

SONOPORATION: THERAPEUTIC AID USING ULTRASONIC WAVES

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Abstract

Ultrasound, a traditional diagnostic modality has emerged as a budding non-invasive tool for drug delivery, gene therapy, and other therapeutic techniques. It is a mechanical wave energy generated in a medium as the oscillating pressure at frequencies above 20 kHz which is beyond the audible range. This exposure causes tissue heating, shear stress, and cavitation, which have been deployed for therapeutic usage. One such ultrasound technique is Sonoporation that employs the acoustic cavitation of micro bubbles generating transient pores on membrane enhancing delivery of large molecules into cells for targeted drug delivery and gene transfection. This review provides the main findings in the field of sonoporation, namely drug delivery, gene delivery, DNA transfer and its possible clinical application in dentistry.

Keywords: Cavitation, piezoelectric transducer, sonophoresis, gene therapy.

Introduction

It is well known that a sound is a form of mechanical energy that is propagated from one point to another by the interaction between the neighboring oscillating particles. [1] Acoustic waves with frequencies between 20 Hz and 20 KHz fall in the audible range. The term ultrasonic refers to sound waves whose frequency is greater than 20 KHz. One of the major triumphs in recent times in the field of medicine is Sonoporation. [2]

Definition: Sonoporation is defined as the interaction of ultrasound with

Ultrasonic contrast agents to temporarily permeabilize the cell membrane allowing for the uptake of various substances such as DNA, drugs, and other therapeutic compounds, from the extracellular environment. [1] It combines the capability of enhancing gene and drug transfer with the possibility of restricting this effect to the desired area and the desired time. [3]

The first case of Sonoporation or sonophoresis was published in the 1950's. Fellingner and Schmidt reported treatment of polyarthritis combining hydrocortisone with sonophoresis.[4] Another case of carbocaine

sonophoresis was successfully reported by Cameron. [3]

Principle

Sonoporation is based on ultrasonic waves, using a piezoelectric crystal transducer made of lead–zirconate–titanium or barium titanate. The waves are produced in relation to electrical impulse in a piezoelectric crystal which converts electrical energy to mechanical or vibrational energy. Subsequent to the outside perturbation, molecules oscillate in phase and transfer the kinetic energy to other molecules. [4]

Mechanism of action

Ultrasound radiation generates cavitation bubbles which collapse and transfer their energy to the skin causing the formation of a pore in the skin area. Ultrasound frequency is approx. 20kHz with intensity between 5-55 W/cm². [5] The tip has a distal end at a distance of 1mm to 10mm from the membrane. The ultrasound radiation can be continuous or intermittent for a period from 30 seconds to 5 minutes. 1 minute time is used for continuous exposure and about 10 to 20 minutes for intermittent exposure with a 5% duty cycle. The pores formed have a diameter ranging from 1µm to 100µm. [4,5]

The ultrasound waves can form pores by following ways:

1. **Cavitation effect:** Formation of gaseous cavities in the medium due to varying pressure in the medium caused by ultrasound waves. This involves both rapid growth and collapse of a bubble or the slow oscillatory motion of a bubble in a medium. Cavitation bubbles produce shock waves leading to disruption of the lipid bilayers and formation of aqueous channels in the skin, allowing entry of extracellular agents into the cytoplasm. [4]
2. **Thermal effects:** Absorption of waves increases the temperature of the medium.

Higher the absorption coefficient, severe the thermal effects. The increase in the temperature of the medium varies directly with the ultrasound intensity, frequency and exposure time. [6]

3. **Convective transport:** Exposure to ultrasound produces Fluid velocities in the porous medium due to waves generated in the diffusion cell and oscillations of the cavitation bubbles. [5]
4. **Mechanical effect:** frequencies more than 1MHz, cavitation ceases. But cyclic stresses due to density changes cause disruption of medium increasing the permeability.

This cavitation induced distortion of the lipid bilayer is the most important cause for ultrasonic augmentation of transdermal transport. [4,5,6]

Advantages [3,4]

1. Enhanced drug penetration
2. Control of transdermal penetration rate
3. Termination of ultrasound causes termination of drug delivery
4. Low risk of infection
5. Skin intact
6. Less pain
7. Less risk of systemic absorption

Disadvantages [3,4]

1. Time-consuming
2. Minor irritation

Applications: [7]

1. Gene delivery
 - Osteoinduction
 - Dental pulp stem cell induction
 - DNA transfer
2. Local drug delivery
3. Targeted drug delivery
4. Tumor cell killing
5. Apoptosis

Gene delivery: Technique for correcting defective gene with the normal gene is employed. A vector is used to deliver a therapeutic gene to target cell. The vector gene complex is used for topical delivery to the target cell. [4,7]

Other applications

Osteoinduction: Bone morphogenic protein is involved in healing and regeneration.[5,7]

Dental pulp stem cell induction: Possible by differentiation into odontoblasts will help in preserving the tooth and function. In vitro studies using Gene transfer of Gdf 11 were done in the canine tooth to induce differentiation of pulp cells into odontoblasts by sonoporation with microbubbles. Reparative dentin formation was stimulated. This could form a rationale for endodontic treatment.[3,4,7]

Drug delivery: Drugs delivered transdermally include NSAIDs, corticosteroids, antibiotics, chemotherapeutic and fibrinolytic drugs, insulin and vasodilators. These drugs can be incorporated into microbubbles, which in turn can target a specific disease site using ligands. The intensity for transdermal drug delivery is 0.5-3W/cm.[5,6,7]

Tumor cell killing: Noninvasive drug delivery system for cancer therapy by the ultrasound-mediated destruction of microbubbles. In vitro studies, using Bleomycin delivery have shown an effective antitumor effect in solid tumors of murine and human cell lines. [2,3]

Induction of apoptosis: Ultrasonic cavitation induced apoptosis compared to the conventionally reported instantaneous cell lysis and necrotic disintegration has been proposed by Ashush et al. [3,7]

Future Scope

Ultrasound-mediated transdermal transport via skin patches provides a sustained delivery of the drug over a period of about 7 days, eliminating the danger posed by the administration of chemotherapeutic agents. [2,3] Future prospective involve ultrasound guided drug release systems providing slow release of vaccines like for tetanus, which may need repeated booster shots. Current research using sonophoresis is in different areas like

cutaneous vaccination, transdermal heparin delivery, treatment of Alzheimer's or bone diseases. The potential appears never-ending. [1,4]

Conclusion

Sonoporation uses ultrasound with ultrasonic contrast agents so as to enhance cell permeabilization making it possible to deliver therapeutic drug agent non-invasively into the target cell.

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