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Study of Electric Field an Magnetic Field Affected Biological Cells

Mohd Zikrillah Zawahir[a], Ruzairi Abdul Rahim[a*], Zulkarnay Zakaria[b], Mohd Saiful Badri Mansor[a], Mohamed Shukri Abdul Manaf[a]

[a]*Process Tomography and Instrumentation Engineering Research Group (PROTOM-i), Infocomm Research Alliance, Faculty of Electrical Engineering, Universiti Teknologi Malaysia, 81310, UTM Johor Bahru, Johor Malaysia*
[b]*Tomographic Imaging Research Group, School of Mechatronic Engineering, Universiti Malaysia Perlis, 02600, Arau, Perlis, Malaysia*

*Corresponding author: ruzairi@fke.utm.my

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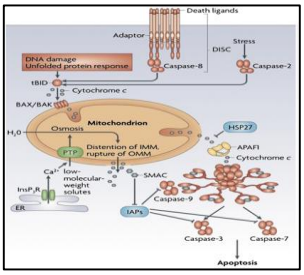
Graphical abstract



Abstract

This paper presents the elaboration on effect of electric field and magnetic field to biological cells. Electroporation has become important parameter in treatment cancer or tumour cells. By using electric field or magnetic field, membrane cell will undergo process electroporation where membrane cell structures being altered for induce apoptosis process.

Keywords: Electric field; magnetic field; electroporation; trans membrane voltage; apoptosis

1.0 INTRODUCTION

Billions of humans around the world are exposed to the risk of being affected by tumours, cancer and many other diseases. There are many methods of prevention, treatment and cure. One of these procedures is therapy. There are also many kinds of therapy and this paper discusses the use of electric field and electromagnetic field for therapeutic purposes. Nowadays, this therapy is being widely explored by researchers because it is involved in medical fields such as the treatment of cancer, tumours, bone healing, hyperthermia, osteoporosis, leukaemia, early stage growth of bone cells, etc. [1-33].

Therapy using electric field is an invasive method, while therapy using magnetic field is non-invasive. Invasive methods involve surgical procedures for the patient while non-invasive methods involve no surgery.

2.0 EFFECT OF ELECTRIC FIELD ON BIOLOGICAL CELLS

Electric field has been investigated by researchers for many years and has been proved to be useful on affected biological cells. Invasive methods use a rod electrode or plates or needles to make an electric field by connecting them to a specific generator. The concept being applied when using electric field involves an alteration of specific membrane cells. This alteration is related to the structure of the functional membrane of a biological cell, such as an animal cell. This alteration is known as "electroporation", meaning making an existing pore in the membrane structure change from intracellular to extracellular or extracellular to intracellular [34, 35, 42].

Electroporation normally occurs in two modes: 1) irreversible and reversible. For irreversible mode, the permeabilization cell is permanent, while reversible mode involves temporary permeabilization. Weaver *et al*. [34] report on the use of an electric field suitable for electroporation to occur, where if the duration of the pulse is long, the membrane cell will be in irreversible mode, while with increasing pulse amplitude the cell will be in reversible mode [34]. In an earlier study, Garcia *et al*. reported that irreversible mode can be safely used in the brain where it is capable of killing brain tissue [36].

Focusing electroporation on cancer and tumour cells will trigger a process call apoptosis. Apoptosis is a process where a cell is programmed to die [1-3, 6, 43, 44]. Other effects of electroporation are intracellular calcium bursts, fast translocation of phosphatidylserine residues in plasma membrane, cell and nuclear shrinkage and necrotic cell death [2]. An experiment by Tang *et al*. demonstrated that an increase of electric field intensity to 200 and 250 V/cm caused the intracellular calcium concentration to decrease [2]. They also found that the change of calcium ions can induce a change of cellular behaviour including the apoptosis

cells, and using a nanosecond pulse did not result in pores on the cell membrane. The use of steep pulse fields triggers a physiological response in cells to release intracellular free calcium which is stored in endoplasmic reticulum compartments and mitochondria [2, 5, 37, 38].

This was different from Ibey *et al*., who applied a nanosecond electric pulse (nsEP) to destroy tumours in animals and conducted a human trial with full elimination of cancerous cells without repeating the treatment and also with no significant side-effects [1,39, 40]. Other than movement of calcium ions, Nesin *et al*. found that using nanosecond electric pulses can open stable nanopores in the cell membrane and affect the cell volume change due to water uptake, as regulated by the osmolality balance of pore-impermeable solutes inside and outside the cell [4]. In their experiment, a 600 nanosecond electric field could open a greater number of larger propidium-permeable pores, but this was insufficient to contribute to cell volume changes. They also found that pores smaller than 0.9 nm in diameter can affect cell volume change for both 60 nanosecond and 600 nanosecond electric field. Moreover, increasing the nanosecond electric field intensity will increase the pore diameter [4, 41].

By contrast with irreversible electroporation that causes membrane damage, reversible electroporation focuses on the delivery of chemotherapeutic drugs into tumour cells, for gene therapy and for transdermal drug delivery [7]. The process of delivering DNA by electroporation into cells or tissues is called gene therapy and has been successful but less efficient than more commonly used methods [45]. Transdermal drug delivery has its own advantages, such as being able to deliver to a specific site, allowing good control of drug dose, and administering drugs that are not suitable for delivery orally or by injection [46].

■3.0 EFFECT OF MAGNETIC FIELD ON BIOLOGICAL CELLS

The other method in therapy uses electromagnetic field. This is a non-invasive method [47], where using a coil, antenna or any material can generate an electromagnetic field when current is supplied to the material or object through a generator. In a previous study, Funk *et al*. found that magnetic field can penetrate cells more deeply than electric field and can also influence chemical and biochemical reactions because the human body is 'semitransparent' to the magnetic field. They also found that magnetic field can penetrate much deeper into cells than electric field, as the cell membranes' high dielectric property has a shielding effect [31, 32].

3.1 Static Magnetic Field

When producing electromagnetic fields, there are many sources of current. One of these is direct current (DC) and the magnetic field produced by DC is called static magnetic field (SMF). A previous study by Murase *et al*. found that the major challenge when using electromagnetic field as therapy is the difficulty of heating the targeted tumour to the desired temperature without damaging surrounding tissues for hyperthermia therapy [9, 24]. In their experiment, they created a method that is useful for controlling the temperature rise in magnetic hyperthermia using a device for generating an alternating magnetic field (AMF) and placed it in the SMF that allows for generating and moving a field free point (FFP). They also derived an empirical equation that is useful for estimating the temperature rise in the presence of both AMF and SMF, for controlling the temperature rise, and for designing an effective local heating system for magnetic hyperthermia [24].

Other than that, magnetic field can also inhibit tumours indirectly via the host immune system, although the available evidence from previous studies is not enough to state a consistent conclusion [48, 49]. Pengfei *et al*.'s investigation found that SMF with values of 0.2-0.4 Tesla could inhibit leukaemia in mice and up-regulated the host immune function either in vivo or in vitro. They also reported that the exposure time and intensity of the magnetic field might play a more important role in the effects [26]. In vivo, the metabolic activity of a human cell HL-60 was retarded to 81% after exposure under 1 Tesla SMF for 72 h, but exposure under the same SMF of 6 mT did not induce any apoptogenic effects in HL-60 [50, 51].

Tofani proposed an exposure system focusing on subjects (mice) exposed to the same total magnetic field but different static and extreme low frequencies (ELF). He proposed six boxes with six mice, separated into two groups. The first group was exposed to high static and low ELF magnetic fields while the second group was exposed to low static and high ELF magnetic fields. The results of the experiment help to clarify which components (shape, size and conductivity) play an important role in the induction of the observed biological effects [11

3.2 Electromagnetic Field/Pulsed Magnetic Field

A pulsed electromagnetic field was also generated by current flow from one position to another position but the current given have frequency or pulse. In Funk *et al*.'s study and investigation, they found that a lower value of electromagnetic field intensity can generate the same result with a high value of static field intensity on the Ca2+/CaM-dependent myosin phosphorylation on neuritis length from embryonic chick ganglia explants. During the development of cells, electromagnetic field (EMF) can also influence the movement of whole organisms [32]. Cifra *et al*. found that there are several biological factors that also play a major role in the response of a biological system to electromagnetic fields. One of the major parameters is the stage of cell differentiation and replication [31].

In an experiment by Yamaguchi *et al*., a combination of repetitive pulsed magnetic stimulation with an anticancer agent was used on a human chronic myelogenous leukemia-derived cell line TCC-S using a molecular target drug (selective tyrosine kinase inhibitor) imatinib mesylate. Magnetic-induced eddy currents in the human body induce neither a pH change nor heat which plays the role in cell death [8]. In the experiment done by Jing *et al*. circadian rhythm (CR) was an important factor involved in determining the preventive effect of pulsed electromagnetic field (PEMF) on osteoporosis in rats [14].

Other researchers focused on generating induction from magnetic field, but Ogiue-Ikeda *et al*.'s group instead focused on the effect of air volume on leukaemia cell growth by using strong magnetic fields up to 8 Tesla. Their experimental results show that the TCC-S (leukaemia cells) growth rate was almost proportional to the growth rate without magnetic field exposure, but they had suspected that magnetic field could affect the cell culture medium, causing it to become homogeneous after exposure to magnetic field. By changing the variety of volume culture medium cell, the results show a dramatic decrease of leukaemia cell growth because of the dissolving oxygen supply from the air to the medium [10]. Even though that situation was clear, it could not be stated which factor inhibited either the magnetic fields or the behaviour of the paramagnetic dissolved oxygen in magnetic fields. A redistribution of dissolved oxygen occurs when oxygen pressure at the atmospheric air is not at equilibrium and the dissolved oxygen concentration is high [52, 53].

Nagae *et al*. and his research group conducted an experiment using two MRI contrasting agents: 1) Feridex and 2) Resovist. They found that Feridex does not show any temperature rise while Resovist, diluted with saline, shows a temperature rise under an alternating current (AC) magnetic field of 4.4 mT at 140 kHz. The effectiveness was increased 6 times by using a high magnetism fraction of Resovist compared with the drug by itself [12]. By contrast, Ogiue-Ikeda *et al*. found that the use of magnetisable beads and pulsed magnetic forces can destroy cancer cells. In a previous study, even though the effectiveness of using magnetisable beads and pulsed magnetic forces was not well known, they found that pulsed magnetic forces caused aggregated magnetisable beads to forcefully penetrate or rupture target cells [13, 54].

Altunc and his group focused on a totally different area from other researchers when they investigated concentrating sub nanosecond electromagnetic pulses (SEP) on a biological target. In their previous study, they had proposed the design of a special dielectric lens for concentrating SEP. By using a prolate-spheroidal impulse radiating antenna (PSIRA) and designing a special lens, their aim is for future applications to penetrate target cells deep within the human body. The results of their experiments show that PSIRAs can deliver faster SEPs, more than 50 picoseconds, with high amplitude. The focusing lens plays an important role in their system [15]. Meanwhile Yamaguchi *et al*. studied the effect of repetitive magnetic stimulation on tumours and immune functions. From their results, they found that proliferation activity increased significantly by 253.7% compared with the control subject (mouse) and that magnetic field stimulation had activated the immune function. They also found that neither local pH alteration nor heat had any effect during the experiment [16, 55].

During electromagnetic hyperthermia treatment, Trujillo *et al*. proposed to use Ferro fluids as an agent to treat deep lesions. Ferro fluids were used to focus the electromagnetic energy in order to avoid heat and damage in healthy tissues, because treatment with microwaves is impossible because of the wave attenuation. According to their results, the physical properties of the materials allow the interaction of the magnetic field generated by the applicator with Ferro fluids. Even though injection of Ferro fluids corroborates the behaviour of nanoparticles in the experiment, it is still hard to control the energy deposition over tumours. More than that, this experiment allowed progress in the nanotechnology research on developing several nanoparticles of Ferro fluids that can be injected into tumours [18, 23]. Laqué-Rupérez *et al*. conducted an experiment on the effects of pulsed electromagnetic field (PEMF) on methotrexate cytotoxicity in MCF-7 breast cancer cells and the effects with exposure to $FeCl_3$. Their results show that PEMF (25 Hz, 1.5 mT) does not induce modulation of the action of methotrexate (with or without iron-III) in MCF-7 cells when exposed for 2 hours/day over a 3-day period [19].

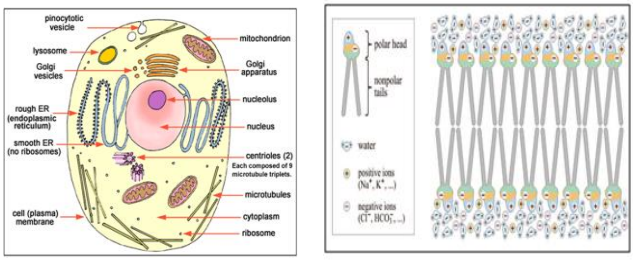
Pang *et al*. investigated the photodynamic effect on cancer cells influenced by electromagnetic fields. The results of their experiment show that treatment enhances the photodynamic effect by more than 40% over the control value. Even though research on this synergism between PEMF and light is still in the early stages, an additional optimization will be possible by photodynamic PEMF synergism for an increased drug delivery if many parameters are considered [20, 29]. In Morita *et al*.'s experiments, MRI with a low duty factor could raise the resonant circuit temperature up to 130 °C. This situation was suitable to use in hyperthermia therapy where hyperthermia elevates the local temperature to between 42.50 °C and 440 °C to kill cancer and most normal tissues are not damaged at temperatures below 440 °C [22, 28].

Stratton *et al*.'s investigation on micro vesicles (MVs) identified various functions including intercellular communication, control of apoptosis, cell proliferation and various immunological and pro-coagulant roles. Their interest was focused on the use of pulsed extremely low-frequency (in the range 3-300 Hz) magnetic fields (ELFMF) to induce cell membrane damage, allowing calcium influx, which then initiates the release from cells of stimulated micro vesicles [27, 56, 57, 58]. Jianyong *et al*., in their previous study, found that low frequency sinusoidal magnetic field has an effect on the treatment of cancer when used to treat fractures and traumas. Other than that, extreme low frequency electromagnetic field (EMF) affected the apoptosis process of tumour cells. Their experimental results showed that the body of the tumour in the control group was bigger than the treatment group. This means that the tumour's weight and shape changed compared to the treatment group and a process of inhibiting tumour growth had occurred [30].

4.0 ELECTROPORATION AND APOPTOSIS

What is electroporation? Electroporation is actually a membrane phenomenon which involves the fundamental behaviour of a cell and artificial bilayer membranes, and is increasingly attracting interest for applications in biology, biotechnology and medicine [34]. Electroporation is also referred to as membrane permeable or membrane electroporation or electropermeabilization. From the electrical aspect, the cell plasma membrane can be viewed as a thin insulator surrounded on both sides by aqueous electrolyte solution. The inside of the cell is surrounded by a plasma membrane called intracellular, while the outside of the plasma membrane is called extracellular. The middle of the plasma membrane is called intercellular. Membrane plasma will undergo electric breakdown when exposed to a sufficiently strong electric field, which make molecules that are unable to cross membrane plasma that is permeable to the molecules [59].

The structure of membrane plasma consists of lipids in the form of a bilayer. This is called the lipids bilayer, which consists of lipids classed as polar (hydrophilic) and nonpolar (hydrophobic). Figure 1 shows the lipid bilayer structure of a membrane cell. The lipid bilayer is a very stable structure because of the relative weakness of the pair-wise interactions between the lipids. It is also an almost impenetrable barrier for polar molecules dissolved in the aqueous electrolyte on both its sides because of its nonpolar interior. More than that, water and some monoatomic ions permeate through it by diffusion through an entirely intact bilayer [59-61].



a) b)

Figure 1 a) Animal cell structure, b) a bilayer of such lipids in an aqueous electrolyte solution

An electric field of pulses going through the cell membrane will make the transmembrane voltage of the membrane cell increase rapidly to a value where suddenly the cell membrane conductance rises. This will cause some changes to the structure orientation of the lipid bilayer by forming pores. From a previous study, irreversible electroporation occurs when a membrane cell receives electric field above the threshold of the transmembrane

voltage, which makes the cell membrane permeable (poration occurs) until the cell is damaged or because the membrane loses its homeostasis. This is different from reversible electroporation, where the membrane cell receives electric field below the threshold of the transmembrane voltage and still makes the cell membrane permeable (poration occurs) but the lipid bilayer can still rearrange its structure back to normal because the electric field received is below the threshold [35, 59, 62].

Electroporation occurs in all membrane cells including organelles in the cell. Initial electroporation releases calcium from the endoplasmic reticulum, which is then followed by delayed calcium redistribution within the cytoplasm. In addition, calcium can also enter the cytoplasm from extracellular space by plasma membrane electroporation. The electroporation also occurs to the mitochondria and calcium penetrates the mitochondrial membrane, causing mitochondrial disruption that releases cytochrome c and other death molecules such as SMAC/Diablo, EndoG, and AIF. The release of all these things from the mitochondria becomes the starting point for programmed cell death, called APOPTOSIS [35, 62]. Figure 2 illustrates how the process going on after electroporation affects the structure and function of a cell.

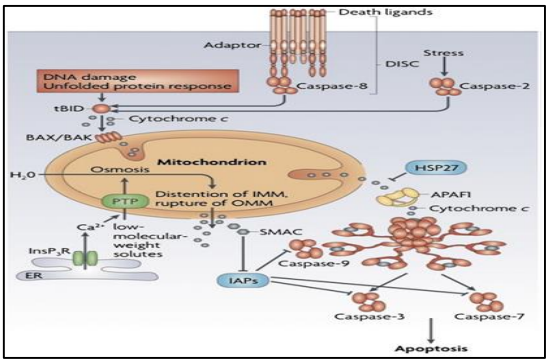


Figure 2 Apoptosis biochemical processes and stimuli

■5.0 CONCLUSIONS

Even though magnetic field is better than electric field, previous findings are not enough to indicate the required value of magnetic field intensity for any given treatment. Moreover, researchers should also consider the results for in vitro and in vivo conditions. The most important thing to determine is the duration of treatment, value of magnetic field, type of cancer, induction value of magnetic field with a specific intensity, and focusing the treatment on cancer cells only. In conclusion, electric field plays a key role during tumour or cancer therapy and in the electroporation that affects the starting point of apoptosis for programmed cell death for the cancer cells.

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