Name-Khiromani Bai
Roll No.-18111031
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REVIEW ON BIOMEDICAL PATHWAYS ASSOCIATED WITH CARDIAC RESPONSES TO EXTERNAL ELECTRIC AND MAGNETIC FILEDS

ABSTRACT-
We discuss a wide range of application of external electric and magnetic fields in biology and medicine. For example, physiological strength (<500V/m) fields are used to improve the healing of wounds, the stimulation of neurons, and the positioning and activation of cells on scaffolds for tissue engineering purposes. The brief, strong pulses used in tumors and DNA into cell nuclei. The references direct readers to detailed reviews of these application. The mechanism by which cell detect physiological strength fields is not well understood. We also describe a field-transduction mechanism that stares features common to the detection of fluid shear by cells. We then provide some experimental evidence that supports our model.

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INTRODUCTION-

The application of external electric and magnetic fields in biology and medicine are many and varied. Physiological strength(~100V/m), direct current(DC) electric fields are important in the development, maintenance and control of cells and tissues.Their role in wound healing, embryonic development, and tissue regeneration is described in detail in the reviews of Pullar, McCaig et al.,and Robinson and Messerli. Endogenous DC electric fields are also important in embryonic patterning. In tissue engineering cell proliferation on scaffolds can be controlled by the application of such fields. At the tissue level electric fields are used for the measurement of body composition and the promotion of wound healing. An important new development has been the use of strong electric fields of drugs through membranes or the insertion of DNA into the nucleus for genetic engineering applications.

There are still unresolved questions regarding the mechanism by which the fields achieve their effects. For physiological strength fields a wide variety of biochemical pathways within the cell following the initial detection of the field have been studied, but the initial transduction mechanism is not well understood. For high voltage, pulsed fields the details of membrane pore formation remain unclear

THE APPLICATION OF PHYSIOLOGICAL STRENGTH DC AND LOW FREQUENCY AC FIELDS TO CELL AND TISSUE-

(a) Wound healing -When tissue is damaged, an electric field is produced at the wound site.
(b) Electrical stimulation of the nervous system-Pulsed and low-frequency alternating current(AC) fields, applied with either implanted or surface neural activity. In Deep Brain Stimulation(DBS) electrodes can be surgically implanted into specific areas of the brain to apply pulse signals that suppress endogenous signals that produce Parkinson's disease tremors or epileptic seizures.
(c) Induced electric fields and bone healing and brain stimulation- (i.)Changing magnetic fields produce electric fields.
(ii.) Two examples illustrate the clinical use of varying magnetic fields.
(d) Electric fields for diagnostic purpose - The preceding sections have described how the application of electric fields to cells and tissue can produce beneficial effects in those targets.Electric fields, however, can also be applied to monitor the physiological state of tissues for diagnostic purposes.
(e) Tissue engineering -The application of electric fields to cellular system can produce a wide variety of physical effects in cells in Addition to galvanotaxis. Such effects are described in detail in the CRC review monograph edited by Pullar.

CELL DOSIMETRY-

In order to understand how cells produce the observed effects, it is first necessary to understand how the applied field is distributed within the cell as a function of time. Suppose that a spherical cell of radius R is placed within a culture medium far from parallel plate electrodes. At time t=0 an electric field E is applied between the plates.The cell behaves as a series RC circuit. When the field is applied, charge flows through the resistor to charge the capacitor. Once the capacitor is fully charged to establish TMVi, the flow of charge through R ceases. The time constant for the process is torque. For times significantly less than torque there is significant charge flow and an associated electric fields within the cell interior(cytoplasm).

ELECTROPORATION-

(a) Basic principles- The application described to this point are for applied fields of physiological strength; that is, less than about 300 V/m. The frequencies of these fields are also less than 1 MHZ with corresponding time scales greater than 1 microsecond. As noted above, for such time scales the resulting cytoplasmic electric field is negligible, so any direct interaction must take place at the cell surface. In this section we discuss applications produced by fields that are on the order of 10kV/m or greater with component frequencies often greater than 1 MHZ. Such fields are strong enough to permeabilise the cell membrane; that is, to permit the passage of atoms and molecules to the interior ion the cell. The principle model used to describe this process involves the opening of small openings or pores. For this reason the process is referred to as electroporation although the term electropermeabilization is sometimes used. In this way previously administered drugs that ordinarily cannot pass through the membrane are able to enter the cell interior or DNA/RNA can be inserted into the cell nucleus.

(b) Clinical applications of electroporation- Important anti-cancer drugs such as cisplatin and bleomycin cannot easily cross the cell membrane. Application of electroporation pulses opens pores in the membrane through which the drugs can pass. Because drug insertion into the cell is now more efficient, the dose given to the patient can be reduced significantly and have fewer side effects. ECT is being used at numerous centres in Europe for a wide variety of tumors. For deep-seated tumors NTIRE is used to destroy the cancer cells while preserving the surrounding tissue. Deep-seated tumors require complex procedures. Typically an MRI is used to provide a detailed mapping of the tissue types surrounding the tumor. Knowledge of the dielectric properties of the various tissue types permits the calculation of the field that would be applied at the tumor site for various possible electrode placements. Once the optimum electrode placement has been decided the MRI can be used to guide the surgeon's placement of the electrodes.

(c) Nanoporation- Recall from Section 3 that for times much less that the membrane time constant, torque, the electric field penetrates the cell interior. It may then be possible to porate the cell nucleus and other sub cellular structures. Because the size of those structures is much smaller than the cell itself.

MECHANISMS AND EXPERIMENTS-

We present here an abbreviated description of the research we have conducted to determine the mechanism by which cell initially detect physiological strength electric fields. Identifying and understanding this mechanism is important for further developing the various applications described above. We also present an abbreviated description of some experiments that support this identification.
(a)How cells detect electric fields-As described above, DC and low-frequency electric fields produce a wide variety of biological effects at the cellular and tissue levels. Although the emphasis here is on cell migration, wound healing and neural stimulation, electric fields produced a wide variety of other effects on cells as described in the CRC review. Once a cell initially detects the field that information is transmitted throughout the cell to produce a wide variety of biochemical effects. A major question is—what is the initial transduction mechanism by which the cell detects the field?
(b)Details of the mechanical model-
(i.)Directionality increase
(ii.)Motility increase
(c)Galvanotaxis experimentation to validate the model-
(i.)Experimental setup
(ii.)Galvanotaxis results

NUMERICAL SIMULATIONS-

The applicability of the methods described above requires knowledge of the detailed electric field distribution depends on the electrical properties and physical shapes of the various cells and tissues involved, numerical methods must be used for the calculation. These methods have evolved considerably over the years. For example, spreadsheet cells can be used to represent small volume elements in a limb.The value of the cell is the electrical potential of the element,Vo.That value is related to the potential of the six surrounding cells in the three-dimensional model. Setting the current entering the cell equal to the current leaving relates Vo the potentials of the surrounding cells via the inter-cell resistivities. The electrical anisotropies of the tissue can be introduced into many similar cells simultaneously and solved by the method of successive over-relaxation in an Excel spreadsheet.This approach was used to determine how the electric field at the site of a tibia fracture evolved as the injury healed during an electrical fracture-healing treatment. The method can even be extended to calculate the electric field distribution induced in a complex distribution of cells in a culture dish.

CONCLUSIONS-

Electric fields have a wide variety of applications in biology and medicine. Physiological strength fields are used to improve the healing of wounds, the stimulation of neurons and the positioning and activation of cells on scaffolds for tissue engineering purposes. The brief, strong pulses used in electroporation are used to improve the insertion of drugs into tumors and DNA into cell nuclei. Numerical simulations must be used to select the proper field strengths to be applied in a clinical setting. Some fundamental issues are still being addressed; in particular, how do cells actually detect the fields? The electromechanical model described here is consistent with the experimental evidence whereas other models are not.