

ORIGINAL PAPERS

## The Biologic Effects and the Therapeutic Mechanism of Action of Electric and Electromagnetic Field Stimulation on Bone and Cartilage: New Findings and a Review of Earlier Work

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### ABSTRACT

**Background:** Muscle, ligament, bone, cartilage, blood, and adult stem-cell production all respond to electric and electromagnetic fields, and these biophysical field agents can be applied in therapeutic contexts. Postulated mechanisms at the cellular, subcellular, and molecular level are discussed. Electric and electromagnetic field stimulation enhance the repair of bone through the mediation of three areas at the cellular level: (1) the complex interplay of the physical environment; (2) growth factors; and (3) the signal transduction cascade. Studies of electric and electromagnetic fields suggest that an intermediary mechanism of action may be an increase in morphogenetic bone proteins, transforming growth factor- $\beta$ , and the insulin-like growth factor II, which results in an increase of the extracellular matrix of cartilage and bone. Investigations have begun to clarify how cells respond to biophysical stimuli by means of transmembrane signaling and gene expression for structural and signaling proteins.

**Methods:** Review of meta-analysis trials of electrical stimulation of all types.

**Conclusions:** Further research in the form of methodologically sound, randomized, controlled studies are needed. *Inter alia*, resolutions are needed for the significant disparities between clinical targets, types of electrical stimulation, and clinical outcomes.

### INTRODUCTION AND BACKGROUND

The use of electric and magnetic forces to treat disease has fascinated the general public and scientists alike since antiquity. Interest in these treatment modalities, both scientific and public, persists today; and, in an era of expanding research in bioelectromagnetics, perhaps it is time the paradigm was reexamined. It has been known for many years that endogenous electrical potentials and currents are generated in wounded tissues and terminate when healing is complete.<sup>1–4</sup>

Despite a growing understanding of the intricate bio-

electrical properties of many tissues, few have researched whether these properties can be manipulated to enhance the healing process. Widespread acceptance and use of this treatment has not followed, probably because of the dearth of objective data. In an exhaustive meta-analysis of the impact of electrical field stimulation on health, Akai and Hayashi<sup>5</sup> concluded that, although definitive judgment was difficult, it was still more difficult to ignore the statistically significant supportive data from the few investigators who have published in this field—mainly scientists who have not been restricted by considerations that weigh against publication before commercialization.

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## CURRENT ELECTROMEDICINE RESEARCH

Existing research strongly points to evidence that the biological effectiveness of electric and electromagnetic field devices depends on their ability to excite transmembrane receptors of cells to act as sites of amplification. This is because the induced electric fields of these devices are considerably weaker than the levels required to depolarize cell membranes.<sup>6–10</sup>

In addition, at the cellular level, electrical stimulation has been shown in experiments to have an effect on three areas: (1) the complex interplay of the physical environment; (2) growth factors; and (3) the signal transduction cascade. With regard to the physical environment, early research by Brighton<sup>11</sup> suggested that PO<sub>2</sub> is lowered and pH is elevated at the level of the cathode, thereby assisting in the formation of bone.

Correlation studies are not straightforward because of the apparent coexistence and inseparable interplay of pulsed electric and magnetic fields, now simply called PEMF energy. This interplay requires attention because Coulomb\* and Gauss† fields can produce different biologic effects.‡ The rate of change of each field is also known to couple and therefore enable electromagnetic field (EMF) effects. For example, the extremely low frequency or static Gauss field cannot produce the displacement current clinically reported (with an extremely low frequency or static Coulomb field). However, the static Gauss field produced by a permanent magnet can be made to induce low-frequency EMF effects via the addition of mechanical vibration. Goodman and Shirley-Henderson were perhaps the first to recognize and report this frequency dependent PEMF synergy, with their *in vitro* study of the transcription and translation of cells exposed to an extremely low frequency PEMF field.<sup>12</sup> Here, the frequency-dependent Gauss rate of change was simply too weak to drive a useful current through high tissue impedance. Rather than vibrate a magnet to induce its frequency-dependent Coulomb field, their apparatus utilized electrode capacity and a variable voltage to induce the required negative (current of injury) electronic displacement current.<sup>§</sup>

In this review, the authors have reported evidence from numerous clinical investigations of accelerated bone and cartilage repair using capacity coupled electrophoresis,<sup>¶</sup> uti-

lizing pulsed Coulombic (PC), pulsed Gaussian (PG) and pulsed electromagnetic fields (PEMF). They have also examined studies of signal transduction at the membrane level and on the stimulation of growth factor synthesis, which may be an intermediary mechanism of action, and possibly a mechanism of amplification, of the PC, PG, and PEMF fields.

## CLINICAL EFFECTS ON CARTILAGE AND BONE

Many hypotheses and postulates have been developed in an attempt to explain the therapeutic or biological effects of electric and magnetic fields on musculoskeletal tissues, particularly those of cartilage and bone.

In 1982, Fukada hypothesized that the growth of bone is regulated to best resist external force, and the controlling signal seems to be the electric potential generated by shear piezoelectricity in collagen fibers and/or steaming potential in canaliculae.<sup>13</sup> He also demonstrated that application of a small direct current or of piezoelectric polymer film stimulates bone formation and that PEMF energy enhances the proliferation of cell culture. More recently, it has been demonstrated that polarized hydroxyapatite ceramics increase bone formation *in vivo* in the early phase of healing and regeneration relative to controls. In 1950, Yasuda<sup>14</sup> conducted experiments to explain the piezoelectric effect in bone. He reported that when bone was under compression, an electronegative potential was induced. Conversely, an electropositive potential was produced by bone under tension.

There exist various techniques through which electrical current may be administered to assist bone healing. The two most popular techniques employed in the orthopedic community have been (1) direct current contact and (2) capacitive coupling. In the first case, current is delivered to the bone through insulated electrodes, which are placed on the skin so current may be induced in bone tissue with pulsed electric fields. Direct current electrodes can be either implanted or applied percutaneously.<sup>15</sup> Implantable devices have the advantages of providing constant stimulation of bone directly at the desired body site, with increased patient compliance, so that optimization of the position of the electrodes is possible over time. Disadvantages include the risk of an infection, the potential for a painful implant, which might necessitate early removal, and in the case of a high-risk patient, the usual stress of any operative procedure.

Electrical field stimulation has been applied with dramatic beneficial effect in the treatment of nonunions in bone. Numerous authors have reported remarkable success in treating these chronic conditions,<sup>16–19</sup> stress fractures,<sup>20</sup> osteotomies,<sup>21–22</sup> spinal fusions,<sup>23–25</sup> and acquired and congenital pseudoarthroses<sup>26</sup> with various forms of electrical stimulation. Unfortunately, the heterogeneity of trial design,

\*Coulomb, Charles A. (1736–1806). In 1777, Coulomb identified the inverse-square force of electronic charge.

†Gauss, Karl F. (1777–1855). In 1839, Gauss published his general treatment of inverse-square magnetic force.

‡A static Gauss field can induce electron-spin precession in living tissue, a more complex effect than the induced electron displacement in living tissue produced by a static Coulomb field—an important area to explore, but beyond the scope of this paper.

§A static Coulomb field can induce electron displacement-current in living tissue.

¶Electrophoresis is the movement of an electrically charged substance under the influence of an electric field. See [wikipedia.org/wiki/electrophoresis](http://wikipedia.org/wiki/electrophoresis).

dosage, and method of delivery throughout this group has failed to lead to the establishment of electrical field stimulation as an everyday treatment modality. Notwithstanding these shortcomings, a consistent finding among the studies is the osteogenic impact of electrical stimulation on the early phase of bone healing. Schubert et al. postulated that this early effect is caused by the restitution of normal, or near normal, piezoelectric properties by the exogenous electric field, which otherwise is lost after fracture and interruption of the Haversian canalicular network.<sup>27</sup> The normal 2-week lag seen in unstimulated bone healing is obviated and healing begins at an accelerated rate. This theory of enhanced reorganization is borne out by observations of improved callus realignment in bone and collagen orientation in skin.<sup>28</sup> Electrical field stimulation is also beneficial in tendon and ligament repair. It has been demonstrated to reduce adhesion formation, increase hydroxyproline content, and beneficially affect breaking strength by altering collagen types.<sup>29</sup> It is likely that these effects are the result of the pronounced modulation of fibroblast function induced by electrical fields.

With respect to growth factors, preclinical studies have shown that PEMF energy stimulation increases the expression of bone morphogenetic proteins (BMP) 2 and 4, transforming growth factor- $\beta$ , and an insulin-like growth factor II.<sup>30-34</sup> Bodamyali reported that PEMF energy simultaneously induced osteogenesis and unregulated transcription of BMP 2 and 4 in osteoblasts of rats.<sup>35</sup> Aaron et al.,<sup>36</sup> using Coulomb and Gauss fields, increased both insulin-like growth factor II (IGF-II) mRNA and protein levels in rat callus after exposing them to a PC and PG stimulus.

One mechanism suggested for the independent actions of PC and PG field stimuli is their effects on charged transmembrane molecules, such as receptors. For example, alteration in chondrocyte receptor activation by a parathyroid hormone and transforming of the growth factor  $\beta$ -1 (TGF- $\beta$ 1) with PC fields have been demonstrated by Goodman et al. and Aaron et al.<sup>37</sup> These authors discovered that an increase in TGF- $\beta$ 1 causes multipotent mesenchymal cells to express a phenotype and committed osteochondral cells to proliferate and differentiate, which then causes an increase in the extracellular matrix mass of cartilage and thereby provides a greater surface to serve as a scaffold for bone formation. The effect on cell proliferation and extracellular matrix production was determined by thymidine and sulfate uptake. Zhuang et al.<sup>38</sup> reported that electrical stimulation increased the level of TGF- $\beta$ 1 mRNA content in osteoblastic cells by 39% compared with unstimulated cultures by a mechanism involving calcium/calmodulin pathway. In another study examining the response of nonunion cells to PEMF, observations supported the central role of TGF- $\beta$ 1 in the cascade of regulatory events initiated by PEMF.<sup>39</sup> PEMF exposure of cells isolated from hypertrophic and atrophic nonunions resulted in a time-dependent increase in TGF- $\beta$ 1 levels of the hypertrophic nonunion cells by day 2

and of the atrophic nonunion cells by day 4. In an *in vivo* model of enchondral bone formation, PEMF unregulated TGF- $\beta$ 1 protein synthesis and mRNA expression coincident with increases in extracellular matrix protein synthesis. In terms of both amplitude and duration of exposure, regulation of protein synthesis occurred in a dose-dependent manner. TGF- $\beta$ 1 mRNA levels increased 68%, the active protein 25%, and number of immunopositive cells 119% compared with control tissues. The pattern of TGF- $\beta$ 1 expression was preserved throughout the developmental sequence, suggesting that PEMF treatment enhances chondrogenesis, endochondral calcification, and the normal physiologic expression pattern of TGF- $\beta$ 1 without disrupting these processes.

Some studies have revealed a significant increase in cell proliferation and extracellular matrix synthesis after exposure to a low-amplitude capacitively coupled electric field *in vitro*. Fitzsimmons et al.<sup>40</sup> showed that after exposing an embryonic chick tibia to a voltage of 0.1 mV for 30 minutes per day for 72 hours, hydroxyproline uptake increased 83%–125% of control, whereas continuous exposure for 72 hours increased hydroxyproline incorporation by 30%. The authors employed a static-capacity-coupled Coulomb electric field for their *in vitro* study of embryonic chick tibia. Static-capacity-coupled meant that the Coulomb force produces a continuous dielectric-displacement, field and electrophoresis.

The above PC and PEMF studies of the stimulation of chondrogenesis in experimental endochondral ossification have been extended to indicate that exposure of ossicles during chondrogenesis results in elevation of extracellular matrix molecules.<sup>41</sup> The authors in this study showed that a significantly greater fraction of the proteoglycan synthesized under conditions of Coulomb field stimulation were also of normal size. PEMF energy also has been shown to regulate the synthesis of extracellular matrix. This may occur through the stimulation of signaling pathways at the cell membrane and resulting in the appearance of intracellular second messengers, particularly cyclic nucleotides.<sup>42-45</sup> However, it is unlikely that the mechanism of action is solely a result of transmembrane potentials, because the potentials generated by extremely low-frequency PEMF energy are much lower than the cell membrane potentials.

Other studies have noted that exposure of osteoblastic cells to PC fields can stimulate a mechanism involving the calcium/calmodulin pathway and resulting in an increase of TGF- $\beta$ 1 mRNA,<sup>46</sup> and TGF- $\beta$ 1 protein in both osteoblastic cells<sup>47</sup> and fibroblasts cultures.<sup>44</sup> These studies show that chondrogenesis is responsive to displacement current stimulus, which supports observations of other authors who conclude that the production of TGF- $\beta$ 1 is an early response of mesenchymal cells to stimulation by both Gauss and Coulomb fields.<sup>48</sup>

The response of increased fibroblasts to a PC field is thought to be caused by the opening of voltage-sensitive cal-

cium channels and a secondary increase in insulin receptors.<sup>49</sup> Unlike bone and cartilage, which mount a regenerative response, soft tissues, which include the dermis, ligaments, and tendons, heal by a process of fibroplasia.

Several thoughts emerge with regard to chondrocytes in articular cartilage and growth plate stimulation by electromagnetic fields. First, one would assume that the longer the period of electromagnetic stimulation, the more accelerated chondrocyte proliferation and extracellular production. However, a question that will have an important biologic implication is: Will the closure of a bone growth plate be delayed more by electric or magnetic stimulation? That is, will specific electronic energy stimuli allow the growth plate to remain open longer than it should so that more longitudinal growth will occur?

Lippiello et al.<sup>50</sup> examined the exposure of a pulsing direct current on osteochondral defects in the distal femoral condyles of rabbits. This is one of the very few studies in which an attempt has been made to correlate the biologic response of tissue exposed to external DC stimulation by *in situ* measurement of the electrical parameters. The stimulation apparatus involved an undefined signal period with a peak value of 2  $\mu$ A, imposing an electric field in the tissue of 20–60 mV/cm<sup>2</sup>, recurring at 100 Hz. It is noteworthy that a shorter exposure period (40 hours versus 160 hours) proved more efficacious. Could DC polarization damage be time dependent? These authors also reported the appearance of unorganized hyaline cartilage on the surface of the repaired tissue of these rabbits. In an attempt to explain a possible mechanism for this action, they postulate similarly with Guerkov et al.<sup>51</sup> that such treatment stimulates differentiation of mesenchymal cells derived from marrow elements into chondrocytes and induces the proliferation of existing chondrocytes at the wound margins.

There have been several studies testing the incorporation of calcium and its relation to various electric and or magnetic field stimulation.<sup>13,52</sup> For example, Norton and Rovetti<sup>53</sup> hypothesized that the incorporation of Ca in the extracellular matrix of cartilage is influenced by electromagnetic field stimulation. They proved that the largest biologic response in chondrocytes occurred after 24 hours of this stimulation, as defined by autoradiography data.

The effect of low-energy, combined AC and DC (unipolar) magnetic fields on the metabolism of articular cartilage was studied by Grande D et al.<sup>13</sup> After 30 minutes of such unipolar magnetic field exposure, there was a significant increase in radioactive calcium uptake. This uptake was insignificant with exposures of only 1 and 2 minutes and also after 24 hours. The authors concluded that the metabolism of articular cartilage can be stimulated by low-energy pulsating-unipolar, effective DC, magnetic fields, and this unipolar effect is associated with an increase in calcium ion uptake by the cells.

The effect of PEMF energy in the treatment of osteoarthritis (OA), particularly that of the knee, has been stud-

ied in several trials. Trock et al.<sup>53</sup> examined the effectiveness of PEMF in the treatment of OA of the knee and cervical spine on 86 subjects. The subjects were exposed to 9 hours of PEMF stimulation during a 1-month period using a magnetic coil device that delivered three signals in stepwise fashion, ranging from 5 Hz to 12 Hz with variable magnetic flux densities from 10 G to 25 Gauss. Pain on motion, joint tenderness, and activities of daily living were evaluated using a 10-cm visual analog scale. The treated patients achieved between 29% and 36% improvement. In 1998, Perrot et al.<sup>54</sup> reported similar findings using the same PEMF device. However, any attempt to delineate the mechanism of pain relief brought about by this form of treatment modality in relation to known biologic effects of PEMF would be purely speculative, because the factors responsible for the pain in patients with OA are varied and often uncertain.

## CONCLUSIONS

How, and at what level, do various electric, magnetic, electromagnetic, and pulsed EM field devices initiate changes in cell behavior? For the time being, answers to these questions remain to be accurately determined. Notwithstanding the limitations of currently accepted insights into the exact mechanism by which electrical field stimulation works, it is clear that it has a potentially beneficial role to play in clinical practice. The problems in accurately delineating the electromagnetic mechanisms are not only complicated by cellular complexities, but also by the complexities inherent in properly defining the electric, magnetic, and pulsed combinations of these energy fields.

Further research should be directed at establishing the parameters of high-frequency electromagnetic, PEMF, PG, PC, and both static Gauss and static Coulomb field transduction. All related phenomena need to be considered in order to provide a viable foundation for interpreting biologic interactions of the different energy fields with living systems. The literature dealing with electric and magnetic energy stimuli is full of a bewildering array of model systems, clinical situations, signal configurations, and stimulation devices. From these data, one can tentatively propose concepts of energy and tissue specificity. Electronic signal specificity involves a very wide range of pulse repetition rates, electric and magnetic waveforms, frequencies energy amplitudes, dose regimens, and other parameters of a particular electromedicine application that result in a favorable biologic response. The concept of tissue specificity refers to the nature of the biological response to the applied energy. The complexity of tissue and energy specificity should not be unexpected; rather, it should help illuminate the wide variety of synthetic and clinical responses presently reported. As the energy responses become better understood, one can anticipate increasingly efficacious techniques for electronic energy stimulation of tissue repair.

What is perhaps most encouraging is the suggestion that electronic energy stimulation may be applied easily, inexpensively and without added risk to the patient undergoing treatment. Any treatment modality that purports to improve healing, both in healthy and at-risk populations, without significantly increased risk, technical challenge, or cost, deserves further investigation. Electronic energy stimulation for healing therapies is indeed a good idea whose time has come.

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