Electromagnetic Field Devices and Their Effects on Nociception and Peripheral Inflammatory Pain Mechanisms

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ABSTRACT

Context • During cell–communication processes, endogenous and exogenous signaling affects normal and pathological developmental conditions. Exogenous influences, such as extra-low-frequency (ELF) electromagnetic fields (EMFs) have been shown to affect pain and inflammation by modulating G-protein coupling receptors (GPCRs), downregulating cyclooxygenase-2 (Cox-2) activity, and downregulating inflammatory modulators, such as tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β) as well as the transcription factor nuclear factor kappa B (NF-κB). EMF devices could help clinicians who seek an alternative or complementary treatment for relief of patients chronic pain and disability.

Objective • The research team intended to review the literature on the effects of EMFs on inflammatory pain mechanisms.

Design • We used a literature search of articles published in PubMed using the following key words: low-frequency electromagnetic field therapy, inflammatory pain markers, cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), opioid receptors, G-protein coupling receptors, and enzymes.

Setting • The study took place at the Wake Forest School of Medicine in Winston-Salem, NC, USA.

Results • The mechanistic pathway most often considered for the biological effects of EMF is the plasma membrane, across which the EMF signal induces a voltage change. Oscillating EMF exerts forces on free ions that are present on both sides of the plasma membrane and that move across the cell surface through transmembrane proteins. The ions create a forced intracellular vibration that is responsible for phenomena such as the influx of extracellular calcium (Ca²⁺) and the binding affinity of calmodulin (CaM), which is the primary transduction pathway to the secondary messengers, cAMP and cGMP, which have been found to influence inflammatory pain.

Conclusions • An emerging body of evidence indicates the existence of a frequency-dependent interaction between the mechanical interventions of EMF and cell signaling along the peripheral inflammatory pain pathway. (Altern Ther Health Med. 2016;22(3):##-##.)

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In humans, electromagnetic-field (EMF) therapy has proven to be a safe, noninvasive, easy-to-use method to treat the site of pain and inflammation. Research has shown that therapeutic applications at extra-low-frequency (ELF) levels (ie, 1-100 Hz) of EMF stimulate the immune system by suppressing inflammatory responses at the cell membrane level. Double-blind, placebo-controlled clinical trials have reported that EMF passes through the skin into the body’s conductive tissue, reducing pain and delaying the onset of edema shortly after trauma. In a randomized, double-blind, sham-controlled clinical study, low-frequency (LF), pulsed EMF (PEMF) at 0.1 to 64 Hz was reported to improve mobility and decrease pain and fatigue in patients with fibromyalgia (FM).

Both clinical and in vitro studies have reported that EMF is effective in the treatment of osteoarthritis (OA). Although many drugs have been used recently for the treatment of OA, the majority of them relieve pain and increase function but do not modify the complex mechanisms that occur in the pathology. PEMF has a number of well-documented physiological effects on cells and tissues, including the expression of the transforming growth factor beta (TGF-β) super family, an increase in the levels of glycosaminoglycan, and an anti-inflammatory action.
to those discoveries, a strong rationale exists for supporting the use of biophysical stimulation with PEMF for the treatment of inflammatory pain that is related to diseases such as OA, FM, and migraine headache. Although the treatment may be a promising therapy, investigators have reported conflicting outcomes, with obvious differences in their measuring techniques. Some studies do not report the frequency and intensity (ie, the field strength) of their treatment device; therefore, it is difficult to compare the parameters being used toward specific outcomes.

For this review, the authors performed a literature search of articles published in PubMed using the following key words: low-frequency electromagnetic field therapy, inflammatory pain markers, cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), opioid receptors, G-protein coupling receptors, and enzymes. The literature search was conducted from October of 2014 to May of 2015.

**EMF NOMENCLATURE**

When discussing cellular influences by either endogenous or exogenous fields, it is important to define the nomenclature. The term EMF is used to summarize the whole field, which includes electric, magnetic, and combined electromagnetic effects.

An electric field (EF) involves a current that can be either direct (DC) or alternating (AC). Units of electrical current are measured in amperes (A), and differences in electrical potential are measured in volts (V). Units of magnetic-flux density (ie, intensity) are measured in either Gauss (G) or Tesla (T), which is 10 000 Gauss.

Faraday’s Law of Induction and Maxwell’s equations explain how an EMF is generated. A static electric field is generated by a static charged particle (q). The electric field or “E” component of an EMF exists whenever a charge (Q) is present. Its strength is measured in volts per meter (V/m) and is expressed as intensity for field strength. An electric field of 1 V/m is represented by a potential difference of 1 volt existing between 2 points that are 1 m apart.

A magnetic field (MF), or the “M” component of an EMF, arises from current flow. The Tesla or Gauss is used mainly to express the flux density or field strength produced by the MF. Both EFs and MFs are generated if a charged particle moves at a constant velocity. Combined, they generate an EMF when the charged particle is accelerated. Most often, the acceleration takes place in the form of an oscillation; therefore, electric and magnetic fields often oscillate. A change in the EF creates an MF, and any change in the MF creates an EF. That interaction suggests that the higher the frequency of the oscillation is, the more the electric and magnetic fields are mutually coupled.

EMFs can affect biochemical reactions and the behavior of charged molecules near cell membranes. The magnetic aspect can influence cell behavior by (1) exerting a force on moving charge carriers, such as ions; (2) generating electric fields in conductive substances; (3) changing the rate of diffusion across membranes\(^\text{13}\); and (4) distorting bond angles, which affects protein-structure binding and, therefore, macromolecule synthesis.\(^\text{14}\)

Unlike EFs, which are shielded by the highly dielectric properties of the cell membrane, magnetic gradients penetrate deeper through layers of living tissue,\(^\text{15}\) acting directly on cell organelles. Pulsing the EMF causes a rise and fall in ion fluxes, whereby changes in the membrane potential cause an inward current flow, resulting in hyperpolarization of its potential.\(^\text{16}\) Depending on the parameters involved in the EMF treatment and the biological process in question, either stimulation or inhibition can occur. In contrast to the membrane, the cytoplasm or fluids in extracellular spaces contain no free electrons to carry a charge; the current is carried by charged ions, such as sodium (Na\(^+\)), potassium (K\(^+\)), chloride (Cl\(^-\)), and extracellular calcium (Ca\(^{2+}\)).

**TYPES OF EMF DEVICES**

EMF devices exhibit varying parameters that include (1) frequency—the number of cycles per time unit (Hz); (2) amplitude—the intensity or magnetic-field strength; and (3) exposure—the time duration.\(^\text{17,18}\) The objective of the devices is the production of a uniform EMF to expose cells or tissue to a consistent set of dosing parameters. For therapeutic purposes, the devices include the transcutaneous electrical nerve stimulation (TENS) and transcranial direct current stimulation (tDCS) devices, the solenoid, and the Helmholz coil (Figure 1).

**Figure 1. EMF Devices**

(A) TENS

(B) Solenoid

(C) Helmholz Coil

Abbreviations: EMF, electromagnetic field; TENS, transcutaneous electrical nerve stimulation.
Transcranial Direct Current Stimulation

TENS has been used to treat a variety of conditions with battery-generated electric current that stimulates nerves to reduce inflammatory pain. The device is connected to the skin via 2 or more electrodes that modulate pulse width, frequency, and intensity. Although typically used at the site of an injury, it is possible that an application outside the injured site can be effective.

Ainsworth et al have confirmed that hypothesis by showing that application of TENS to the contralateral hind limb of rats reduces the hyperalgesia of an inflamed limb.\(^{19,20}\)

The study presented the results for each animal by showing the differences in pressure between the measurements performed on the right hind paw, which had been injected with carrageenan, and those performed on the left hind paw, which had been injected with saline. A reduction in thresholds was interpreted as hyperalgesia; however, it must be taken into consideration that the analgesic effects of TENS might have been stress induced. Greater hyperalgesia stemming from the inflammatory process that had been induced by the carrageenan in the right paw would have required less pressure to provoke the removal of the paw from the algometer, thereby leading to a more negative value when comparing the inflamed and noninflamed paw.

Exposure applications in those 2 studies were either (1) an HF of >50 Hz, with an intensity below motor contraction (ie, sensory intensity) or (2) an LF of <10 Hz, with an intensity that produced motor contraction (ie, 20-40 pulses per second).\(^{21,22}\)

It is generally thought that TENS produces analgesia by activation of cutaneous afferent fibers at the site of application; however, other reports have shown the importance of deep-tissue afferents in analgesia produced by TENS.\(^{23}\)

Various theories have been proposed to explain the analgesic mechanism of TENS. Recent in vivo studies have demonstrated that part of the analgesia is mediated through neurotransmitters acting at peripheral sites. Sabino et al\(^{24}\) have interpreted TENS effects to be mediated by many neurotransmitters, including opioids, serotonin, acetylcholine, norepinephrine, and gamma-aminobutyric acid. In that study, LF but not HF TENS was shown to involve the mu-opioid 5-HT2 and 5-HT3 receptors.

HF but not LF TENS has been reported to involve delta-opioid receptors and to reduce aspartate and glutamate levels in the spinal cord. Santos et al have reported the effects of an LF at 10 Hz and an HF at 130 Hz of TENS on hyperalgesia and edema when applied before serotonin (5-HT) was administered to rats’ paws.\(^{25}\) In that study, both LF and HF TENS were applied to the right paw for 20 minutes, and 5-HT was administered immediately after the TENS.

Santos et al used the Hargreaves method\(^{26}\) to measure noiception, and a hydroplethysmometer was used to measure edema. That method measures the level of cutaneous hyperalgesia from thermal stimulation in carrageenan-induced inflammation in rats’ paws, showing greater bioassay sensitivity and providing measurements of other behavioral parameters in addition to paw withdrawal, as well as supplying a measurement of the nociceptive threshold. In the Santos et al study, neither the LF nor the HF TENS inhibited 5-HT-induced edema; however, the LF TENS, but not the HF, significantly reduced 5-HT-induced hyperalgesia.

Fang et al\(^{28}\) have shown in an in vivo study that TENS may be an effective therapy in controlling inflammatory pain by inhibiting the activation of the spinal extracellular signal-regulated kinase (ERK) 1/2-cyclooxygenase (COX)-2 pathway. Those researchers induced inflammatory pain in rats using carrageenan. Treatment was applied using TENS at an LF of 2 Hz and an HF of 100 Hz, with intensities ranging from 1 to 2 mA at 5 hours and 24 hours after the injection, with each treatment lasting 30 minutes. Although the outcome related to control of peripheral inflammation was found to be independent of anti-inflammatory activity, the analgesic effects of TENS on the inhibition of the ERK1/2-COX-2 pathway was statistically significant at 2 Hz, but not at 100 Hz. Those trials suggest that adequate dosing, particularly the correct frequency, is critical to obtaining pain relief with TENS. Basic scientific studies using animal models of inflammation also report changes in the peripheral nervous system as well as in the spinal cord and descending inhibitory pathway in response to TENS.\(^{22}\)

Transcranial Direct Current Stimulation

In clinical trials, tDCS devices have also been reported to be effective in the treatment of migraine headache. Those devices look very similar to the TENS device, with electrodes placed on the patient’s forehead. In randomized, double-blind, controlled study, Rocha et al\(^{29}\) studied 23 adults, 11 with and 12 without an aura, and compared them with 11 healthy patients to test the effects of 12 sessions of tDCS treatment on the visual cortex during a 90-day period. The phosphene threshold (PT) induced by the tDCS was recorded to measure the excitability of the visual cortex before and after each session. The measurements at baseline showed a higher level of cortical excitability in patients with migraines when compared with healthy volunteers. After the tDCS application, a significant decrease was observed in the number of migraine attacks, frequency of painkiller intake, and duration of each attack in the intervention group. PT analysis indicated that no differences existed in cortical excitability after treatment. The clinical improvements of the patients after tDCS treatment were not correlated with changes in cortical excitability.

Laste et al\(^{30}\) has reported that tDCS can induce changes in cortical excitability in rats (N = 18, with 9 in the treatment...
group and 9 in the sham group) and in humans, which lasted beyond the duration of the stimulation. To evaluate the effects of eight 20-minute treatments with tDCS for chronic inflammatory pain, the rats were injected with complete Freund’s adjuvant (CFA) in the right footpad to induce inflammation. Both the intervention and sham groups were exposed to a hot plate; then, Von Frey tests were applied immediately and at 24 hours after the last tDCS session of 500 µA. The results showed significant, lasting, neuroplastic effects related to the analgesic effects of tDCS on a chronic-pain model of peripheral inflammation.

To study the analgesic effects of tDCS on post procedural pain in healthy patients with abdominal pain after endoscopic retrograde cholangiopancreatography (ERCP), a randomized, sham-controlled study was conducted involving 21 patients who were exposed to 20 minutes of 2-mA treatment with tDCS immediately after the ERCP procedure. As outcome measures, the study used a visual analog scale, the McGill Pain Questionnaire, and a brief pain inventory and also documented the patient-controlled use of analgesics and adverse events. In the intervention group, 22% less hydromorphone was used by patients versus the sham group. The tDCS patients also reported significantly less interference with sleep because of pain, with $t_{17} = 3.70$ and $P = .002$, and less throbbing pain as well, with $t_{16} = 2.37$ and $P = .03$. The visual-analog pain scale and mood scores at 4 hours post-ERCP showed no significant differences, despite hydromorphone use. The side effects of the tDCS treatment were limited to mild tingling, itching, and stinging under the site of the electrode placement.

As to the frequency-specific effects of tDCS, Khadka et al tested a range of 3 signals—39 and 76 µA at 1, 10, and 100 Hz—in an in vitro test creating electrode-failure modes. Both the DC and AC components of the voltages across the electrodes were compared, and participants were asked to rate subjective pain. The researchers’ results showed that average voltage and pain scores were not significantly different across the test-current intensities and frequencies.

Solenoids

A solenoid consists of a thin loop of coiled wire that produces a uniform MF when an electric current passes through it. The device is used by exposing the painful or inflamed area to the field for a prescribed amount of time. The EMF produced by solenoids has been used to affect the inflammatory biomarkers that are associated with oxidative-stress plasma fibrinogen, nitric oxide (NO), L-citrulline, carbonyl groups, and superoxide dismutase (SOD) in rats with experimental myopathy.

Vignola et al have compared an EMF treatment with a sham treatment at a 50-Hz frequency and a 20-mT intensity, for 30 minutes per day per rat. The researchers’ results showed that the EMF decreased the levels of fibrinogen, L-citrulline, NO, SOD, and carbonyl groups, with significant muscle recovery.

Sanserverino et al have reported that a solenoid at 50 Hz, which emitted field intensities between 3 mT and 6 mT, had relieved pain and improved joint mobility with 15 sessions at 15 to 40 minutes daily. Subsequently, an 82% improvement was observed when single-joint disease was considered as compared to a 66% improvement for multiple-joint disease (polyarthritis). The absence of side effects also proved to be an added benefit. The researchers’ hypothesis for the mechanisms of action included transmembrane ionic activity.

Helmholtz Coils

The Helmholtz coil consists of 2 identical, circular, magnetic coils (ie, solenoids), which are placed symmetrically along a common axis, 1 on each side of the experimental area and separated by a distance that is equal to the radius of the coil. Each coil carries an equal amount of electric current flowing in the same direction, producing a uniform MF via Faraday’s law.

Helmholtz coils have been used as the intervention in various studies (eg, animal models of arthritis, cell -culture systems, and clinical trials). In a review of these studies, Ganesan et al indicated that EMF not only alleviated the pain of arthritic conditions, but also afforded chondrocyte protection, exerted anti-inflammatory action, and helped bone remodeling. Although clinical trials have reported beneficial effects with PEMF therapy, Ganesan et al stated the results were not consistent, reporting little evidence was available showing PEMF is more effective than placebo.

Li et al have assessed both the beneficial and harmful effects of EMF for the treatment of OA as compared with placebo or sham. Evaluating controlled trials using EMF for OA with 4 or more weeks of treatment duration, the researchers found 9 studies of 636 patients in the Cochrane Database of Systemic Reviews that found EMF treatment provides a moderate benefit for OA sufferers in terms of pain relief. The researchers, however, suggested that further studies are required to confirm whether the treatment can provide clinical benefits in terms of physical function and quality of life.

In 2014, Adravanti et al reported as much as one year after total knee arthroplasty (TKA), a significant percentage of 33 patients had not attained complete recovery and indicated the patients’ long-term pain outcomes were unfavorable. Patients were treated 4 hours per day for 60 days and assessed before surgery at 1, 2, and 6 months postoperatively, using international scores. One month after TKA, the pain level of knee swelling and functional scores were significantly better in the treatment group as compared with the control group. Pain was significantly lower in the treatment group at the 6 month follow-up. Three years after surgery, severe pain and occasional walking limitations were reported in a significantly lower number of patients in the treatment group.
Studies conducted by Qin et al\textsuperscript{37} have reported that a low-intensity, LF EMF from a Helmholtz coil provided substantial relief to rats with various types of chronic pain that triggered the activity of the thoracic spinal neurons in response to noxious visceral stimuli. In their study, the researchers recorded the T3-T4 spinal neurons in male rats that had been anesthetized with pentobarbital and administered with noxious chemicals producing cardiac stimulation. Noxious esophageal distention was also produced via inflation of a latex balloon. EMF frequencies of <1 Hz and <0.05 µG were applied to both sides of the rats’ chests.

The study’s results showed a 75% decrease in excitatory neuronal responses to intrapericardial chemicals for the intervention group. The inhibitory effect on the spinal neurons occurred at 10 to 20 minutes after EMF application, and the effects continued 1 to 2 hours after termination of the application. Seven of the 18 excitatory-response neurons related to esophageal distention (39%) were inhibited; 5 were excited (28%); and 6 were not affected by the treatment (33%). The authors concluded that application of EMF could reduce the nociceptive responses of the spinal neurons to noxious, cardiac chemical stimuli, whereas the treatment was not effective for nociceptive responses to esophageal mechanical stimulation.

Regarding responses to thermal stimuli in animal studies, Schaible\textsuperscript{38} exposed rats (n = 24) to EMF using a Helmholtz coil, either sham or frequency-modulated, at 2 mT for 30 minutes on 2 consecutive days. The rats exhibited strong analgesic effects to thermal stimulation applied to footpads immediately after treatment, and up to 30 minutes later. Schaible’s generalized speculations as to the mechanisms of action included an EMF modulation of ion flux.

**MECHANISMS AT MOLECULAR LEVEL**

Tissue trauma, immune reactivity, and nerve injury are frequently associated with an inflammatory pain response. Within peripherally damaged tissue, such as skin, muscles, joints, and viscera, the primary afferent neurons transduce noxious chemical, chemical, and/or thermal mechanisms to activate specific receptors and ion channels in peripheral nerve endings.\textsuperscript{40} Those events result in the initiation of action potentials that propagate along the axons of primary afferent fibers to synaptic sites in the spinal cord’s dorsal horn. Peripheral sensory neurons express opioid receptors and opioid peptides, and the function of those neurons can be modulated by endogenous opioids derived from immune cells that seek to affect the mechanisms of inflammatory pain and its inhibition.

Peripheral sensitization contributes to the pain hypersensitivity found in inflammation and at the site of tissue damage. Peripheral inflammation in primary sensory neurons consists of changes in their neurochemical character due to alterations in transcription and translation. The electrical activity of primary afferent neurons is primarily governed by the expression and function of ion channels that define the resting membrane potential, action-potential initiation, depolarization and repolarization, and transmitter release from terminals in the dorsal horn.\textsuperscript{39}

LF EMF passes unobstructed through living tissue\textsuperscript{40,41} and has been shown to modulate ion flux along the cell membrane, thereby achieving opioid-mediated analgesia.\textsuperscript{42,43} Because EMF can alter ion flux, it can influence subsequent cellular events in the signal-transduction cascade.\textsuperscript{44,45} The effects of EMF on pain, nociception, and opiate-mediated analgesia have a number of potential cellular targets that are closely related (ie, Ca\textsuperscript{2+} ion fluxes, kinases, NO, and GPCRs), establishing a chain of events leading to an increase in analgesic affects.

Although the basic transduction mechanisms of EMF are still being investigated, a substantial body of theoretical work has focused on ion/ligand binding as a possible factor for the biomechanical interaction of exogenous EMF with the cell membrane. The application of any mechanical stimulus, such as fluid-shear stress or exogenously applied EMF, to the cell surface can activate mechanically sensitive ion channels, G-protein kinases, and other membrane-associated signal-transduction molecules, which trigger downstream signaling cascades that can lead to force-dependent changes in gene expression.\textsuperscript{46}

It is now known that mechanical action at a distance occurs in living cells,\textsuperscript{47-50} and that a unique form of mechanical signaling provides a more rapid and efficient way to convey information over long distances during cell communication than does diffusion-based chemical signaling.

Panagopoulos et al proposed a simple hypothesis that an oscillating, external EMF can exert an oscillating force on each of the free ions that exist on both sides of the plasma membrane and that the force can move across the membrane via transmembrane proteins.\textsuperscript{51} The researchers have theorized that the external oscillating force can produce a forced vibration on each free ion, and when the amplitude of the ions’ force-vibration transcends some critical value, the oscillating ions can give a false signal to gating channels that are electrically sensitive, or even mechanically sensitive, thereby interrupting the electrochemical balance of the membrane and, therefore, of the entire cell function (Figure 2).

The types of channels include (1) voltage-gated channels (ie, voltage-sensitive channels); (2) mechanically gated channels (ie, channels gated by ion pressure); and (3) ligand-gated channels (ie, chemically sensitive channels).\textsuperscript{52} Mechanical stimulation of the channels may help to explain how mitochondria located far from the cell surface can sense and respond to mechanical stressors by releasing reactive oxygen species (ROS) and activating signaling molecules, such as the GPCRs, that contribute to pain as well as nuclear factor kappa B (NF-κB), a transcription factor that contributes to the inflammatory response.\textsuperscript{53} Voltage-dependent Ca\textsuperscript{2+} channels play a significant role in the cell-differentiation process by triggering intracellular events, such as the activation of enzymes that catalyze modulators of inflammatory pain.\textsuperscript{54,55}
Figure 2. Hypothesis for Mechanism of EMF

(A) Polarized Membrane

(B) Depolarized Membrane

Nonconductive Medium = ~3 nm
Insulating Membrane

Note: The figure shows (A) a voltage-gated ion channel that controls intra- and extracellular ion flux due to a positive surface charge, prior to application of EMF; and (B) a voltage-gated ion channel that can attenuate the opening and closing of the ion channels, after application of EF or EMF, to trigger intracellular events due to a negative charge (-Q) that depolarizes the plasma membrane.

Abbreviations: electromagnetic field (EMF); EF, electric field.

One common theme in those studies is the biomechanics of Ca\(^{2+}\) and its ability to alter the cell membrane to play a significant role in the effects that EMF has on inflammatory pain mechanisms.\(^{56}\) For an effect to occur in ligand-gated ion channels, the interacting system must contain a Ca\(^{2+}\)-molecular structure.\(^{57}\) For the EMF activation of the opioid receptors against inflammation of peripheral tissue, for the increased functionality of opioid receptors on peripheral sensory neurons, and for the local production of endogenous opioid peptides that have been observed in lymphocytes, Ca\(^{2+}\) appears to be the principal cellular component affected by the EMF exposure.\(^{58}\) And the Ca\(^{2+}\)/calmodulin (CaM)-dependent signaling to intracellular enzyme systems appears to act specifically as a primary transduction mechanism for EMF treatment. As for cytokines and chemokines, the NO activation of voltage-sensitive Ca\(^{2+}\) channels responds to EMF exposure through Ca\(^{2+}\)/CaM stimulation of NO synthesis. Beneficial responses may be largely a result of the stimulation of the NO-cGMP-protein-kinase-G pathway.\(^{59}\)

It has been reported that opiates induce analgesia by diminishing the cellular-Ca\(^{2+}\) flux,\(^{60,61}\) and EMF has the capability to reduce that flux to induce the same effect.\(^{42,64}\) It has also been documented that Ca\(^{2+}\) channel blockers can potentiate the effects of opiates by diminishing the inward Ca\(^{2+}\) flux, and that action has been reported to occur in snails and mice exposed to EMF.\(^{63,64}\) The Ca\(^{2+}\) channel agonists have been investigated, with the researchers observing the attenuating effects of opiates through enhancement of the inward Ca\(^{2+}\) flux and potentiation of the effects of EMF.\(^{58,65,66}\)

The mechanisms through which the EMF exchanges information between cells and the ways in which the conversion of that biomechanical signaling is translated have been researched for decades. It has been reported that EMF can permeate both the plasma and nuclear membranes of cells, thereby affecting different types of tissues.\(^{67-69}\) The concept that the extended membrane regions may be sensitive to EMF was first proposed by Adey in 1974.\(^{70}\) Liboff has suggested that the transport of calcium ions through channels of the cell membrane involves a resonance-type response to the applied EMF, which is the mechanism that activates ion flux, receptors, kinases, and even transcription factors.\(^{71}\)

Ursu et al\(^{72}\) found a strong correlation between the kinetics of calcium flux and transient receptor potential vanilloid 1 (TRPV1), the ligand-gated ion channel expressed predominantly in nociceptive primary afferents that plays a key role in pain processing. In that study, current-clamp recordings were performed in the neurons of rats’ dorsal root ganglia (DRG) to assess the consequences of TRPV1 activation on neuronal excitability. The researchers reported that the Ca\(^{2+}\) ion flux and the TRPV1 influenced the trigger-of-action potentials in sensory neurons. Due to that phenomenon, the electrical-potential gradient that exists across the cells exposed to the EMF can increase the activation of voltage-gated, Ca\(^{2+}\) ion channels on either side of the cell membrane, giving rise to a gradient of intracellular Ca\(^{2+}\) that alters cell morphology. That effect modulates the changes by intracellular actin filaments in levels of cytosolic calcium\(^{73}\) and also produces a significant decrease in the production of cyclic adenosine triphosphate (ATP), which is a known master regulator of the functioning of innate immune cells and of the generation of inflammatory mediators.\(^{74,75}\)

EFFECTS OF EMF

Effects on Ion-ligand Binding

Another focus of EMF biomechanics involves the ligand-gated ion channels, which are a group of transmembrane, ion-channel proteins that open to allow ions such a Ca\(^{2+}\), Na\(^{+}\), Cl\(^{-}\), and K\(^{+}\) to pass through the cell membrane in
response to the binding of an electrical or chemical messenger.76-80 Ion fluxes such as those moving through voltage-gated sodium and calcium channels are widely used to treat inflammatory pain. In particular, voltage-gated calcium channels (VGCCs) are the main source of depolarization-induced calcium entry into neurons.81

Primary afferent neurons express multiple types of VGCCs, with specific, subcellular, expression patterns and functions. Those channels are clinically validated drug targets for pain, and their roles in pain transmission have been extensively reviewed.82 On peripheral nociceptors, they are critical for nociceptive transmission beyond the peripheral transducers and are responsive to exogenous stimuli, such as waveform patterns emitted by EMFs.83

Although ion channels have a pervasive distribution, recent studies have identified a number of channels, in particular those of sodium and calcium, that appear to have a more selective role in nociception.84 Many cationic channels are responsible for the excitation of sensory neurons, and the activation of those channels in sensory neurons is critical to the generation of nociceptive signals. The main channels responsible for inward membrane currents in nociceptors are voltage-activated sodium and calcium channels, whereas outward current is carried mainly by potassium ions.85 In addition, the activation of nonselective cation channels is also responsible for the excitation of sensory neurons. Thus, the excitability of neurons can be controlled by regulating the expression of or by modulating the activity of those channels.

It is well known that large numbers of free ions, such as Ca^{2+}, Na^{+}, and K^{+}, reside on both sides of every cell membrane and play an important role in signal transduction. Ion fluxes through cell membranes are elucidated by the ion concentration and voltage gradients between the 2 sides of the membrane. Those ion fluxes affect primary afferent nociceptors that are the initial part of the pain pathway86,87 and the accumulation of ions creates an intense electric field on either side.18

Radhakrishnan and Sluka88 investigated cutaneous vs knee-joint afferents and the antihyperalgesia that was produced by TENS. The research showed differentially blocked, primary afferents on use of local anesthetics. In the study, hyperalgesia was induced by kaolin-carrageenan and assessed by measuring a rat’s paw-withdrawal latency to heat. Both HF and LF TENS were applied. Control experiments were conducted using vehicles. Both frequencies completely reversed hyperalgesia, and an injection of lidocaine into the knee joint prevented the antihyperalgesia that would have been produced by the HF or LF TENS. Application of an anesthetic cream was shown to reduce the amplitude of the cord-dorsum potential by 40% to 70% for both HF and LF TENS, confirming the loss of large-diameter, primary-afferent input. Therefore, the activation of joint afferents, but not cutaneous afferents, prevented the antihyperalgesia effects of the TENS. The researchers concluded that large-diameter primary-afferent fibers from deep tissue are required and that activation of cutaneous afferents is not sufficient for TENS-induced antihyperalgesia.

Effects on G-protein Coupled Receptors

EMF has also been reported to affect inflammatory pain by modulating GPCRs, which are 7-transmembrane domain receptors that sense molecules outside the cell and activate inside signal-transduction pathways.89 When the molecules bind to a GPCR, that action is followed by a series of conformational changes in the activated receptors, which are capable of signaling to downstream molecules. When it comes to the peripheral-pain pathway, inflammatory cells, such as polymorphonuclear leukocytes (PMN), monocytes, and macrophages, express a large number of GPCRs for chemoattractants and chemokines.90 GPCRs are critical to the migration of those phagocytes and their accumulation at sites of inflammation, where they not only can exacerbate inflammation but also can contribute to its resolution.

It has been hypothesized that the activation of GPCRs is affected by voltage,91,92 due to reports that nonactivated GPCRs do not appear to show any voltage-dependent activity.93 That effect is in line with the hypothesis that the binding of a charged agonist within an EMF that is present on a cell membrane, is a major mechanism for the voltage dependence of GPCR activation, indicating a definite voltage-dependent activation of GPCRs at the receptor level. The existence of voltage gradients on the cell surface and the ways in which the gradients respond to EMF is of great importance to inflammatory pain mechanisms.

Because endogenous EFs are generated by polarized ion transport and conductive extracellular pathways, polarized ion transport, which leads to the movement of a charge, can create electrical-potential differences across immune cells.93 In that process, the ion transport is dependent on the amount of energy per unit of charge that is needed to move the ion across the membrane. That amount is a measure of voltage potential. Voltage potentials, such as those measured on lymphocyte membranes, can reach +50 mV,94 due to the net positive charge coming out of the cell by ions such as Na^{+}, K^{+}, and Ca^{2+}.

The idea that the immune system can communicate with peripheral sensory neurons to modulate pain is based mainly on reported interactions between opioid receptors and their environments.95-97 One of the main aspects of inflammatory pain pathways is the presence of opioid receptors that are expressed on peripheral sensory nerve endings, cutaneous cells, and immune cells, such as granulocytes, monocytes, macrophages, and lymphocytes. During an inflammatory response, those cells can produce the opioid peptides of 3 different receptors (ie, µ, δ, and κ), which on activation, can cause the dissociation of the GPCR subunits that inhibit cyclic adenosine monophosphate (cAMP) production and/or can interact with a membrane’s ion channels.98,99

Inflammation of peripheral tissue leads to the increased functionality of opioid receptors on peripheral sensory neurons and to local production of endogenous opioid peptides. Opioid receptors are widely expressed in the central and peripheral nervous systems as well as in numerous nonneuronal tissues. Both animal models and human clinical data support the involvement of peripheral opioid receptors.
in analgesia, particularly in inflammation, where both the opioid-receptor expression and efficacy are increased.\textsuperscript{100} EMF has been reported to reduce hyperalgesia and pain through the release of endogenous opioids into the central nervous system (CNS)\textsuperscript{101-106}; specifically, LF EMF at <10 Hz can activate mu-opioid receptors, and HF at >50 Hz can activate delta-opioid receptors in the spinal and rostral ventral medulla (RVM).\textsuperscript{107}

Different frequencies used under the same conditions affect different opioid receptors. Experimental evidence has shown that using the same time exposure and field strength of EMF at ELF's <100 Hz, such as 4 Hz, will cause a spinal blockade of mu-opioid receptors, preventing hyperalgesia, while the same parameters used for EMF exposure at 100 Hz will prevent hyperalgesia in delta-opioid receptors but not in mu-opioid receptors.\textsuperscript{106,108} That frequency-dependent effect has been reported at 60 Hz and 141 µT, with a 15-minute exposure, in both mice\textsuperscript{109} and land snails.\textsuperscript{110} A 2-hour exposure of EMF at 1 Hz and a 20- to 27-µT field strength decreased the mu-opioid receptors concentration in the brain of pigeons,\textsuperscript{111} with similar outcomes at 50 Hz and 100 µT for 8 hours in rats.\textsuperscript{112}

Studies have shown that exposure to a LF TENS device produces endogenous opioids in both humans\textsuperscript{113} and rats.\textsuperscript{114} According to the investigators in those studies, the activation of both the mu-opioid receptors and delta-opioid receptors induced a reduction of hyperalgesia and pain. It is important to note that animal studies tend to rely on reflex-based pain assessments, which are increasingly recognized as being a poor model of the pain experienced in humans compared to operant assays.\textsuperscript{115} That statement is especially true in studies pertaining to the effects of EMF on pain sensation in land snails.

### Effects on Cytokines and Chemokines

Cytokines and chemokines are the mediators of inflammation from within minutes to hours after injury during the activation of inflammatory pain. They serve as signals to engulf damaged tissue, destroy infectious agents, and clear the wound bed for healing.\textsuperscript{116} Damaged cells respond by activating stress-signaling pathways which produce trauma-associated molecular patterns that activate cue and chemotactic factors for other immune cells in the area.\textsuperscript{117,118} The mechanistic effects of EMF on protein molecules focus on the effects of gradients dependent on ion flux on cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6), and chemokines, such as interleukin 8 (IL-8) and regulated on activation, normal T-cell expressed and secreted (RANTES).

In vitro studies have demonstrated the effects of EMF on NF-κB, a downstream signal-transduction molecule,\textsuperscript{119} whereby researchers have reported that results can depend on frequency, indicating that 8-µL/mL concentrations of lipopolysaccharide (LPS)-challenged macrophages exposed to EMF with a Helmholtz coil emitted at a range of frequencies between 0 and 30 Hz. Those results showed a significant downregulation of both TNF-α and NF-κB at 5 Hz but not at 10, 15, 25, or 30 Hz.\textsuperscript{120}

A selective inhibition of NF-κB by ELF EMF may also be involved in the decrease of chemokine production as reported by Vianale et al.,\textsuperscript{121} where the ELF-EMF exposure modulated NF-κB activation as well as the proinflammatory cytokines TNF-α and interleukin 1 beta (IL-1β), growth factors, and viruses known to cause infections.

In OA fibroblasts in the presence of EMF under 24-hour exposure at 75 Hz and 1.5 mT, other investigators have reported that adenosine receptors downregulated the proinflammatory cytokine IL-6 and the chemokine IL-8 while stimulating the release of interleukin 10 (IL-10), an anti-inflammatory cytokine.\textsuperscript{122} At 50 Hz and 2.5 mT, EMF exposure was reported to increase IL-1β in mouse macrophages that had been activated with LPS after 24 hours but to decrease IL-1β in human fibroblasts when using the same parameters. Under those same conditions, EMF decreased IL-6 in LPS-activated human fibroblasts, and TNF-α decreased when the researchers used the same 50 Hz with a 2.5 mT field on human fibroblasts activated with LPS.

Other in vitro studies have shown that human keratinocytes decrease IL-8 at an exposure to an EMF of 50 Hz and 1 mT for 4 hours, although they also have been shown to decrease RANTES in the same cell line under the same conditions.\textsuperscript{123} Mouse macrophages stimulated with LPS and exposed to a time-varying EMF at 30 Hz and 400 Gauss, were also reported to downregulate IL-6 and TNF-α after a 1-hour exposure.\textsuperscript{124} A range of EMF frequencies between 0 and 100 Hz appear to affect various proteins in inflammatory processes when studied in vitro.

In vivo studies have reported that a 27.12-MHz radio frequency emitted from a solenoid device, with 3-ms bursts repeating at 2 Hz, can suppress significantly the proinflammatory cytokine IL-1β, an early responder to injury in rats with traumatic brain injury.\textsuperscript{125} That same frequency has also been reported to cause a significant reduction in IL-1β cytokines in wound exudate of human patients who had been exposed to EMF for 20-minute treatments every 4 hours for the first 3 days postoperatively and then every 8 hours for the next 3 days.\textsuperscript{60,61} EMF modulation of both cytokines and chemokines may contribute to an increase in the NO that is involved in the regulation of inflammatory pain modulators, such as CaM, which in turn leads to the activation of endothelial NO synthase (eNOS), increasing NO, and, thereby, modulating cytokine expression through adenosine receptors and an early decrease in the activity of NF-κB.

### Effects on Enzymes

COX enzymes control the initial steps of the inflammation process.\textsuperscript{126} Among the proteins mediating that effect are dynorphin, an endogenous opioid that increases neuronal excitability, and COX-2, the enzyme that produces prostaglandin E\textsubscript{2} (PGE\textsubscript{2}). PGE\textsubscript{2} is a known lipid mediator that contributes to inflammatory pain.\textsuperscript{127} PGE\textsubscript{2} increases the phosphorylation of NO production through the activation of cAMP-dependent protein kinase A (PKA).
In vitro studies have shown that adenosine receptors modulate PGE2 in OA fibroblasts after 24 hours of exposure to EMF at 75 Hz and 1.5 mT.\textsuperscript{122} EMF at 15 Hz and 0.6 mT for 72 hours has also been shown to affect that same analgesic process by acting on PGE2 and PKA, initiating the release of NO from osteoblasts and, thereby, increasing NO synthesis.\textsuperscript{128} NO appears early in biochemical cascades that are involved in the inflammatory phase of tissue repair and has been reported to be involved in the mechanism by which EMF devices achieve pain relief.\textsuperscript{129}

At 15 Hz and 0.6 mT, no significant differences have been reported between unstimulated human monocytes that either had been exposed or had not been exposed to EMF; however, inducible NO synthase (iNOS) activity was significantly reduced in LPS-stimulated human monocytes that had been exposed to EMF at 15 Hz when compared to LPS-stimulated cells that had not been exposed. That reduced enzyme activity has been reported to be related to the reduction of iNOS mRNA and immunoreactive iNOS proteins that has been observed in rats induced with experimental myopathy.\textsuperscript{33}

Evidence linking EMF exposure to protein kinase C (PKC) activity and analgesia provides an example of calcium-activated, phospholipid-dependent PKC that plays an important role in relaying transmembrane signaling inside diverse, calcium-dependent, cellular processes during an inflammatory pain response.\textsuperscript{130-132} Although the activation of endorphins is a recurring theme in the process, compelling evidence has indicated that EMFs can modulate opioid gene expression.

Ventura et al\textsuperscript{133} found that the expression of opioid genes was significantly increased following the exposure of myocardial PKC inhibitors that suppressed the transcriptional effects of cells exposed to an EMF at 50 Hz and 1.74 mT. The researchers found that EMF-enhanced, myocardial, opioid gene expression and a direct exposure of isolated myocyte nuclei to EMF markedly enhanced prodynorphin gene transcription in the intact cell. That EMF action was mediated by nuclear PKC activation but occurred independently from changes in PKC-isozyme expression and enzyme translocation, suggesting the involvement of a nuclear endorphinergic system in the regulation of gene transcription.

**DISCUSSION**

EMF, when used to affect inflammatory pain, has been shown to produce noninvasive outcomes while involving the application of different frequencies, field strengths (intensities), and time points that can affect nociception and analgesia.\textsuperscript{134,135} Several parameters, including the doses, frequencies, and phases of EMF devices are decisive as to whether or not the cells respond, and if they do respond, in what manner. For use of a TENS device, an application at 4 Hz and 10 to 18 mA for 20 minutes appears to activate the mu-opioid receptor best, whereas an application at 100 Hz and 10 to 18 mA for 20 minutes appears to activate the delta-opioid receptors. Thermal analgesic effects have been reported for applications at 20 Hz and 0.03 µT for 30 minutes in rats; however, a debate still exists as to whether the analgesic effect was stress induced.

Because various parameters of frequency, intensity, and time of exposure are used for humans, animals, and cells, the consistency of outcomes is difficult to ascertain. For example, in a human keratinocyte model, Patruno et al have reported a healing effect that is related to the effects on enzymes of an EMF using an ELF of <100 Hz,\textsuperscript{136} and McKay et al have reported that the EMF waveform is what generates the effects. On the other hand, Kalra et al and Fleming et al have suggested that the effects occur in the opioid receptors when using a 4 Hz or a 1 µT field, respectively.\textsuperscript{43,137} What Fleming does not explain is how an EMF would affect the receptor. Table 1 identifies the different EMF frequencies, field strengths, and exposure times and how the proposed mechanisms along the peripheral inflammatory pain pathways are affected.

As shown in Table 1, the parameters of time and frequency can remain constant, but a change in field strength will elicit a different outcome. Martin et al has reported that the thermal analgesic effects were amplitude-(intensity-) dependent in producing analgesia more quickly in male rats.\textsuperscript{135} In that study, solenoids were used to emit an EMF, with burst-firing configurations at once every 4 seconds for 30 minutes. Using a maximum strength of exposure at 0.25 µT, the researchers reported an analgesic response that was significantly greater than the normal sham-field responses, whereas the exposure at 0.30 µT did not produce responses that differed significantly from the sham; the standard error of the mean (SEM) for sham exposure was 2.2 and for EMF exposure was 0.4.\textsuperscript{135}

Fleming et al\textsuperscript{138} reported that the whole-body exposure of rats to a burst-firing EMF with intensities of 1 µT once every 4 seconds for 20 minutes, displayed the minimum intensity of stimulation needed to trigger the signal from the axon to the spinal cord. When the electric current was delivered to the rats’ footpads, its analgesic effect was still apparent at 20 minutes after the removal of EMF and was equivalent to the analgesia produced by 4 mg/kg of morphine.

Kalra et al\textsuperscript{106} reported that hyperalgesia and pain were attenuated in rats using 100 ms of exposure with a 10- to 18-mA field strength for 20 minutes; at 4 Hz, the outcome was due to the activation of the mu-opioid receptor, and at 100 Hz, the EMF activated the delta-opioid receptor.

The time of exposure appears to make a difference in the outcome, as shown by Kavaliers et al,\textsuperscript{63} who reported for snails that an application of EMF at 60 Hz and 100 µT altered the Ca\textsuperscript{2+} flux, and the channels associated with opioid receptors were dependent on the time of exposure. A significant reduction in the analgesic effects of mu- and kappa-opioid agonists occurred at 2 hours and 12 hours, but at 48 to 120 hours showed no more effects than the 12-hour application, and the 0.5-hour exposure had similar outcome to that of the controls.
EMF frequencies were able to limit OA progression, but the sham 75 Hz, EMF counteracted cartilage thinning, as demonstrated the histological score and the FI than did EMF at 37 Hz. At EMF at 75 Hz produced significantly more beneficial effects on spacing), which basic bone research has shown are key measures increases; and (3) the trabecular numbers. The EMF also (3) the subchondral bone thickness, which reflects the fact that cartilage pathology both frequencies the EMF significantly reduced (1) the histomorphometric analyses of the guinea pigs stimulation w.

Some evidence has shown that PEMF can counteract degradation and inflammation is currently the most important course.

In conditions such as OA, controlling chondrocyte degradation and inflammation is currently the most important target. Some evidence has shown that PEMF can counteract late-stage OA progression at 2 different frequencies, 37 Hz and 75 Hz, in 21-month-old guinea pigs. After 3 months of stimulation with EMF for 6 hours per day, both histological and histomorphometric analyses of the guinea pigs’ knees were performed. In comparison to the nontreated sham group, at both frequencies the EMF significantly reduced (1) the histological cartilage score, which measures the severity of cartilage pathology, (2) the Fibrillation index (FI), which measures the pathological characteristic of fibrillation in OA; (3) the subchondral bone thickness, which reflects the fact that the damage in the cartilage matrix increases as the load duration increases; and (3) the trabecular numbers. The EMF also increased the trabecular thickness and separation (trabecular spacing), which basic bone research has shown are key measures characterizing the 3-dimensional structure of cancellous bone. EMF at 75 Hz produced significantly more beneficial effects on the histological score and the FI than did EMF at 37 Hz. At 75 Hz, EMF counteracted cartilage thinning, as demonstrated by significantly higher cartilage thickness values than either the sham or the group treated at 37 Hz. In cases of severe OA, both EMF frequencies were able to limit OA progression, but the 75-Hz stimulation achieved better results.

During clinical trials, certain frequencies and field strengths have produced different outcomes depending on the condition. In a randomized, double-blind, sham-controlled clinical trial, a total of 50 patients with either chronic generalized pain from FM or chronic localized musculoskeletal or inflammatory pain were exposed to extremely weak pulses of EMF at 400 µT and 1000 Hz or less for 800 mT per second, using a portable solenoid device that fitted to patients’ heads during the twice-daily, 40-minute treatments for 7 days. The outcomes were recorded using a visual analog scale. A differential effect of EMF over sham treatment was noted in patients with FM that approached statistical significance at P = .06 for n = 17 but was not evident in those treated who did not have FM (ie, had musculoskeletal or inflammatory pain), P = .93 for n = 15.

In a double-blind, placebo-controlled clinical trial, 22 patients were assigned to treatment (n = 28) or sham (n = 26) groups to test the analgesic and antinociceptive effects of low-intensity (ie, 8 Hz) EMF on FM patients. Pressure pain thresholds before and after treatment were determined using an algometer during the 8 consecutive, weekly sessions. Also, blood serotonin levels were measured and patients completed questionnaires to monitor symptoms. Repeated-measures analysis of variance (ANOVA) indicated a statistically significant improvement in the treatment group compared with the controls with respect to somatosensory pain thresholds, ability to perform daily activities, perceived chronic pain, and sleep quality. Although improvement in pain thresholds was apparent after the first session, improvement in the other 3 measures occurred after week 6.

### Table 1. Conditions, Treatment Parameters, Mechanisms of Action, and Results

<table>
<thead>
<tr>
<th>Inflammatory Pain Condition</th>
<th>Hz</th>
<th>Field Strengths</th>
<th>Time Courses</th>
<th>Molecular Mechanisms</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflamed knee-joint pain²⁴</td>
<td>4</td>
<td>100 ms 10-18 mA</td>
<td>20 min</td>
<td>Activation of mu-opioid receptor was frequency-dependent.</td>
<td>The treatment produced antihyperalgesia by activation of mu-opioid receptors in the rostral ventral medulla of rats.</td>
</tr>
<tr>
<td>Inflamed knee-joint pain²⁴</td>
<td>100</td>
<td>100 ms 10-18 mA</td>
<td>20 min</td>
<td>Activation of delta-opioid receptor was frequency dependent.</td>
<td>The treatment produced antihyperalgesia by activation of delta-opioid receptors in the rostral ventral medulla of rats.</td>
</tr>
<tr>
<td>Thermal analgesic effects⁷³</td>
<td>20</td>
<td>0.03, 0.3, 3 µT</td>
<td>30 min</td>
<td>Analgesic effects were EMF intensity dependent.</td>
<td>The 0.03-µT field strength exhibited an analgesic response (rat-paw reflex) that was significantly greater than that of the sham treatment.</td>
</tr>
<tr>
<td>Effect on endogenous opioid systems in burns⁵⁶</td>
<td>60</td>
<td>100 µT</td>
<td>30 min, 2 h, 12 h, 48 h, 120 h</td>
<td>Alterations in the Ca²⁺ flux and channels associated with opioid receptors were time-dependent.</td>
<td>The treatment produced a significantly attenuated, morphine-induced analgesia and reduced basal nociceptive responses in snails via the reduced analgesic effects of the mu- and kappa-opiate agonists. The 0.5-h time course showed no significant effects. The 2-h and 12-h time courses showed significant effects. The 48-h and 120-h time courses showed effects that were more significant than the 12-h course.</td>
</tr>
<tr>
<td>Effect on endogenous opioid systems in burns¹³⁰</td>
<td>60</td>
<td>100 µT</td>
<td>30 min, 1 h, 2 h</td>
<td>Alterations in the Ca²⁺ flux and channels associated with opioid receptors were time-dependent.</td>
<td>The 2-h time course had greater inhibitory effect than the 0.5-h course, with the 1-h course having an intermediate effect in land snails for aversive thermal (nociceptive) responses and morphine-induced analgesia.</td>
</tr>
</tbody>
</table>

Abbreviation: EMF, electromagnetic field.

Patruno et al¹³⁰ reported that EMF at a 50-Hz frequency and a 1-mT field strength, with overnight exposure, enhanced the re-epithelialization of keratinocytes by decreasing the COX-2 expression and the downstream, intermediate PGE₂ in vitro. In conditions such as OA, controlling chondrocyte degradation and inflammation is currently the most important target. Some evidence has shown that PEMF can counteract late-stage OA progression at 2 different frequencies, 37 Hz and 75 Hz, in 21-month-old guinea pigs. After 3 months of stimulation with EMF for 6 hours per day, both histological and histomorphometric analyses of the guinea pigs’ knees were performed. In comparison to the nontreated sham group, at both frequencies the EMF significantly reduced (1) the histological cartilage score, which measures the severity of cartilage pathology, (2) the Fibrillation index (FI), which measures the pathological characteristic of fibrillation in OA; (3) the subchondral bone thickness, which reflects the fact that the damage in the cartilage matrix increases as the load duration increases; and (3) the trabecular numbers. The EMF also increased the trabecular thickness and separation (trabecular spacing), which basic bone research has shown are key measures characterizing the 3-dimensional structure of cancellous bone. EMF at 75 Hz produced significantly more beneficial effects on the histological score and the FI than did EMF at 37 Hz. At 75 Hz, EMF counteracted cartilage thinning, as demonstrated by significantly higher cartilage thickness values than either the sham or the group treated at 37 Hz. In cases of severe OA, both EMF frequencies were able to limit OA progression, but 75-Hz stimulation achieved better results.
of treatment. No significant differences were reported in depression, fatigue, severity of headaches, or serotonin levels, and no adverse side effects were reported. EMF is usually more effective at less than 3 mT, with frequencies lower than 100 Hz.

Various research studies have given different outcomes, either beneficial or with no effects, due to a lack of standardization in the dosing parameters. Although most therapeutic dosages are <100 Hz and in the micro- and milli-Tesla and Ampere ranges, times of exposure have varied greatly. If the mechanism of action does indeed occur at the plasma membrane, and as is suggested by many investigators, if it is driven by ion flux, then hours of exposure would not be necessary to obtain results. Ion diffusion and transport occur in seconds to minutes; therefore, fewer sessions of shorter periods would prove to be far more beneficial than 1 or 2 sessions of long duration.

Of high importance is the lack of standardized nomenclature and experimental protocols when it comes to running trials. Like pharmaceuticals, where dosages vary from patient to patient, EMF treatments also are dose and tissue dependent. It has been suggested that the following dosing parameters should be required for all practitioners using EMF therapies: (1) the type of tissue that the EMF is targeting; (2) the specific site of EMF application; (3) the distance between the EMF field and tissue; (4) the frequency of the EMF field; (5) the EMF field strength; (6) the exact composition of the EMF device; and (7) the exact time of exposure. Otherwise, it is difficult to compare results.

CONCLUSION

When it comes to modulating inflammatory pain mechanisms, numerous experimental findings have reported that EMF affects cell function through mechanical action on both the intracellular and plasma membrane levels, which includes ion channels, receptors, cytokines, and enzymes. Various EMF dosing parameters—frequency, intensity and duration of exposure—all contribute to different outcomes; however, frequencies of less than 100 Hz and intensities in the mT or mA range are reported to be most effective in the downregulation of peripheral inflammatory pain modulators.

From a clinical standpoint, the tDCS device appears to be the most beneficial for migraine headache, using dosing parameters of 100 Hz or less and intensities of 1 mA or less for twelve 90-minute sessions. For postprocedural abdominal pain in patients after endoscopy, treatment with a tDCS device set at 0.2 mA for 20 minutes is reported to be most beneficial. In conditions such as OA, controlling chondrocyte degradation and inflammation is optimized at 75 Hz and a 1.5-mT field strength, with treatment for 15 minutes twice daily for up to 42 days. The same parameters have been shown to be beneficial after arthroplasty. For FM, treatment at 8 Hz and 1 mA is reported to be beneficial if applied for 40 minutes twice daily for 7 days.

Although a multitude of research articles investigating the effects of EMF on inflammatory pain mechanisms exist, the methods for gathering the data have included an overwhelming array of experimental models, EMF devices, waveforms, and clinical applications. Therefore, a consensus of standardized methods for experimentation is greatly needed to determine which responses directly result from the EMF exposure. Because various parameters of treatment produce similar results, a report cross-referencing the frequencies, field strengths, and times of exposure of EMF treatments on inflammatory responses would be beneficial to both researchers and clinicians working in the field.

REFERENCES


