

Therapeutic Effects of Electromagnetic Fields in the Stimulation of Connective Tissue Repair

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Abstract The therapeutic effects of electric and magnetic fields have been studied largely for their promotion of connective tissue repair. The most widely studied application concerns bone repair and deals with acceleration of the healing of fresh fractures, delayed and non-unions, incorporation of bone grafts, osteoporosis, and osteonecrosis. More recently the effects of these fields upon the repair of cartilage and soft fibrous tissues have been described. In all these experimental systems and clinical applications an acceleration of extracellular matrix synthesis and tissue healing has been observed. A degree of specificity, in terms of the parameters of applied energy and biological response, is hypothesized. ~ 1993 Wiley-Liss, Inc.

Key words: fractures, bone grafts, osteoporosis, osteonecrosis, cartilage

Therapeutic effects of electromagnetic fields are largely concerned with the promotion of tissue repair. The molecular architecture of the extracellular matrix is critical to the functioning of connective tissues, and successful repair implies the synthesis and organization of an extracellular matrix appropriate to the functioning of the tissue in its biophysical environment. A previous Prospect review dealt with the augmentation of endochondral ossification by electric stimulation. This biological process is central to the repair of skeletal fractures. This review will discuss the therapeutic effects of electromagnetic fields on clinical bone repair and will also present information on the synthesis of bone extracellular matrix (osteoid) in adaptation and remodeling, cartilage matrix reconstitution, and soft tissue repair.

The regulation of extracellular matrix synthesis and repair is of major interest, both clinically and biologically. Matrix homeostasis and repair of defects have been shown to be subject to regulation by chemical agents (cytokines, morphogens, and growth factors) and physical agents, primarily mechanical and electrical signals. A number of laboratories have explored the

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relationship between mechanical and electrical events in bone and cartilage [29,30,35]. While the precise nature of electromechanical signal transduction is not yet known, quantitative relationships have been described especially with regard to amplitude and frequency. Both mechanical and electrical signals have been shown to regulate the synthesis of extracellular matrix and may do so through the stimulation of signaling pathways at the cell membrane resulting in the appearance of intracellular second messengers, particularly cyclic nucleotides [19]. The therapeutic use of electric fields has derived from the observation that when bones are placed under mechanical load (stress) the deformation of the bone (strain) is accompanied by an electrical signal and the signal is related to strain characteristics. This strain-related, or strain-generated, electric potential has been hypothesized to consist of information transfer to the osteocyte regarding the nature of its mechanical environment and the state of the extracellular matrix. The origin of the electric signal was thought initially to be related to deformation of the crystalline structure of extracellular matrix collagen, the piezoelectric effect. Other data, however, have suggested that alterations in fluid flow might produce electrokinetic events, specifically streaming potentials, which might be partly or wholly responsible for the observed electric potential. Clinical and animal studies employing stimulation

with direct current have indicated that bone is deposited at the cathode when an appropriately configured signal is applied [11]. The osteogenic range of the signal is thought to be 1-10 mV/cm and 10-20 μ A/cm². Two general types of stimulation devices have been developed for clinical or animal experimental use: DC stimulation for invasive use and inductively coupled techniques for external or noninvasive use. These techniques have been briefly discussed in another Prospect and reviewed in more detail elsewhere [4,11].

BONE REPAIR

The most widespread therapeutic application of electromagnetic fields has been to augment skeletal repair. Five major aspects of bone repair have been addressed: fracture non-unions; incorporation of bone grafts; fresh fractures, osteotomies, and arthrodeses; disorders of adaptation (e.g., osteoporosis); and osteonecrosis.

In vitro studies with osteoblast cell cultures have generally shown an increase in proliferation measured by thymidine incorporation and an increase in DNA content associated with changes in cAMP [18,19,28]. Bone formation in calvarial explant cultures has been shown to be enhanced by exposure to electric stimulation [25]. Fracture callus cells, harvested from healing tibial fractures in rats, have been studied in cell culture under conditions of electric stimulation [7]. These cells proliferate spontaneously between 40 and 80 h of culture. If stimulated with a DC electric field just prior to their proliferative phase, an increase in thymidine incorporation was observed. Other osteoprogenitor cells, derived from marrow, have been stimulated by exposure to an electric field to increase calcium deposition in the extracellular matrix [21]. In a study of matrix synthesis by marrow osteoprogenitor cells, an increase in collagen synthesis was observed in cultures exposed to electromagnetic fields [20].

A large number of studies have been done examining the role of electric stimulation in the repair of fracture non-unions. Non-unions can be thought of as a failure to produce an extracellular matrix suitable to the biophysical functioning of the tissue. With regard to fracture nonunion, the matrix consists of fibrocartilage which does not calcify and which is ill suited to bearing load. Union rates of 77-85% have been reported with electrical stimulation in self-controlled studies [8,16]. A double-blind, placebo controlled study

of tibial non-unions has recently been reported [37]. In this study, radiographic union was observed in 2/25 (8%) of placebo treated non-unions and 10/20 (50%) of non-unions treated with an active signal ($P < 0.002$).

The role of electric stimulation in the treatment of fresh fractures and osteotomies is less well established clinically, and most studies have been carried out in animal models [23]. One study in humans reported the results of electric stimulation of femoral intertrochanteric osteotomies [12]. The study was placebo controlled and blinded. The density of the healing osteotomy was measured radiographically with an image analyzer and normalized to the patient's iliac bone and soft tissue. A significant increase in the relative density of the healing osteotomy was observed in the electrically treated group. In animal models of fresh osteotomies, those exposed to electric stimulation have been reported to heal more rapidly and with more mechanical stability [9,17].

The effects of electric stimulation in accelerating bone graft incorporation in both animal models and clinical applications have recently been reviewed [5]. Briefly, animal studies suggest that a variety of signal configurations can enhance the incorporation of cancellous bone grafts. Opinion is divided on the efficacy of electric stimulation in cortical grafting [32]. Electric stimulation has been reported to enhance bone graft incorporation in several clinical situations, including spinal fusions and resistant fracture non-unions. Three studies, involving over 200 patients, demonstrated that 77-92% of spine fusions with graft and electric stimulation demonstrated incorporation of the graft in a solid union [27,33,38]. The effectiveness of combined bone grafting and electric stimulation in resistant non-unions has also been reported [10]. In this study, 83 patients with complicated resistant non-unions were treated with autogenous cancellous bone grafting and electric stimulation. These patients had a mean of 1.5 years from the initial fracture to treatment and had undergone an average of 2.4 prior surgical procedures unsuccessfully. One-third of these patients had a history of infection. An overall healing rate of 87% was achieved. Electric stimulation has also been shown to enhance the induction of bone by decalcified bone matrix allografts [2]. Ossicles formed in response to decalcified bone matrix implants treated with electric stimulation calcified earlier and exhibited more rapid formation of

more mature trabeculae than did control ossicles.

Bone undergoes a process of adaptive remodeling to a variety of environmental stimuli including mechanical strain and hormonal influences. Reduction in mechanical strain by protected weight bearing or microgravity environments results in disuse osteoporosis. Several studies have suggested that electric stimulation is able to prevent or restore disuse osteoporosis. Using a model of protected functional loading, an increase of 20-23% of bone mass was observed in electrically stimulated bones as compared to controls [36]. This effect was observed with a specific pulse power level and was ascribed to a decrease in endosteal resorption as well as to an increase in new bone formation. Similar studies have been carried out in dogs [39]. This study examined the usefulness of an inductively coupled electric field in preventing combined hormonal and disuse osteoporosis. Control animals lost 23% of bone mass while treated animals lost only 9% ($P < 0.03$). The mechanism of preservation of bone mass was thought to be due to a reduction of resorption. Similar electric stimulation configurations have been studied for their effect upon human osteoporosis [41]. Twenty post-menopausal women with longitudinal bone density measurements were treated at the radius with an inductively coupled electric field for 12 weeks. The patients were followed for 48 weeks. A limited increase in cortical bone was observed during the treatment period. I

Electrical and electromagnetic stimulation has been shown to be useful in the treatment of osteonecrosis of the femoral head. Osteonecrosis is defined as the death of osteocytes with an accompanying resorption of bone, femoral head collapse, and secondary osteoarthritis [4]. This is generally regarded as a progressive condition and surgical interventions have had variable success rates. Several studies have suggested that DC or inductively coupled electric stimulation may be useful in the retardation of collapse and the preservation of the femoral head [1,4]. DC electric stimulation via wires implanted at a surgical procedure has been shown to provide pain relief for a substantial number of patients with osteonecrosis. Compared to a surgical grafting procedure, the addition of electric stimulation decreased the percentage of patients requiring hip arthroplasty by 20%. The use of inductively coupled external electric stimulation without a surgical procedure has been shown to result in the

preservation of 80% of hips with stage II lesions (pre-collapse) and 45% of patients who have suffered structural compromise of the femoral head. These results are substantially better than those seen with a variety of surgical procedures.

CARTILAGE REPAIR

Articular cartilage is comprised of highly negatively charged macromolecules (proteoglycans) immobilized by collagen fibers within a hyperhydrated aqueous gel. Under conditions of mechanical load, the water phase and associated ions flow past the stationary charged phase creating streaming potentials and current flow [29]. These potentials have been quantitated and related to the magnitude of the fixed charged density. The biological consequences of the electrical signal are not clear but may include information transfer to the chondrocytes concerning the nature of their mechanical environment and the state of the extracellular matrix. The effects of electrical and mechanical stimulation of embryonic chondrocytes have been reported [30]. A two- to threefold increase in glycosaminoglycan synthesis was observed with either stimulate :t-Y modality. In the same study a general decrease in protein and collagen synthesis was noted. These data suggested that chondrocyte synthesis of glycosaminoglycans is subject to regulation by mechanical and electrical signals of specific amplitude, frequency, and dose. Chondrocytes derived from neonatal calf articular cartilage have been stimulated with a capacitively coupled electric field in high density culture in vitro [15]. At a specific and limited electric potential (250 V) an increase in sulfate incorporation was observed. Our laboratory has carried out detailed studies of the effects of inductively coupled electric fields on proteoglycan synthesis in bovine articular cartilage explants [6]. The incorporation of sulfate into cartilage macromolecules was increased within 5 days of culture and increased further by 12 days. Newly synthesized proteoglycans were retained within the cartilage matrix. Cultures exposed to fields retained 9510 of glycosaminoglycans compared to 70% in control cultures. The proteoglycans synthesized were of normal size distribution on Sepharose 2B. Glycosaminoglycans derived by papain digestion also had normal size distribution on Sepharose 6B and a normal chemical composition by selective enzyme digestion. The catabolic rate of proteoglycans appears

to be unaffected by exposure to the field. In vivo studies with rabbit articular cartilage exposed to similar fields demonstrated a 22% increase in glycosaminoglycan content [40]. The collagen content remained unchanged during exposure to the electric field.

Appropriately configured electric fields appear to have a regulatory effect on articular chondrocytes to selectively increase proteoglycan synthesis but not collagen production. The molecules synthesized appear to be normal in size and composition. This is of great potential importance since articular cartilage does not mount a repair response that results in matrix reconstitution in either trauma or arthritis. Clinical studies of the efficacy of electric stimulation in arthritis are in progress but no data is yet available.

SOFT TISSUE REPAIR

Unlike bone, which mounts a regenerative response, and cartilage, which heals poorly if at all, soft tissues, including dermis, ligament, and tendon, heal by the process of fibroplasia. Therefore, basic studies of the effects of electric stimulation upon soft tissue repair have focused on the response of fibroblasts. Certain electric fields have been reported to increase protein and DNA synthesis in human skin fibroblasts [13]. The stimulation of fibroblasts by electric fields is thought to be due to the opening of voltagesensitive calcium channels and a secondary increase in insulin receptors [14]. Other in vitro studies have demonstrated specific increases in collagen synthesis by fibroblasts [34]. In vivo studies have shown increases in tensile strength of healing skin wounds [26,31]. Several clinical studies have been reported on the effects of electric stimulation in chronic skin and dermal ulcerations. The effects of electric stimulation have been reported in venous stasis ulcers [24].

Forty-four patients were studied in a placebo controlled, blinded trial. At 90 days of follow-up, 32% of patients treated with a placebo unit healed compared to 67% treated with active units ($P < 0.02$). At one year follow-up, 42% of controls and 89% of treated patients had healed ($P < 0.005$). Granulation tissue was observed to a greater degree in patients treated with active units. Other studies have demonstrated reduction in wound size and an increase in granulation tissue in patients with chronic decubitus ulcers [22]. Wounds treated with electric stimulation healed at

almost twice the rate of control wounds with a reduction in infection and wound drainage and an increase in granulations and epithelialization.

CONCLUSIONS

The literature dealing with electric stimulation of repair 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 signal and tissue specificity. Signal specificity refers to a range of frequencies, amplitudes, dose regimens, and other physical parameters of energy application which result in a favorable biological response. The concept of tissue specificity refers to the nature of the biological response to the applied energy. This is most certainly offered by the individual cell or tissue stimulated and, probably, by the position of the predominant cell population in the cell cycle [3]. Therefore, proliferative or synthetic responses may occur to the same signal depending upon the state of the biological tissue at the time of stimulation. Similarly, bone and cartilage cells, for example, will respond to the same signal in different ways but ways which are characteristic of the specific cell type.

These concepts of tissue and signal specificity should not be unexpected and explain the variety of synthetic and clinical responses observed. As these concepts are explored more definitively one might anticipate increasingly efficacious techniques for the electric stimulation of tissue repair.

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