International Journal of Pharmaceutics 423 (2012) 3–6

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Mini review

Drug delivery by electropulsation: Recent developments in oncology

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ARTICLE INFO

Article history:
Received 15 February 2011
Received in revised form
13 September 2011
Accepted 26 September 2011
Available online 1 October 2011

Keywords:
Drug delivery
Electro-pulsation
Electro-permeabilisation
Electro-poration
Photodynamic therapy
Cancer
Bleomycin
Cis-platin

ABSTRACT

Electro-permeabilisation allows the free access of polar compounds to the cytoplasm by a reversible alteration of the cell membrane. It is now used in clinics for the eradication of cutaneous solid tumors. New developments predict its future applications for other anti-cancer treatments.

1. Introduction

Among the physical methods for drug delivery, electric field induced membrane permeabilisation (electro-permeabilisation, electroporation) appears as one of the most mature ones. For almost 20 years, it was developed for an in vivo use and clinical applications. This is now a loco-regional therapy for disseminated cutaneous and subcutaneous tumor lesions (such as melanoma). In this mini-review, after a short description of the biophysical mechanisms supporting electro-permeabilisation and their consequences for more practical applications, the present state of the art on electro-chemotherapy will be reported. In a final part, promising developments for a targeted delivery in connection with nano-biotechnologies will be described with the first reports for photodynamic therapy.

2. Electrodelivery at the single cell level

From Maxwell equations and electrodynamics of dielectric, a cell can be considered as a hollow sphere of dielectrics (the plasma membrane) embedded in and containing a conductive medium. In simpler words, when the field is present, the cell behaved as a closed capacitor. As a result, the field induces a size and position dependent membrane voltage modulation. This is present after a loading time of the order of the microsecond. Membranes become permeabilised when the field induced trans-membrane voltage reaches locally (on the cellular caps facing the electrodes) a critical value. At the single cell level, different steps can be observed (Teissie et al., 2005):

(1) "Induction step" (time scale microsecond or less): the field induced the membrane potential difference increase which gave local defects (may be due to kinks in the lipid chains) when it reached a critical value (about 200 mV). A mechanical stress was present with a magnitude that depends on the buffer composition.
(2) "Expansion step" (micro to millisecond): these defects expended as long as the field was present and with a strength larger than a critical value. Again, an electromechanical stress remained present.
(3) "Stabilization step" (millisecond): as soon as the field intensity was lower than the threshold value, that is mentioned in step 1, stabilization processes were taking place within milliseconds, which brought the membrane to the permeabilised state for small molecules.

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doi:10.1016/j.ijpharm.2011.09.038

(4) "Resealing step": a slow resealing was then occurring on a scale of minutes. It was a first order process with a strong temperature control.
(5) "Memory effect": some changes in the membrane properties (a potency for macro-pinocytosis) remained present on a longer time scale (hours) but the cell behavior was finally back to normal (ability to grow).

Concerning drug delivery, the main fact is that permeabilisation stays present for seconds after the pulse (so-called resealing period). The post pulse repair mechanism appears as an active process involving energy provided from the cell (starved cells cannot reseal). There is a general agreement that very little is known about what is really occurring at the molecular level during membrane electro-permeabilisation. Lipids appear as the primary target of the field effect as in the case of liposomes. Nevertheless membrane proteins appear to be affected by a direct or by a back effect.

It is well accepted that the entry of small molecules, such as anticancer drugs, occurs mostly through simple diffusion after the pulse. A short lived electrophoretic loading is indeed present along the millisecond duration of the pulse (Pucihar et al., 2008). The passive loading during the slow resealing results in a fast and significant increase of drug concentration (100×), for products where no effective membrane transport is present. This is of major importance for drug delivery as it induces a high cytotoxicity in tumor cells when polar toxic drugs (bleomycin or cis-platin) are introduced in the cytoplasm. This is obtained even if their external concentration is low. Secondary effects are therefore limited.

The entry of charged macromolecules, such as plasmid DNA, occurs through a multistep mechanism involving the electrophoretically driven interaction of DNA molecules with the destabilized membrane during the pulse, a stabilization step during the second following the pulse and then its passage across the membrane. Successful DNA electro-transfer into cells depends not only on cell permeabilisation but also on the way plasmid DNA interacts with the plasma membrane. In tissues (i.e. for clinical developments), a critical problem is the limits for plasmid diffusion due to the extracellular matrix (Mesojednik et al., 2007; Henshaw and Yuan, 2008).

But gene electro-transfer is not the focus of the present mini-review. Recent pertinent reviews can be found in several papers (Escoffre et al., 2009; Andre and Mir, 2010).

3. Electrodelivery in tissues

This description at the single cell level can be adapted to be valid on tissues (cell associate). A fair agreement was found between mathematical simulation and experimental observations. The local field at the cell level is not the "macro-field" present externally on the assembly (tissue). The free diffusion of the drug can be hindered by the close contact of the cells and by the external matrix (Pucihar et al., 2007; Abidor et al., 1994a,b; Wasungu et al., 2009).

From the technology (design of applicators), it is possible to very specifically target certain tissues within the body with whatever drug, isotope, or other product. Delivery is desired in a specific situation (Cemazar and Sersa, 2007; Hojman, 2010).

Permeabilisation (and associated local delivery) occurs as long as it is possible to locally provide a field strong enough to be larger than the critical value reported in step 1. This is obtained by a proper design of the electrodes taking into account their geometry and the specific dielectric properties of a tissue. The efficiency in delivery is then under the control of the pulse cumulated duration. This parameter acts on the permeabilisation extend (step 2) and on the kinetic of the slow resealing (step 4). Drug delivery is obtained and appears to be further enhanced by a tissue response the so-called vascular lock. The application of electric pulses to the tumors induced instant but transient tumor blood flow reduction. This is followed by a vascular disrupting action due to an indirect action on the endothelial cells of the blood vessels (Hudej et al., 2010; Sersa et al., 2008).

This means that the drug does not need to be locally injected (IT) but its IV injection will be effective on the local tissue (tumor) where the electric pulse is applied. Again a massive inflow occurs allowing injecting a very limited amount of the drug.

4. Electrodelivery in clinics

The most impressive success of electro-pulsation in drug delivery is the clinical development of electro-chemotherapy (ECT). From the efforts of several teams with supports of the European Union (FP5 Cliniporator, FP6 Esope), standardized protocols are now provided to treat cutaneous tumors (Mir et al., 2006).

Basically, the drug (bleomycin or cisplatin) is injected at a low dose either IV or IT, then a series of 8 pulses of 0.1 ms (frequency up to 5 kHz) at a 1300 V to electrode width (cm) is delivered with plate or needle electrodes. It is observed to be painless for the patient. EU approved technologies are available associated to these protocols (Colombo et al., 2008; Hampton, 2011).

Local electro-loading of bleomycin or cis-platin is obtained on skin tumors submitted to local electric pulses after IV injection of the drug. More than 80 hospitals spread all over Europe are using this technology (almost as a routine practice). ECT is now proved to be an effective treatment in the palliative management of un-resectable recurrent disease in solid cutaneous and subcutaneous tumors of varying histology (mostly melanoma) with overall objective response rates of approximately 80–90%. ECT is now a loco-regional therapy for disseminated cutaneous and subcutaneous tumor lesions to be used as a new treatment modality to improve patient's quality of life (Campana et al., 2009; Quaglino et al., 2008; Giardino et al., 2006, 2010; Möller et al., 2009; Gaudy et al., 2006; Sadadcharam et al., 2008; Gehl, 2008; Testori et al., 2010; Kaehler et al., 2010; Landstroem et al., 2010; Jarm et al., 2010).

A key feature is that 0.1 ms pulses are applied to bring an efficient delivery for drugs (MW about 1000 Da) with almost no direct effect on the cell viability. Death can be "delivered" by inducing an irreversible permeabilisation (so-called IRE) by using more stronger pulses (Edd et al., 2006; Al-Sakere et al., 2007). No drug injection is required. Recent results showed that indeed very short ns pulses can eradicate skin tumors in a more effective way than longer pulses by an IRE process (Nuccitelli et al., 2010; Chen et al., 2011; Garon et al., 2007). The associated mechanisms are clearly different. No drug is needed. Furthermore it is observed that even if permeabilisation is triggered for divalent ions, it cannot support the inflow of drugs large as bleomycin (Deng et al., 2003; Bowman et al., 2010). While ECT does not appears to have a cell selectivity (as long as cells are sensitive to bleomycin), this is clearly not the case for ns IRE (Ibey et al., 2010).

5. Safety issues

The concerns of the safety of electro-delivery were accessed. They can be linked to the physical effects of the technology. Burning can be induced due to the high currents that are delivered. This is a main concern when using needles electrodes with a very small diameter. Their shapes result in a very high local current density. But burning is avoided when the standard operating procedures are followed.

The occurrence of a "molecular" response was recently investigated. No toxicity appears to be linked to "classical"

electro-permeabilisation in vivo. Differentially expressed genes were investigated by microarray analysis. ECT (and EGT) pulses induce a heat shock protein (HSP70) stress response mechanism. Nuclear effects are present such as repression of histone protein H4, a major protein involved in chromatin assembly, and down-regulation of components involved in protein synthesis. But no change in the expression profile of major tumor suppressor genes or oncogenes, no change in the expression of genes involved in the stability of DNA and no promotion of tumor genesis were detected. The expression of metastasis promoting genes was not increased after electro-chemotherapy (Todorovic et al., 2010; Mlakar et al., 2009).

The effects on muscle fibers were transient as the expression profiles 3 weeks after treatment were closely related with the control muscles (Rubenstrunk et al., 2004; Hojman et al., 2007). This was observed with plate electrodes. Nevertheless some deleterious damages were observed in old investigations when using needle electrodes where current induced effects may be present. Limited muscle damage and regeneration structural changes with loss of cell integrity and striation pattern were observed in some fibers after EGT (i.e. electrical conditions that are more drastic that those required for ECT in the standardized protocols). No difference in the force generation capacity was observed in the muscles 2 weeks after EGT.

6. New developments on delivery by electropulsation

6.1. Improved photodynamic therapy (PDT)

During many years due to the success in preclinical and clinical treatments, electro-delivery was mostly used to enhance the effect of bleomycin (and of cis platin). But the biophysical description of the processes supporting the trans-membrane transport predicts that it was effective for any kind of polar molecule (with a MW about 1 kDa). The effectiveness of the photodynamic therapy (PDT), a low-invasive and targeted therapy of cancer, could be intensified by increasing the intracellular transport of a photosensitizer. A disadvantage of photodynamic therapy is linked to the slow accumulation of photosensitizer in tumor tissue. Its accumulation is passive and therefore very limited when the product is hydrophilic. It is a slow process with a poor selectivity for the tumor. The dose that can load in the tumor can be too low to give a therapeutic effect. Electro-permeabilisation gives a free access the cytoplasm in the tissue volume where the field pulse is delivered. Recent studies in vitro showed on different cell systems an enhancement of photodynamic tumor therapy effectiveness by electroporation in vitro. Low doses of photosensitizers can therefore be used improving the safety of the treatment. Photosensitizers chlorine e(6) (C e(6)) at the dose of 10 μg/ml and aluminium phthalocyanine tetrasulfonate (AlPcS4) at the dose of 50 μg/ml were electro-loaded under ECT conditions and brought a fourfold increase in PDT cytotoxicity after light irradiation. This is a clear illustration of the difference in cellular uptake of foreign materials and of the associated therapeutic results between the normal cells and the cells treated electromagnetically. This conclusion allows reducing drug doses and exposure time of the cells to those drugs as compared with conditions routinely used in standard PDT (Labanauskiene et al., 2007; Labanauskienė et al., 2009; Saczko et al., 2010).

6.2. Metal nanoparticles delivery

Metal nanoparticles are proposed as new vehicles for drug delivery besides their use as contrast agents in MRI or other spectroscopic approaches (intracellular surface-enhanced Raman spectroscopy (SERS)). Loading is conventionally obtained by passive entry (endocytosis). This is a slow process with a rather poor reproducibility in the cellular localization. For imaging, electro-loaded nanoparticles are localized only in the cell cytoplasm by a very fast process (polylysine coating of the nanoparticle, a short incubation to give some surface absorption, a 1 ms ECT pulse). The procedure is reported to be completed in a very short period of time (less than 1 min) in the in vitro procedure (Tai et al., 2006; Lin et al., 2009).

6.3. Targeted PDT with metal nanoparticles

In all previous studies, targeting of electrodelivery is limited to a volume. Delivery is obtained where permeabilisation is triggered, i.e. the part of the tissue where the local field is high enough to induce membrane permeabilisation. This is controlled by the design of the electrodes and by the voltage applied between them. No specific recognition is provided. This was shown to be provided by the conjugation of the TiO_2 nanoparticles with a monoclonal antibody and the combination with electroporation (Xu et al., 2007). Labeling nanoparticles with the antibody is a routine procedure and can be easily monitored by using FITC tagged antibodies. The specificity of cell recognition brought by the antibody gives a targeted accumulation of TiO_2 nanoparticles on the target cancer cells. Cellular delivery is obtained by electro-pulsation with electrical parameters used for delivery of drugs (0.1 ms pulse duration). Photo killing is obtained after UV irradiation of the cells. Eradication of the cancer cells can be obtained when the particle cell mixture is pulsed while a very limited effect is observed without electro-pulsation. Furthermore the photo-killing is specific for the cells bearing the antigen specific of the monoclonal antibody.

7. Conclusions

Electric mediated drug delivery is now at a mature state. Electrochemotherapy is now used as a routine practice in oncology after almost 20 years of preclinical research. Electro-delivery is indeed open for more applications even if the molecular mechanisms remain poorly understood. One should mention that even it was developed on an empirical approach, it is a safe method. In connection with the newly introduced nano-biotechnologies, improvements in a more specific targeting can be reached to obtain a more specific targeting in the drug delivery.

Acknowledgements

This work was supported by grants from the ANR (Cemirbio, CMID) and of the EU FP7 (Oncomir). This was partly presented by JT as an invited lecturer along the "XVèmes Journées du GTRV "in Toulouse (December 6–8, 2010).

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