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Sonoporation – The Healing Sound and Its Applications in Dentistry.

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ABSTRACT

Sonoporation employs the acoustic cavitation of microbubbles to enhance delivery of large molecules such as DNA into the cells of applied to heart, blood vessel, lung, kidney, muscle, head and neck tumour , in a cell disruption process called transformation and increases the permeability to bioactive materials which is usually used in molecular biology and gene therapy. Sonoporation is a promising drug delivery and gene therapy technique .This review helps us to understand the importance of Sonoporation and its applications in Dentistry.
Keywords: Sonoporation, gene delivery, microbubbles, cavitation

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INTRODUCTION

Ultrasound is an oscillating sound pressure wave with a frequency greater than the upper limit of the human hearing range that is 20,000 cycles per second (Hz) [1]. Ultrasound has wide and varied range of applications in the diagnostic field of medicine and dentistry.

The therapeutic effects of ultrasound are derived from its thermal and non-thermal properties. Sound waves at high intensity (1 – 1.5 Watts/cm^2) cause tissue vibration that produces heat in the treatment field. The production of heat increases blood flow to tissues, which delivers essential nutrients and removes waste. This thermal property of ultrasound is traditionally used for therapy in musculoskeletal conditions [2].

At low intensity (<0.3 – Watts/cm^2) the non-thermal property of sound waves are utilized in therapeutic field. At this intensity sound waves exert pressure on the cell wall, caused by cavitation and micro-streaming. These effects cause changes in the cell membrane permeability and thus the diffusion of cellular metabolites causing reduction in edema, pain modulation and increased capillary density which increases local circulation [3]. This low intensity ultrasound therapeutics encompasses sonoporation.

SONOPORATION

Definition

Sonoporation or cellular sonication is the use of ultrasound to temporarily modify the permeability of the cell membrane allowing for the uptake of various substances such as drugs, DNA and other therapeutic compounds, from the extracellular environment [4]. This transient membrane alteration leaves the compound trapped inside the cell after ultrasound exposure.

Principle

The technique of sonoporation is based on ultrasonic waves. These waves are produced in the sonoporator that converts the electric energy into mechanical or vibrational energy. The ultrasound radiation is given from ultrasound machine to the microparticles suspension. The ultrasound radiation is applied effectively to generate cavitation bubbles [5]. Thus; sonoporation employs the acoustic cavitation of microbubbles to enhance delivery of these large molecules through formation of transient pores in the cell membrane facilitating trans-membrane transport of drugs into the cell. Inertial cavitation is the process of formation, oscillation and collapse of gaseous bubbles driven by an acoustic field [6].

These sound waves provoke the formation of pores by possible five mechanisms, as follows: [6] (Figure 1)

- Push – During its expansion phase, a microbubble might touch a cell membrane surface, possibly pushing it apart.

- Pull – During the contraction phase of an oscillating microbubble, the plasma filling the void left by the contracting bubble might pull the cell membrane towards the microbubble, possibly disrupting the plasma membrane.
- Jetting – Jetting is the asymmetric collapse of a bubble, creating a funnel-shaped protrusion through the bubble which is directed towards a boundary.
- Streaming – If a microbubble is attached to a cell membrane, the fluid streaming around the oscillating bubbles creates enough shears that could induce cell membrane rupture.
- Translation – Owing to radiation forces, lipid-encapsulated microbubbles could translate through cell membrane. The microbubble may lose part of its shell whilst passing through the cell membrane.

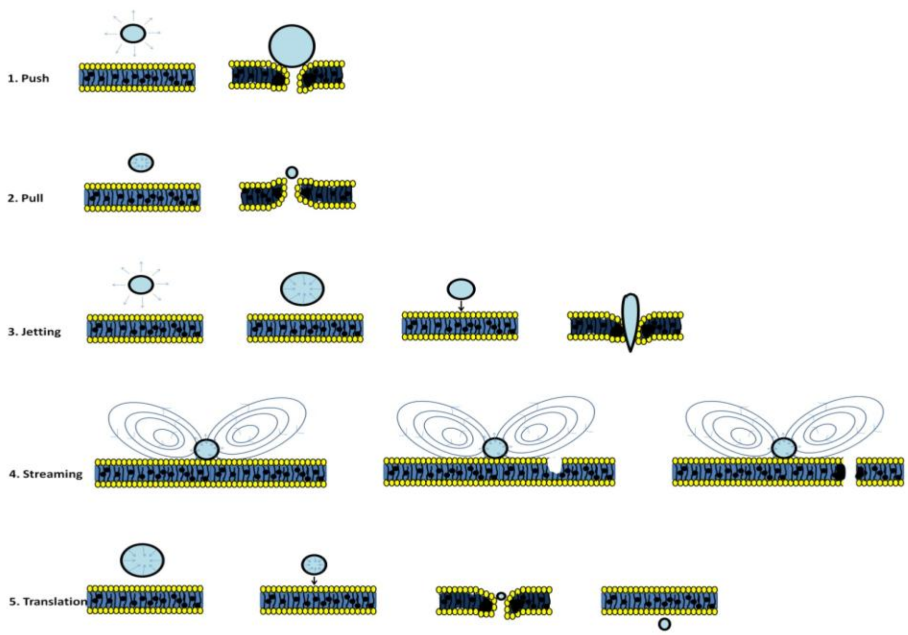

Figure 1: Mechanism of pore formation.

Figure 2: Sonoporator

Application of sonoporation in dentistry

- Gene delivery
- Local drug administration
- Tumor cell destruction
- Induction of Apoptosis

Gene delivery

Induction of reparative dentin formation:

Misako Nakashima studied that gene therapy has the potential to induce reparative dentine formation for potential pulp capping [8, 9] In their research acoustically active materials, microbubbles, have been developed to bind or trap genes. The sonotransfection was performed in the amputed dental pulp. Gene transfer of *Gdf1 1* was optimized to induce differentiation of pulp cells into odontoblasts in vitro by sonoporation with microbubbles. Dental pulp tissue irradiated by ultrasound showed significant efficiency of gene transfer which stimulated the reparative dentin formation during pulpal wound healing in canine teeth. These results provide the scientific basis and rationale for gene therapy in endodontic treatment.

Local drug administration

Transdermal drug delivery is an attractive alternative to conventional drug delivery methods such as oral administration and injections. Local drug delivery ensures sufficient drug concentration at the diseased site while limiting toxicity for healthy tissues. Drugs that can be delivered transdermally includes NSAIDS, anesthetic agents, antibiotics, anti-cancer drugs, fibrinolytic drugs, corticosteroids, insulin and vasodilators [5]. These drugs can be incorporated into microbubbles, which in turn can target a specific disease site using ligands such as the antibody [5]. The drugs can be released ultrasonically from microbubbles that are sufficiently robust to circulate in the blood and retain their corgo of drugs until they enter an insonated volume of tissue. The intensity commonly used for transdermal drug delivery is 0.5 – 3.0 W/cm^2.

Sonothrombolysis

Recent studies have concluded that ultrasound can aid the dissolution of blood clot either on its own or in combination with microbubble contrast agents and fibrinolytic drugs.[10] This method is known as sonothrombolysis. This may facilitate the permeation of the drug into the clot, or the mechanical action of the ultrasound affects the fibrin mesh, allowing better access for the drug.

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Tumor cell destruction

Destruction of tumor cells using ultrasound has been proposed as an innovative drug delivery system for cancer chemotherapy. Sonoporation in cancer chemotherapy not only act by destructing cancer cells but also avoids the adverse effects of anticancer drugs. Iwanga et al., evaluated the efficiency of sonoporation towards growth inhibition of human gingival squamous carcinoma cells Ca9-22 [11]. Sonoporation was used to deliver bleomycin and transfect a edtB-expessing plasmid into Ca9-22 cells. The result showed that tumor almost disappeared during the four week experimental period. Takagi et al., administered a low dose of bleomycin by sonoporation with the anti-EGFR antibody producing a marked growth inhibition of Ca9-22 cells in vitro [12].

Induction of Apoptosis

Apoptosis is an organized process of cell death occurring naturally for unneeded cells. Ashush et al., [13] and Ando et al., [14] concluded that exposure of cells to ultrasonic cavitation induced apoptosis in addition to the conventionally reported instantaneous cell lysis and necrotic disintegration. This process may be used in future for killing cancerous cells and other cells of benign growths before malignant change takes place or reduction in size of the growth before surgeries [5].

CONCLUSION

In advent of many new and advanced technologies, Sonoporation serve as a boom in the field of therapeutic dentistry. The possibility of transfer of therapeutic genes and controlling of gene release would be a advancement in the field of Gene therapy. The non-invasiveness and simplicity of this technology has made it superior to other physical methods like electroporation. Ultrasound mediated sonoporation is an upcoming research area in the therapeutic field of medicine and dentistry.

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