

Pilla, A. 2008, A proposed electrochemical mechanism for EMF Bioeffects. Bioelectromagnetics Society, June, 2008. San Diego, CA.

Introduction: This study proposes PEMF accelerates tissue repair by directly affecting the kinetics of  $\text{Ca}^{2+}$  binding to calmodulin (CaM). This allows a priori configuration of EMF signals to optimally couple to the  $\text{Ca}^{2+}$ /CaM transduction pathway, from which further molecular signaling can be modulated. This work shows how effective EMF signals may be configured a priori to be first messengers by evaluation of signal to thermal noise ratio (SNR) in a two step pathway involving  $\text{Ca}^{2+}$  binding to CaM, followed by  $\text{Ca}^{2+}$ /CaM binding to epithelial or neuronal nitric oxide synthase (eNOS and nNOS, respectively) which modulates nitric oxide (NO) release.

Methods: The EMF target is considered to be  $\text{Ca}^{2+}$  binding to CaM followed by CaM binding to eNOS or nNOS, both of which control the CaM-dependent release of the signaling molecule nitric oxide (NO). Analysis of the kinetic equations describing this two step process yields a two time constant electrical equivalent circuit analog, as shown in fig 1. Here RACA and RBCB are the time constants for  $\text{Ca}^{2+}$  binding to CaM, and CaM binding to, e.g., NOS, respectively; and Cd and RM are the membrane capacitance and leak resistance, respectively. Knowledge of the actual time constants, allows any EMF signal to be assessed in the frequency domain with respect to its ability to produce a detectable (i.e.  $\text{SNR} \gg 1$ ) voltage in the target. This is shown in fig 2, wherein SNR for pulsed radio frequency (PEMF) signals consisting of a 2000  $\mu\text{sec}$  burst of 27.12 MHz sinusoidal waves repeating at 5/sec (configured a priori for the Ca/CaM pathway), a 65  $\mu\text{sec}$  burst at 600/sec (a diathermy based signal in clinical use for soft tissue repair), and the original PEMF bone healing signal consisting of a 5 msec burst of 200/20  $\mu\text{sec}$  pulses repeating at 5/sec, are shown. Both PEMF signals were predicted effective, the 65  $\mu\text{sec}$  signal significantly less so since it was not matched to the bandpass of  $\text{Ca}^{2+}$  binding. The PEMF bone repair signal was predicted ineffective. This validity of this approach was reported on Achilles tendon repair in the rat (Strauch, 2006).

Objectives: The activation of calmodulin (CaM) by  $\text{Ca}^{2+}$  has been found to be the initial stimulus for many biochemical cascades involved in tissue repair, starting with the inflammatory phase. The initial steps of the Ca/CaM-dependent cascades often start with activation of eNOS which causes an immediate release of NO. This causes an immediate vasodilation which is subsequently followed by increased, e.g., cGMP formation which can enhance growth factor release. It is shown here how an PEMF signals may be configured to modulate Ca/CaM binding leading to increased tissue repair. with a subsequent effect Figure 3 summarizes a proposed scheme for PEMF acceleration of tissue repair.

The Clinical Results: A PEMF signal configured a priori for the Ca/CaM pathway was tested clinically in a randomized double-blind study for its effect on pain reduction immediately post breast augmentation. Active patients received the PEMF signal every 4 hours, days 1-3, every 8 hours, days 4-6, and every 12 hours thereafter. Pain was assessed twice daily using a validated VAS. The results are shown in figure 3. Bars represent the mean VAS pain score at Day 1 for all breasts and at Day 7 for both the active and sham groups. Mean ( $\pm$  SD) VAS score was  $54 \pm 9$  mm for all groups on Day 1. Mean VAS decreased to  $17 \pm 4.4$  mm in the treated group (218%,  $P < 0.001$  vs Day 1) and to  $31 \pm 5.6$  mm in the sham group (74%,  $P < 0.001$  vs Day 1). The difference in mean pain between the active and sham cohorts was also statistically significant ( $P < 0.001$ ), suggesting post surgical use of PEMF therapy could produce a clinically meaningful reduction in pain by nearly a factor of 3. Active patients also had a concomitant decrease in pain medication by a factor of 2.5 (Heden, 2007)

Conclusions: It is proposed EMF signals configured via SNR analysis to match the bandpass of a second messenger target can act as a first messenger to modulate biochemical cascades related to tissue growth and repair. The likely second messenger is  $\text{Ca}^{2+}$  binding to CaM which activates eNOS or nNOS. The result is PEMF acts to reduce the inflammatory phase of tissue repair and then acts to accelerate the remaining phases of repair by directly modulating the appropriate growth factor release at the appropriate time and with the correct kinetics.