REGENERATIVE EFFECTS OF PULSED MAGNETIC FIELD ON INJURED PERIPHERAL NERVES

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Previous studies confirm that pulsed magnetic field (PMF) accelerates functional recovery after a nerve crush lesion. The contention that PMF enhances the regeneration is still controversial, however. The influence of a new PMF application protocol (trained PMF) on nerve regeneration was studied in a model of crush injury of the sciatic nerve of rats. To determine if exposure to PMF influences regeneration, we used electrophysiological recordings and ultrastructural examinations. After the measurements of conduction velocity, the sucrose-gap method was used to record compound action potentials (CAPs) from sciatic nerves. PMF treatment during the 38 days following the crush injury enhanced the regeneration. Although the axonal ultrastructures were generally normal, slight to moderate myelin sheath degeneration was noted at the lesion site. PMF application for 38 days accelerated nerve conduction velocity, increased CAP amplitude and decreased the time to peak of the CAP. Furthermore, corrective effects of PMF on the abnormal characteristics of sensory nerve fibers were determined. Consequently, long-periodic trained-PMF may promote both morphological and electrophysiological properties of the injured nerves. In addition, corrective effects of PMF on sensory fibers may be considered an important finding for neuropathic pain therapy. (Altern Ther Health Med. 2006;12(5):42-49.)

Peripheral nerve injury can result in both structural and physiological changes. After the crush injury, the axon cylinder is disrupted, whereas the basement membrane of the Schwann cells remains intact. These intact basement membranes provide pathways to guide the regenerating axon sprouts. The regenerating fibers enlarge and become myelinated after contact with the periphery target tissue. Even minimal myelin retraction results in conduction or impulse blockade caused by both increased membrane capacitance and decreased membrane resistance. This causes significant reorganization of ion channels at both paranodes and nodes, which are critical for the proper electrophysiological function of the peripheral nerves.

The production and conduction of nerve electrical signals (i.e., action potentials) most frequently require the coordinated opening and closing of Na⁺ and K⁺ channels. In the axons, the majority of ion channels are Na⁺ and K⁺ channels. Na⁺ channels, which are concentrated at the Node of Ranvier, are mainly responsible for the axonal depolarization that is required for action potential induction. In general, K⁺ channels cluster in the internodal regions (paranodal/juxtaparanodal). The functions of these channels prevent aberrant neuronal firing during development and modulate action potential duration and frequency.

Animal models provide an excellent avenue for establishing injury to a nerve to enable an understanding of what methods are successful in the repair of the injury. Experimental animal models of peripheral nerve crush injury resembling the clinical cases provide opportunities for electrophysiological research of peripheral mechanisms. These models have indicated that the relative success or failure in re-establishing functionally appropriate connections depends upon the combined effects of several neuronal and non-neuronal factors. The successful and reliable recovery of injured nerves is currently an area of considerable research interest. It is well known that physical agents, such as electrical or magnetic applications, may positively influence the regeneration process of peripheral nerves.

Pulsed magnetic field (PMF) application is one of the basic techniques that is currently being used to treat injured peripheral nerves. Investigations in several laboratories have demonstrated that functional recovery of the peripheral nerves after the injury can be accelerated by PMF. Furthermore, PMF can promote peripheral nerve regeneration to an extent similar to that observed with conditioning lesions, growth factors, and hormones in experimental models.
The contention that PMF enhances peripheral nerve regeneration is still controversial, however.12

To our knowledge, no attempt to use the trained-PMF (t-PMF) application protocol on peripheral nerve regeneration has been made. Therefore, we decided to investigate the effects of PMF, which was presented in trains, including the different frequencies, on rat sciatic nerve after a crush injury. In the present study, we used electrophysiological recording techniques and electron microscopy for ultrastructural examinations to show the effect of PMF on morphologic properties and electrophysiologic functions of the injured nerve. Specifically, we focused our attention on the effects of t-PMF on the remyelination process and electrophysiological properties of regenerating nerves.

MATERIALS AND METHODS

Animals and Surgical Procedure

Thirty female Wistar rats weighing 220-240 g were used for the experiments. These animals were obtained from the Medical Sciences Research Center of Cukurova University, Adana, Turkey. For the crush injury, the animals were anesthetized with Ketamine (80 mg/kg) plus Xylazine (2.5 mg/kg) intraperitoneally. The left lateral thigh was shaved and prepped with Betadine solution. A longitudinal incision was made along the lateral thigh, the hamstring and gluteal muscles were exposed, and a 10-15-mm length of the sciatic nerve was identified. The nerve was crushed with surgical forceps (Martin, no: 13-324-14) for 30 sec, and then the incision was closed using 4-0 silk sutures. All surgical procedures were conducted under sterile conditions.

After the surgical operation, the rats were randomly housed in groups of 5 in plastic boxes and allowed to recover for 15-38 days. The rats were maintained in a climate-controlled room (23-25 °C) on a 12-hour light/dark cycle (6 AM-6 PM), and food and water were available ad libitum. The experimental protocols were reviewed and approved by the Institutional Animal Care and Use Committee of the University of Cukurova. All efforts were made to minimize animal suffering, and the number of animals used was the minimum for obtaining significant data.

In a preliminary study, when sham-exposed (non-t-PMF in application system) groups, including rats with a crushed nerve, were compared with control groups, including rats with a crushed nerve, at the same time points (15 days post-crush [dpc] or 38 dpc), no clear differences between groups were observed. Based on these findings, experimental groups were designed as below.

For the electrophysiological studies, 30 experimental rats were divided into 2 main groups: PMF and control (non-t-PMF) after the crush injury. Each group was separated into 2 subgroups; 15 dpc (n=7), 15 dpc+PMF (n=7), 38 dpc (n=8), and 38 dpc+PMF (n=8). In addition, 20 rats that had not received crush injury (ie, intact) were grouped as intact (n=8) and intact+PMF (for 15 days [n=6] and 38 days [n=6]). In addition, similar groups were designed for the histological examinations. In addition to these groups, 5 dpc and 5 dpc+PMF groups were examined for Wallerian degeneration. Each group included 5 rats/nerves in histological examination groups.

Pulsed Magnetic Field Treatment

Following recovery from anesthesia, 15 injured rats were randomly assigned to 2 experimental groups for t-PMF treatments. The animals were treated with whole-body exposure to t-PMF (Figure 1) for the 15 days and 38 days. Each animal was placed in an all-plastic restrainer (30 cm long, 20 cm wide, 15 cm high) located between Helmholtz coils at approximately the same hours (9-11 AM). PMF was applied using Helmholtz coils.8,10-15 60 cm in diameter, placed 30 cm apart. When connected to a signal generator, these coils produced magnetic field peak amplitude of 1.5 milliTesla (mT). To our knowledge, this t-PMF application procedure has not been studied until now. Our t-PMF application was presented in 3 train sets. Each train set was composed of the following frequencies: 1, 10, 40, and 100 Hz. The duration of each frequency train was 6 minutes; a 2-minute interval occurred between each frequency train, and a digital timing device controlled the timing of the pulses. The rats were located in the homogeneity region of the magnetic field between the coils (Figure 1).

Effects of Pulsed Magnetic Field on Injured Nerves

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Electrophysiological Experiments

Before the sucrose-gap recordings, nerve conduction velocities were measured at day 15 and day 18 after crush. After the rats were re-anesthetized, the sciatic nerves were exposed and stimulated with supramaximal stimulus intensity through a pair of stimulating platinum electrodes (distance of the electrodes; AL=1 cm) placed directly on the sciatic nerve, 2 mm proximal (S1) and distal (S2) to the crushed site (Figure 2B). For the determination of the conduction velocity (CV) at the crushed site of the nerve, the latency of the evoked compound muscle action potentials were recorded from gastrocnemius muscle with a bipolar concentric needle electrode with platinum surface (Type 13K59). The latency was measured from stimulus artifact to the first deflection from the baseline. The difference between latencies recorded from proximal and distal location from the crushed site was used to calculate the CV.

After the measurements of CV, the rats were exsanguinated by carotid section, and the sciatic nerves were rapidly removed and carefully desheathed in Krebs solution. Sucrose-gap recordings were performed as previously described. Before starting the recordings, the de-sheathed sciatic nerves were superfused with an oxygenated Krebs solution for 30 minutes to achieve a stable baseline and to record reproducible compound action potentials (CAPs). Following this period, individual nerves (the nerve segment with the crush lesion was positioned in the test pool) were placed in a sucrose-gap apparatus (Figure 2A) partitioned into pools by Petroleum jelly-silicon oil mixture for stimulation and recording. The nerve segments in pools superfused with the appropriate solutions at a flow rate of 1-2 mL/min. In the sucrose-gap apparatus, there are 4 pools: stimulating pool contains a pair of platinum electrodes and is filled with Krebs solution (in mM 124.0 NaCl, 3.0 KCl, 1.3 NaH$_2$PO$_4$, 2.0 MgCl$_2$, 2.0 CaCl$_2$, 26.0 NaHCO$_3$, and 10.0 dextrose); test pool contains Krebs or test solution; sucrose pool contains 320 mM isotonic sucrose; and iso-KCl pool contains isotonic KCl solution (in mM 120.0 KCl, 7.0 NaCl, 1.3 NaH$_2$PO$_4$, 2.0 MgCl$_2$, 2.0 CaCl$_2$, 26.0 NaHCO$_3$, and 10.0 dextrose). During the sucrose-gap recordings, agar-bridged Ag/AgCl recording electrodes positioned in the test and iso-KCl pool of the apparatus were connected to the inputs of a high-impedance DC amplifier (Grass P-16). The nerve was stimulated with voltages 1.5-2 times supramaximal for 0.05-ms duration at 1 stimulation per minute with a Grass S-48 stimulator and stimulus isolation unit (SIU5).

The changes in CAP amplitude and time to peak, delayed depolarization (Del-Dep), and hyperpolarizing afterpotentials (HAPs) were recorded, and all data were entered into a computer to be evaluated later. The experiments were carried out at 23-25°C. The pH of the solutions was adjusted to 7.4 with NaOH or HCl.

In the experiments, after the steady state condition, during the next 30 minutes, 2 mM 4-Aminopyridine (4-AP) was tested. This concentration was based on earlier studies and was chosen because it permits the pharmacological differentiation of distinct channel types in intact and regenerating nerves.

Histological Examinations

At the time of sacrifice, the rats were terminally anesthetized. After opening the thoracic cavity, the vascular system was intracardially perfused using a phosphate buffer solution (pH 7.2-7.4, 200 mL), followed by a 4% paraformaldehyde+1% glutaraldehyde solution (200 mL).

The crushed site of the left sciatic nerves and the same sites in the nerves of intact animals were dissected and immediately placed in 5% glutaraldehyde buffered at pH 7.3 with Millonig phosphate buffer for 3 hours. The tissue samples were subsequently fixed in 1% osmium tetroxide solution for 2 hours and dehydrated in graded ethanols, embedded in araldite. Ultrathin sections (0.5 μm) were obtained using a Reichert Ultrcut S ultramicrotome (Reichert Inc, Depew, NY), and these sections were stained with uranyl acetate and lead citrate. Electron microscopy was performed under Zeiss EM 10 B electron microscope (Carl Zeiss, Oberkochen, Germany).

In addition, these sections were examined with light microscopy (Optiphot trinocular, Nikon Corp, Tokyo, Japan) after staining with 1% toluidine blue (x1000) and semi-quantitatively scored for myelinated nerve fibers in whole sciatic nerve bundle. The myelinated nerve fibers within 1 mm$^2$ were counted.

Statistical Analysis

All the data given here are reported as mean ± standard error.
of the mean (SEM). The existence of group differences among the electrophysiological and histological parameters of animals (eg, CV, CAP amplitude and duration, and the number of myelinated fibers of 15 dpc, 38 dpc, and intact were compared to determination of regeneration process with or without t-PMF) were evaluated with 1-way analyses of variance (ANOVA) using the Statistical Package for Social Sciences (SPSS 11.0, SPSS Inc, Chicago, Ill). Post-hoc analyses were done with Turkey's Honestly Significant Different (HSD) or Tamhane tests (ANOVAs were computed with 95% confidence levels). Furthermore, F test was used to detect the statistical significance of the observed differences among the means. For comparison of parameters of 2 groups with and without PMF (eg, 38 dpc and 38 dpc+PMF) in single time points, the nonparametric Mann-Whitney U was used. P values <.05 were considered significant.

RESULTS

Comparison of Conduction Velocities

Nerve conduction changes were dependent on the temperature, and thus in this study, all nerve conduction velocities (CV) recordings were done in stable room temperature (23-25°C). Nerve conduction velocity is calculated by dividing the inter-electrode distance by the latency of the first positive deflection in the waveform.

Under these conditions, CV of the intact sciatic nerve was calculated as 38±1 meters per second (m/s). No nerve conduction was evoked in the animals evaluated after 15 days, while the mean CV recorded after 38 days was approximately 50% (19±2 m/s) of the normal value (P<.05).

Application of t-PMF for 15 or 38 days to intact animals did not cause any changes in the nerve CVs. In the other part of the experiment, CV markedly increased at 38 dpc+t-PMF (28±2 m/s) as compared with 38 dpc (P<.05). However, due to absence of signal conduction in the crushed site or insufficient axonal regeneration, CV was not determined in both 15-dpc groups (with or without PMF).

Compound Action Potentials Recorded From Injured and Intact Nerves

In a series of experiments, after the crush injury, CAPs of regenerating and intact nerves were recorded at various times. CAPs recorded from injured (15 dpc and 38 dpc) and intact sciatic nerves showed significant differences between their amplitudes or time parameters (Figure 3). The mean amplitudes of CAPs were 9.0±0.4, 44±2 mV, and 79±2 mV for 15-dpc, 38-dpc, and intact nerves, respectively (P<.05). The time to peak was 2.09±0.02 ms for 15 dpc, 0.98±0.02 ms for 38 dpc, and 0.67±0.01 ms for intact (P<.05).

Application of t-PMF for 15 days did not cause any changes in the nerve CVs. In the other part of the experiment, CV markedly increased at 38 dpc+t-PMF (28±2 m/s) as compared with 38 dpc (P<.05). However, due to absence of signal conduction in the crushed site or insufficient axonal regeneration, CV was not determined in both 15-dpc groups (with or without PMF).

Compound Action Potentials, Delayed Depolarizations, and Hyperpolarizing Afterpotentials in the Presence of 4-Aminopyridine

There was enhanced sensitivity to 4-aminopyridine (4-AP) in injured nerves as compared to intact nerves. Application of 4-AP markedly increased the amplitude and time to peak of the CAP by 53±1% and 90±1%, and produced the HAP following the CAP at 15-dpc. The mean HAPs amplitudes and durations were 1.10±0.03 mV and 215±5 ms, respectively. In the t-PMF-treated rats during 15 days following the crush, neither CAP nor HAP parameters significantly changed (P>.05).

In contrast to 15 dpc, after application of 4-AP, while CAP amplitude and duration did not significantly change, the Del-Dep appeared as another waveform following the CAP in both groups of 38 dpc and intact (Figure 4A). The amplitudes and durations of Del-Dep were 23.2±0.4 mV and 44±1 ms at 38 dpc, and 9.8±0.5 mV and 105±3 ms at intact (P<.05). t-PMF application during 38 days following the crush significantly changed the parameters of Del-Dep only at 38 dpc. Amplitude (12.8±0.6 mV) and duration (88±1 ms) of the Del-Dep values were close to intact nerve values by t-PMF therapy (Figure 4A).

Furthermore, the amplitude ratio of Del-Dep to CAP (V\text{Del-Dep}/V\text{CAP}) significantly decreased from 52±1% to 24±2% in crushed nerves of 38 dpc group following the t-PMF application. This proportion was 12.9±0.5% in intact nerves. The proportions of these 3 groups were significantly different from each other (P<.05).
FIGURE 4 The representative recordings of 4-AP-induced delayed depolarization (Del-Dep) and hyperpolarizing afterpotential (HAP) recorded from 38 dpc injury. (A) Amplitude and duration of the Del-Dep significantly decreased by t-PMF. In addition, beginnings of the Del-Dep were significantly changed by t-PMF (empty arrow). (B) t-PMF decreased the amplitude of the HAP.

Application of 4-AP led to a much larger HAP (2.10±0.04 mV and 269±6 ms) in the injured nerves from the group of 38 dpc, but not in the intact group (Figure 4B). In the t-PMF-treated group (38 dpc+t-PMF), while amplitudes of the HAP decreased to 1.2±0.1 (P<.05), its duration insignificantly changed (281±6 ms) (P>.05) compared with 38-dpc values.

The Number of Myelinated Nerve Fibers
To quantify the effect of t-PMF on demyelination or remyelination after the crush injury, we counted total myelinated fibers per mm² and estimated the proportions of damaged (D) and undamaged (UD) myelinated nerve fibers in nerve bundles (Figure 5). The myelinated fibers were counted as 10,920±11 in intact nerves. The number of myelinated fibers was small at the early recovery periods; 2,030±4 (UD: 20%; D: 80%) at 5 dpc and 3,000±6 (UD: 40%; D: 60%) at 15 dpc, but had increased to 3,750±5 (UD: 80; D: 20%) at 38 dpc (P<.05). t-PMF application during 5 and 15 days after crush did not cause any changes in the number of myelinated nerve fibers and damaged and undamaged nerve proportions. However, t-PMF application for 38 days caused a significant increase in the number of myelinated fibers (4390±5) (P<.05) and a significant decrease in proportion of damaged myelinated fibers (7%) (P<.05) compared with non-t-PMF group (38-dpc).

Electron Microscopy
Most of the axons in crushed sites of the sciatic nerves showed regular type of Wallerian degeneration 5 days after crush injury (Figure 6A). The myelin sheaths were disintegrated, and axons were condensed and degenerated. Some Schwann cells contained myelin debris. The basal lamina tubes contained amorphous myelin fragments.

Fifteen days after crush injury, although the axonal ultrastructures were almost normal, some myelinated nerve fibers showed myelin sheath degeneration (Figure 6B). The endoneurial fibro-
lasts showed cytoplasmic degeneration, and they contained intensive lipid droplets. Furthermore, a great many myelinated nerve fibers formed between the gaps in the axon and the myelin sheath.


t-PMF application during 15 days following the crush injury did not cause any differentiation in the ultrastructural appearance of the crushed sciatic nerve fibers. However, the most conspicuous changes were found between 38 dpc and 38 dpc+PMF.

Although most of the nerve fibers appeared quite mature in size and shape, with thick myelin sheaths at 38 dpc, some of the myelinated nerve fibers showed slight to moderate myelin sheath degeneration (Figures 7A and 7B). Phagocytic cells were numerous, and they contained cytoplasmic myelin ovoids and lipid droplets (Figure 7B). In addition, myelin sheath lamellar separation and disruption were frequently seen in this group (Figure 7A).

Ultrastructures of the crushed sciatic nerve fibers exposed to-PMF application during 38 days were quite similar to intact nerves (Figures 8A and 8B). However, gaps between axon and myelin sheath were noted in some of the myelinated nerve fibers (Figure 8A).

DISCUSSION

The 3 basic techniques that are currently being used to treat damaged nerves include electrical or magnetic applications, chemical or drug therapy, and surgical manipulations. One of these, PMF, has been used as a therapeutic agent during the last 40 years. Many previous studies conducted with different PMF application protocols have demonstrated that PMF applications can promote peripheral nerve regeneration. The accelerated functional recovery measured by the pinch test or behavioral tests observed was attributed to enhancement of the regeneration rate, which in nerve crush models was found to be a significant 22% (0.3 mT, 2 Hz) and 24% (0.1 mT, 1000 Hz). Rusovan et al suggested that frequencies of 250, 500, and 1,000 Hz significantly increase the regeneration distance, but higher (2,000 Hz) and lower (50 Hz) frequencies have no effect. Furthermore, positive effects of PMF have also been reported, including an increased rate of regeneration and improved functional recovery. These studies confirm that functional recovery after nerve crush lesion is accelerated by PMF. The regeneration rate following PMF exposure was enhanced to approximately the same degree as obtained by other treatment methods, including conditioning lesions, growth factors, and hormones.

In the present study, t-PMF application was carried out with trained different pulsed frequencies (1, 10, 40, and 100 Hz). The t-PMF protocol may shorten the exposure time of the animals to magnetic field and may prevent a probable accommodation of the animals to single frequency application. In addition, this protocol may include a useful frequency for the therapy due to the broad frequency range or diversities of frequencies.

The current study demonstrated that t-PMF application did not cause any significant changes in ultrastructural appearance or electrophysiological properties during 15 days post-crush. However, significant electrophysiological and ultrastructural differences were noted in t-PMF-treated 38-dpc nerves. Many of the ultrastructural, cellular, and molecular events in the peripheral nerve regeneration after injury have been identified previously.
nerve fibers was noted at the lesion site even in this group. This may offer evidence that long-periodic t-PMF application may promote the peripheral nerve regeneration.

The recording of sciatic nerve conduction velocity by directly stimulating and recording the surgically exposed nerves may be one approach to nerve regeneration. Recordings of the nerve conduction velocity and time-to-peak measurements of the CAP (which is time between artifact and peak of the CAP) showed that t-PMF treatment during 38 days after injury could accelerate nerve conduction by increasing myelin formation. Conduction velocity of the regenerated nerve at 38 dpc was markedly slowed because of lost electrical insulation or myelin when compared with intact nerves. Increase of myelination and better electrical properties of isolated nerves fibers by t-PMF may be the result of acceleration of the nerve conduction caused by both decreased membrane capacitance and increased membrane resistance. These findings may indicate that the myelin sheath is crucial for faster transmission of the nerve impulse along the axon. Further evidence of the effect of t-PMF was the enhanced amplitude and a decrement in duration of the CAP recorded from the crushed site in the t-PMF-treated 38-dpc group. These rectifier effects suggest that PMF may change the activities of some ion channels that are involved in the electrophysiological properties of regenerating nerves.

During the regeneration process, ion channel organization is drastically altered, and the electrical properties of the nerve fibers are markedly improved. Some indication of the functional consequences of this period can be seen through the compound action potential (CAP). Electrophysiological properties of the regenerating nerves after crush injury have been detailed in previous studies. According to these studies, 4-AP–sensitive fast K+ channels are highly concentrated in the internodal/paranodal regions in close proximity to the nodes, and when myelin structures are damaged, these K+ channels are exposed and can be activated during signal propagation. These studies suggest that 4-AP–sensitive fast K+ channels can play a decisive role before and during the process of myelin formation. Therefore, in this study, changes in 4-AP–sensitive fast K+ channel activity were used as electrophysiological criteria in the evaluation of the myelin sheath formation.

4-AP application to an injured site markedly increased the amplitude and duration of CAPs at 15 dpc but only slightly affected the CAP parameters at 38 dpc and intact nerves. These findings show that 4-AP has a more pronounced effect on injured nerves than on intact nerves, and 4-AP–sensitive fast K+ channels appear after damage to the myelin sheath, consistent with other studies' findings. In myelinated damaged nerves, 4-AP may provide better access to the periaxonal space and better access to K+ channels located at the paranodal region. This may be due to the expansion of the periaxonal space separating the axon from its myelin and breaks in the myelin sheath.

Previous studies have demonstrated that responses of sensory and motor fibers in the injured sciatic nerve bundle are different than fast K+ channel block with 4-AP. These criteria were used to distinguish sensory and motor fibers characteristics. After 4-AP application to the injured nerves, sensory fibers give rise to a delayed depolarization and hyperpolarizing afterpotential, whereas motor fibers exhibit broadening of action potential. These function reflect distinct distributions of various ion channels. Del-Dep results from the activation of kinetically slow Na+ currents elicited by the blockage of the fast K+ channels with 4-AP, whereas HAP can be elicited by activation of slow K+ channels.

Although t-PMF treatment during 15 days did not cause any change in 4-AP–induced CAP parameters, t-PMF elicited more pronounced effects on 4-AP–induced Del-Dep and HAP activities at PMF-treated 38 dpc. t-PMF application during 38 days following crush resulted in reduction of the Del-Dep and HAP activities. This may be due to a decrease in the effects of 4-AP to the fast K+ channels located at the paranodal region. These findings suggest that t-PMF may provoke the process of myelin compaction or may decrease the expansion of the periaxonal space and breaks in the myelin sheath. These corrective effects of t-PMF on the aberrant characteristics of sensory nerve fibers may be evidence that t-PMF application contributes to neuropathic pain therapy, as abnormal impulse characteristics caused by slow Na+ and K+ currents play a critical role in the generation and transmission of the neuropathic pain information.

In summary, the current study may suggest that long-periodic t-PMF treatment may promote both morphologic properties and electrophysiological functions in the crushed sciatic nerve of rats in experimental conditions, probably by accelerating myelin sheath regeneration. Present electrophysiological and ultrastructural findings, consistent with those of other studies, may suggest that long-periodic t-PMF treatment also may reduce the time required for healing and rehabilitation in peripheral nerve injury. There is a good deal of speculative comment about the acceleration of nerve regeneration rate following PMF exposure. Present electrophysiological and electron microscopy findings would justify these positive comments. However, in the present study, the mechanism of action of PMF (systemic effects of PMF) is still unclear. Further studies are required to clarify the mechanisms of action and bio-effects of t-PMF.

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REFERENCES


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