ELECTROMAGNETIC FIELDS IN BIOMEDICINE: CYTOPROTECTION AND GENE THERAPY

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Introduction. Electromagnetic (EM) fields as a tool for stimulation of biological effects offer many distinct advantages: bioelectromagnetic techniques are non-invasive, the fields can be easily directed, and they require low energy. The low thresholds at which EM fields stimulate biological processes, including the protective stress response, are below the level of perception, so they have the further advantage of not interfering with the subject. Here we describe two potential medical applications based on EM stimulation of the stress response and the use of EM field-responsive elements (EMREs) in genetic engineering .

EM fields stimulate gene expression. EM fields initiate gene expression, and the well-established stimulation of the stress response has now been found over a wide range of frequencies, including RF. Electromagnetic response elements (EMREs) in the promoters of genes are required for EM field interaction with DNA. A 900 base pair segment containing EMREs in the hsp70 promoter is needed for the response to EM fields. Removal of the segment eliminates the response, and transfection into a promoter construct renders the construct EM field-responsive (1).

EM field-induction of hsp70 for use in cardiac by-pass surgery. Induction of the stress protein hsp70 by electromagnetic (EM) fields is often used as an indication of the normal response of cells to biological hazards, but it should be emphasized that the same stress protein serves to protect against potential hazards. We have utilized the protective aspect of EM field induced stress proteins to develop two new beneficial medical tools (patents pending).

Elevating hsp70, usually through hyperthermia (high temperatures), protects the myocardium during reperfusion ischemic stress and helps prevent heart attack and stroke. Induction of increased hsp70 with EM fields eliminates patient discomfort associated with hyperthermia. EM fields are non-invasive, penetrate all cells, and have longer-lasting effects than hyperthermia. Within 30 minutes hsp70 levels are elevated at least 2-fold and remain elevated for more than 3 hours. Unlike hyperthermia, hsp70 levels can be augmented by restimulation for extended surgical procedures (2).

Results of cytoprotection studies. The increase in hsp70 levels by EM fields *in vivo* and *in vitro* depends on the field strength. EM field-preconditioning produces a higher survival rate than thermal preconditioning in fertilized dipteran eggs and cultured rodent cardiomyocytes (1).

Beneficial use of EM fields for gene therapy. We have identified three nCTCTn EM field-responsive elements (EMRE) in the DNA sequences in the HSP70 promoter are EM field-responsive. Inactivating these sequences, by removal or mutation, renders reporter gene constructs unresponsive to EM fields. Inserting this sequence in an unresponsive reporter construct, renders the gene EM field-responsive (2). This innovation in gene therapy provides a non-invasive and precise technique for gene activation. For example, an exogenous insulin gene containing one or more EMREs introduced upstream of the gene, can be simply and safely regulated by the EM fields. The procedure can be made automatic with an EM field generating circuit activated by an implanted glucose sensor that responds immediately to changes in pre-set blood glucose levels.

References

1. Carmody et al (2000) ***J Cell Biochem*** 79: 453-459.
2. Lin et al (2001) ***J Cell Biochem*** 192: 1622.