of ESWT on peripheral nerves, a large body of evidence suggests that shock wave doses greater than 900 impulses combined with a flux density of 0.08 mJ/mm^2 induce damage to the affected nerves, manifested in impaired electrophysiological conduction parameters (Wu et al., 2007), a disrupted neurofilament staining pattern of the treated axons (Hausner et al., 2012), and degeneration of the myelin sheaths at the levels of light and electron microscopy (Bolt et al., 2004). These doses appeared to damage motor and sensory nerves equally (Bolt et al., 2004; Wu et al., 2007). Our experimental and clinical experience indicates that the therapeutically applicable dose for the promotion of nerve regeneration without side effects is likely to be lower than 500 impulses (0.1 mJ/mm^2 , 4 Hz) (Hausner et al., 2012). The effect of such doses is highly dependent on the depth of the target tissue and the treated surface area.

4.2. Effects of ESWT on motor nerves

The question arose of whether doses of shock wave treatment that did not cause degenerative events in the affected peripheral nerve segments would foster the regeneration of injured axons in a rodent model. It was clearly demonstrated that ESWT applied at a dose of 300 impulses and 0.1 mJ/mm^2 did not induce the disintegration of neurofilaments within the axons of the sciatic nerve (Hausner et al., 2012). The efficacy of this ESWT scheme was tested in an autologous rat sciatic nerve model, where an 8-mm long autograft was excised and coapted with the proximal and distal stumps. When shock wave treatment was applied immediately after surgical reconstruction, a significantly improved rate of axonal regeneration was observed as early as 3 weeks after the injury. Not only were more regenerating axons found in the reinnervated distal stump of the shock wave-treated nerves, but also this early reinnervation was accompanied by moderate values of axon conduction beyond the distal coaptation site. The morphological and functional reinnervation of the denervated hind limb muscles could be expected only at later time points. Functional tests revealed a clear improvement in the ESWT animals from 4 weeks onward, but this difference in improved

locomotor pattern was no longer detectable from week 10 after surgery. Twelve weeks after injury, none of the morphological, functional, or electrophysiological parameters indicated differences between the treated and the untreated animals, with the exception of the conduction velocity, which was still significantly higher in the ESWT group (Fig. 3.2).

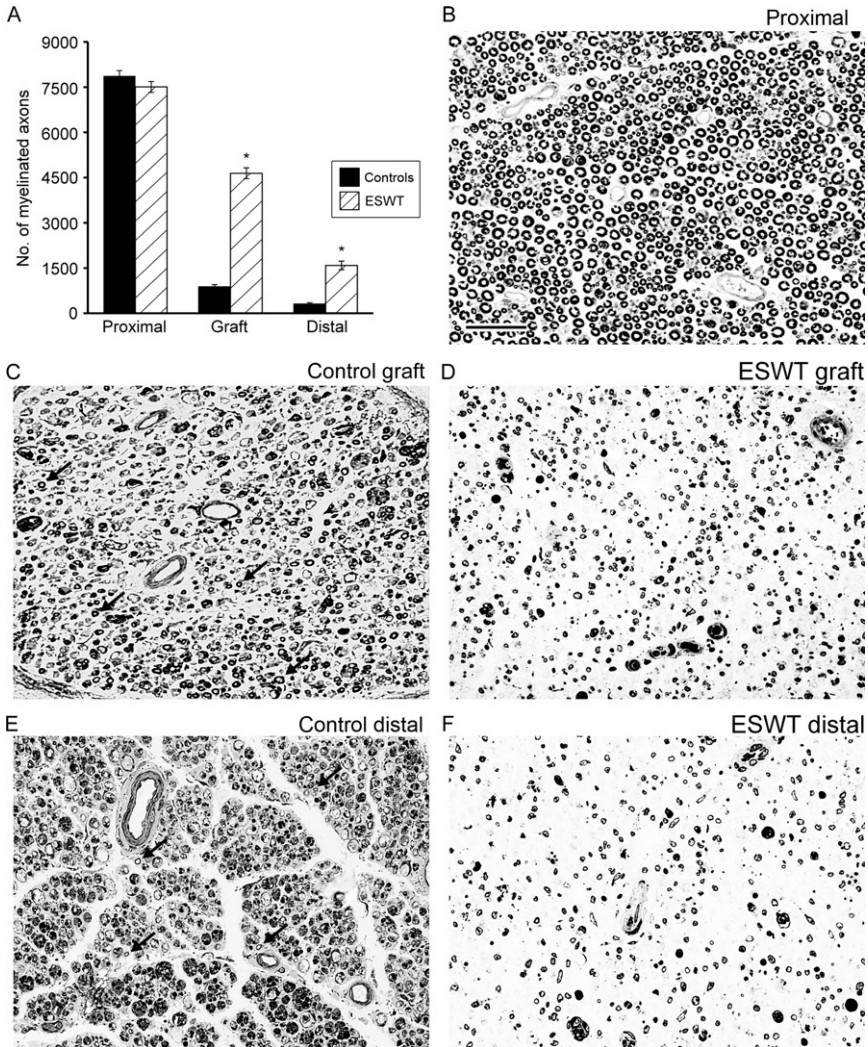


Figure 3.2 Axonal regeneration in control and extracorporeal shock wave-treated (ESWT) peripheral nerves 3 weeks and 3 months after surgery. (A) The columns show the numbers of myelinated fibers found in the middle of the graft and 2 mm proximal and distal to the graft in ESWT and control animals 3 weeks after axotomy (left). The

Ultrastructural analysis of the nerve grafts 3 weeks after the injury revealed that not only were there more regenerated and well-myelinated axons in the ESWT nerves, but also the endoneurium was free from reactive cells and degenerated myelin profiles, which were present in abundance in the untreated nerves (Fig. 3.3; Hausner et al., 2012). These findings indicated that the improved rate of axonal regeneration and the clearing-up of the degenerated structures in the denervated nerves are strongly related. It remains for future studies to establish whether either of these processes enjoys priority over the other in the temporal sequence of events.



5. CONCLUSION

Shock waves were introduced into the arsenal of modern human medical therapy some 30 years ago (Shrivastava and Kailash, 2005; Thiel, 2001). Following the initial treatment trials on urolithiasis, extracorporeal shock waves were introduced both preclinically and clinically for the treatment of acute and chronic soft and hard tissue healing problems (Ogden et al., 2001). In most cases, improvements in the soft and hard tissue healing processes were found to be associated with increased levels of vascularization, and this mechanism of action was therefore considered to be a general, but not overall scenario for shock wave-induced improvement (Wang et al., 2004; Yan, Zeng, Chai, Luo, & Li, 2008; Zimpfer et al., 2009). However, it has subsequently been demonstrated that other nonvascular mechanisms contribute to the tissue repair (for details, see Fig. 3.1).

numbers of myelinated axons in the graft and distal to the grafting site are much higher in the ESWT animals than in the controls. There was no significant difference between the controls and the ESWT animals in the numbers of myelinated axons distal to the graft 3 months after axotomy and grafting (right). *Significant difference ($p < 0.05$) between the control and the ESWT groups by ANOVA, computed by using Tukey's all pairwise multiple comparison procedures. (B–F) Photographs of semithin cross-sections from the proximal stump (B), the middle of the graft (C, D), and the distal stump (E, F) 3 weeks after axotomy. The shock wave-treated peripheral nerves (ESWT) contain more myelinated axons, while the control nerves display far fewer regenerated axons (arrows) and are full of degenerated myelin sheaths and reactive cells. (G, H): Photographs of semithin cross-sections from the distal stump 3 months after axotomy. There is no striking difference between the ESWT and control nerves, although the myelin sheaths of the regenerated axons appear thinner than those seen in the intact proximal stump (B). Methylene blue–thionin staining according to R udeberg, scale bar = 25 μm . This figure is reproduced from the publication by Hausner et al. (2012), with the kind permission of Elsevier/Rightslink.

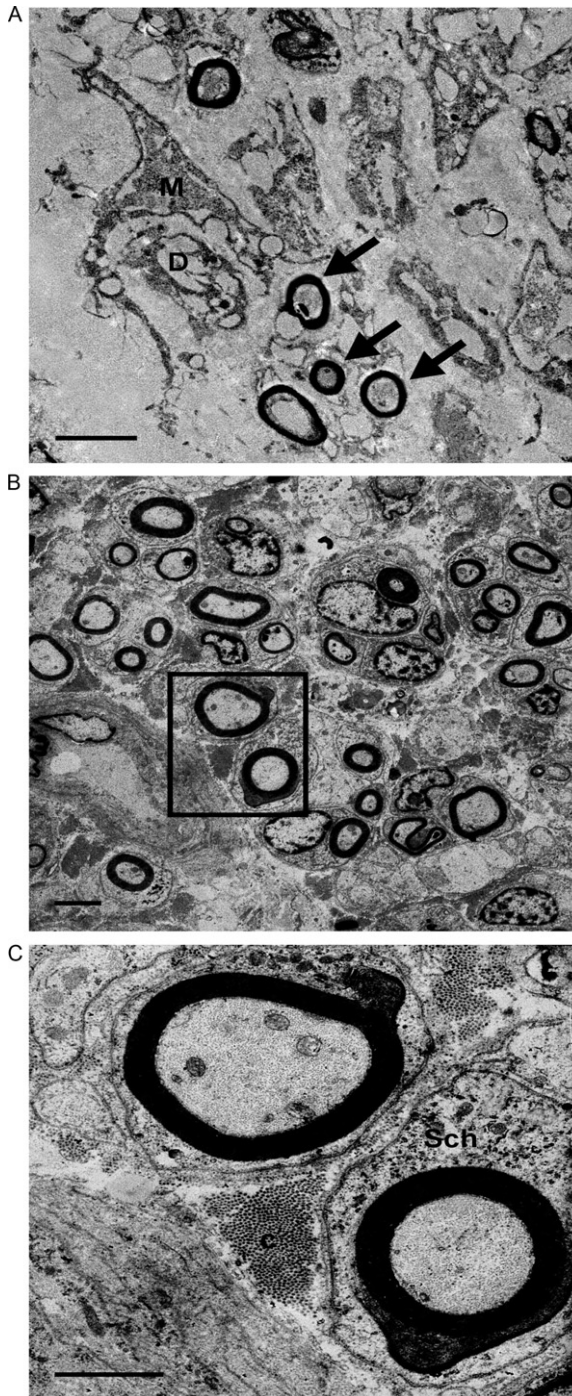


Figure 3.3 Electron microscopic photographs of control (A) and shock wave-treated peripheral nerves 3 weeks after surgery. Panel (A) shows several degenerated myelin sheaths (D) engulfed by macrophages (M). A few myelinated regenerated axons (arrows) too can be seen. In panel (B), a high number of myelinated axons are present

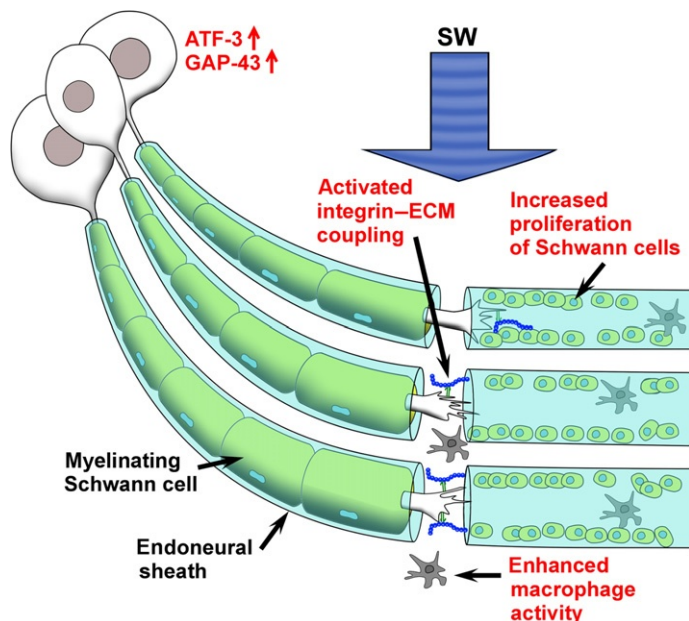


Figure 3.4 Schematic drawing displaying the possible sites of action of ESWT in a regenerating peripheral nerve and related cell bodies. In an untreated peripheral nerve, regenerating neurites enter the vacated endoneurial sheaths of the degenerated distal peripheral nerve stump and grow along the aligned proliferating Schwann cells (bands of Büngner), provided that the proximal and distal stumps are sufficiently close to each other. It is suggested here that ESWT may improve the rate of axonal regeneration through the activation of integrin molecules expressed on the axonal growth cones, thereby promoting stronger binding to the various extracellular molecules, such as laminin and fibronectin. The rate of proliferation of Schwann cells in the distal stump may also increase, in conjunction with a more pronounced macrophage activity, which results in the faster and more effective clearance of myelin debris. These actions may have a cumulative effect on nerve regeneration, leading to a faster and more accurate reinnervation process. The changes in the distal stump of the nerve and the more effective axonal regeneration is accompanied by molecular changes in the related cell bodies, that is, upregulation of transcription factor ATF-3 and GAP-43. Apart from these actions marked in red, it appears conceivable that many other molecular mechanisms too are upregulated in order to support extensive axonal growth. The term endoneurial sheath refers to the fine network of reticular fibers and extracellular matrix molecules around each myelinated axon as part of the endoneurium (ATF-3, activating transcription factor-3; ECM, extracellular matrix; GAP-43, growth-associated phosphoprotein-43; SW, shock waves).

without reactive cells, but surrounded by Schwann cells. Panel (C) presents a higher magnification of the framed area in (B). Note the remyelinating Schwann cells (Sch) and some collagen bundles (C) in the endoneurium. Scale bar in (A) and (B) = 2 μm , in (C) = 1 μm . This figure is reproduced from the publication by Hausner et al. (2012), with the kind permission of Elsevier/Rightslink.

The present review has surveyed the findings that describe the effects of shock waves on intact and injured peripheral nerves. Although only limited information is available on the mechanism of action of shock wave treatment on peripheral nerves, improved vascularization does not appear to play a direct role in promoting axon regeneration after axotomy. Axonal regeneration in the peripheral nerves is known to be promoted by several cellular and molecular components of the nerve, including the coupling of integrin molecules situated on the axonal growth cone membrane with the abundant extracellular molecules (Lefcort, Venstrom, McDonald, & Reichardt, 1992; Low, Nógrádi, Vrbová, & Greensmith, 2003; Tomaselli et al., 1993), the proliferation of activated Schwann cells in the degenerated distal stump of the nerve (Stoll and Müller, 1999), and the clear role played by activated macrophages (Dailey, Avellino, Benthem, Silver, & Kliot, 1998; Horie et al., 2004; Hughes and Perry, 2000) in the removal of myelin debris (Fig. 3.4). We therefore suggest that ESWT may augment and potentiate the mechanisms described earlier in a regenerating peripheral nerve segment. It is to be expected that ESWT will become more widely used in the treatment of injuries and pathological conditions affecting peripheral nerves.

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