The Good and the Bad of Cell Membrane Electroporation

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Abstract

Electroporation is used to increase the permeability of the cell membrane through high-voltage electric pulses. Nowadays, it is widely used in different areas, such as medicine, biotechnology, and the food industry. Electroporation induces the formation of hydrophilic pores in the lipid bilayer of cell membranes, to allow the entry or exit of molecules that cannot otherwise cross this hydrophobic barrier. In this article, we critically review the basic principles of electroporation, along with the advantages and drawbacks of this method. We discuss the effects of electroporation on the key components of biological membranes, as well as the main applications of this procedure in medicine, such as electrochemotherapy, gene electrotransfer, and tissue ablation. Finally, we define the most relevant challenges of this promising area of research.

Keywords: Electroporation; cell membrane; electrochemotherapy; gene electrotransfer; tissue ablation; nanotechnology

1. Introduction

Cell membrane electroporation, also known as electroporation,1 is an effective method for internalization of various molecules into biological cells, with increasing number of applications in oncology,2,3 gene therapy,4–6 tissue ablation,7–9 food technology10,11 and nanotechnology.12

Electroporation depends on the nature of the molecular constituents of biological membranes and their behavior in electric field. The first part of this article thus dissected out the structure of the cell membrane and describes the main transport mechanisms across this barrier. In the second part, the mechanistic principles of electroporation are presented, followed by a description of the influence of an externally applied electric field on specific cell-membrane components, such as lipids and proteins, as well as the cytoskeleton. Finally, the advantages, disadvantages, and remaining challenges of electroporation are critically discussed.

1. 1. Structure of the Cell Plasma Membrane

The plasma membrane is basically a 6–10 nm-thick biological structure that surrounds every living cell, and it provides a selective barrier between the intracellular and extracellular environments.13 Plasma membrane thickness of some cells can however be much larger than this basic value, for example due to glycocalyx, a highly charged layer of membrane-bound biological macromolecules attached to the membrane (e.g., endothelial and epithelial cells), or the membrane skeleton, a specialized part of the cytoskeleton closely coupled to the plasma membrane. The main function of the plasma membrane is to keep the constituents of the cell inside, while preventing unwanted substance to enter the cell. At the same time, it mediates the selective transport of essential nutrients into the cell, and of waste products in the opposite direction.14

The cell membrane provides a selective barrier due to its unique structure, which consists mainly of amphiphilic phospholipid molecules. These form a continuous double layer (the ‘phospholipid bilayer’) that has a profoundly hydrophobic core. The proteins embedded in or associated with this structure endow it with specific functions, such as the selective passage of molecules and ions. Cell shape is primarily determined by interactions between the cell-membrane components, the cytoskeleton, and the extracellular matrix,14,15 however factors contributing to the cell shape are much more complex.16–19
As well as the major lipid constituents of the plasma membrane, the phospholipids, there are two other lipid species that are very important: sterols and glycolipids. Cholesterol is the main sterol-based lipid molecule in the plasma membrane. It is intercalated between the lipid tails of the adjacent phospholipid molecules in the phospholipid bilayer thus increasing their ordering. In this way, it reduces membrane fluidity. Glycolipids (e.g., glycosides) are very important cell-surface markers that serve as specific determinants for cellular recognition and cell-to-cell communication, and as receptors for different biomolecules. The fatty acid chains in the phospholipids and glycolipids usually contain an even number of carbon atoms, and can be saturated or unsaturated, i.e., they can contain one or more double bonds. The length of a fatty-acid chain and the number of double bonds that it contains have profound effects on the internal energy of the cell membrane; i.e., on its order and fluidity.

1.2. Molecular Transport Through the Plasma Membrane

The cell plasma membrane is selectively permeable, whereby the passage into the cell of molecules needed for its survival is highly regulated. The transport of molecules through the plasma membrane can be passive or active. Passive transport does not require energy, and its rate is governed by the physicochemical properties of the cell membrane, visco-elastic properties on both sides of the membrane, physicochemical and electrical properties of the media on both sides of the membrane, and the number of double bonds that it contains have profound effects on the internal energy of the cell membrane; i.e., on its order and fluidity.

### Table 1. Different methods used to manipulate cell-membrane permeability.

<table>
<thead>
<tr>
<th>Method</th>
<th>Main characteristics</th>
<th>Applications</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sonoporation mediated by microbubbles</td>
<td>Transient perforation of the plasma membrane; noninvasive</td>
<td>Drug and gene delivery</td>
<td>29-31</td>
</tr>
<tr>
<td>Lipid or lipid-like vesicle fusion</td>
<td>Oral delivery; protects a loaded drug; release of a drug in a controlled way</td>
<td>Drug delivery</td>
<td>32,33</td>
</tr>
<tr>
<td>Virus fusion</td>
<td>Injection; can trigger an immune response</td>
<td>Gene delivery</td>
<td>34</td>
</tr>
<tr>
<td>Cytolytic toxins</td>
<td>Bacterial cytotoxic proteins</td>
<td>Virulence-targeted therapies</td>
<td>35</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>High intensity focused ultrasound; generation of cavities due to ultrasound oscillation</td>
<td>Drug and gene delivery; tissue ablation</td>
<td>36-38, 27,39</td>
</tr>
<tr>
<td>Electroporation</td>
<td>High voltage electric pulses; formation of hydrophilic pores in the plasma membrane</td>
<td>Drug and gene delivery; tissue ablation</td>
<td></td>
</tr>
</tbody>
</table>

The main physiological role of the cell plasma membrane is to control and regulate the flux of molecules or ions into and out of the cell. The selectivity of the plasma membrane for the passage of molecules or ions is very high, and therefore for therapeutic or biotechnological reasons, the aim is to create procedures that enable the manipulation of transmembrane transport, ideally in a relatively controlled fashion. Caution is however needed, as treatments to increase the permeability of the plasma membrane can also result in increased molecular efflux, which can then induce cell death. On the other hand, the efflux of molecules from cells can also be exploited under certain conditions in biotechnology, to extract bioproducts.

Several methods to increase the permeability of biological membranes have been described. Table 1 gives the main characteristics and applications of the main biochemical (lipid and polymer particles, microbubbles), biological (viral), and physical (ultrasound, electroporation) methods for plasma-membrane permeabilization.

In this article, the focus is on electroporation, as the alteration of the cell membrane permeability induced by exposure to an externally applied electric field. Due to the membrane exposure to pulsed electric field, pores are formed in the cell membrane and increase its conductance for various hydrophilic molecules, such as peptides, nu-
cleic acids, and drug molecules. Electroporation is used in medicine and biotechnology for the delivery of drugs or genes into cells, for tissue ablation, for extraction of bioproducts from cells, and for microbial inactivation in food preservation.3,40–42

2. Principles of Plasma-Membrane Electroporation

Electroporation leads to increased permeability of the cell membrane as a consequence of the application of electric pulses. The term electroporation was coined by Neumann and colleagues in 1982.43 It originally described the process of electrically induced hydrophilic pore formation in the lipid bilayer (Figure 1).

![Figure 1](image-url) Formation of a hydrophilic pore in the membrane lipid bilayer. Exposure of the membrane to the electric field (E) allows the penetration of water molecules into the lipid bilayer. This induces reorientation of the polar headgroups of the lipids towards the penetrating water molecules, which ultimately leads to the formation of a hydrophilic pore, i.e. electroporation.

From the electrical point of view, the cell membrane can be regarded as a thin insulation sheet that is surrounded on both sides by an electrolyte. The transmembrane voltage is the difference in the electric potentials between outside and inside of the cell, which is due to the difference between the intracellular and extracellular ion concentrations. Specifically, different ions are present on either side of the membrane plane and have a concentration gradient across it, which results in formation of the transmembrane voltage. An electrical double layer is formed when a charged membrane plane is in contact with an electrolyte solution consisting of charged ions and oriented dipoles, resulting in accumulation of oppositely charged ions (counter-ions) and depletion of ions with the same charge (co-ions).44–46 Membrane itself has a net charge, which is dependent on the lipid composition, due to charged lipid head groups. The hydrophobic region of the membrane has a zero net charge. When the membrane is surrounded by an electrolyte, an interface forms, due to the separation of charged ions on either side of the membrane causing the formation of electrical double layer and consequently the transmembrane voltage.47–49 In the resting state, the cell membrane acquires the so called ‘resting (trans)membrane voltage, which is typically between –40 mV and –70 mV.1

Due to the opening or closing of ion channels in the cell membrane, the resting voltage can shift to more negative or more positive values, i.e., the membrane becomes hyperpolarized or depolarized.13 When a cell is exposed to an external electric field, an induced transmembrane voltage is superimposed on the existing resting transmembrane voltage. The resting transmembrane voltage is always different from zero, and is equal all around the cell since the membrane is an isotropic dielectric medium with constant dielectric permittivity. On the other hand, the induced transmembrane voltage is present only for the duration of the external electric pulse, and it is anisotropic, or dependent on the position on the cell membrane.50 Due to this induced transmembrane voltage, the structure and function of the cell membrane is locally modified.1 The membrane undergoes electrical breakdown, which results in increased permeability for virtually all molecules. As the cell membrane behaves as a two-dimensional liquid, it can return to its pre-breakdown state, and thus the cell can survive. In such a case, we talk about reversible electroporation. However, when the exposure of the cell membrane to an electric field is very intensive, the cell will die, even if the membrane manages to reseal. This type of electroporation is referred to as irreversible (IRE).40,51

In electroporation, three general levels have been defined: (1) no detectable electroporation; (2) reversible electroporation; and (3) IRE. The range over which each of these occur is characterized by the strength of the external electric field applied (V/cm) and the duration of exposure (seconds) to it. To achieve electroporation, longer pulse durations require lower electric field strengths. For example, for a pulse of 1 millisecond, no detectable elec-
Electroporation is seen from 0 V/cm to 250 V/cm, reversible electroporation occurs between 250 V/cm and 1750 V/cm, and IRE occurs above 1750 V/cm.\cite{52} In the first range for no detectable electroporation, if pores are formed, they are too small and/or too unstable to be detected. For reversible electroporation, the pores can provide a temporary pathway for molecular transport across the membrane, although once the electric pulse ceases, the membrane gradually reseals, the induced transport stops and most of these cells will survive and remain viable. For IRE, the membrane may not reseal or will reseal too slowly for cell to maintain its viability. These cells then lose their integrity, with the release of their contents, and ultimately die.\cite{51,53}

From a mechanistic point of view, electroporation is best described by the theory of hydrophilic pore formation. The external electric field induces a drop in the electric potential across the lipid bilayer, which leads to the formation of hydrophilic pores in the bilayer.\cite{43} Both, theoretical considerations and molecular dynamics simulations suggest that electroporation is initiated by the penetration of water molecules into the hydrophobic core domain of the lipid bilayer, which then causes a re-orientation of the adjacent lipid molecules, whereby their polar headgroups will follow the direction of the invading water molecules (Figure 1).\cite{54} First, single water molecules penetrate the hydrophobic core of the bilayer due to local defects in the lipid headgroup region. Then, these so-called water fingers expand into the hydrophobic core of the bilayer, and firstly form a hydrophobic pore.\cite{1,54,55} Subsequently, these pores are stabilized by re-orientation of the lipid headgroups adjacent to the water molecules, thus stabilizing the pore into its hydrophilic state and allowing more water, as well as other polar molecules and ions, to enter.\cite{40,55,56} After the electric field is eliminated, the pores that are formed and stabilized have lifetimes from milliseconds to minutes (Table 2).\cite{1} As indicated experimentally and theoretically, stability of the pores can be increased by intercalation of different molecules in the lipid bilayer.\cite{57-59}

Furthermore, membrane tension and mechanical stress can also play a role in formation of hydrophilic pores in the lipid bilayer.\cite{60-62} Applied electric field can cause lateral stress to the membrane influencing interfacial tension and pore formation.\cite{55} With a reduction in membrane tension in the lateral plane a decrease in the interaction between the phospholipid molecules occurs and with it an increase in ion permeability.\cite{63}

### Table 2. Steps in the formation of hydrophilic pores during electroporation of a lipid bilayer.\cite{1}

<table>
<thead>
<tr>
<th>Step</th>
<th>Main characteristics</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>Membrane electrical conductivity and permeability start to increase</td>
<td>Nanoseconds (conductivity for electric current);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>microsec (perm for ions and molecules)</td>
</tr>
<tr>
<td>Expansion</td>
<td>Conductivity and permeability persist and intensify</td>
<td>Until the end of the pulse (up to milliseconds)</td>
</tr>
<tr>
<td>Partial recovery</td>
<td>After the external voltage ceases, membrane conductivity and permeability decrease rapidly, but not to zero (i.e. not to the pre-poration state)</td>
<td>Microsec (perm for electric current);</td>
</tr>
<tr>
<td>Resealing</td>
<td>The membrane recovers to its physiological state of impermeability</td>
<td>Seconds to minutes</td>
</tr>
<tr>
<td>Memory</td>
<td>The cell can show alterations to stressors before finally returning to its normal state</td>
<td>Hours</td>
</tr>
</tbody>
</table>

**3. Effects of an Electric Field on Cellular Structures**

Cells consist of many different components, and an external electric field can affect these in different ways. Some of these alterations are necessary for the cell membrane electroporation to occur. However, others are not wanted, as they can induce cell death. Thus, attempts are made to reduce the unwanted effects as much as possible.

We are focusing here on the effects of an external electric field on three main cellular structures: the lipids that form the plasma membrane; the proteins associated with the plasma membrane; and the cytoskeleton that lies under the plasma membrane and imposes shape to the cell (Figure 2).
packed, and with lower internal order. Such lipid bilayers are no longer stable and are prone to undergo lateral phase separation. The cumulative result here is that the physiological functions of the cell membrane are altered, which can lead to cell damage, and even to cell death.\textsuperscript{69–71}

It has been reported that electroporation induces lipid peroxidation in bacteria, plant cells, and mammalian cells, as well as in liposomes made from polyunsaturated phospholipids.\textsuperscript{1} The origins of ROS are diverse. It has been suggested that electric pulses can generate ROS by triggering redox reactions in the water medium, on the membrane surface, and at the electrode–electrolyte interface.\textsuperscript{72,73} However, electric pulses initiate creation of ROS also inside the lipid bilayer and in the cell. In addition, there are always some ROS already present in the system.\textsuperscript{74,75} All ROS, no matter their origin, can result in peroxidation of lipids during electroporation; however, as ROS are short-lived, only those generated in close proximity to the cell membrane will cause lipid damage. It has been demonstrated that ROS peroxidize only the parts of the membrane that are electroporepermeabilized. These reactions reach their peak a few seconds after application of electric pulses, and then gradually diminish.\textsuperscript{76}

3. 2. Effects of an Electric Field on the Membrane Proteins

Membrane proteins are molecules associated with (i.e., peripheral) or embedded in (i.e., integral) the lipid bilayer of the cell membrane, and they are mainly responsible for all of the specific functions of the biological membranes.

Cell membrane electroporation affects membrane proteins to different extents, where the worst case scenario leads to their inactivation by denaturation, due to the local increase in temperature induced by the electric pulses.\textsuperscript{77} For example, it was shown that exposure of cells to electric pulses increased the conductivity of transmembrane Na\textsuperscript{+}/K\textsuperscript{+}-ATPases\textsuperscript{1} and decreased transmembrane ionic currents through voltage-gated ion channels.\textsuperscript{78} Gating potentials of voltage-gated ion channels are in the range of 50 mV. Therefore, when electric pulses are applied, these channels will open and can experience very large ion currents. This can also inflict irreversible damage to the channel proteins as a result of the local Joule heating or chemical modifications.\textsuperscript{79} The recovery of damaged membrane proteins is much slower than their opening and closing. While channel closing occurs in microseconds, their opening can take even tens of minutes.\textsuperscript{79} The consequences for the cell can therefore be serious, and even fatal.

3. 3. Effects of an Electric Field on the Cytoskeleton

The cytoskeleton is a cytoplasmic protein structure that is attached under the cell plasma membrane. As it is attached to the plasma membrane, it shapes the cell and has important roles in cell adhesion and migration. The
main components of the cytoskeleton are microfilaments, intermediate filaments, and microtubules.\textsuperscript{13}

The application of electric pulses can affect the integrity of the cytoskeleton. Exposure of cells to electric pulses can disrupt the network of microfilaments and microtubules. These effects are voltage-dependent and reversible, as the cytoskeleton can fully recover within hours without significant loss of cell viability.\textsuperscript{1,80} The disruption of microfilaments was shown to even protect the cell from being killed by external electric pulses.\textsuperscript{81} Electroporation of vesicles with actin filaments showed that membrane rigidification occurs, which blocks any large deformation of the vesicles, and prevents the formation of large membrane pores.\textsuperscript{82} The mechanism of cytoskeleton disruption includes conformational changes and electromechanical processes, although it remains not entirely clear to date.\textsuperscript{83,84} Atomic force microscopy has revealed a decrease in membrane stiffness, leading to the rippling and destabilization of microfilaments. The main reason for the morphological changes observed was shown to be the impaired attachment of the cytoskeleton to the cell membrane. Electroporation often results in cell swelling due to the induced osmotic imbalance, and the resulting swelling force is an important factor in the dislocation of the cytoskeleton from the membrane.\textsuperscript{1}

4. Advantages and Disadvantages of Cell Electroporation

Electroporation is an efficient method for the manipulation of cell membrane permeability. It can be applied to all types of cells, and no matter which stage of the cell cycle they are in. Its efficiency depends on the size of the cell, as stronger electric fields are required for induction of pore formation in smaller cells than in larger cells. Moreover, the electrical properties of the tissue also greatly influence the electroporation process, such as its conductivity.\textsuperscript{85} As the transport of materials into and out of electroporated cells is not specific, an ionic imbalance can occur, which can be harmful for the cell. Thus, for each specific application of electroporation, the electric pulse parameters need to be appropriately adjusted to minimize unwanted cell damage, or even cell death.\textsuperscript{53}

The most widely used applications of electroporation in medicine, electrochemotherapy (ECT), electro-transfer of genes (GET), and irreversible electroporation (IRE) for tissue ablation are illustrated in Figure 3.

4.1. Electrochemotherapy

Electrochemotherapy (ECT) is a local treatment that includes chemotherapy followed by tumor-directed elec-

Figure 3. The main applications of electroporation in medicine. (a) Electrochemotherapy uses electroporation to increase the uptake of chemotherapeutic drugs into cells, thus boosting their cytotoxic effects. (b) Gene electrotransfer uses electroporation to transfer DNA or RNA molecules into cells, to induce expression of the desired proteins. (c) Irreversible electroporation (IRE) causes cell death and is used to nonthermally ablate tissue (Figure adapted from reference 86).

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tric pulses, to increase the drug delivery into the malignant cells. Electric pulses are applied through metal plate or needle electrodes, to permeabilize the membranes of the cells, and hence to increase the uptake and effectiveness of the drug that was injected prior to the application of the electric pulses.77

Electrochemotherapy is simple and easy to perform. It is also a relatively inexpensive treatment. To perform ECT, we need an electric pulse generator (i.e., an electroporator) and suitable electrodes. The treatment can be performed on practically any part of the body. After the treatment, patients do not require special care, nor post-treatment medication. The main advantage of ECT when compared to other techniques is that it combines chemotherapy and the application of electric pulses. The targeted cells die in a more controlled manner, which results in slower shrinkage of the tumor, without development of massive necrosis that represents a major burden for patients and is accompanied by the risk of complications, such as infections.88

As well as these advantages, ECT also has some disadvantages. One of these is the pain that patients can experience during the application of the electric pulses as well as muscle contraction.85 The factors that can limit the use of ECT include the size of the tumor89 and difficult accessibility of a tumor by electrodes. For safety reasons, ECT is currently contraindicated for patients with cardiac pacemakers and patients on anticoagulant therapy.3,90

4. 2. Gene Electrotransfer

Gene electrotransfer (GET) uses high-voltage electric pulses to deliver DNA or RNA molecules into cells. In oncology, this is used to induce anticancer effects in tumor cells.4,6 GET can also be used for DNA or RNA vaccination, or for gene therapy, as it improves the expression of pertinent proteins.91 GET can be used to treat cardiovascular, autoimmune, and infectious diseases. Two specific benefits of GET are that it does not induce unwanted specific immunity, and that it lowers the risk of integration of therapeutic nucleic acids into the host genome, or their environmental spread.6 Nowadays GET is among the most promising nonviral methods for gene delivery to cells, due to its safety, efficacy, flexibility, ease of application, and relatively low cost.4,92

The main obstacle against the more widespread use of GET, particularly in human medicine, is that when applied in vivo, there can be substantial increases in the local temperature and large changes in the pH close to the electrodes, both of which reduce the efficacy of the therapy.3,92

4. 3. Irreversible Electroporation Ablation

Electroporation, as IRE, is used as a minimally invasive surgical technique for tissue ablation.7 With this procedure, it is possible to ablate undesirable tissue in a controlled and precise manner, without damaging the surrounding critical structures.93

There are different minimally invasive methods for tissue ablation, but IRE has certain advantages over these. IRE is not temperature based, and therefore the target tissue can be destroyed without overheating of the tissue. IRE is easy to apply, the local blood flow does not influence its efficacy, and it does not require the use of supportive drugs. It affects only the membranes of living cells, while the extracellular structures remain intact. The result is less scarring and faster healing of the treated tissue.94–96 One of the most promising applications of IRE in medicine is for cardiac ablation after atrial fibrillation.97,98 This is a catheter-based ablation, and due to its advantages over the contemporary ablation procedures, it has also been recently transferred to human cardiology.99,100

On the other hand, IRE can damage the entire tissue that is exposed to the electric pulses if the operating parameters are not correctly selected. Therefore, meticulous treatment planning and setting of the correct electroporation parameters are important, to avoid such damage.101

5. The Challenges Ahead

Electroporation of biomembranes has been studied and developed over the past 40 years; nevertheless, there remain some challenges for further improvement of this methodology.

One fundamental challenge that remains to be resolved for biomembrane electroporation is to identify the underlying molecular mechanisms. Only full understanding of the phenomenon at molecular level will allow unraveling its full potential and its reliable control. For example, the contribution of electric pulses to increased cell membrane permeability due to lipid peroxidation and protein modifications are far from being well understood today.

Preclinical and clinical trials have confirmed the great potential for electroporation-based treatments for cancer and gene therapy, as well as in tissue ablation. However, it is evident that there remains room for further technical improvements to increase the precision and specificity of these treatments, one of the possibilities is through the use of nanoparticles for enhanced electroporation efficiency.102 Furthermore, the reduction or elimination of the serious side effects that sometimes occur is of great importance.6,85,103 In this context, the processes that occur directly at the electrodes inserted into the tissue during pulse applications need to be better controlled, such as the electrochemical reactions, bubble formation, and local large changes in pH.

Last, but not least, a major problem for the use of electroporation in medicine that awaits resolution is reduction of the intensity and the extent of muscle contraction during the treatments. This would attenuate or even...
eliminate the pain that treated patients experience today, without the need for muscle relaxants. In this respect, trials that are investigating high-frequency bipolar electroporation pulses appear to be very promising.  

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